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Palladium complexes as promising antimicrobial agents

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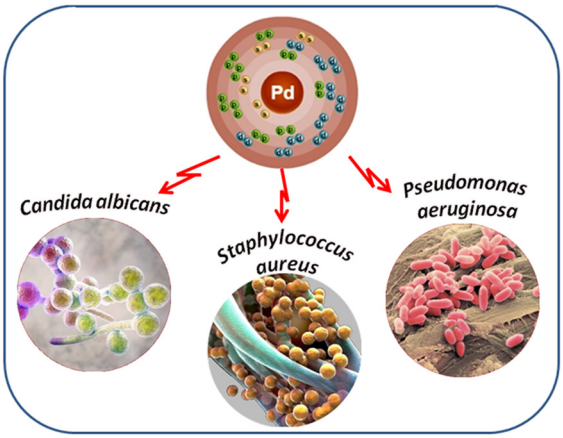
The review presents a summary and systematic analysis of the literature data on the antibacterial and antifungal activity of palladium complexes with organic ligands published over the past three years. The structures of different types of stable complexes are discussed. Taking into account the great structural diversity of the compounds under consideration, the classification of the complexes is performed in terms of the nature of donor centres of the initial ligands. A group of palladium phthalocyanine complexes for photodynamic therapy is considered separately. The final section is devoted to palladium complexes with terpene ligands, which are of scientific interest to the authors of this review.
The bibliography includes 97 references.
Keywords: palladium complexes, organic ligands, antibacterial activity, antifungal activity.



Contents

1. Introduction 1
2. Palladium complexes with N- and O-donor ligands 2
3. Cyclopalladated compounds. Palladium carbene complexes 11
4. Palladium complexes with sulfur-containing ligands 12
5. Palladium complexes for antimicrobial photodynamic therapy 20
6. Palladium complexes with terpene ligands 22
7. Conclusion 23
8. List of abbreviations and designations 24
9. References 24

1. Introduction

Almost all publications on the evaluation of antimicrobial activity of metal complexes begin with the discussion of a pressing problem of the rapidly growing resistance of abundant pathogenic strains to available clinical antibiotics and antifungal drugs. According to the World Health Organization,[†] antibiotic resistance is one of the top ten global public health threats to humanity in the 21st century.

The international scientific team with the participation of Australian researchers has made significant progress in addressing this problem.[1] Within the framework of the not-for-profit initiative Community for Open Antimicrobial Drug Discovery (CO-ADD), a large number of metal-containing compounds were screened for antimicrobial activity. Out of 906 compounds, 88 were found to show activity against at least one of the tested strains, including fungi, while displaying no cytotoxicity against mammalian cell lines. An analysis of the results of the publication[1] demonstrated that palladium complexes are in the top three of 16 tested groups of compounds in terms of activity. For example, palladium compounds account for 14% of active and nontoxic agents, being second only to platinum complexes (18%). Unfortunately, palladium complexes have not been adequately addressed in the study.[1] In the review,[2] the prospects of metal complexes as antimicrobial agents are also considered, but no data on palladium compounds are reported. The lack of information stimulated us to analyze the studies aimed at evaluating the antimicrobial activity of palladium complexes, which were published in 2021–2023, summarize and systematize these results. We limited this review to the past three years because there is a number of previous review papers,[3–8] in which the results of the evaluation of metal complexes (including palladium compounds) as antibacterial

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[†] See https://www.who.int/ru/news/item/21-09-2016-at-un-global-leaders-commit-to-act-on-antimicrobial-resistance

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and antifungal agents are summarized. The knowledge of the types of active compounds is important for the design of new antibiotics with high antimicrobial potential.

The general strategic issues of the design of effective antibiotics require a knowledge of the target of the attack, the molecular target, and a possible mechanism of action.[5,9] Bacteria are prokaryotic cell organisms, which do not contain certain cell organelles compared to eukaryotic cells. Bacteria do not have a nucleus, and their genetic material is found in the cytoplasm in the form of nucleotide. Besides, these organisms are classified as either Gram-positive or Gram-negative, which is attributed to the structure of their cytoplasmic membranes. Gram-positive bacteria have a cell wall composed of a relatively thick peptidoglycan layer. Gram-negative bacteria have a difficult-to-access plasma membrane composed of lipopolysaccharides and use a porin (efflux) pump to export the required compounds into the cell and remove any unwanted waste from the cell. There are also other organelles found in both Gram-positive and Gram-negative bacteria, for example, a polysaccharide membrane called a capsule around their outer membrane. This capsule prevents the phagocytosis of bacteria by other organisms or human phagocytic cells. Bacterial cells have a cytoplasm, in which cellular processes take place. The cytoplasm contains all important cell organelles and macromolecules, such as ribosomes, plasmids and chromosomes. Bacterial cells also contain a cytoplasmic membrane consisting of proteins and phospholipids. This membrane is important for bacteria, controling the flow of molecules into and out of the cells. Some bacteria have flagella, which are whip-like structures, responsible for bacterial locomotion. Since bacteria have a single chromosome, their double-stranded DNA is located in the membrane-free region known as the nucleoid. Most of bacteria contain pili, which are whip-like appendages on the outer membrane of bacterial cells that help bacteria attach to surfaces. Finally, all bacteria have ribosomes that translate their genetic code.

Therefore, bacteria have multiple targets and each class of antibacterial agents is characterized by a specific mode of action against bacterial cells. Certain agents cause the mechanical disruption of the structures of bacterial cells, *e.g.*, of the cell membrane. Other agents act on bacteria through inhibition of the biosynthesis of particular macromolecules that are produced during bacterial cell division, growth and differentiation. Bacteria resist antibiotics through two main mechanisms: by decreasing the concentration of the antibiotic before it reaches the target or by changing the structure of bacterial organelles, that are antibiotic targets, in order to prevent the cell death.

In the review,[9] Boros *et al*. emphasized that the understanding of the mechanism, by which metal compounds exert their biological effects, and the knowledge of the key parameters required for enhancing these properties will allow the more rational design of new compounds. For example, palladium complexes can justifiably be compared with the known platinum-based clinical anticancer drugs, such as cisplatin, carboplatin and oxaliplatin. One of the key characteristics of many metal complexes is the active chemical ligand exchange responsible for the mechanism of action of the well-known metal-based agents used in the clinical practice, namely Pt^{II} complexes. In fact, the metal ion is covalently bound to important biomolecules, *e.g.*, DNA, proteins, enzymes, *etc*., inhibiting their function and leading to different types of cell death (*e.g.*, through the apoptosis and necrosis). After the intravenous infusion of cisplatin, the complex remains to a large extent unchanged due to a high concentration of chloride ions in the blood. After entering the cell, the complex undergoes aquation, *i.e.*, one or two ligands (chloride ions) are replaced by water molecules (because the chloride concentration in the cell is significantly lower than that in the blood). The resulting Pt^{II} particles are activated and then are bound to nuclear DNA, predominantly to the N(7) atom of guanine, to form mainly intrachain cross-links. These cross-links block the replication and cell division, interfering with RNA processing. Based on this mechanism, cisplatin and related DNA-binding agents are referred to as alkylating agents; in organic medicinal chemistry, these agents are termed as covalent inhibitors.

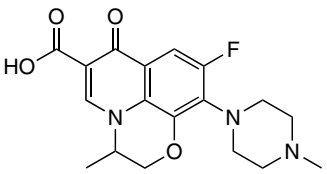
With a few exceptions, the studies on the comparative evaluation of biological activity of metal complexes and the corresponding initial ligands demonstrated that the complexes are significantly more active than the ligands. This is evidence of an important role of the metal ion in the mechanism of antimicrobial or anticancer activity of metal-containing agents. Numerous examples can be found below. Most of the authors explained this fact as follows. The complexation leads to an increase in the lipophilicity of transition metal ions due to the delocalization of π or p electrons of the ligands in the metal coordination sphere. This, in turn, improves the diffusion of the complex molecule through the cell membrane. Although the chelation plays an essential role in the antimicrobial behaviour of the complexes, other factors can also enhance and control this activity of metal complexes compared to the free ligands. These factors include the size and geometry of the complex, its dipole moment, the solubility, the nature of the donor centre, the redox potential of the metal ion, the bond length between the ligand and the metal, steric and pharmacokinetic parameters and the concentration of the compound. Besides, the changes in the behaviour of metal complexes towards different microbes can depend on the difference in the cell wall permeability of microorganisms.

This review presents examples of different types of palladium complexes with known antibacterial and antifungal activity. Selected results of relevant studies are given in the tables, the most significant activity values being highlighted in bold. These data demonstrate that palladium complexes are promising antimicrobial agents.

2. Palladium complexes with N- and O-donor ligands

Chemical modification of structures of the known drugs is a promising strategy for discovering more effective compounds in a particular pharmaceutical group, called 'the next in the class'. For example, three palladium complexes (**Pd1**–**Pd3**, Table 1) containing ofloxacin (**L1**) and the amino acids glycine or alanine as the ligands were evaluated as antimicrobial materials.[10]

Structure L1



L1 (Ofloxacin)

Ofloxacin is a broad-spectrum second-generation fluoroquinolone antibiotic against anaerobic and aerobic microorganisms and a specific inhibitor of bacterial DNA gyrase. The antibacterial activity of complexes **Pd1**–**Pd3** was evaluated against *Klebsiella pneumoniae* and *Escherichia coli*

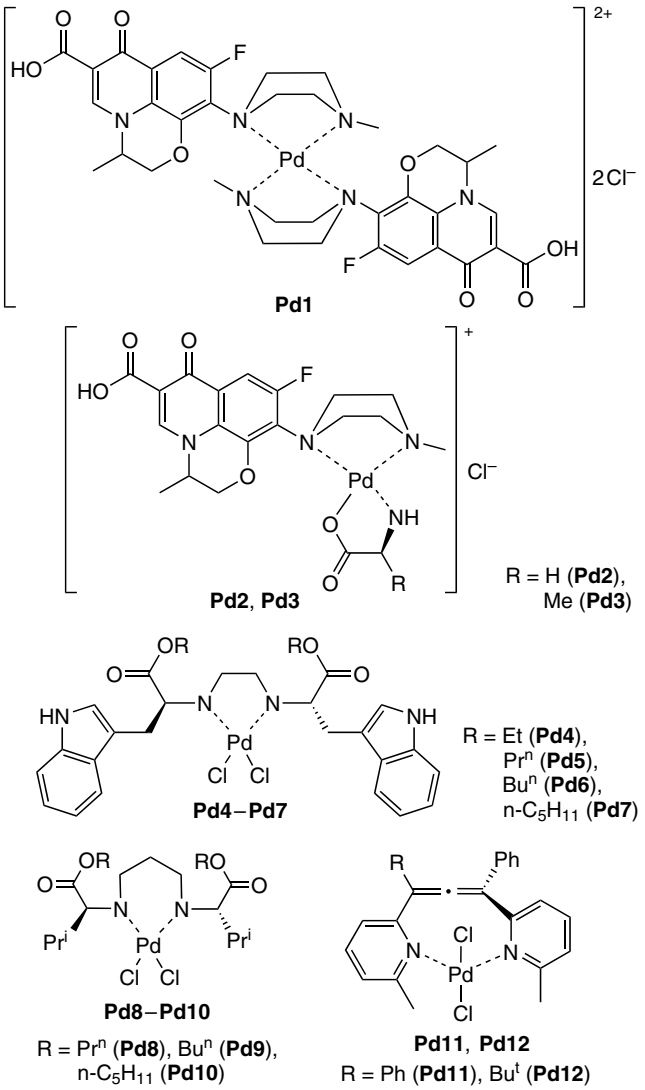
Table 1. Antibacterial activity of compounds **Pd1**–**Pd3** and the related ruthenium complex (ofloxacin as the reference drug).[100]

Compound	Inhibition zone[a]		Ref.
	K. pneumonia	*E. coli*	
Ofloxacin (**L1**)[b]	0.0	0.0	10
Pd1	**1.5**	**1.2**	10
Pd2	1.1	0.9	10
Pd3	1.4	0.6	10
$[Ru(\mathbf{L1})_2Cl_2]Cl$	0.4	0.3	11

[a] The diameter of the growth inhibition zone of microorganisms (in mm) in the presence of the agent (1 mg); [b] hereinafter, the number of the ligand corresponds to the number of the metal complex, in which it is involved.

strains. Ofloxacin was used as the reference drug (positive control), which proved to be inactive in these experiments.[‡] The coordination of ligand **L1** to palladium(II) gives rise to complexes **Pd1**–**Pd3** exhibiting bactericidal activity. It is worth noting that the activity of homoleptic complex **Pd1** is somewhat higher than that of mixed-ligand complexes **Pd2** and **Pd3**. For comparison, the authors cited the data for ofloxacin-based Ru^{III} complexes obtained previously,[11] which showed that it is preferable to use the corresponding palladium compounds.

Structures Pd1–Pd12



Ethylene- and propylenediamine derivatives were extensively studied as N,N-donor chelating ligands by Serbian researchers.[12–14] Chiral ligands containing amino acid moieties and their complexes with palladium are also of obvious interest. A wide screening of the antimicrobial activity of complexes **Pd4**–**Pd7** and the corresponding ligands containing a tryptophan moiety was performed (Table 2).[12] The authors used 19 microorganisms: 15 bacterial strains, including three probiotics, five standard strains and seven isolates, as well as four types of yeast. The antibacterial activity of the tested ligands and complexes was quite selective. The distinguishing feaeture of this group of compounds is that the activity of the complexes is very similar to the activity of the corresponding ligands, except for compounds **L6** and **L7**. The latter exert a stronger effect on Gram-negative bacteria and yeast compared to their complexes. Bacterial *E. coli* cells showed the highest sensitivity to all the tested complexes and ligands. The minimum inhibitory concentration (MIC) of complex **Pd6** is 7.81 μg mL^{-1}, which is significantly higher than the activity of tetracycline (15.63 μg mL^{-1}). It is worth noting that there is no clear dependence of the antibacterial activity of the tested compounds on the length of the hydrophobic alkyl group (R = Et, Pr^n, Bu^n, $n\text{-}C_5H_{11}$).

Propylenediamine ligands containing O-alkylated valine moieties were used to synthesize chiral complexes **Pd8**–**Pd10**.[13] The antimicrobial activity of these ligands and complexes was evaluated against 12 microorganisms. Generally, the tested compounds exhibit selective and moderate activity. The difference in the antimicrobial activity of the ligands and the corresponding complexes **Pd8**–**Pd10** is insignificant. The MIC values vary from 31.25 to >1000 μg mL^{-1}, but these compounds exhibit low antibacterial activity compared to the positive control (MIC of tetracycline varies from 0.11 до 62.5 μg mL^{-1}, which is indicative of the selectivity of action of the agent on different strains).

Bis(pyridyl)allene ligands can be assigned to 'exotic' scaffolds for the preparation of metal complexes.[15] These ligands provide an approach to compounds with axial chirality. Complexes **Pd11** and **Pd12** were synthesized based on racemic ligands. Within the framework of the CO-ADD project, the complexes and the corresponding ligands were tested for the antimicrobial activity against the following panel of microorganisms: *S. aureus* ATCC 43300, *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603, *Actinetobacter baumannii* ATCC 19606, *Cryptococcus neoformans* and *Candida albicans*. The primary screening of the antimicrobial activity showed that, when taken at a single concentration of 32 μg mL^{-1}, complexes **Pd11** and **Pd12** are quite active (the inhibition of the growth of microorganisms was higher than 80%). The dose-dependent experiment demostrated that complex **Pd12** is a lead compound (MIC against *S. aureus*, *C. albicans* and *C. neoformans* < 0.25 μg mL^{-1}). Complexes **Pd11** and **Pd12** are characterized by high toxicity towards the human embryonic kidney cell line HEK293. The CC_{50} value[§] of these complexes against the cell line HEK-293 was ~1 μg mL^{-1}.

Two tridentate pyridine-based ligands, benzimidazole and tetrapyridine, were used to synthesize ionic palladium complexes

[‡] Since the activity of the agent depends on a particular strain, it is more important to compare the activity of the ligand and the complexes.

[§] CC_{50} is the concentration of the agent, at which the cell growth is inhibited by 50%.

Table 2. Antibacterial and antifungal activity of complexes **Pd4**–**Pd7** and the corresponding ligands (tetracycline as the reference drug).[12]

Compound	MIC, μg mL^{-1}				
	B. animalis subsp. lactis	*E. coli* ATCC 25922	*S. aureus* ATCC 25923	*B. subtilis* IP 5832	*P. aeruginosa* ATCC 27853
L4	250	15.63	500	500	1000
Pd4	**15.63**	**15.63**	500	250	1000
L5	125	3.61	500	250	1000
Pd5	62.50	31.25	125	125	1000
L6	125	7.81	125	250	500
Pd6	62.50	**7.81**	125	125	1000
L7	7.81	3.91	62.50	125	62.50
Pd7	125	31.25	500	250	250
Tetracycline	31.25	15.63	0.22	1.95	62.50

Note. The following abbreviations are used: *B. animalis subsp. lactis* for *Bifidobacterium animalis subsp. lactis*, *S. aureus* for *Staphylococcus aureus*, *B. subtilis* for *Bacillus subtilis*, *P. aeruginosa* for *Pseudomonas aeruginosa*.

(**Pd13**, **Pd14**) and platinum complexes (**Pt13**, **Pt14**).[16] The antimicrobial screening of the metal complexes was performed by CO-ADD according to the standard protocol. Although these compounds exhibited low antibacterial activity, their antifungal activity deserves attention. Palladium complex **Pd13** with the benzimidazole ligand showed the best inhibitory activity against the fungi *C. neoformans* and *C. albicans* (MIC was 1 and 0.5 μg mL^{-1}, respectively), while MIC of the ligand was >32 μg mL^{-1}.

Triazole derivatives of pyridine containing perfluoroalkyl substituents and their complexes **Pd15** and **Pd16** were synthesized in order to evaluate their bactericidal activity.[17] Both complexes exhibited high activity against the Gram-negative bacteria *E. coli*. Thus, the zone of inhibition was about 80–90 mm (in the presence of 5 μmol L^{-1} (μM) compound), which is larger than that of vancomycin (60 mm) and is comparable with that of ampicillin (100 mm).

Imidazo[1,2-*a*]pyridine was successfully used as a precursor for the preparation of broad-spectrum drugs.[18] The bactericidal activity of three palladium(II) complexes of the composition PdL_2Cl_2 (**Pd17**), $[PdL_4]Cl_2$ (**Pd18**) and $[PdL_4]Cl_2(4H_2O)L$ (**Pd19**), where L is imidazo[1,2-*a*]pyridine, was evaluated against the microorganisms *S. aureus*, *B. subtilis*, *B. spizizenii*, *E. coli* and *P. aeruginosa*. It was found that complex **Pd19** exhibited moderate bactericidal activity against *S. aureus*; the MIC value and the minimum bactericidal concentration (MBC) were 18.75 μg mL^{-1} (22 μM) and 75.00 μg mL^{-1} (89 μM), respectively. Two other compounds (**Pd17** and **Pd18**) proved to be inactive against the whole range of the tested pathogenic strains. Although the authors gave no explanation for these observations, we agree with their optimistic conclusion that this 'finding may encourage other researchers to join in designing newer palladiums as antibiotics'.

Aryl-substituted biguanidine ligands can be used to synthesize bischelate ionic metal complexes.[19] Such complexes (**Ni20**,

Structures M13–M19

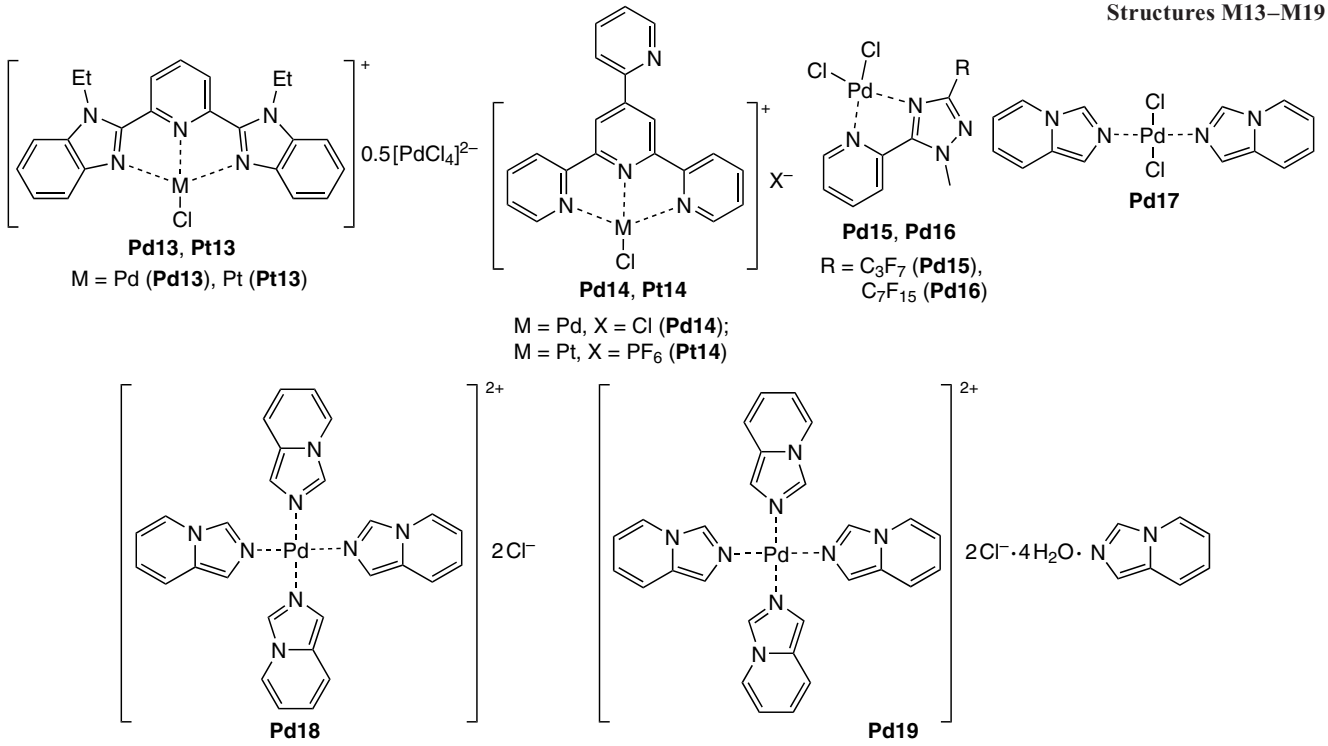
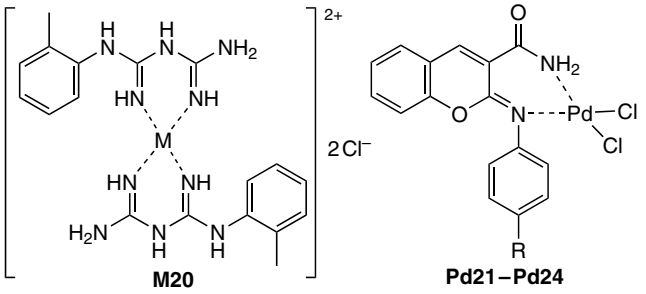


Table 3. Antibacterial and antifungal activity of complexes **M20** and initial ligand **L20**.[19]

Compound	MIC, mg mL^{-1}					
	E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*	*E. faecalis*	*C. albicans*
L20	>1000	1000	>1000	>1000	>1000	1000
Ni20	>1000	125	>1000	500	125	>1000
Pd20	500	15.62	**62.50**	**31.25**	125	**62.50**
Pt20	62.50	7.81	125	125	125	125

Pd20 and **Pt20**) were evaluated as antimicrobial agents against the following strains: *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, *B. subtilis* ATCC 6633, *Enterococcus faecalis* ATCC 29212 and *C. albicans* 22 (Table 3). The metal complexes exhibited significantly higher activity compared to ligand **L20** used as hydrochloride. The palladium complex proved to be the best inhibitor of the growth of the bacteria *S. aureus*, *B. subtilis*, *E. faecalis* and *C. albicans*.

Structures M20–M24



M20

M = Ni (**Ni20**), Pd (**Pd20**), Pt (**Pt20**)

Pd21–Pd24

R = H (**Pd21**), Br (**Pd22**), Me (**Pd23**), OMe (**Pd24**)

Schiff bases are the most popular ligands used for the synthesis of metal complexes. Iminocoumarin ligands and their complexes **Pd21**–**Pd24** were synthesized and tested as antimicrobial agents.[20] The antibacterial activity was evaluated against the strains *E. coli* ATCC 25922, *K. pneumoniae* ATCC 13883, *S. aureus* ATCC 25923 and *E. faecalis* ATCC 19433. The ligands and complexes were found to exhibit weak antibacterial activity against the Gram-positive bacteria. For complexes **Pd21**–**Pd24**, the diameter of the growth inhibition zone of the Gram-positive bacteria was in the range of 10–14 mm. The Gram-negative bacteria proved to be insensitive to the tested compounds. This fact was attributed to the difficulty of penetration of the agent through the lipid layer of these bacteria. A significant improvement of the antifungal activity against the strains *C. albicans* ATCC 24433, *C. tropicalis* ATCC 10233 and *Aspergillus niger* ATCC 135550 was observed when using complexes **Pd21**–**Pd24** instead of the corresponding ligands. For example, the growth inhibition zone of the fungi *C. albicans* in the presence of compounds **Pd22** and **Pd24** containing more polar groups are in the range of 20–40 mm; of the corresponding ligands, ~ 10 mm.

Complexes **Pd25**, **Co25**, **Ni25**, **Cu25** and **Zn25** with the azomethine ligand contain a polar carboxyl group responsible for their hydrophilicity (Table 4).[21] Different types of biological activity, including antimicrobial activity, of these compounds were studied. Complex **Pd25** was found to have a broad spectrum of antibacterial activity against *Proteus vulgaris*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus* and *B. subtilis* strains. In all experiments, the coordination of the ligand to palladium

Table 4. Antibacterial and antifungal activity of complexes **M25** and initial ligand **L25** (streptomycin and ketoconazole as the reference drugs).[21]

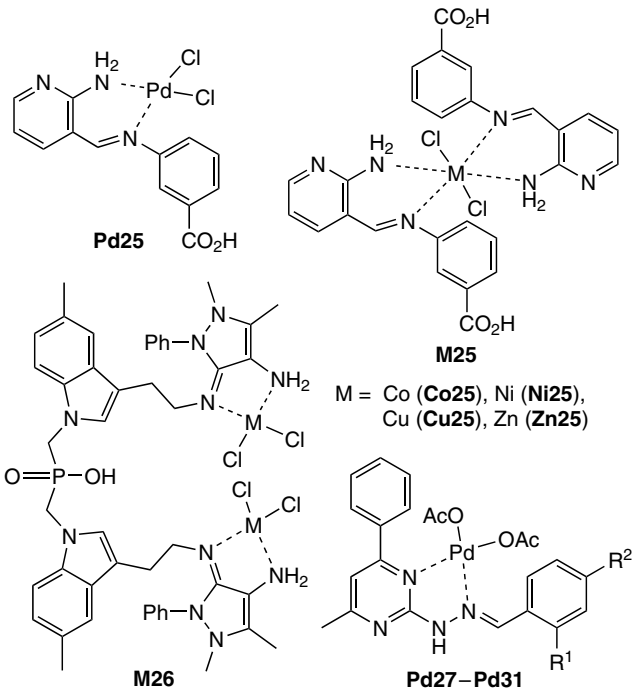
Compound	MIC, μg mL^{-1}				
	S. aureus	*B. subtilis*	*P. aeruginosa*	*A. niger*	*R. botaticola*[a]
Co25	21.87	25.79	10.91	>100	50
Ni25	18.15	14.35	24.86	3.94	>100
Cu25	4.21	5.13	6.01	4.17	6.24
Zn25	>100	11.50	29.63	19.24	21.73
Pd25	**5.17**	**7.69**	**7.25**	**4.03**	26.49
L25	50	>100	38.94	>100	35.29
Streptomycin	3.24	3.15	4.27	–	–
Ketoconazole	–	–	–	2.92	4.57

Note. Hereinafter, the dash means that the data are absent. [a] *R. botaticola* is *Rhizoctonia botaticola.*

led to the enhancement of antimicrobial activity. In terms of activity, palladium complex **Pd25** is second only to the related copper complex (**Cu25**).

Compounds **M26**, where M = Ni, Cu, Zn, Pd, Cd or Hg,[22] are examples of metal complexes containing a N,N-donor ligand with a coordination mode similar to that described above. The distinguishing feature of these complexes is the presence of a phosphoric acid moiety. The antibacterial activity of these compounds was evaluated against the microorganisms *S. aureus* and *E. coli*. Only qualitative results of the evaluation were reported, which are indicative of a low inhibitory activity of complex **Pd26**; the best results were observed for its analogue **Ni26**.

Structures M25–M31



Pd25

M25

M = Co (**Co25**), Ni (**Ni25**), Cu (**Cu25**), Zn (**Zn25**)

M26

M = Co (**Co26**), Ni (**Ni26**), Cu (**Cu26**), Zn (**Zn26**), Pd (**Pd26**), Cd (**Cd26**), Hg (**Hg26**)

Pd27–Pd31

R^1 = H: R^2 = Me (**Pd27**), F (**Pd28**), Br (**Pd29**), CF_3 (**Pd30**); R^1 = R^2 = Cl (**Pd31**)

Table 5. Antibacterial and antifungal activity of complexes **Pd27**–**Pd31** and the corresponding ligands (ciprofloxacin and amphotericin B as the reference drugs).[23]

Compound[a]	Inhibition zone, mm				
	B. subtilis	*S. aureus*	*P. aeruginosa*	*C. albicans*	*S. cerevisiae*
L27	11.2	11.2	10.1	11.1	13.1
Pd27	**22.1**	**20.1**	10.0	13.0	15.0
L28	9.3	–	9.0	10.0	13.0
Pd28	16.2	**20.2**	12.2	**18.7**	**18.1**
L29	13.1	12.3	11.1	15.0	15.7
Pd29	18.3	15.9	**22.2**	15.9	**20.2**
L31	10.0	9.3	10.0	–	10.0
Pd31	**22.0**	9.9	14.2	14.9	16.2
Ciprofloxacin	24.1	26.4	22.1	–	–
Amphotericin B	–	–	–	16.3	19.2

[a] The concentration of the agent was 4 mg mL^{-1}.

Hydrazones containing the diazine core were synthesized and used to prepare complexes **Pd27**–**Pd31** containing different halogen substituents on the benzylidene moiety (Table 5).[23] The antimicrobial screening of this series of compounds was carried out against the bacterial strains of *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*, the fungi *C. albicans* and the yeast *Saccharomyces cerevisiae*. In all tests, the ligands were significantly less active than the corresponding palladium complexes. The bactericidal activity of complexes **Pd27**–**Pd31** against the *S. aureus*, *B. subtilis* and *P. aeruginosa* strains was comparable to that of ciprofloxacin used as the reference drug. The Gram-negative bacteria *E. coli* were less sensitive to these agents. In this series, the clear structure–property relationship was not revealed. Complexes **Pd27**–**Pd31** can be considered as effective antimicrobial agents.

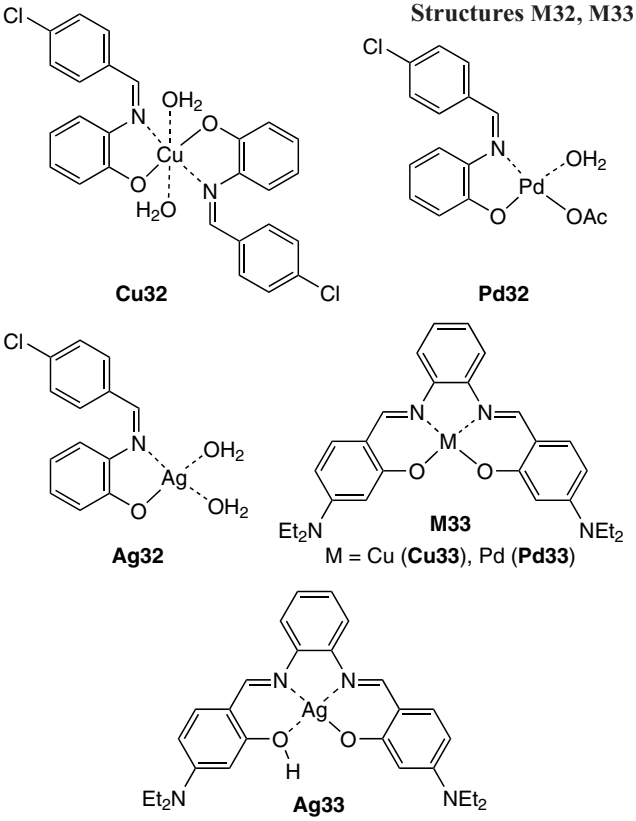
Metal complexes with azomethine ligands were extensively studied by international teams of United Arab Emirates and Egyptian researchers.[24–29] Complexes **Cu32**, **Pd32** and **Ag32** with 2-[(4-chlorobenzylidene)amino]phenol (**L32**) were synthesized (Table 6).[24] The antibacterial activity of these compounds was evaluated against three bacterial strains of *E. coli*, *B. subtilis* and *S. aureus*; the antifungal activity, against *C. albicans*, *A. flavus* and *Trichophyton rubrum*. In this series of three metal complexes, **Pd32** did not exhibit satisfactory activity.

Table 6. Antibacterial and antifungal activity of complexes **M32** and initial ligand **L32** (gentamicin and fluconazole as the reference drugs).[24]

Compound[a]	Inhibition zone, mm					
	E. coli	*B. subtilis*	*S. aureus*	*T. rubrum*	*A. flavus*	*C. albicans*
L32	4	5	4	5	4	3
Cu32	14	17	15	16	15	11
Pd32	13	16	14	14	12	9
Ag32	17	20	13	19	17	14
Gentamycin	20	26	25	–	–	–
Fluconazole	–	–	–	24	16	15

[a] Here and in Tables 7, 9, 16, 31, 32 and 37, the concentration of the agent was 10 mg mL^{-1}.

Structures M32, M33



The best results were observed for compound **Ag32**. In the study,[24] a significant effect of the coordination to metal was demonstrated once again. Thus, free ligand **L32** was almost inactive.

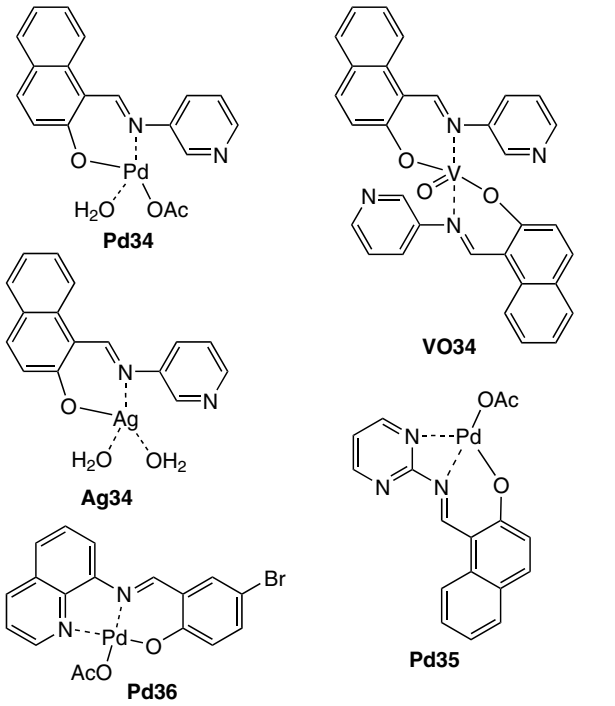
A similar dependence was observed for complexes **M33**, where M = Cu, Pd or Ag, based on the tetradentate salen-type ligand (Table 7).[25]

However, in another series of three metal complexes (**Pd34**, **VO34** and **Ag34**), which were synthesized based on 1-(3-pyridyliminomethyl)-2-naphthol (**HL34**), the palladium complexes were found to be the lead compounds (Table 8).[26] These compounds were tested *in vitro* against three bacteria (*E. coli*, *Serratia marcescens*, *Micrococcus luteus*) and three fungi (*Geotrichum candidum*, *A. flavus*, *Fusarium oxysporum*). The antimicrobial activity of azomethine ligand **HL34** was found to be significantly lower than the activity of its metal complexes. Complex **Pd34** proved to be the most effective. It showed the lowest MIC values against the tested bacteria and fungi compared to the other compounds.

Table 7. Antibacterial and antifungal activity of complexes **M33** and initial ligand **H2L33** (gentamicin and fluconazole as the reference drugs).[25]

Compound	Inhibition zone, mm					
	E. coli	*B. subtilis*	*S. aureus*	*T. rubrum*	*A. flavus*	*C. albicans*
H_2L33	5	7	6	4	5	6
Cu33	16	19	17	14	16	18
Pd33	15	18	16	9	14	16
Ag33	19	23	20	16	18	22
Gentamycin	21	27	26	–	–	–
Fluconazole	–	–	–	14	18	23

Structures M34–M36



Structures M37, M38

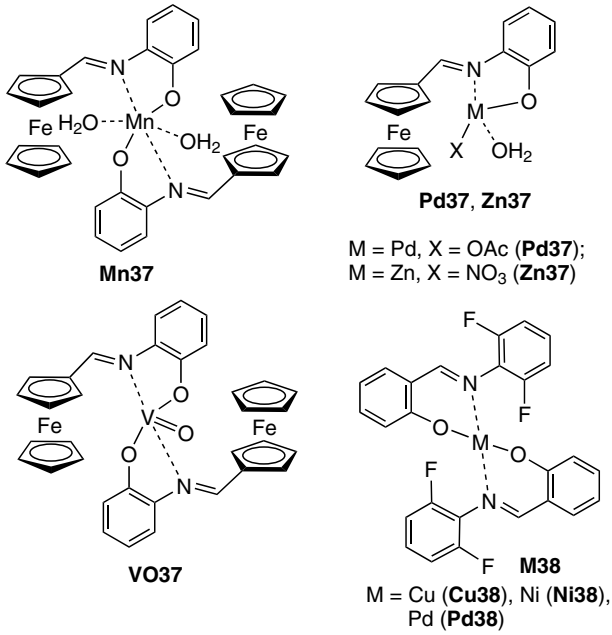


Table 8. Antibacterial and antifungal activity of compounds **M34** and initial ligand **HL34** (ofloxacin and fluconazole as the reference drugs).[26]

Compound	MIC, μg mL^{-1}					
	S. marcescens	*E. coli*	*M. luteus*	*F. oxysporum*	*G. candidum*	*A. flavus*
HL34	4.25	5.25	3.50	5.00	4.75	5.25
Pd34	**2.00**	**2.25**	**1.50**	**2.75**	**2.50**	**3.00**
VO34	2.75	3.25	2.25	3.75	3.25	4.00
Ag34	2.50	2.75	2.00	3.25	3.00	3.50
Ofloxacin (**L1**)	1.25	1.75	0.75	–	–	–
Fluconazole	–	–	–	2.00	1.75	2.50

Complex **Pd35** with a related ligand, which was synthesized in the study,[27] has an unusual structure consisting of six- and four-membered palladacycles. The screening demonstrated that complex **Pd35** exhibited the strongest inhibitory activity against the growth of the bacteria *S. marcescens*, *E. coli* and *M. luteus* (MIC was 3.25, 3.75 and 3.00 μM, respectively) compared to the related zinc(II), chromium(III) and vanadyl(II) complexes. Structure **Pd36**, proposed for the Pd^{II} complex with quinoline imine,[28] seems to be more reliable than the above formula **Pd35**. In the study,[28] a comparative analysis of the antimicrobial and antifungal activity of compound **Pd36** and related Zn^{II}, Cr^{III} and VO^{II} complexes was performed, and the palladium derivative was found to have advantages because it inhibited the growth of the bacteria *S. marcescens*, *E. coli* and *M. luteus* (MIC was 2.25, 2.75 and 1.50 μM, respectively). High biological activity of Pd^{II} complexes was confirmed by molecular docking, assuming that the square-planar geometry of the palladium centre promotes a more efficient interaction with the active sites of biomolecules.

Transition metal complexes were synthesized based on the azomethine ferrocenyl ligand (Table 9).[29] The screening of biological activity of complexes **M37**, where M = Mn, Pd, Zn or VO, and uncoordinated ligand **HL37** was carried out against pathogenic bacterial (*S. marcescens*, *E. coli* and *M. luteus*) and fungal (*A. flavus*, *G. candidum* and *F. oxysporum*) strains. As expected, free ligand **HL37** showed lower antimicrobial activity than the corresponding metal complexes. The results of this study demonstrated that complex **Pd37** possessed the best antibacterial and antifungal activity compared to the other complexes, which is comparable with the activity of ofloxacin and fluconazole used as the reference drugs.

Table 9. Antibacterial and antifungal activity of compounds **M37** and initial ligand **HL37** (ofloxacin and fluconazole as the reference drugs).[29]

Compound	Inhibition zone, mm					
	S. marcescens	*E. coli*	*M. luteus*	*A. flavus*	*G. candidum*	*F. oxysporum*
HL37	4.5	3.5	6.1	3.1	7.2	5.2
Mn37	11.5	9.8	15.9	9.6	17.3	10.2
Pd37	**14.2**	**13.1**	**21.2**	**12.5**	**20.7**	**14.1**
Zn37	13.5	11.9	19.3	11.3	19.6	12.8
VO37	12.8	10.70	17.60	10.1	18.0	11.5
Ofloxacin	15.7	14.5	23.8	–	–	–
Fluconazole	–	–	–	13.6	22.5	15.5

Fluorine-containing salen-type imine was used as the ligand for the synthesis of chelate complexes **Cu38**, **Ni38** and **Pd38** (Table 10).[30] In this series of three compounds, complex **Pd38** exhibited higher antimicrobial activity against both pathogenic bacterial strains (*E. coli*, *S. aureus*, *P. aeruginosa*) and fungal microorganisms (*A. niger*, *A. flavus*, *C. albicans*). This difference of complex **Pd38** was attributed to its high antioxidant activity established in this study as well. Amali *et al*.[30] suggested that the resulting reactive oxygen species (ROS) and metal ions attack the negatively charged cell wall of bacteria and lead to its disruption, which causes death of microbes.

Halogen-substituted quinolinols, 5-chloro-8-hydroxy-7-iodoquinoline (**HL39**), 5,7-dichloro-8-hydroxyquinoline (**HL40**) and 5,7-dibromo-8-hydroxyquinoline (**HL41**), which

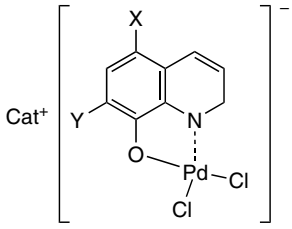
Table 10. Antibacterial and antifungal activity of complexes **M38** and initial ligand **HL38** (amoxicillin and ketoconazole as the reference drugs).[30]

Compound[a]	Inhibition zone, mm					
	E. coli	*S. aureus*	*P. aeruginosa*	*A. niger*	*A. flavus*	*C. albicans*
HL38	8	9	9	9	10	9
Cu38	12	13	13	12	14	12
Ni38	10	10	11	11	12	10
Pd38	**13**	**16**	**15**	**15**	**17**	**14**
Amoxicillin	7	6	8	–	–	–
Ketoconazole	–	–	–	9	9	8

[a] The concentration of the agent was 2 and 1 mg mL^{-1} for the evaluation of the antibacterial and antifungal activity, respectively.

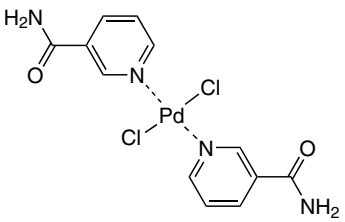
are used as ligands for the coordination to metals, are known as antiviral, antibacterial, antifungal and antiprotozoal drugs.[31] In order to determine the metal complex state of these ligands, the authors synthesized a series of ionic palladium complexes **Pd39**–**Pd41** of the general formula Cat[PdCl2(L)] (Cat = K or Cs) and evaluated their antimicrobial activity against 19 strains of pathogenic microorganisms, including 15 bacteria and 4 fungi

Structures Pd39–Pd45

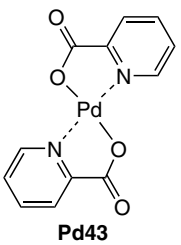


Pd39–Pd41

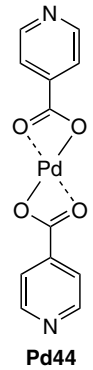
Cat = K (**a**), Cs (**b**);
X = Cl, Y = I (**Pd39**);
X = Y = Cl (**Pd40**), Br (**Pd41**)



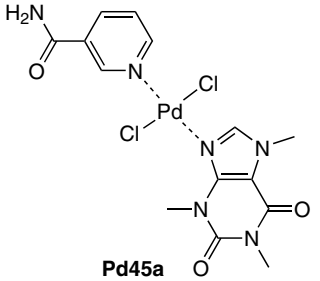
Pd42



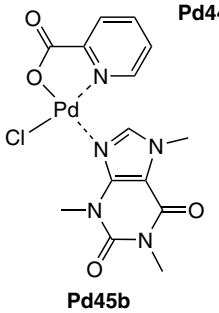
Pd43



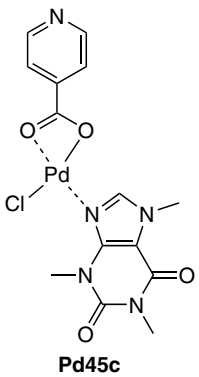
Pd44



Pd45a



Pd45b



Pd45c

(Table 11, selected data are given).[31] As opposed to most of the above results, the activity of the initial ligands appeared to be comparable with the activity of the corresponding metal complexes. The test using *P. aeruginosa* strains was the only example, in which the complexes were more active than the ligands. The yeast strains were the most sensitive to the presence of these compounds. The Gram-positive bacteria showed higher sensitivity to these compounds compared to the Gram-negative bacteria. No clear dependence of the antibacterial activity on the nature of the substituents and the nature of the cation was revealed.

Mononuclear complexes **Pd42**–**Pd44** containing nicotinamide (**L42**), picolinic acid (**L43**) and isonicotinic acid (**L44**) as the ligands and mixed-ligand analogues **Pd45a**–**c** containing the caffeine moiety (**L45**) were screened for antibacterial activity.[32] The experiments demonstrated that all the tested compounds exhibited no antibacterial activity against four bacterial strains (*K. pnuemoniae*, *E. coli*, *S. aureus* and *S. epidermidis*). Despite the negative results, this study deserves mention because any data are important for the comparative structural analysis.

The introduction of a pharmacophoric moiety into the target structure is a promising approach to the design of effective drugs, which was used in the study.[33] The aim of this study was to synthesize and characterize three new palladium complexes with Schiff bases (**Pd46**–**Pd48**), which were prepared from pyrrole-2-carboxaldehyde and L-methionine, L-histidine or L-tryptophan, and test their antibacterial activity (Table 12). The antibacterial activity of the compounds was evaluated against Gram-positive (*S. aureus* ATCC 25923, MRSA ATCC 33591, *S. epidermidis* ATCC 12228 and *Streptococcus pyogenes* ATCC 19615) and Gram-negative bacteria (*P. aeruginosa* ATCC 27853 and *K. pneumoniae* ATCC 13883). It was found that the ligands inhibited the growth of none of the tested bacterial strains. The MIC values of all ligands were lower than 2.5 mg mL^{-1}. The lowest MIC value (0.078 mg mL^{-1}) was observed for complex **Pd48** against the microorganisms *S. epidermidis*, *S. aureus* and the methicillin-resistant *Staphylococcus aureus* strain (MRSA). A similar MIC value was observed for compound **Pd47** against *S. epidermidis*. In all other cases, the MIC values were higher than 0.078 mg mL^{-1}. The highest MIC value (0.625 mg mL^{-1}) was found for complex

Table 11. Antibacterial and antifungal activity of complexes **Pd39**–**Pd41** and the corresponding initial ligands (tetracycline as the reference drug).[31]

Compound	MIC, μg mL^{-1}					
	P. mirabilis	*P. aeruginosa*	*B. subtilis*	*S. aureus*	*S. enterica*	*C. albicans*
HL39	15.63	62.50	7.81	7.81	7.81	>7.81
HL40	7.81	7.81	15.63	62.50	7.81	>7.81
HL41	7.81	125	7.81	7.81	7.81	>7.81
Pd39a	7.81	15.63	3.90	7.81	7.81	>7.81
Pd40a	7.81	31.25	7.81	7.81	7.81	>7.81
Pd41a	7.81	31.25	**>0.98**	7.81	7.81	>7.81
Pd39b	7.81	7.81	3.90	7.81	7.81	>7.81
Pd40b	7.81	31.25	**>0.98**	7.81	7.81	>7.81
Pd41b	7.81	15.63	7.81	7.81	7.81	>7.81
Tetracycline	500	62.50	1.95	0.22	15.63	0.98

Note. *S. enterica* is *Salmonella enterica*.

Structures Pd46–Pd54

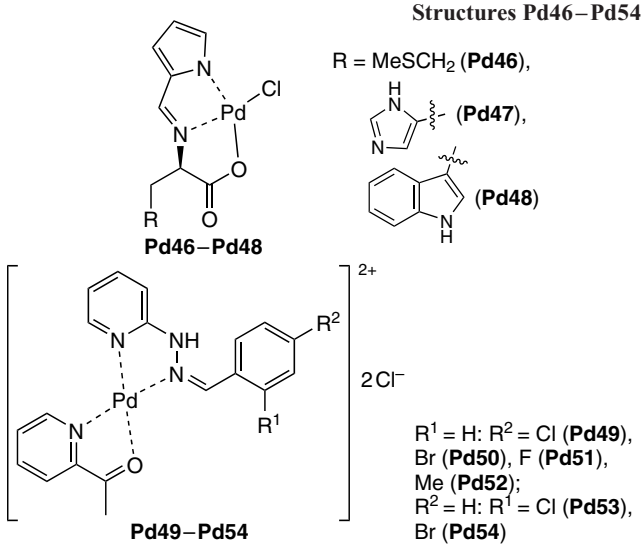


Table 12. Antibacterial and antifungal activity of compounds **Pd46**–**Pd47** and the complex (COD)PdCl2 (ampicillin as the reference drug).[33]

Compound	MIC, mg mL^{-1}				
	S. epidermidis	*S. pyogenes*	*K. pneumoniae*	MRSA	*S. aureus*
Pd46	0.315	0.625	–	0.625	0.625
Pd47	**0.078**	0.156	–	**0.156**	0,156
Pd48	**0.078**	0.156	–	**0.078**	0.078
(COD)$PdCl_2$	0.315	0.625	0.625	0.625	0.625
Ampicillin	0.040	0.020	0.630	0.310	0.020

Pd46 against the *S. pyogenes*, *S. aureus* and MRSA strains. An analysis confirmed that *P. aeruginosa* is resistant in the presence of all the tested complexes **Pd46**–**Pd48**. The higher antibacterial activity of compounds **Pd47** and **Pd48** was attributed to the presence of important pharmacophoric units, such as the imidazole or indole core, respectively. It should be emphasized that the dichloro(1,5-cyclooctadiene)palladium(II) complex ((COD)$PdCl_2$) containing no amino acid ligands was studied as the reference. The fact that the antibacterial activity of the latter complex appeared to be much lower and the absence of activity of the free ligands provide unambiguous evidence that the presence of a biogenic ligand coordinated to the palladium ion is the main structural factor responsible for this type of activity. It is this combination that determines the optimal lipophilicity(hydrophilicity) of the molecule and ensures the penetration of the latter through the membrane of the pathogenic cell.

Diverse biological activity of heteroleptic complexes **Pd49**–**Pd54** containing acetylpyridine and substituted 2-(2-benzylidenehydrazinyl)pyridines (**L49**–**L54**) was investigated (Table 13).[34] For all ligand–complex pairs, it was clearly established that the chelation of the metal ion leads to the enhancement of antibacterial activity of the ligand by a factor of 3–4. It is noteworthy that the palladium salt Na_2PdCl_4 did not possess bactericidal properties. The subtle dependence of the antimicrobial activity of the synthesized complexes **Pd49**–**Pd54** on the character of substitution in the benzene ring of the imine ligand was revealed. Complex **Pd54** proved to be active against all the tested bacterial strains with MIC values in the range of 30–50 μM. Compound **Pd54** exhibited higher activity (MIC was 30 μM against *B. subtilis* and 40 μM against *P. aeruginosa*),

Table 13. Antibacterial activity of complexes of **Pd49**–**Pd54** and the corresponding ligands (sodium tetrachloropalladate as the reference drug).[34]

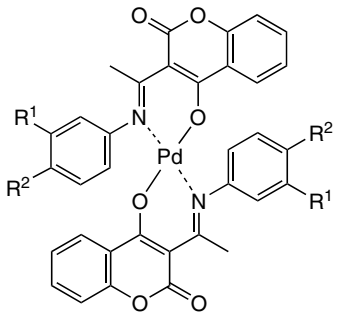
Compound	MIC, μM				
	S. aureus	*B. subtilis*	*S. marcescens*	*P. aeruginosa*	*E. coli*
L49	200	160	215	185	190
L50	185	185	175	190	170
L51	190	170	165	175	175
L52	205	190	195	190	215
L53	180	160	180	165	185
L54	170	165	185	160	170
Pd49	50	45	65	75	40
Pd50	40	55	45	65	35
Pd51	**35**	**30**	45	40	55
Pd52	55	50	65	75	45
Pd53	50	45	**40**	**35**	**30**
Pd54	45	**30**	45	40	50
Na_2PdCl_4	2240	2490	2145	1940	2820

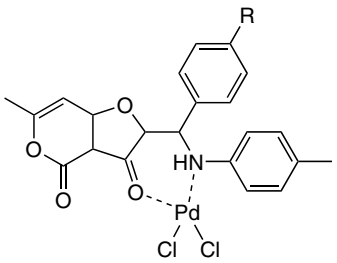
while complex **Pd53** was the most effective against *E. coli* (MIC = 30 μM).

Coumarins, phenolic compounds, are widely distributed secondary plant metabolites. Coumarin complexes with transition metals exhibit significant biological activity.[35] Numerous Pd^{II} complexes with coumarins were synthesized, and their antimicrobial and cytotoxic activity was confirmed. The antibacterial activity of complexes **Pd55** and **d56** based on 4-hydroxycoumarin derivatives was evaluated against 16 strains of microorganisms.[36] Generally, these ligands and their complexes with palladium showed low activity.

Compounds **Pd57**–**Pd59** with furopyran-3,4-dione derivatives were investigated as antimicrobial agents against three bacterial (*E. coli*, *P. aeruginosa* and *S. aureus*) and two fungal strains (*C. albicans* and *C. tropicalis*) (Table 14).[37] Metal complexes **Pd57**–**Pd59** exhibited higher antimicrobial and

Structures Pd55–Pd63





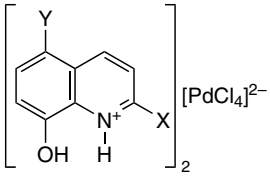


Table 14. Antibacterial and antifungal activity of complexes **Pd57**–**Pd59**, the corresponding ligands and reference drugs.[37]

Compound[a]	Inhibition zone, mm				
	E. coli	*P. aeruginosa*	*S. aureus*	*C. albicans*	*C. tropicalis*
L57	11	10	28	28	28
Pd57	**15**	**20**	**30**	30	29
L58	12	15	30	31	30
Pd58	**15**	**20**	**35**	33	30
L59	15	20	35	36	34
Pd59	**18**	**23**	**38**	38	37
Ampicillin	15	–	25	–	–
Cephalexin	–	20	–	–	–
Ketoconazole	–	–	–	40	40

[a] The concentration of the agent was 5 mg mL^{-1}.

antifungal activity than the corresponding ligands, which is comparable with the activity of the reference drugs. As regards the nature of the substituent, it should be noted that hydroxy-containing derivative **Pd59** showed higher activity. Dechouk *et al*.[37] suggested that this fact is associated with a higher polarity of this compound due to the presence of the hydroxy group, which provides an interaction (through hydrogen bonding) with the bacterial cell membrane and penetrates the latter.

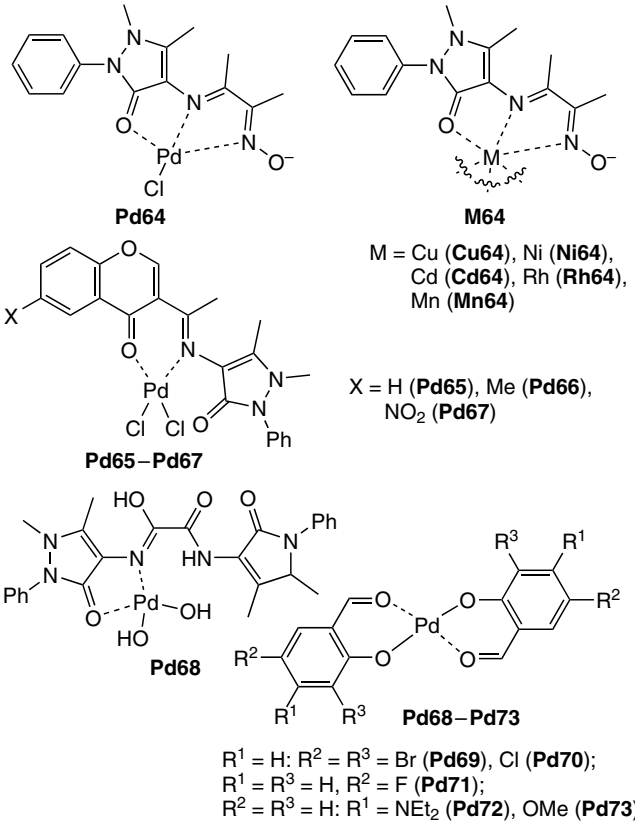
Organic-inorganic complexes **Pd60**–**Pd63** containing the substituted 8-hydroxyquinolinium cation and the tetrachloropalladate anion are effective against 14 strains of microorganisms with MIC values from <1.95 to 250 μg mL^{-1} (Table 15).[38] Despite the fact that these metal complexes contain the $[PdCl_4]^{2-}$ anion, they exhibit different antimicrobial activity. The observations demonstrated that the cationic part, 8-hydroxyquinolinium derivatives, have a significant effect on the antimicrobial activity. For this reason, the authors tested free ligands **L60**–**L63** against these microorganisms. In the study,[38] the complexes were found to have higher activity compared to that of the corresponding ligands, as is often the case. Among the most significant results, noteworthy is the antimicrobial activity of complex **Pd61**. This complex has MIC < 1.95 μg mL^{-1} in all tests, which is several times higher than the activity of the initial ligand.

Table 15. Antibacterial activity of complexes **Pd60**–**Pd63** and the corresponding ligands (tetracycline as the reference drug).[38]

Соединение	MIC, μg mL^{-1}			
	B. animalis subsp. lactis	*S. aureus* ATCC 25923	*E. coli* ATCC 25922	*A. flavus*
L60	<7.81	<7.81	<7.81	<7.81
Pd60	**<1.95**	**<1.95**	31.25	62.50
L61	<7.81	<7.81	<7.81	<7.81
Pd61	**<1.95**	**<1.95**	**<1.95**	**<1.95**
L62	<7.81	<7.81	<7.81	<7.81
Pd62	7.81	31.25	**<1.95**	31.25
L63	<7.81	<7.81	31.25	250
Pd63	7.81	7.81	31.25	31.25
Tetracycline	31.25	0.22	0.98	0.98

Complexes **M64**, where M = Pd, Cu, Ni, Cd, Rh or Mn, based on imino derivatives of 4-aminoantipyrine (**L64**) were found to exhibit diverse, including antibacterial, activity.[39] The experiments demonstrated that all metal complexes were more active than the initial ligands against the microorganisms *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *S. mutans* and *C. albicans*. However, in most cases the activity was not higher than that of the reference drug. Thus, the diameter of the inhibition zone was in the ranges of 13–41 and 21–30 mm, respectively. An exception is the palladium derivative. For example, initial ligand **L64** is inactive against *S. mutans*; in the presence of complex **Pd64**, the growth inhibition zone of bacteria is 24 mm, which is comparable with the activity of ampicillin (22 mm).

Structures M64–M73



4-Aminoantipyrine was also used as a scaffold for the synthesis of Schiff bases by the condensation with substituted chromones.[40] The reaction of ligands **L65**–**L67** with palladium chloride affords the corresponding complexes **Pd65**–**Pd67**. The antimicrobial activity of these complexes was evaluated against two human bacterial pathogens, such as *S. aureus* and *E. coli*. Complexes **Pd65**–**Pd67** showed a larger growth inhibition zone of the bacteria *S. aureus* (12–21 mm) compared to streptomycin used as the positive control (11 mm). These complexes proved to be inactive against *E. coli*.

The screening of a series of complexes **M68**, where M = Pd, Mn, Co, Ni, Cu, Zn, Fe or Ru, which were synthesized based on the polyfunctional imino derivative of 4-aminoantipyrine (**L68**), demonstrated that complex **Pd68** exhibited the best antifungal activity and the highest antimicrobial activity (Table 16).[41] It was mentioned that free ligand **L68** displayed no activity. The *in vitro* testing of these compounds was carried out against *S. aureus*, *B. subtilis*, *E. coli*, *P. vulgaris*, *C. albicans* and *A. fumigates* strains.

Table 16. Antibacterial and antifungal activity of complexes **M68** and free ligand **L68** (gentamicin and ketoconazole as the reference drugs).[41]

Compound	Inhibition zone, mm					
	S. aureus	*B. subtilis*	*E. coli*	*P. vulgaris*	*A. fumigatus*	*C. albicans*
L68	0	0	0	0	0	0
Pd68	18	23	21	18	**15**	**22**
Co68	19	25	19	15	14	18
Cu68	15	19	15	20	9	12
Zn68	19	18	20	20	0	0
Ru68	15	17	16	12	0	0
Gentamycin	24	26	30	25	–	–
Ketoconazole	–	–	–	–	17	20

Table 17. Antibacterial activity of complexes **Pd69**–**Pd73** and the corresponding ligands.[42]

Compound	MIC, μM			
	S. aureus	*B. subtilis*	*E. coli*	*X. campestris*
HL69	89	89	179	89
HL70	262	262	262	262
HL71	1427	1427	1427	1427
HL72	>1035	>1035	>1035	>1035
HL73	1314	1314	1314	1314
Pd69	**38**	**38**	**38**	**38**
Pd70	51	103	51	51
Pd71	259	259	259	259
Pd72	204	204	204	407
Pd73	245	245	245	245

The biological profile of complexes **Pd69**–**Pd73** and corresponding substituted salicylaldehydes **HL69**–**HL73** as the ligands was determined (Table 17).[42] The antimicrobial activity was evaluated against two Gram-negative bacteria (*Xanthomonas campestris* and *E. coli*) and two Gram-positive bacteria (*B. subtilis* and *S. aureus*). All metal complexes proved to be more active than the initial ligands. The best results were obtained for the bromo derivatives both in the group of the ligands (the MIC values of **HL69** were in the range from 89 to 179 μM) and complex **Pd69** (MIC = 38 μM).

3. Cyclopalladated compounds. Palladium carbene complexes

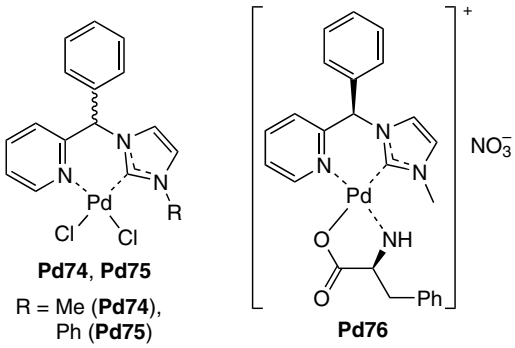
Cyclopalladated compounds, including carbene complexes **Pd74**–**Pd76** with a N-donor pyridine moiety, are a special group.[43] In this study, a series of palladium complexes both in the racemic form and as individual enantiomers were synthesized. The latter compounds were obtained by the resolution of a racemic mixture using an additional amino acid ligand as the chiral reagent. The antimicrobial activity of the initial ligands and the corresponding complexes was evaluated against 13 strains of pathogenic microorganisms (Table 18, selected data are given).[43] This investigation is a rare example of studies, in which not only the structural factors but also stereochemical characteristics of the tested agents are considered. For chiral compounds, it is very important to perform a comparative analysis of the racemic form and individual enantiomers. This

Table 18. Antibacterial activity of complexes **Pd74**–**Pd76**, the corresponding ligands and palladium(II) chloride (chloramphenicol as the reference drug).[43]

Соединение	MIC, mM					
	B. cereus	*B. subtilis*	MRSA	*E. coli*	*K. pneumoniae*	*P. aeruginosa*
HL74	5	5	5	>5	>5	>5
HL75	2.5	2.5	1.25	5	2.5	>5
(*R*,*S*)-**Pd74**	>0.5	>0.5	>0.5	>0.5	>0.5	>0.5
(*R*)-**Pd74**	0.125	0.25	**0.031**	0.125	0.125	0.125
(*R*,*S*)-**Pd75**	0.25	0.063	0.5	0.5	>0.5	>0.5
(*S*)-**Pd75**	>0.5	>0.5	>0.5	>0.5	>0.5	>0.5
(*R*,*S*)-**Pd76**	>0.5	>0.5	0.125	0.5	0.5	0.5
$PdCl_2$	>0.5	>0.5	>0.5	>0.5	>0.5	>0.5
Chloramphenicol	0.006	0.006	0.025	0.025	0.003	>0.05

issue is confirmed by the results obtained in the study.[43] Racemic complex (*R*,*S*)-**Pd74** did not exhibit antimicrobial activity at the highest tested concentration (0.5 mM), while the corresponding enantiomer (*R*)-**Pd74** inhibited the growth of the tested microorganisms. For the pair of phenyl-substituted structures of racemate (*R*,*S*)-**Pd75** and optically pure enantiomer (*S*)-**Pd75**, no significant differences were observed because both forms did not show antimicrobial activity at the highest tested concentration (0.5 mM).

Structures Pd74–Pd76



N-Heterocyclic carbene (NHC) complexes are promising compounds for searching for new pharmacological agents.[44–48] Among different NHC systems, air-stable and convenient-to-handle complexes stabilized by pyridine, so-called PEPPSI complexes (PEPPSI stands for pyridine-enhanced precatalyst preparation, stabilization and initiation), have attracted great attention.

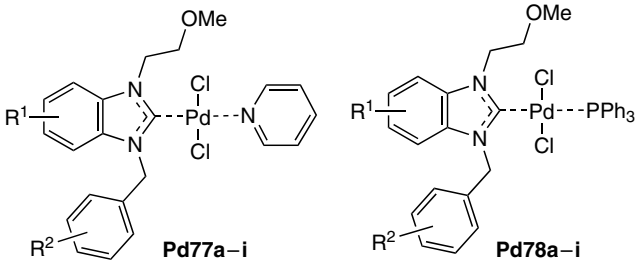
In order to evaluate the effect of structural factors on the biological activity of the PEPPSI-type complexes, a large library of benzimidazolium salts and related palladium carbene complexes was synthesized.[45] The following two groups of complexes should be distinguished: one group (**Pd77a**–**i**) contains pyridine as the stabilizing ligand; another group (**Pd78a**–**h**) contains triphenylphosphine (Table 19). In each group, the number and positions of alkyl substituents in aromatic rings of the benzimidazole ligand were varied. A broad biological activity profile of the synthesized compounds was investigated. The antimicrobial activity was evaluated using *E. coli*, MRSA and *C. albicans* strains as the tested microorganisms. Eight compounds exhibited higher antibacterial activity against *E. coli* compared to that of tetracycline. Complexes **Pd77g** and **Pd78f** were found to be the most active (the inhibition zone was 26.3 mm at a concentration of the

Table 19. Antibacterial and antifungal activity of compounds **Pd77a**–**h** and **Pd78a**–**h** (tetracycline and fluconazole as the reference drugs).[45]

Compound	Inhibition zone, mm		
	E. coli	MRSA	*C. albicans*
Pd77a	20.3	17.4	18.0
Pd78a	**25.0**	22.0	26.0
Pd77b	18.3	17.5	32.0
Pd78b	**23.0**	26.0	27.0
Pd77c	19.3	19.0	12.0
Pd78c	**25.0**	**27.0**	**28.0**
Pd77d	18.3	15.0	19.0
Pd78d	18.5	19.5	19.0
Pd77e	12.0	18.0	20.0
Pd78e	19.3	18.5	**29.0**
Pd77f	**25.0**	**28.5**	26.0
Pd78f	**26.3**	**28.0**	15.0
Pd77g	**26.3**	**26.5**	**29.5**
Pd78g	18.3	15.0	22.0
Pd77h	**22.4**	23.0	**28.0**
Pd78h	**24.0**	20.0	23.0
Tetracycline	22.3	26.5	–
Fluconazole	–	–	28.0

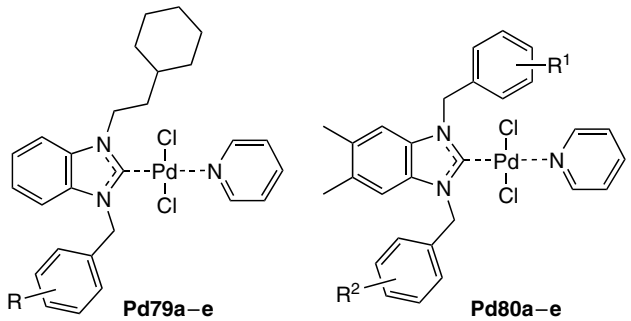
compounds equal to 50 μg per disc). Compounds **Pd77f**, **Pd78f** and **Pd78c** showed higher activity against MRSA compared to the reference drug (the inhibition zones were 28.5, 28.0 and 27.0 mm, respectively). Complexes **Pd77b**, **Pd77g** and **Pd78e** exhibited the best antifungal activity against the yeast-like fungi *C. albicans* with the inhibition zone of 32.0, 29.5 and 29.0 mm, respectively. Generally, the triphenylphosphine complexes were more active in most of the tests (the ratio of the active compounds with triphenylphosphine and pyridine ligands was 18 : 9). However, these results did not allow a definite conclusion about the effect of the character of substitution in the benzene ring of the ligand on the antibacterial activity.

Structures Pd77–Pd80



Pd77a–i **Pd78a–i**

R^1 = H: R^2 = 2,3,4,5,6-Me_5 (**a**), 2,4,6-Me_3 (**b**), 3,5-Me_2 (**c**), 3-Me (**d**);
R^1 = 5,6-Me_2: R^2 = 2,3,4,5,6-Me_5 (**e**), 2,4,6-Me_3 (**f**), 3,5-Me_2 (**g**), 3-Me (**h**), 3-Bu^t (**i**)



Pd79a–e **Pd80a–e**

R = 2-Me (**a**), 3-Me (**b**), 2,3,4,5,6-Me_5 (**c**), 2,4,6-Me_3 (**d**), 2,3,5,6-Me_4 (**e**)

R^1 = R^2 = 4-Bu^t (**a**), 4-Me (**b**);
R^1 = 3,5-Me_2: R^2 = 4-Me (**c**), 4-Bu^t (**e**)

Table 20. Antibacterial activity of compounds **Pd79a**–**e** and **Pd80a**–**e** (ampicillin as the reference drug).

Compound	MIC, mg mL^{-1}			Ref.
	L. monocytogenes	*S. typhimurium*	*M. luteus*	
Pd79a	1.235	1.260	0.323	46
Pd79b	0,615	0.040	0.314	46
Pd79c	**0.0042**	**0.0045**	**0.0025**	46
Pd79d	0.045	0.720	0.215	46
Pd79e	0.063	0.655	0.126	46
Pd80a	0.524	1.260	0.624	48
Pd80b	0.310	0.313	0.421	48
Pd80d	0.212	0.213	0.223	48
Pd80e	0.426	1.340	0.125	48
Ampicillin	0.039	0.6235	0.0134	46

As a continuation of these studies, a new series of benzimidazolium salts **HL79a**–**e** and related palladium carbene complexes **Pd79a**–**e** were synthesized (Table 20).[46] The antimicrobial activity of these compounds was evaluated against the strains *M. luteus* LB14110, *Listeria monocytogenes* ATCC 19117, *S. typhimurium* ATCC 14028 and *S. aureus* ATCC 6538. Most of ligands **HL79a**–**e** showed low activity against all the tested bacterial and fungal strains. Complexes **Pd79a**–**e** displayed moderate selective activity, except for compound **Pd79c**, which showed high inhibitory activity against all the tested strains. In the study,[46] this fact was not explained. It can be suggested that the presence of the maximum number of nonpolar methyl substituents on the aromatic ring in compound **Pd79c** provides the required hydrophilic lipophilic balance for the penetration into the microbial cells.

In the studies,[47,48] a number of new related Pd^{II} carbene complexes were investigated. The antimicrobial activity of compounds **Pd80a**–**e** was evaluated against the same range of pathogenic microorganisms. The comparative results given in Table 20 demonstrate that these structural changes did not lead to a significant improvement of the activity.

Binuclear palladacycles can be used to synthesize mononuclear mixed-ligand complexes.[49] Compounds **Pd81** and **Pd82** thus synthesized were tested as antibiotics against *E. coli*. The distinguishing feature of these structures is the presence of substituents of different nature. Thus, complex **Pd81** contains an OH group, while its analogue **Pd82** contains a remote amino group as a quaternary salt, thereby providing better solubility of **Pd82** in an aqueous medium and allowing the use of more concentrated solutions in the testing. It was found that the palladium complexes exhibited satisfactory antibacterial activity, which is higher than that of the initial organic ligands. At a concentration of 0.1 mM, complex **Pd81** caused 50% inhibition of complex-forming units (compared to the control). The same result with the use of compound **Pd82** was achieved at a concentration of 0.6 mm; the 70% inhibition, at 1 mM.

4. Palladium complexes with sulfur-containing ligands

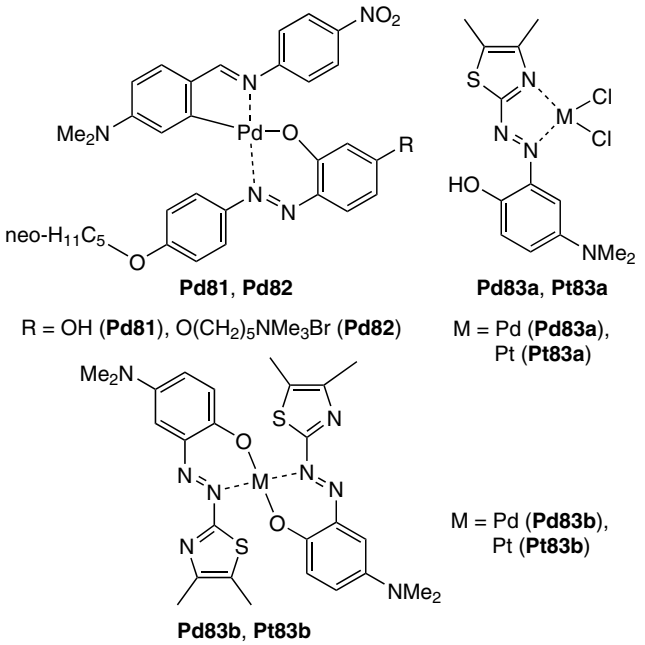
Palladium(II) complexes with sulfur-containing ligands, including S-donor ligands, are extensively investigated as

antimicrobial agents. A large series of Pd^{II}, Pt^{II} and Zn^{II} complexes of this structural type were synthesized by the research group headed by Al-Janabi.[50–53]

Polydentate diazene ligand **HL83** allows the synthesis of different types of palladium(II) and platinum(II) complexes depending on the reaction conditions.[50] In a neutral medium, the reaction affords compounds **Pd83a** and **Pt83a**; in an alkaline medium, dimers **Pd83b** and **Pt83b** are produced. The evaluation of their antibacterial activity against *S. aureus*, *E. coli*, *K. pneumoniae* and *P. aeruginosa* strains demonstrated that palladium complexes **Pd83a** and **Pd83b** exhibited the highest activity (Table 21). However, all the tested compounds were less effective than gentamicin used as the reference drug.

This research group also tested the antifungal activity of complexes **Pd84**–**Pd86** with thiol ligands against two types of fungal strains of *C. albicans* and *A. niger* (Table 22).[51] These complexes are distinguished by the structure of the second chelating N,N-donor ligand. Generally, these compounds did not exhibit satisfactory antifungal activity. However, it is worth mentioning the following interesting issue. Complex **Pd85** exhibited abnormally high inhibitory activity against the fungi *C. albicans* comparable with the activity of fluconazole used as the reference drug.

Structures M81–M83



Pd81, **Pd82** — **Pd83a**, **Pt83a**

R = OH (**Pd81**), $O(CH_2)_5NMe_3Br$ (**Pd82**) — M = Pd (**Pd83a**), Pt (**Pt83a**)

M = Pd (**Pd83b**), Pt (**Pt83b**)

Pd83b, **Pt83b**

Table 21. Antibacterial activity of compounds **M83** and initial ligand **HL83** (gentamicin as the reference drug).[50]

Compound[a]	Inhibition zone, mm			
	S. aureus	*P. aeruginosa*	*K. pneumoniae*	*E. coli*
HL83	18	14	11	19
Pd83a	23	21	16	23
Pt83a	20	19	15	20
Pd83b	25	23	19	27
Pt83b	21	21	16	22
Gentamicin	29	30	25	31

[a] Here and in Tables 26 and 28, the concentration of the agent was 10^{-3} M.

Table 22. Antifungal activity of complexes **Pd84**–**d86** (fluconazole as the reference drug).[51]

Compound[a]	Inhibition zone, mm	
	C. albicans	*A. niger*
Pd84	0	7
Pd85	**16**	1
Pd86	0	0
Fluconazole	14	15

[a] The concentration of the agent was 10^{-5} M.

The study[52] is a continuation of the above investigations. In this study, a series of mixed-ligand dithiocarbamate complexes of palladium (**Pd87**–**Pd90**) and zinc (**Zn87**, **Zn88**) were synthesized. The antimicrobial activity of these compounds was evaluated against three types of pathogenic bacteria (*E. coli*, *S. aureus* and *S. pyogenes*) and two types of fungi (*C. albicans* and *A. niger*) (Table 23). First of all, it should be noted that the dithiocarbamate ligand, sodium piperidine dithiocarbamate (NaPipDT), used for the comparison has low activity. Based on the analysis of the structure–property relationship, the authors concluded that the specificity of antibacterial activity does not depend on the nature of metal. Thus, the related Pd and Zn complexes (**Pd87** and **Zn87**, **Pd88** and **Zn88**) exhibited comparable activity against the whole series of the tested strains. The complexes possessed moderate to good activity compared to the standard antimicrobial drug streptomycin. Complexes **Pd89** and **Pd90** with the phosphine ligand appeared to be more effective antimicrobial agents than the other complexes and the free ligand. It is worth noting that complex **Pd90** containing, unlike compound **Pd89**, the oxidized sulfamide moiety showed higher antibacterial activity than streptomycin and higher antifungal activity compared to that of fluconazole.

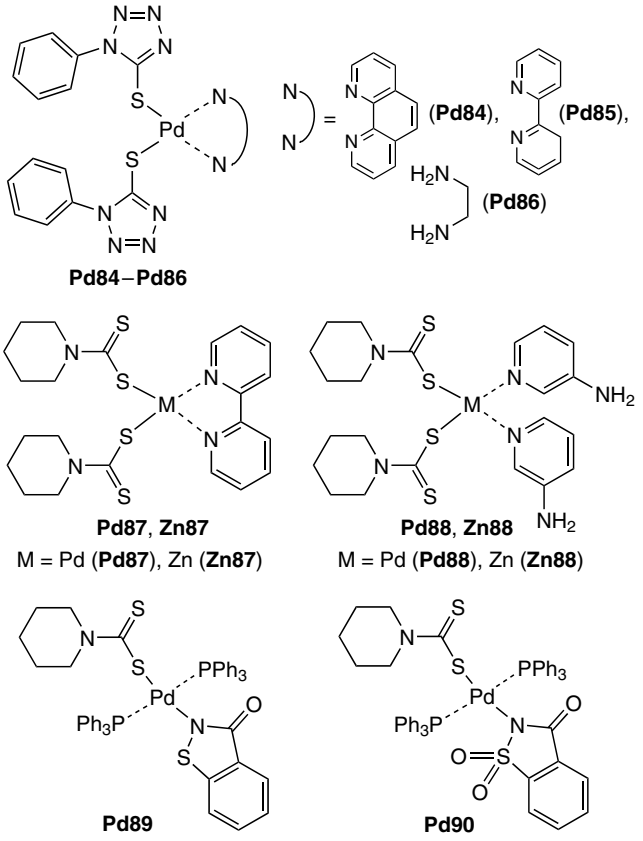
Dithiocarbamate ligands derived from the primary amines *N*-phenylaniline, 4-methylaniline and 4-ethylaniline were used to prepare Ni^{II}, Pd^{II} and Pt^{II} complexes.[54] Table 24 gives selected data on the activity of complexes **Pd91**–**Pd93**. Unlike the previous study, Bobinihi *et al*.[54] proposed the bidentate S,S-chelating mode of coordination of the dithiocarbamate ion to the metal cation. The antimicrobial screening demonstrated that complexes **Pd91**–**Pd93** exhibited moderate activity against Gram-negative (*E. coli*, *K. pneumoniae* and *P. aeruginosa*) and Gram-positive bacteria (*Bacillus cereus* and *S. aureus*) and

Table 23. Antibacterial and antifungal activity of compounds **M87**–**M90** and NaPipDT (streptomycin and fluconazole as the reference drugs).[52]

Compound[a]	Inhibition zone, mm				
	E. coli	*S. aureus*	*P. aeruginosa*	*C. albicans*	*A. niger*
NaPipDT	8	8	11	7	9
Zn87	12	16	14	11	10
Zn88	19	17	18	16	12
Pd87	12	11	12	14	10
Pd88	17	18	16	13	16
Pd89	20	20	14	18	15
Pd90	**24**	**22**	**20**	**22**	**19**
Streptomicin	23	20	25	–	–
Fluconazole	–	–	–	21	23

[a] The concentration of the agent was 10^{-3} μg mL^{-1}.

Structures M84–M90



Structures M91–M95

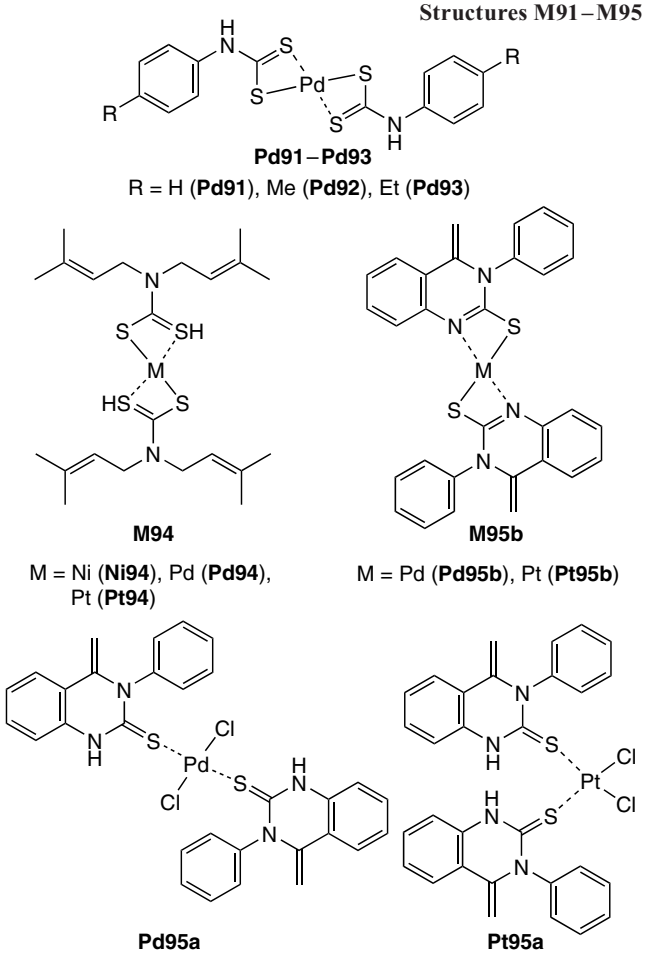


Table 24. Antibacterial and antifungal activity of complexes **Pd91**–**Pd93** (sulfamethoxazole and ketoconazole as the reference drugs).[54]

Compound[a]	Inhibition zone, mm				
	S. aureus	*K. pneumonia*	*E. coli*	*P. aeruginosa*	*C. albicans*
Pd91	10	–	17	11	13
Pd92	–	13	15	11	11
Pd93	19	19	16	14	08
Sulfamethoxazole	23	26	30	28	–
Ketoconazole	–	–	–	–	27

[a] The concentration of the agent was 50 mg mL^{-1}.

Table 25. Antibacterial and antifungal activity of compounds **M94** (ciprofloxacin and ketoconazole as the reference drugs).[55]

Compound[a]	Inhibition zone, mm				
	S. aureus	*B. cereus*	*P. aeruginosa*	*E. coli*	*C. albicans*
Ni94	14.1	13.1	20.3	19.0	19.2
Pd94	17.0	**16.8**	19.3	17.5	13.0
Pt94	18.0	10.0	14.0	21.0	17.3
Ciprofloxacin	19.0	21.0	20.0	22.0	–
Ketoconazole	–	–	–	–	21.0

[a] The concentration of the agent was 10^{-3} μg mL^{-1}.

against fungi (*C. albicans* and *A. flavus*) at a concentration of 50 μg mL^{-1}. Ethyl-substituted dithiocarbamate complex **Pd93** showed better antimicrobial activity compared to that of the unsubstituted (**Pd91**) and methyl-substituted (**Pd92**) analogues.

Thiocarbamate complexes **Ni94**, **Pd94** and **Pt94** were synthesized and characterized (Table 25).[55] The tested *S. aureus*, *B. cereus*, *P. aeruginosa*, *E. coli* and *C. albicans* strains proved to be resistant to the free ligand. The metal complexes exhibited moderate antimicrobial activity comparable with the activity of the reference antimicrobial drugs.

Complexes **Pd95a**,**b** and **Pt95a**,**b** were synthesized by the reaction of Na_2PdCl_4 or K_2PtCl_4 with 4-methylidene-3-phenyl-3,4-dihydroquinazoline-2(1*H*)-thione (**HL95**). In the presence of an alkali, the reaction proceeds through the deprotonation to give complexes **Pd95b** and **Pt95b**; in the absence of an alkali, the reaction affords complexes **Pd95a** and **Pt95a**.[53] The antibacterial activity of these compounds was evaluated against five pathogenic bacteria: *P. aeruginosa*, *K. pneumoniae*, *E. coli*, *S. epidermidis* and *S. aureus* (Table 26). It was found that all metal complexes were more effective than the free ligand. It should be noted that the palladium compounds were slightly less effective than the platinum analogues. Generally, the activity of these complexes is similar to the activity of tetracycline used as the reference drug.

A series of mononuclear complexes **Pd96**–**Pd101** with pyrazolylsulfonamide ligands were investigated in the study.[56] The antibacterial activity was evaluated against Gram-negative (*Citrobacter freundii*, *E. coli*, *S. typhi*, *P. mirabilis*, *Vibra cholerae*, *K. pnuemoniae*) and Gram-positive bacteria (*S. aureus*, *E. faecalis*, *S. epidermidis*) (Table 27). The MIC values

Structures Pd96–Pd102

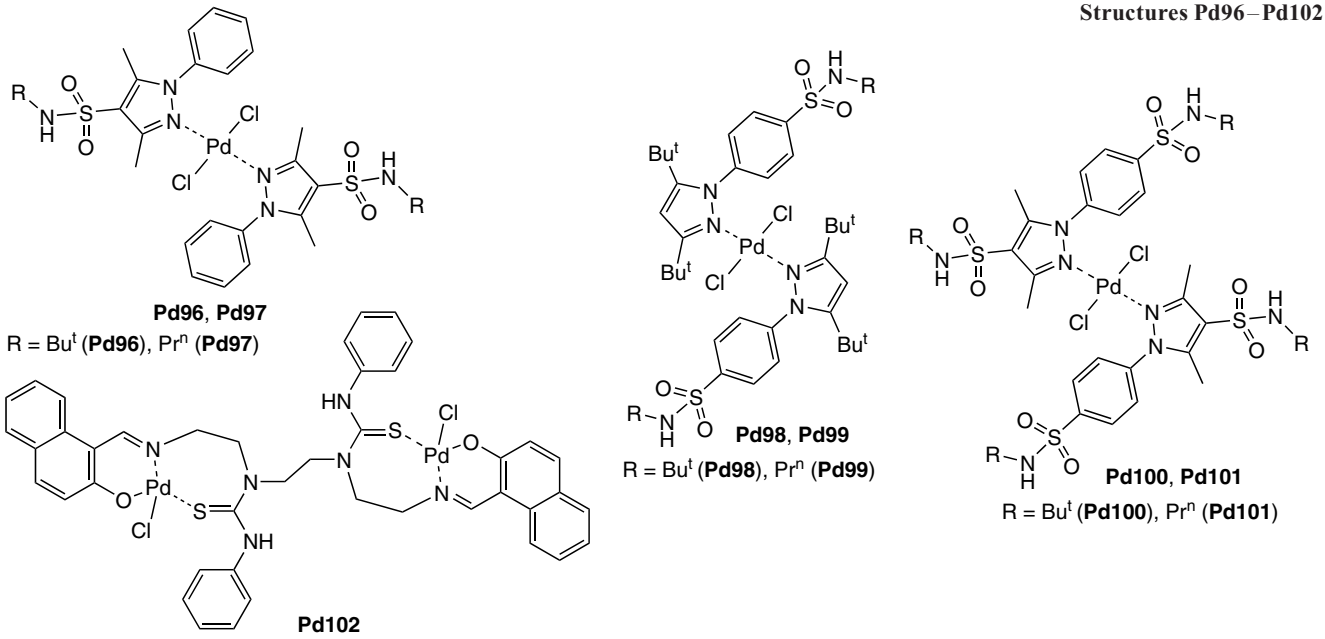


Table 26. Antibacterial activity of complexes **M95** and initial ligand **HL95** (tetracycline as the reference drug).[53]

Compound	Inhibition zone, mm				
	E. coli	*S. epidermidi*	*S. aureus*	*P. aeruginosa*	*K. pneumoniae*
HL95	18	14	18	16	14
Pd95a	21	24	22	20	21
Pt95a	24	25	23	22	26
Pd95b	22	23	22	19	20
Pt95b	23	23	24	20	23
Tetracycline	29	28	27	32	30

Table 27. Antibacterial activity of complexes **Pd96**–**Pd101** and the corresponding ligands (gentamicin as the reference drug).[56]

Compound	MIC, μg mL^{-1}					
	S. epidermidis	*E. coli*	*P. aeruginosa*	*C. freundii*	*K. pneumoniae*	*S. typhi*
L96	32.58	10.79	9.55	3.83	47.86	7.64
L97	7.24	5.23	7.12	21.23	34.83	4.92
L98	–	27.35	–	14.43	46.88	14.50
L99	23.01	–	–	–	46.70	–
L100	60.67	–	>1000	–	–	–
L101	–	64.41	6.40	8.51	>1000	10.19
Pd96	**3.36**	5.12	**6.52**	–	**9.05**	–
Pd97	**1.61**	3.66	**4.88**	**10.25**	**4.30**	**3.26**
Pd98	–	10.55	–	**11.23**	31.21	12.01
Pd99	**1.05**	41.59	**33.73**	–	21.35	–
Pd100	40.23	–	>1000	–	–	–
Pd101	–	20.58	**4.69**	**7.01**	>1000	8.64
Gentamicin	7.01	0.031	33.73	36.00	10.70	6.90

demonstrated that the tested compounds are more active against Gram-negative bacteria compared to Gram-positive bacteria. Note once again that, in general, the palladium complexes possess higher antibacterial activity than the corresponding ligands.

Complexes **Pd102** and **Ru102** were synthesized using an appropriate polydentatc ligand belonging to Schiff bases.[57] The antibacterial activity of ligand **L102** and its metal complexes was evaluated against five bacterial strains: MRSA ATCC 43300, *S. aureus* ATCC 25923, *P. aeruginosa* ATCC 278530, *M. luteus* and *E. coli* ATCC 25922. It was found that free ligand **L102** was inactive against all the tested bacterial strains. Complex **Pd102** exhibited activity only against methicillin-resistant *Staphylococcus aureusm* (the diameter of the inhibition zone was 19 mm at a concentration of 10 mg mL^{-1}) and methicillin-sensitive *S. aureus* (16 mm). A significant difference in the bactericidal activity against the *E. coli* strain was observed between complexes **Ru102** (20 mm) and **Pd102** (0 mm).

The applied aspect of using of these metal complexes for the analytical detection of free cholesterol in human blood was investigated.[57] Fluorometric measurements showed significant fluorescence quenching induced by the reaction of complex **Pd102** with cholesterol, which is indicative of a sensitive fluorometric response, allowing the detection of cholesterol. The detection limit of cholesterol using complex **Pd102** at a concentration of 4.6 μM was much lower than the detection limit achieved using other known sensors in the cholesterol concentration range of 0–5 mM.

A comparative analysis of the antimicrobial activity of chelate complexes **M103**, where M = VO, Zr, Pd, Pt or U, with 2-cyano-2-[(2-nitrophenyl)hydrazono]acetamide (**L103**) was performed (Table 28).[58] The bactericidal effect was evaluated against two Gram-positive (*S. aureus* K1 and *B. subtilis* K22) and two Gram-negative bacteria (*E. coli* K32 and *P. aeruginosa* SW1) compared to the positive control (ampicillin, amoxicillin and cephalexin). Complex **Pd103** exhibited the highest antibacterial activity. However, the fungicidal activity of this compound against two pathogenic fungi (*A. flavus* and *A. fumigatus*) proved to be lower than that of complexes **Zr103** and **Pt103**. The activity of initial ligand **L103** was much lower than that of the metal complexes in all tests. It is worth noting that the structures of the complexes presented in the original study[58] are doubtful.

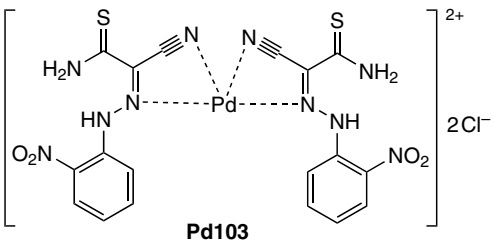
A comprehensive theoretical and physicochemical study of palladium complex **Pd104** with Schiff base **HL104**, which was

Table 28. Antibacterial and antifungal activity of complexes **M103**, initial ligand **L103** and reference drugs.[58]

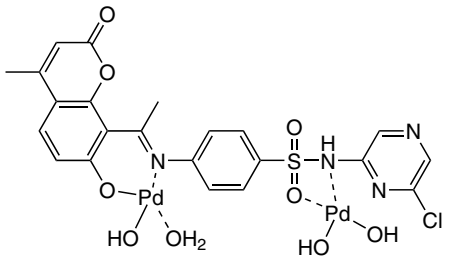
Compound	Inhibition zone, mm					
	E. coli	*P. aeruginosa*	*B. subtilis*	*S. aureus*	*A. flavus*	*A. fumigatus*
L103	15	18	25	28	–	–
VO103	25	17	35	30	5	5
Zr103	30	25	35	25	15	20
Pd103	**30**	**28**	**55**	**60**	7	9
Pt103	25	16	49	48	11	18
U103	18	27	44	35	7	8
$PdCl_2$	9	–	5	–	–	–
Ampicilin	–	13	28	–	–	–
Amoxycillin	–	23	22	–	–	–
Cefaloxin	24	–	27	–	–	–
Ketoconazole	–	–	–	–	17	20

synthesized by the condensation of 8-acetyl-7-hydroxy-4-methylcoumarin with sulfaclozine (sulfachloropyrazine), was performed.[59] This is yet another example of a multimodal ligand with pharmacophoric moieties. Sulfaclozine is an effective sulfonamide derivative with antibacterial activity, which is widely used for the treatment of various poultry diseases. It was found that the antibacterial activity of complex **Pd104** against *S. faecalis*, *E. coli* and *Neisseria gonorrhoeae* strains is higher than the activity of initial ligand **HL104**. Complex **Pd104** proved to be generally less active against a series of pathogenic strains (*B. subtilis*, *S. aureus*, *S. faecalis*, *E. coli*, *N. gonorrhoeae*, *P. aeruginosa*) compared to complex **Zn104** described in the same study but is more active than complex **Cu104**.

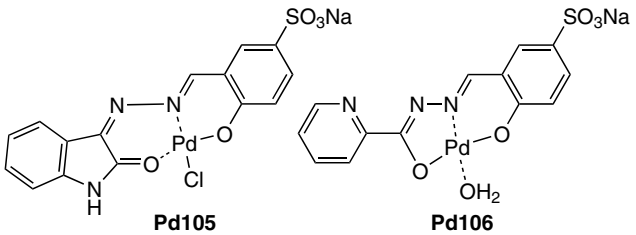
Structures Pd103–Pd106



Pd103



Pd104



Pd105 **Pd106**

The solubility of these agents in aqueous solutions is an important issue. Metal complexes **Pd105** and **Pd106** were synthesized using water-soluble sulfonate ligands.[60,61] The antimicrobial potential of ligand **HL105**, which was prepared based on isatin, and corresponding complex **Pd105** was evaluated against three known bacterial strains of *E. coli*, *S. marcescens* and *S. aureus*; the antifungal activity, against *A. flavus*, *C. albicans* and *T. rubrum* strains.[60] The MIC values of ligand **HL105** varied in the range of 6.50–8.05 μM; of complex **Pd105**, in the range of 1.75–2.20 μM. In the case of the fungal strains, the MIC values were 6.65–7.85 μM (for **HL105**) and 2.05–2.50 μM (for **Pd105**). Therefore, complex **Pd105** proved to be more active than the corresponding free ligand.

Related ligand **HL106** was synthesized based on picolinic acid hydrazide[61] and was used to prepare a series of metal complexes **M106**, where M = Co, Fe, Hg or Pd. These complexes were subjected to antimicrobial screening against the following microorganisms: *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa* and *C. albicans*. Unlike complex **Pd105**, compound **Pd106** did not exhibit sufficiently high activity against the tested strains.

Picolinic acid hydrazide was used also in the study[62] to synthesize thiosemicarabazides **H2L107**–**H2L109** and heterocyclic complexes **Pd107**–**Pd109** and **Pt107**–**Pt109**. Analyzing the results of antimicrobial screening of these ligands and their metal complexes, it can be stated that only two results are worth discussing. Thus, complexes **Pd108** and **Pt108** containing a cyclohexyl substituent possessed high antibacterial activity against *B. subtilis* and *Lactobacillus fermentum*. The MIC values of these compounds were lower than 16 μg mL^{-1}, which is smaller than the value of 32 μg mL^{-1} for ampicillin taken as the control.

Abu-Dief and co-workers[63–65] tested thiazolopyrazole complexes of Pd^{II}, Cu^{II} and Fe^{III} as antimicrobial agents. The antibacterial screening was carried out against the bacteria *M. luteus*, *E. coli* and *S. marcescens*; the fungicidal activity, against the fungi *F. oxysporum*, *G. candidum* and *A. flavus*. In all tests, complexes **Pd110**–**Pd112** proved to be more effective than the corresponding ligands and complexes **Cu110**–**Cu112** and **Fe110**–**Fe112** (Table 29, selected data are given).

As mentioned by de Lacerda *et al*.,[66] the resistance of the zoo bacterium *Campylobacter jejuni*, which causes foodborne gastroenteritis, to clinical antimicrobial agents is a challenging problem. The antibacterial activity of two new complexes (**Pd113** and **Pt113**) was evaluated against three resistant *C. jejuni* strains. The *in vitro* antibacterial activity of these complexes was investigated in isolation and synergistically with ciprofloxacin (CIP) and erythromycin (ERY). Complex **Pd113** proved to be ineffective, while its analogue **Pt113** gave an interesting synergistic effect with CIP. The grouped analysis of the mean MIC values showed that complex **Pt113** was effective both alone (MIC = 21.4±10.6 mg L^{-1}) and in synergy with the antimicrobial drugs (in the presence of CIP, MIC = 0.9±0.5 mg L^{-1}; in the presence of ERY, MIC = 21.4±10.6 mg L^{-1}) compared to the assays, in which only these antibiotics were used (MIC = 32 mg L^{-1}).

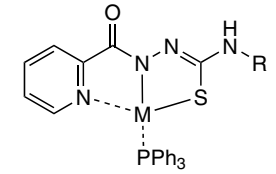
The antimicrobial activity of complexes **Pd114** and **Pd115** with aminothiazole ligands was evaluated against a wide range of pathogenic microorganisms (Table 30, selected data are given).[67] The experiment included eight bacterial strains (four standard strains and four clinical isolates) and three types of yeast. In most cases, the bactericidal activity of complexes **Pd114** and **Pd115** was higher than that of the corresponding ligands **L114** and **L115**. The tested complexes exhibited better

Table 29. Antibacterial and antifungal activity of complexes **M110**–**M112** and the corresponding ligands.

Compound	Strains						Ref.
	M. luteus	*E. coli*	*S. marcescens*	*A. flavus*	*G. candidum*	*F. oxysporum*	
	MIC, mg mL^{-1}						
L110	–	–	6.75	–	4.75	–	63
Cu110	–	–	2.50	–	2.25	–	63
Pd110	–	–	**2.25**	–	**1.75**	–	63
Fe110	–	–	4.00	–	2.50	–	63
L111	7.00	7.75	7.25	6.00	5.25	6.75	64
Cu111	3.00	3.50	3.25	3.00	2.75	3.00	64
Pd111	**2.50**	**3.50**	**3.00**	**2.50**	**2.00**	**2.75**	64
Fe111	4.25	4.75	3.75	3.75	3.00	4.25	64
	Activity index A, % (see [a])						
L112	36.53	33.33	22.72	25.00	25.00	26.92	65
Cu112	80.76	89.74	77.27	85.71	84.09	89.74	65
Pd112	**86.53**	**92.30**	**84.09**	**89.28**	**88.63**	**92.30**	65
Fe112	75.00	83.33	63.63	82.14	79.54	85.89	65

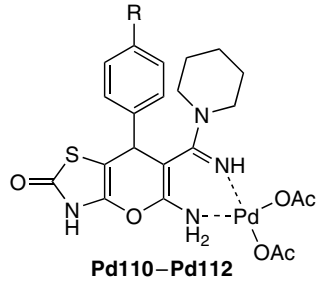
[a] The activity index *A* is the ratio of the diameter of the inhibition zone of the compound (mm) to the diameter of the inhibition zone in the presence of the reference drug (mm) expressed in percentage.

Structures M107–M116



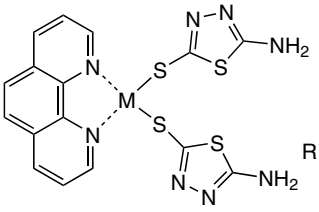
Pd107–**Pd109**

M = Pd: R = Et (**Pd107**), Cy (**Pd108**), Ph (**Pd109**); M = Pt: R = Et (**Pt107**), Cy (**Pt108**), Ph (**Pt109**); Cy = cyclo-C_6H_{11}



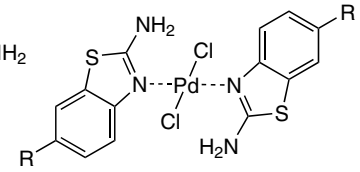
Pd110–**Pd112**

R = Cl (**Pd110**), OMe (**Pd111**), H (**Pd112**)



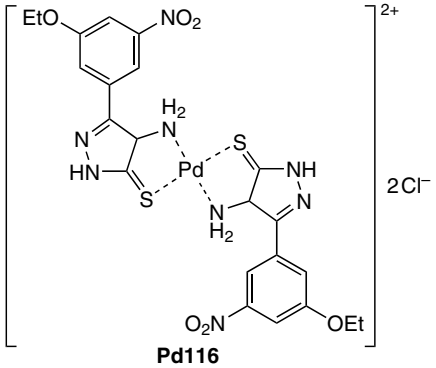
Pd113, **Pt113**

M = Pd (**Pd113**), Pt (**Pt113**)



Pd114, **Pd115**

R = Me (**Pd114**), Cl (**Pd115**)



Pd116

Table 30. Antibacterial and antifungal activity of complexes **Pd114**, **Pd115** and the corresponding ligands (tetracycline and fluconazole as the reference drugs).[67]

Compound	MIC, μg mL^{-1}				
	B. subtilis ATCC 6633	*S. aureus* ATCC 25923	*E. coli* ATCC 25922	*C. albicans* ATCC 10231	*R. mucilaginosa*
L114	500	1000	62.50	250	62.50
L115	500	1000	125	500	62.50
Pd114	31.25	250	125	500	125
Pd115	31.25	500	125	500	250
Tetracycline	1.95	0.22	15.63	–	–
Fluconazole	–	–	–	31.25	62.50

activity against Gram-positive bacteria (standard and clinical strains of *S. aureus* and *B. subtilis*). The effect on Gram-negative bacteria was low. These compounds exhibited moderate antifungal activity. In this case, ligands **L114** and **L115** showed higher activity than the complexes. The yeast strain of *Rhodotorula mucilaginosa* was the most sensitive within the positive control (fluconazole).

Complexes **Pd116**, **Ni116** and **Zn116** were synthesized by the coordination of the corresponding metals with sulfur-containing triazole ligand **L116** (Table 31).[68] The evaluation of antimicrobial activity of these compounds against bacterial (*S. aureus*, *E. coli*) and fungal strains (*C. albicans*, *A. flavus*) demonstrated that the bactericidal activation of the ligand occurs only upon coordination to palladium (the diameter of the inhibition zone varied from 6–8 to 11–12 mm). Besides, only complex **Pd116** exhibited antifungal activity comparable with the activity of miconazole used as the reference drug.

Aminotriazole and oxodiazole thiones are close analogues of the above ligands. These ligands were used to synthesize mononuclear (**Pd117a** and **Pd118a**) and binuclear (**Pd117b** and **Pd118b**) palladium(II) complexes (Table 32).[69] All the synthesized compounds were tested as antimicrobial agents against eight bacterial strains (*S. aureus* ATCC 25923, *S. aureus* (laboratory isolate), *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853) and three fungi (*A. niger*, *C. albicans*, *Trichosporon*). No significant antifungal activity was observed in this series. The patterns of changes in the antibacterial activity are significantly differen for the aminotriazole and oxodiazole derivatives. Thus, aminotriazole sulfone **HL117** exhibited high bactericidal activity against the whole range of strains (the diameter of the growth inhibition zone of bacteria was 15–34 mm), while corresponding complexes **Pd117a**,**b** proved to be inactive. On the contrary,

Table 31. Antibacterial and antifungal activity of complexes **M116** and initial ligand **L116** (azithromycin and miconazole as the reference drugs).[68]

Compound	Inhibition zone, mm			
	S. aureus	*E. coli*	*C. albicans*	*A. flavus*
L116	8	8	0	0
Pd116	**12**	**11**	**13**	**18**
Ni116	6	8	0	0
Zn116	4	5	0	0
Azithromycin	18	22	–	–
Miconazole	–	–	17	23

Structures Pd117–Pd123

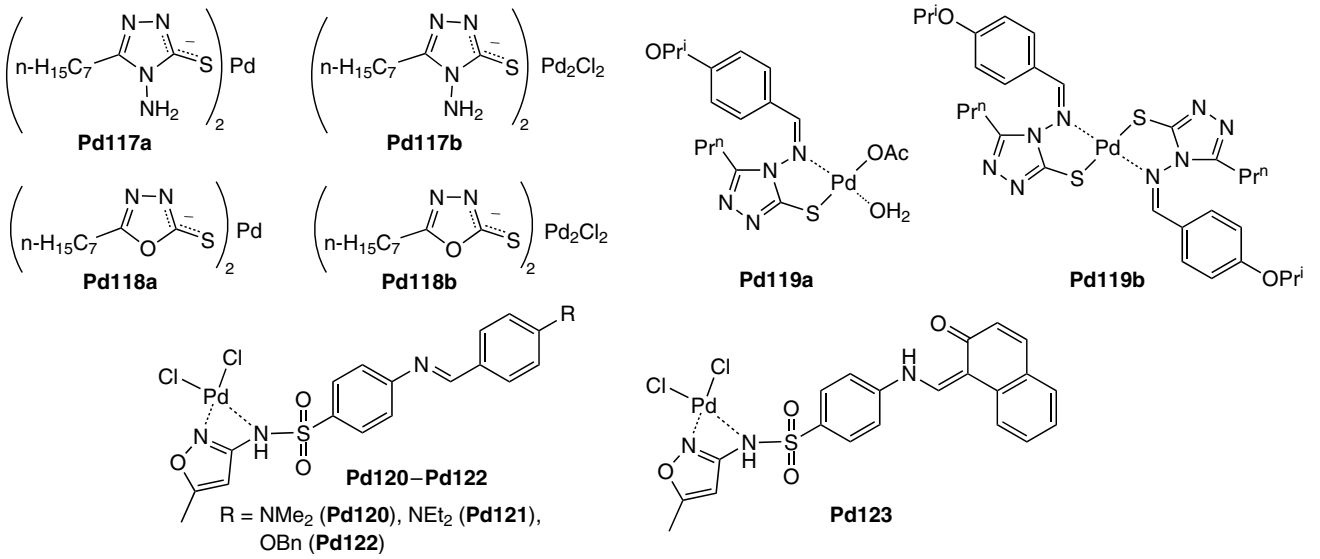


Table 32. Antibacterial and antifungal activity of complexes **Pd117**, **Pd118** and the corresponding ligands (vancomycin and colistin as the reference drugs).[69]

Compound	Inhibition zone, mm				
	S. aureus ATCC 25923	*S. aureus*	*E. faecalic* ATCC 29212	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853
HL117	29	15	19	22	34
Pd117a	0	0	0	0	0
Pd117b	0	0	0	0	0
HL118	12	14	9	0	0
Pd118a	0	0	0	0	7
Pd118b	7	9	0	**7**	**11**
Vancomycin	18	30	23	–	–
Colistin	–	–	–	14	11

ligand **HL118** was inactive against Gram-negative bacteria (*E. coli*, *P. aeruginosa*), while its complex **Pd118b** inhibited the growth of bacteria (the diameters were 7 and 11 mm, respectively).

The imine [(4-isopropoxybenzylidene)amino]-5-propyl-3-sulfanyl-4*H*-1,2,4-triazole (**HL119**) was synthesized based on aminotriazole thione and was used to prepare a series of cobalt(II), nickel(II), zinc(II), copper(II) and platinum(II) complexes.[70] Depending on the ligand : metal molar ratio, the coordination results in the formation of mono- and bischelate complexes (*e.g.*, **Pd119a** and **Pd119b**). The antibacterial activity of these compounds was tested against the standard strains *S. aureus* MTCC 96, *S. pyogenes* MTCC 442, *E. coli* MTCC 443 and *P. aeruginosa* MTCC 1688 (Table 33). The tested compounds showed moderate activity (MIC = 62.5–250 μg mL^{-1}); however, the lead compound was not found. The dependence of the activity on the nature of metal and the type of the complex was also not revealed. For compounds **Pd119a** and **Pd119b**, only the effective bactericidal activity against *Pseudomonas aeruginosa* and *Streptococcus pyogenes* was observed (MIC = 62.5 μg mL^{-1}), which is comparable with the activity of the clinical drug, the antibiotic chloramphenicol (MIC = 50 μg mL^{-1}). For comparison, note that the MIC value of free imine **HL119** was in the range of 100–125 μg mL^{-1}.

Table 33. Antibacterial and antifungal activity of complexes **Pd119** and initial ligand **HL119 (**chloramphenicol and nystatin as the reference drugs).[70]

Compound	MIC, μg mL^{-1}					
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenus*	*C. albicans*	*A. niger*
HL119	250	125	125	100	500	1000
Pd119a	125	**62.5**	250	100	1000	1000
Pd119b	125	100	100	**62.5**	250	500
Chloramphenicol	50	50	50	50	–	–
Nystatin	–	–	–	–	100	100

Unlike the antibacterial activity, the antifungal effect of the tested metal complexes against *C. albicans*, *A. niger* and *A. clavatus* strains was low (MIC = 250–1000 μg mL^{-1}), which is lower than that of nystatin (100 μg mL^{-1}). Nevertheless, it is clearly seen that the fungicidal activity of the bischelate complexes is higher than that of the monochelate analogues. For example, compound **Pd119a** is almost inactive (MIC = 1000 μg mL^{-1} and higher); the MIC value of complex **Pd119b** is in the range of 250–1000 μg mL^{-1} against all the tested pathogenic fungi.

As it was mentioned many times above, and efficient and promising approach to tackle the problem of resistance of clinical drugs is based on their modification through complexation with metal ions. An example of this approach is the study,[71] in which complexes **Pd120**–**Pd122** with sulfamethoxazole imines were synthesized and characterized. The evaluation of the antibacterial activity against the microorganisms *E. coli*, *K. pneumoni*, *S. aureus* and *B. subtilis* showed that corresponding ligands **L120**–**L122** exhibited moderate activity, which is, in some cases, enhanced upon their coordination to metal ions (Table 34). For example, the MIC value of ligand **L120** for *Staphylococcus aureus* is 200 μg mL^{-1}, while this value for corresponding complex **Pd120** is 50 μg mL^{-1}. The results of this study demonstrate that sulfamethoxazole derivatives and their metal complexes possess low activity against the pathogenic fungi *C. albicans* and *A. niger*.

Sulfamethoxazole was used also to synthesize ligand **L123** and related complexes **Pd123** and **Pt123** (Table 34).[72]

Table 34. Antibacterial and antifungal activity of complexes **Pd120**–**Pd123** and the corresponding ligands (ampicillin as the reference drug).

Compound	Strains					Ref.
	E. coli	*K. pneumoniae*	*S. aureus*	*B. subtilis*	*P. aeruginosa*	
	MIC, μg mL^{-1}					
L120	75	25	200	12.5	–	71
L121	75	25	100	6.25	–	71
L122	6.25	6.25	6.25	6.25	–	71
Pd120	75	25	**50**	12.5	–	71
Pd121	100	25	100	6.25	–	71
Pd122	6.25	6.25	6.25	6.25	–	71
	Inhibition zone, mm					
L123	16	–	10	–	0	72
Pd123	16	–	15	–	15	72
Pt123	–	–	15	–	10	72
Ampicillin	20	–	40	–	10	72

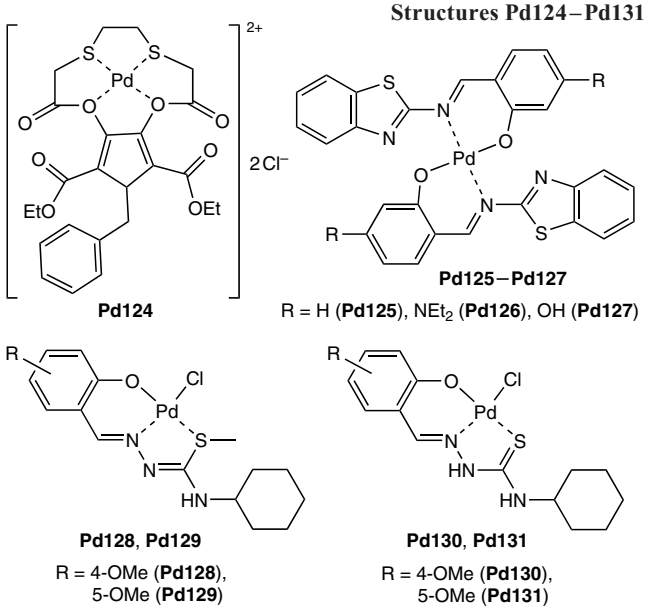
Unfortunately, it is impossible to compare the results of these two studies (see Refs 71 and 72) because the antimicrobial activity of the synthesized compounds was expressed in different units. Nevertheless, it is worth noting that ligand **L123** and corresponding complex **Pd123** exhibited good antibacterial activity against *E. coli* (the diameter of the inhibition zone was 16 mm, the concentration was not reported). Complexes **Pd123** and **Pt123** possessed higher activity against the bacteria *S. aureus* (15 mm) compared to free ligand **L123** (10 mm). The free ligand was inactive against *P. aeruginosa*, whereas complexes **Pd123** and **Pt125** inhibited this bacterial strain, compound **Pd123** exhibiting higher inhibitory activity than complex **Pt123** (the diameters of the inhibition zone were 15 and 10 mm, respectively). Notably, complex **Pd123** was more active against the bacteria *P. aeruginosa* compared to the standard drug ampicillin.

Original macrocyclic ligand **L124** and complex **Pd124** were synthesized and characterized.[73] The antimicrobial activity of this pair of compounds was evaluated against *S. aureus*. It was found that the coordination to the metal causes a decrease in the activity compared to free ligand **L124** (MIC = 6.25 μg mL^{-1} for the ligand; MIC = 25 μg mL^{-1} for **Pd124**). The ligand and the complex had equal antifungal activity against the yeast *C. albicans* (MIC = 6.25 μg mL^{-1}).

A wide screening of complexes **Pd125**–**Pd127** with thiazole azomethine ligands for antimicrobial activity was performed (Table 35).[74] In this study, 16 bacterial strains and two fungal strains were used. All compounds proved to be the most effective against Gram-positive bacteria, particularly against *B. megaterium*. Generally, complexes **Pd125**–**Pd127** exhibited higher antibacterial and antifungal activity compared to corresponding ligands **HL125**–**HL127**. The best results were observed for compound **Pd126** containing an amine substituent. For example, the activity of this compound against the microorganisms *S. aureus* is comparable with that of the reference drug vancomycin.

Salicylidene derivatives of thiosemicarbazones were used as polydentate ligands to synthesize chelate complexes **Pd128**–**Pd131** having N,O,S-coordination mode.[75] The antimicrobial activity of these ligands and palladium(II) complexes was evaluated against a panel of pathogenic bacterial and fungal strains (Table 36). It was found that thiosemicarbazone ligands **HL129**–**HL131** did not exhibit inhibitory activity

Structures Pd124–Pd131



Pd124

Pd125–**Pd127**

R = H (**Pd125**), NEt_2 (**Pd126**), OH (**Pd127**)

Pd128, **Pd129**

R = 4-OMe (**Pd128**), 5-OMe (**Pd129**)

Pd130, **Pd131**

R = 4-OMe (**Pd130**), 5-OMe (**Pd131**)

Table 35. Antibacterial and antifungal activity of complexes **Pd125**–**Pd127** and the corresponding ligands (vancomycin as the reference drug).[74]

Compound	Inhibition zone, mm				
	S. aureus 6538 P	*B. subtilis* ATCC 6337	*B. megaterium* DSM 32	*B. brevis*	*B. sereus* EMC 19
HL125	4	5	3	2	3
HL126	5	6	4	3	2
HL127	4	2	4	3	6
Pd125	4	4	6	5	7
Pd126	**7**	**8**	**6**	**7**	**6**
Pd127	6	4	8	3	**3**
Vancomycin	7	–	–	–	–

against this panel of strains, except for the fungi *C. tropicalis*. The test cultures of Gram-negative bacteria (*P. aeruginosa*, *E. coli*, *K. pneumoniae*, *P. mirabilis*) and *S. aureus* proved to be resistant to all these compounds. Complexes **Pd128** and **Pd129** with thioalkylated ligands possessed significant activity against *E. faecalis* and *S. epidermidis* strains, whereas thione complexes **Pd130** and **Pd131** did not inhibit the growth of these bacteria. All complexes **Pd128**–**Pd131** displayed fungicidal activity. For example, complex **Pd128** appeared to be more active against *C. albicans* (MIC = 3.17 μg mL^{-1}) than the reference drug clotrimazole (MIC = 4.9 μg mL^{-1}).

Selenium is an essential natural microelement. Therefore, it is reasonable to introduce this heteroatom into potential pharmaceticals.[76] Chiral selenium-containing imines **HL132**, **HL133** and related complexes **Pd132**, **Pd133** were tested for biological activity. The antimicrobial activity was evaluated against the microorganisms *K. aerogenes*, *E. coli*, *P. desmolyticum*, *S. aureus* and *C. albicans* using the clinical drugs ciprofloxacin and fluconazole as positive controls. However, all the tested compounds exhibited very low activity. Thus, the diameter of the growth inhibition zone of the tested microorganisms for the reference drugs (ciprofloxacin, fluconazole) was in the range of 11–14 mm, whereas this parameter for complexes **Pd132**–**d133** was smaller than 5 mm even at a concentration of 10 mg mL^{-1}.

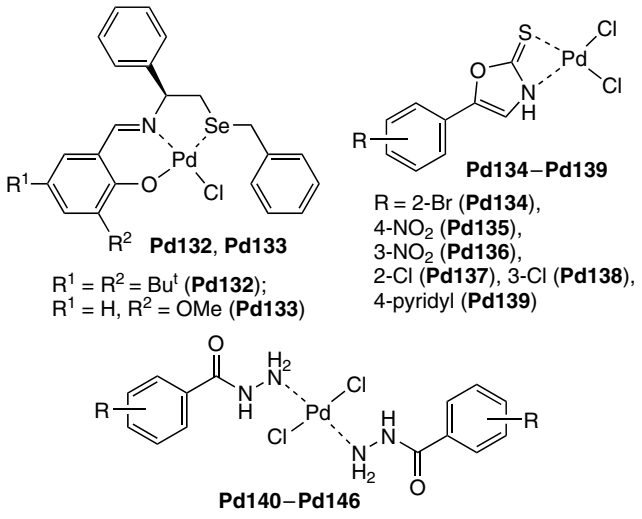
Table 36. Antibacterial and antifungal activity of complexes **Pd128**–**Pd131**, the corresponding ligands and reference drugs.[75]

Compound	MIC, μg mL^{-1}				
	E. faecalis ATCC 2912	*S. epidermidis* 8	*C. albicans* ATCC 10231	*C. parapsilosis* ATCC22019	*C. tropicalis* ATCC 750
HL128	–	–	–	–	375
HL129	–	–	–	–	187.5
HL130	–	–	–	–	–
HL131	–	–	–	–	46.78
Pd128	**12.69**	**6.34**	**3.17**	3.17	–
Pd129	**39.06**	19.53	19.53	19.53	19.53
Pd130	–	–	101.5	25.39	–
Pd131	–	–	78.12	19.53	78.12
Reference product	128[a]	9.8[b]	4.9[c]	0.5[d]	1[d]

[a] Amikacin, [b] Cefuroxime, [c] Clotrimazole, [d] Amphotericin B.

The cycloaddition of aryl-substituted benzoic acid hydrazides to CS_2 afforded a series of oxadiazolothiones **L134**–**L139**, which were used as ligands to synthesize complexes **Pd134**–**Pd139**.[77] Hydrazides **L140**–**L146** and their complexes **Pd140**–**Pd146** were also investigated in order to perform a comparative analysis and reveal the structure–property relationships. The antibacterial and antifungal activity of two types of complexes, with the N,S-chelating thio ligand (**Pd134**–**Pd139**) and the monodentate N-coordinated hydrazide ligand (**Pd140**–**Pd146**), was evaluated. The structural diversity of the compounds was ensured by the nature and positions of substituents in the aromatic ring of the ligands. The antimicrobial potential of palladium complexes **Pd134**–**Pd146** and free ligands **L134**–**L146** was evaluated against a wide range of pathogenic bacteria (*M. luteus*, *S. aureus*, MRSA, *E. coli*, *S. typhi*, *P. aeruginosa*) and fungi (*A. niger*, *C. albicans*, *A. flavus*, *Microsporum gypseum*, *Mucor*, *Penicillium*, *Saccharomyces*, *T. mentagrophytes*) (Table 37, selected data are given). The following distinguishing features were observed in the group of hydrazide ligands and complexes **Pd140**–**Pd146**: in most tests, the ligands are less active than the corresponding palladium(II) complexes; the powerful antibacterial agent **Pd142** (R = 4-NO_2) was found, which provided the inhibition zone with a diameter of 11–16 mm for four of the six tested bacterial strains (the activity against the bacteria *P. aeruginosa* and MRSA is comparable with that of ampicillin). Unlike the hydrazide compounds, oxadiazolothiones **L134**–**L139** exhibited stronger antibacterial activity than the corresponding palladium complexes against most of bacterial strains. Compounds **Pd134**–**Pd139** are also weaker antibacterial agents than related complexes **Pd140**–**Pd146**. This fact was attributed to the higher structural stability of the bidentate chelate complexes. In the series of complexes **Pd134**–**Pd139**, compounds **Pd138** (R = 2-Cl) and **Pd135** (R = 4-NO_2) showed the highest antibacterial potential against strains of *P. aeruginosa* (the diameter of the inhibition zone was 12 mm) and *E. coli* (10 mm). The effect of the position of the substituent on the antibacterial activity of compounds **Pd134**–**Pd139** and **Pd140**–**Pd146** is almost the same. Thus, compounds containing electron-withdrawing substituents in *ortho* or *para* positions possess the highest activity. As opposed to antibacterial activity, such patterns were not observed for antifungal activity. 4-Pyridyl derivatives **Pd139** and **Pd146** are rather active fungicidal agents.

Structures Pd132–Pd146



5. Palladium complexes for antimicrobial photodynamic therapy

Photodynamic therapy (PDT) is an efficient method used in clinical practice to overcome the antibiotic resistance of known

Table 37. Antibacterial and antifungal activity of complexes **Pd134**–**Pd146** and the corresponding ligands (ampicillin and nystatin as the reference drugs).[77]

Compound	Inhibition zone, mm					
	MRSA	*P. aeruginosa*	*A. niger*	*C. albicans*	*M. gypseum*	*Mucor*
L142	8.6	9.0	2.8	0	0	4.2
Pd142	**16.0**	**14.5**	1.0	4.2	2.9	0.7
L135	14.0	6.7	2.4	0	0	4.0
Pd135	**0**	**9.8**	0.9	2.8	2.8	3.6
L144	3.3	0	1.2	0	3.6	3.0
Pd144	**16.0**	0	0.9	0.5	1.5	0.6
L137	19.1	0	1.0	0	0.3	2.7
Pd137	0	**12.2**	0.8	2.7	2.5	0
L146	0	0	4.0	0	3.9	3.4
Pd146	0	0	3.0	**3.9**	**4.5**	**5.3**
L139	8.5	0	3.6	4.3	0.1	3.2
Pd139	0	7.9	**4.0**	2.2	0.2	3.0
Ampicillin	20.3	15.0	–	–	–	–
Nystatin	–	–	5.0	4.5	3.5	6.0

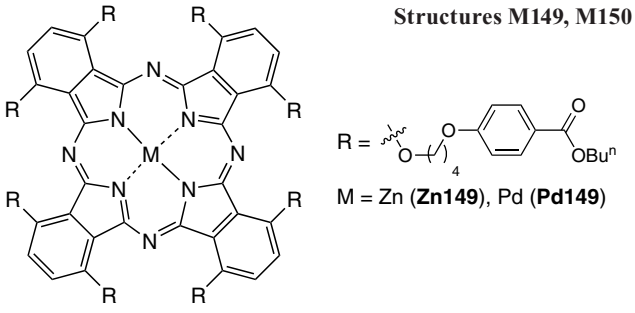
pathogenic microorganisms. This method is based on the combined action of a photosensitizer, oxygen and light of a particular wavelength. The reaction affords singlet oxygen and other reactive oxygen species, which can inactivate pathogenic cells. Porphyrin complexes of transition metals, in particular palladium, are extensively studied as photosensitizers.[78–82] It is worth noting that the palladium-containing agent padeliporfin (**Pd147**) is currently used for PDT.[83]

In the studies,[78,79] phthalocyanine complex **Pd148a** with four peripheral *N*-methylpyridiniomethoxy substituents was found to be effective against the heterotrophic Gram-negative rod-shaped bacterium *Aeromonas hydrophila*. Compound **Pd148a** was synthesized and characterized as a mixture of structural isomers with different arrangement of cationic substituents on the aromatic ring. Strains of the heterotrophic Gram-negative rod-shaped bacterium *A. hydrophila*, resistant (R) and sensitive (S) to antibiotics, were investigated. Peripherally substituted complex **Pd148a** showed complete photoinactivation at a concentration of 8 μM for the sensitive *A. hydrophila* strain. At a concentration of 20 μM, this compound exhibited dark toxicity against both tested strains (S and R). At lower concentrations (<2 μM), **Pd148a** did not show phototoxicity against either S or R strains.

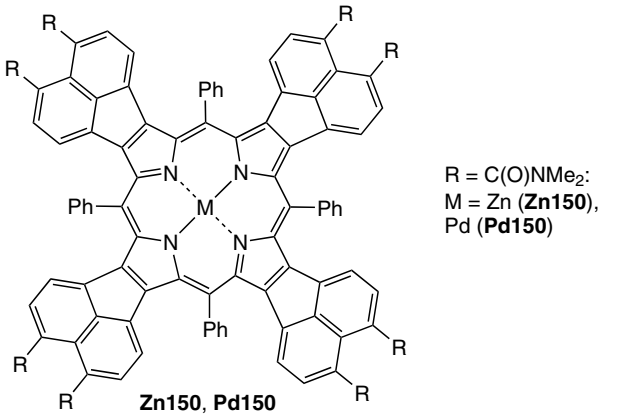
In the subsequent study,[79] these authors applied this procedure to clinical isolates of the Gram-negative bacterium *F. hydatis*, namely multiresistant (R) and sensitive (S) strains. Different structural isomers of palladium(II) phthalocyanine complexes containing one of *N*-methylpyridiniomethoxy groups in the *meta* (**Pd148a**) or *ortho* position (**Pd148b**) were used as bacterial growth inhibitors. It was found that dark toxicity was absent in all tests. Only complex **Pd148b** was shown to have relatively high antibacterial photoefficiency; lower efficiency was observed for its analogue **Pd148a**. It was found that the photodynamic response was similar regardless of the resistance of the bacterial strain; it depended only on the photosensitizing ability of the applied phthalocyanine complex.

Phthalocyanine **L149** containing nipagin-functionalized substituents and its metal complexes **Pd149** and **Zn149** were investigated as photosensitizers for antimicrobial photodynamic therapy.[80] The photoactivity of compounds **L149**, **Pd149** and **Zn149** encapsulated into a liposomal formulation was tested against a wide range of microorganisms, including the bacteria MRSA and *E. coli* (ESBL+), the fungi *C. albicans* (fluconazole-resistant) and *C. auris* and the dermatophytes *T. mentagrophytes* and *T. rubrum*. The first thing to note is that, in the absence of irradiation, no growth inhibition was observed across all the tested strains or compounds even at a concentration two times

Structures M149, M150



Zn149, **Pd149**



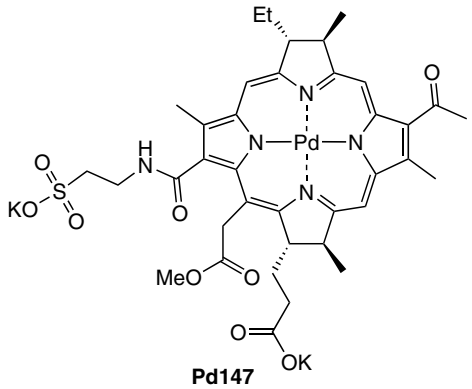
Zn150, **Pd150**

higher than that used in the experiments with irradiation. There was a clear relationship between the presence of Zn^{II} or Pd^{II} in the macrocyclic core and their phototoxicity against the tested microorganisms. Free ligand **L149** appeared to be the least active, whereas derivative **Pd149** exhibited significantly better bactericidal activity compared to its zinc analogue **Zn149**.

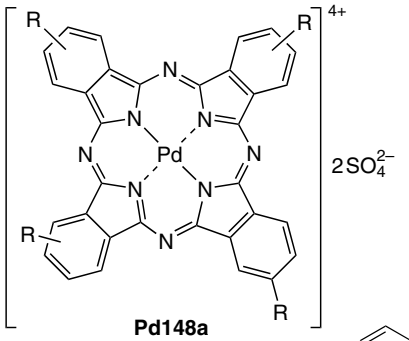
Porphyrins with an extended π system were synthesized and used to prepare corresponding complexes **Zn150** and **Pd150**.[82] The electronic modification of the structures makes it possible to significantly extend the absorption spectrum and, correspondingly, the field of application of these agents. The antibacterial activity of metalloporphyrins **Zn150** and **Pd150** was evaluated against two resistant strains, *S. aureus* 3150/12 and *B. subtilis* DB104. Complex **Pd150** showed significantly higher activity than its zinc analogue **Zn150**. For example, in the presence of compound **Pd150**, bacterial colonies *S. aureus* 3150/12 were not found under continuous irradiation at a dose of 18 J cm^{-2} for 60 min.

Porphyrins containing peripheral positively charged Pt^{II} (or Pd^{II}) dipyridyl complex moieties are of biological and

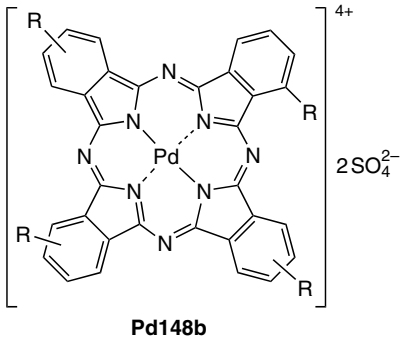
Structures Pd147, Pd148



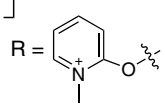
Pd147



Pd148a



Pd148b



photochemical interest.[84–86] As mentioned in these studies, such compounds are the best generators of ROS. Two isomeric Pd^{II} porphyrins, **Pd151** and **Pd152**, were used in experiments on the photoactivation of *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *S. aureus* bacterial cells, (Table 38).[84] It was found that complexes **Pd151** and **Pd152** did not exhibit antimicrobial activity without exposure to light. Under irradiation, the death of the cells of all the tested microorganisms was observed. The study demonstrated that porphyrin **Pd151** containing a positively charged group in the *meta* position was the most efficient photosensitizers.

In the subsequent studies,[85,86] this team of Brazilian researchers investigated this type of complexes for PDT against such pathogenic microorganisms as mycobacteria and fungal dermatophytes. In the latter case, related platinum(II) complexes were used for comparison. The latter complexes appeared to be more efficient photosensitizers than the palladium(II) complexes.

Another example of active photosensitizers is Pd^{II} complexes with *meso*-substituted porphyrins, which were prepared both in the neutral amino form (**Pd153**) and as quaternary ammonium salts (**Pd154**).[87] Chitosan conjugates of these compounds were also synthesized. The *in vitro* photodynamic antibacterial activity of these agents was evaluated against *S. aureus*. The highest activity was observed for positively charged porphyrin **Pd154** and its chitosan conjugate. Almost complete degradation of bacterial cells was achieved after 15–30 min irradiation time at a photosensitizer concentration of 0.5 μM. This result was attributed to the fact that the presence of positively charged centres in palladium porphyrin provides better cell accessibility of this compound.

Structures Pd151–Pd154

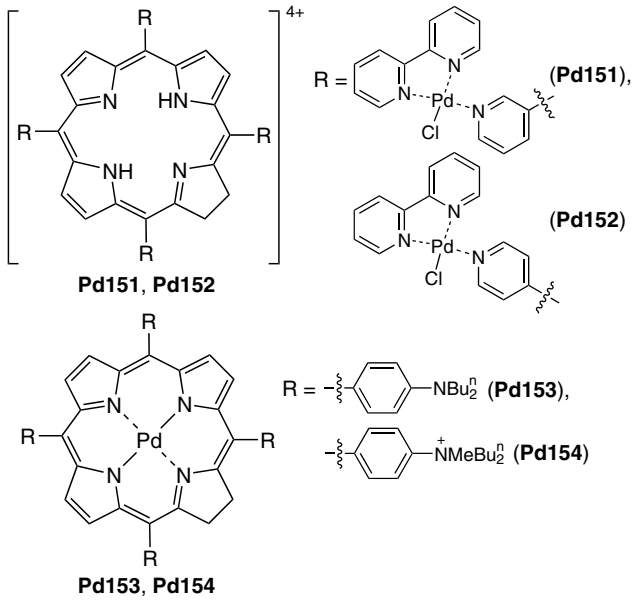
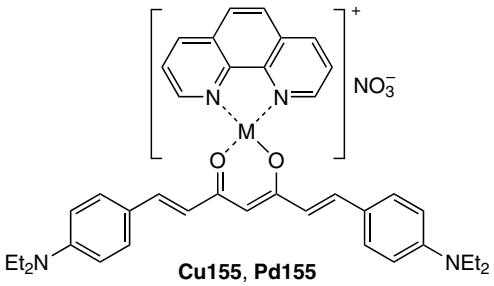


Table 38. Light and dark (in parentheses) antibacterial activity of complexes **Pd151**, **Pd152** and the corresponding ligands.[84]

Compound	MIC, μg mL^{-1}			
	S. aureus	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
L151	20.62 (165.00)	41.25 (82.50)	41.25 (41.25)	165.00 (165.00)
L152	41.25 (330.00)	41.25 (82.50)	41.25 (41.25)	165.00 (330.00)
Pd151	**2.00 (132.50)**	33.10 (33.12)	33.10 (33.10)	**2.00 (132.50)**
Pd152	8.30 (132.50)	33.12 (66.20)	33.12 (33.10)	8.30 (132.50)

Derivatives of coumarin (diferoylmethane), a natural β-diphenolic diketone pigment, are highly promising photosensitizers.[88] The coordination to metal ions makes it possible to significantly change the photophysical properties of these ligands. Heteroleptic complexes **Cu155** and **Pd155** with an additional phenanthroline ligand were synthesized. The *in vitro* antimicrobial photoactivity of these compounds was evaluated against fungi (*C. albicans*, *Sporothrix brasiliensis*, *M. canis*, *M. gypseum* and *Epidermophyton floccosum*) and protozoa (*Leishmania amazonensis*), which cause clinically essential surface skin diseases in humans. The results obtained in this study demonstrate that metal coumarin complexes are promising candidates for PDT. In particular, it was found that the antifungal activity of complexes **Cu155** and **Pd155** against *S. brasiliensis* strains is enhanced when using light instead of dark testing (MIC is 10 μM *vs*. 100 and 25 μM).

Structures M155



6. Palladium complexes with terpene ligands

Palladium complexes with terpene ligands are in the focus of our research.[89] A series of diverse Pd^{II} complexes containing pinane- or bornane-type ligands were evaluated for antimicrobial activity. Below, two compounds belonging to cyclopalladated benzylamines (**Pd156** and **Pd157**) and two chelate complexes (**Pd158** and **Pd159**) with terpene derivatives of ethylenediamine are given as examples. Biological tests were performed *in vitro* in collaboration with the not-for-profit initiative CO-ADD. The activity of the compounds was evaluated based on the inhibition of cell growth of five types of bacteria (*S. aureus*, *P. aeruginosa*, *K. pneumoniae*, *A. baumannii*, *E. coli*) and two types of fungi (*C. albicans*, *C. neoformans*). These types of commonly occurring bacteria and fungi have numerous mechanisms of resistance to a series of clinical drugs, making the search for new bactericidal and fungicidal agents against them a challenging problem.

According to these studies, palladium(II) complexes with different structures showed high selective inhibitory activity against a series of bacterial strains (Table 39). All the tested compounds were found to be inactive against the Gram-negative bacteria *P. aeruginosa*, *K. pneumoniae*, *A. baumannii* and *E. coli*. Complexes **Pd156** and **Pd157** belonging to cyclometallated compounds exhibited high inhibitory activity for Gram-positive bacteria, *e.g.*, *S. aureus*. Palladacycle **Pd156** with the MIC value of 1 μg mL^{-1}, which is comparable with the activity of the standard antibiotic vancomycin, was a lead compound.

According to the tests, complexes **Pd156**–**Pd159** exhibited high antifungal activity against *C. albicans* and *C. neoformans*

Structures Pd156–Pd159

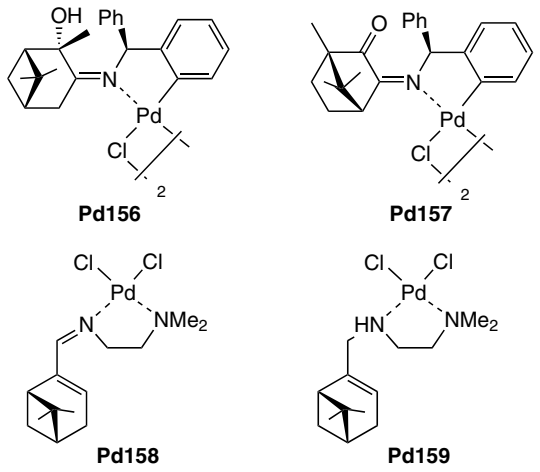


Table 39. Antibacterial and antifungal activity of compounds **Pd156**–**Pd159** and reference drugs.[89]

Compound	MIC, μg mL^{-1}			CC_{50}, μg mL^{-1}	HC_{10}, μg mL^{-1}
	S. aureus ATCC 43300	*C. albicans* ATCC 90028	*C. neoformans* ATCC 208821		
Pd156	1	0.5	⩽0.25	12.4	1.8
Pd157	16	2	0.5	6.0	>32
Pd158	>32	⩽0.25	⩽0.25	10.8	>32
Pd159	>32	2	⩽0.25	>32	>32
Vancomycin	1	–	–	–	–
Fluconazole	–	0.12	8	–	–
Tamoxifen	–	–	–	9	–
Melittin	–	–	–	–	2.7

strains. The MIC values were lower than 16 μg mL^{-1}; in some cases, <0.25 μg mL^{-1}. There was no clear structure–property relationship.

To evaluate the cell cytotoxicity of complexes **Pd156**–**Pd159**, the CC_{50} parameter was determined using human embryonic kidney cells HEK293 as the test system. The hemolytic activity (HC_{10})[¶] of the tested agents against human red blood cells (RBC) was assessed. All samples with the CC_{50} and HC_{10} values larger than the maximum tested concentration (32 μg mL^{-1}) were classified as nontoxic. Only complex **Pd159** met these conditions. This result suggests that the toxicity of palladium coordination compounds depends on the ligand environment of the metal ion and, therefore, can be specifically decreased.

7. Conclusion

An analysis of the literature data allows us to definitely conclude that palladium(II) complexes possess a high pharmacological potential. Palladium-containing agents have attracted interest mainly as anticancer agents (by analogy with cisplatin), but the evaluation of their antimicrobial activity also has good prospects.

[¶] HC_{10} is the hemolytic concentration of the agent (μg mL^{-1}) corresponding to 10% hemolysis.

This review presents numerous examples of high antibacterial and fungicidal activity of Pd^{II} complexes, which is higher than the activity of antibiotics and antifungal drugs widely used in clinical practice. It is worth noting the great structural diversity of the characterized palladium-based compounds. The review gives original, sometimes quite controversial, structural formula of metal complexes. The detailed discussion of synthetic issues is beyond the scope of this review. All relevant literature can be found in the corresponding references to original papers.

In many studies included in this review, the biological profile of palladium(II) complexes was determined. We selected the most significant results of research on the antibacterial and antifungal activity of these complexes. An analysis of the literature data suggests that even very fine structural changes can lead to significant changes in the biological activity of Pd^{II} complexes. It is virtually impossible to select the most promising type of ligands for the design of effective palladium-based antimicrobial agents. A promising approach is based on the use of multifunctional compounds with known biological activity, including those used in clinical practice, as ligands. It can only definitely be stated that metal complexes are more active than the corresponding ligands (this fact was experimentally confirmed in more than 90% publications).

It is worth noting that many publications included theoretical (*in silico*) studies of the biological activity of Pd^{II} complexes.[20,21,24,25,27–30,36,37,50,52–55,57,61,63,65,71,72,77] The molecular docking is a fashionable approach, which allows the identification of the active site for interaction (or the absence of this site) of the tested compound with biomolecules. We did not discuss these results because there is generally no clear correlation between the experimental data on the antimicrobial activity of metal complexes and theoretical calculations.

The elucidation of the mechanism of antibacterial and cytotoxic activity of metal-containing agents is a challenging problem. In a number of studies, interactions of these agents with such biomolecules as DNA or proteins were investigated by photometric or viscosimetric methods.[13,15–18,23–29,31,34,38,40,64,65,67,69] The available data do not allow one to make a general conclusion although the interaction of metal complexes with biomolecules is clearly detected.

The facts that, on the one hand, many Pd^{II} complexes with high antimicrobial activity were fond and, on the other hand, there are no clear structure–property relationships suggest that the high-throughput screening of libraries of different derivatives is the most promising method for searching for effective antibiotics and antimicrobial drugs. Chemists synthesized a large number of new compounds, which are generally difficult to characterize by biological assays. These issues are usually solved individually, which is inefficient. In our opinion, there is a need to establish an all-Russian centre for biological tests of different classes of chemical compounds, in particular promising metal-containing agents.

In concluding this review, we cannot say about such an important form of palladium-containing antimicrobial agents as biogenic palladium nanoparticles (Pd-NPs). This group of compounds is not included in the present review devoted to palladium complexes with organic ligands. Nevertheless, taking into account great prospects of biomedical applications of Pd-NPs, let us refer to a number of reviews[90–97] focused on this issue. In the past years, the scientific community was interested in the biogenic synthesis of Pd-NPs according to the principles of green chemistry. This is a facile, fast, cost-efficient and environmentally friendly method for the preparation of NPs

based on the naturally occurring biomolecules or metabolites of different plants and organisms as reducing and stabilizing agents. It was demonstrated that biogenic processes allow for a very high level of control over such important properties of Pd-NPs as the size and shape.

We hope that the data considered in this review will be interesting and useful for researchers dealing with investgations in medicinal chemistry and chemistry of metal complexes.

8. List of abbreviations and designations

CC_{50} — concentration of the agent at which the cell growth is inhibited by 50%,
CIP — ciprofloxacin,
CO-ADD — Community for Open Antimicrobial Drug Discovery,
Cy — cyclohexyl,
ERY — erythromycin,
HC_{10} — hemolytic concentration of the agent corresponding to 10% hemolysis,
HEK293 — human embryonic kidney cells,
MBC — minimum bactericidal concentration,
MIC — minimum inhibitory concentration,
NHC — N-heterocyclic carbene complexes,
Pd-NP — palladium nanoparticles,
PDT — photodynamic therapy,
PEPPSI — pyridine-enhanced precatalyst preparation, stabilization and initiation,
PipDT — piperidine dithiocarbamate,
RBC — human red blood cells,
ROS — reactive oxygen species.

Full names of microorganisms:[††]
A. baumannii — *Actinetobacter baumannii* (–),
A. clavatus — *Aspergillus clavatus* (*f*),
A. flavus — *Aspergillus flavus* (*f*),
A. fumigatus — *Aspergillus fumigatus* (*f*),
A. niger — *Aspergillus niger* (*f*),
A. hydrophila — *Aeromonas hydrophila* (–),
B. animalis subsp. lactis — *Bifidobacterium animalis subsp. Lactis*,
B. brevis — *Bacillus brevis* (+),
B. cereus — *Bacillus cereus* (+),
B. megaterium — *Bacillus megaterium* (+),
B. spizizenii — *Bacillus spizizenii* (–),
B. subtilis — *Bacillus subtilis* (+),
C. albicans — *Candida albicans* (*f*),
C. auris — *Candida auris* (*f*),
C. freundii — *Citrobacter freundii* (–),
C. jejuni — *Campylobacter jejuni* (–),
C. neoformans — *Cryptococcus neoformans* (*f*),
C. parapsilosis — *Candida parapsilosis* (*f*),
C. tropicalis — *Candida tropicalis* (*f*),
E. coli — *Escherichia coli* (–),
E. faecalis — *Enterococcus faecalis* (+),
E. floccosum — *Epidermophyton floccosum* (*f*),
F. oxysporum — *Fusarium oxysporum* (*f*),
G. candidum — *Geotrichum candidum* (*f*),
K. aerogenes — *Klebsiella aerogenes* (–),
K. pneumonia — *Klebsiella pneumonia* (–),
L. amazonensis — *Leishmania amazonensis*,
L. fermentum — *Lactobacillus fermentum* (+),
L. monocytogenes — *Listeria monocytogenes* (+),
M. canis — *Microsporum canis* (*f*),
M. gypseum — *Microsporum gypseum* (*f*),
M. luteus — *Micrococcus luteus* (+),
MRSA — methicillin-resistant *Staphylococcus aureus*,
N. gonorrhoeae — *Neisseria gonorrhoeae* (–),
P. aeruginosa — *Pseudomonas aeruginosa* (–),
P. desmolyticum — *Pseudomonas desmolyticum*,
P. mirabilis — *Proteus mirabilis* (–),
P. vulgaris — *Proteus vulgaris* (–),
R. botaticola — *Rhizoctonia botaticola* (*f*),
R. mucilaginosa — *Rhodotorula mucilaginosa* (*f*),
S. aureus — *Staphylococcus aureus* (+),
S. brasiliensis — *Sporothrix brasiliensis* (*f*),
S. cerevisiae — *Saccharomyces cerevisiae* (*f*),
S. enterica — *Salmonella enterica* (–),
S. epidermidis — *Staphylococcus epidermidis* (+),
S. marcescens — *Serratia marcescens* (–),
S. mutans — *Streptococcus mutans* (+),
S. pyogenes — *Streptococcus pyogenes* (+),
S. typhi — *Salmonella typhi* (–),
S. typhimurium — *Salmonella typhimurium* (–),
T. mentagrophytes — *Trichophyton mentagrophytes* (*f*),
T. rubrum — *Trichophyton rubrum* (*f*),
V. cholerae — *Vibro cholera* (–),
X. campestris — *Xanthomonas campestris* (–).

[††] The type of the bacterium, namely Gram-positive (+) or Gram-negative (–), is indicated in parentheses after the name; the symbol *f* indicates fungi.

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