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Antibacterial and antifungal properties of guanylhydrazones

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Abstract: A series of novel guanylhydrazones were designed, synthesized and characterized. All the compounds were screened for their antibacterial and antifungal activity. Compounds **26** and **27** showed excellent antibacterial activities against *Staphylococcus aureus* ATCC 25923 and *Micrococcus luteus* ATCC 379 with minimal inhibitory concentrations of 4 μg mL^{-1}, and good antifungal activity against *Candida parapsilosis* ATCC 22019. These results suggested that the selected guanylhydrazones could serve as promising leads for improved antimicrobial development.

Keywords: guanylhydrazones; iminoguanidines; antibacterial activity; antifungal activity; *Candida* spp.

INTRODUCTION

Infectious diseases caused by human pathogens, both bacteria and fungi, result in significant morbidity and mortality worldwide. Treatment of these diseases is often hampered by limited therapeutic options and the development of resistance. Bacteremia is a major cause of life-threatening complications in patients in intensive care units, neonates, or cancer patients, who are at extremely high risk for infections caused by antibiotic resistant bacteria.[1] Invasive candidiasis is the fourth most common bloodstream infection with mortality rates remaining disturbingly high at 40 %.[2] This makes the quest for new molecules that are effective against the threat of drug resistance a significant issue in modern medicine.

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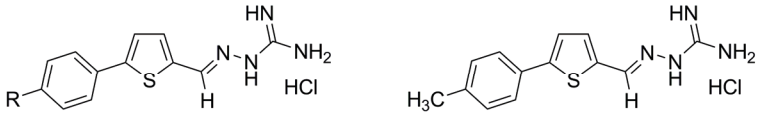
Guanylhydrazones have been a long-standing point of interest in medicinal chemistry.[3] Recently, a two-step procedure was demonstrated for the preparation of simple guanylhydrazones **1** (Fig. 1).[4] The synthesized compounds were evaluated for their *in vitro* antifungal activities against a wide range of medically important fungal strains. Among the series, compound **2** proved to be an effective, broad-spectrum antifungal compound (Fig. 1). In particular, compound **2** exhibited excellent activity against the voriconazole-resistant *Candida albicans* CA5 strain.

Given the good antifungal properties shown by selected guanylhydrazones and as a continuation of research on the development of new antimicrobial agents, in the present work, the synthesis, characterization and evaluation of the antibacterial and antifungal properties of new guanylhydrazone derivatives are reported.



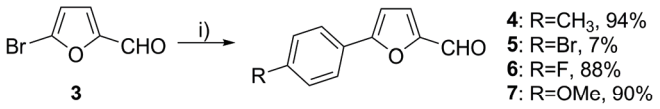
1 **2**

Fig. 1. Guanylhydrazones.

RESULTS AND DISCUSSION

Chemistry

The Suzuki–Miyaura reaction enabled access to a range of aldehydes **4**–**7** from easily obtainable starting compounds (Scheme 1). The low yield of aldehyde **5** is associated with problems during purification and isolation of the desired product from the crude reaction mixture. The reported yield is also non-optimized and certainly could be further improved through variation of the reaction conditions.



3

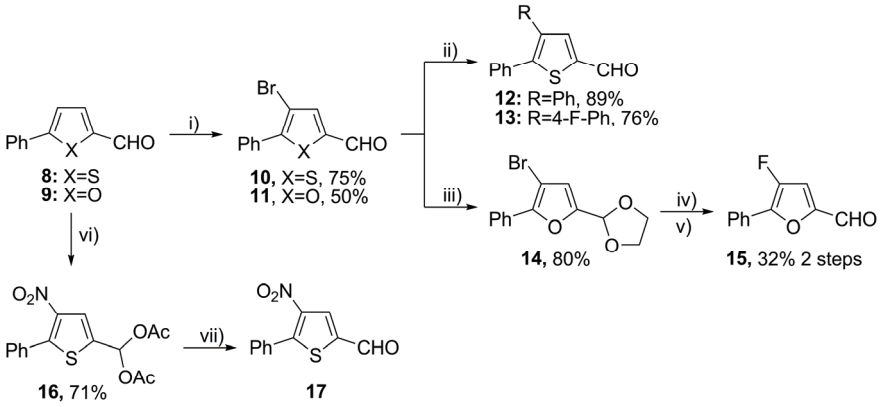
4: R=CH_3, 94%
5: R=Br, 7%
6: R=F, 88%
7: R=OMe, 90%

i) R=CH_3, F, OMe; $ArB(OH)_2$, $Pd(OAc)_2$, PPh_3, DME, $Na_2CO_{3(aq)}$, 90 °C
R=Br; $ArB(OH)_2$, $Pd(OAc)_2$, TBAB, H_2O, K_2CO_3, r.t.

Scheme 1. Synthesis of aldehydes **4**–**7**.

Bromination of aldehydes **8**[5] and **9** with bromine and *N*-bromosuccinimide afforded the corresponding monobromo derivatives **10** and **11**, respectively (Scheme 2). Aldehydes **12** and **13** were prepared by a Suzuki–Miyaura reaction starting from bromide **10** (Scheme 2). Access to 4-fluoro-5-phenyl-2-furaldehyde **(15**) was accomplished by a halogen/metal exchange reaction. The lithiated intermediate formed in the reaction medium was trapped with the electrophilic fluor-

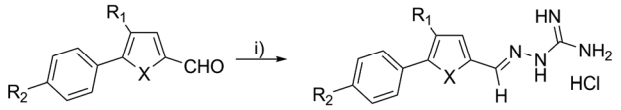
inating reagent *N*-fluorobenzenesulfonimide (NFSI, Scheme 2). The thiophene aldehyde **8** underwent nitration with a mixture of nitric acid and acetic anhydride affording the corresponding 4-nitro derivative **16** in 71 % yield (Scheme 2). Subsequent acid hydrolysis of **16** gave the nitroaldehyde **17** (Scheme 2).



i) X=S; Br_2, $CHCl_3$, r.t.; X=O; NBS, MeCN, r.t.; ii) $ArB(OH)_2$, $Pd(OAc)_2$, PPh_3, DME, $Na_2CO_{3(aq)}$, 90 °C
iii) $HOCH_2CH_2OH$, *p*-TsOH, PhMe, Δ; iv) (a) *n*-BuLi, THF, -78 °C, (b) $FN(SO_2Ph)_2$, THF, -78 °C;
v) THF, 2M HCl, r.t.; vi) HNO_3, AcOH, Ac_2O, r.t.; vii) H_2SO_4, MeOH, H_2O, r.t.

Scheme 2. Synthesis of aldehydes **10**–**13**, **15** and **17**.

The guanylhydrazones **18**–**27** were synthesized using a one-step condensation reaction of aminoguanidine hydrochloride and the corresponding aldehyde in good to excellent yields (Scheme 3). All the guanylhydrazones were obtained as hydrochlorides.



18: X=O, R_1=H, R_2=CH_3, 99%
19: X=O, R_1=H, R_2=OMe, 100%
20: X=O, R_1=H, R_2=F, 100%
21: X=O, R_1=H, R_2=Br, 100%
22: X=O, R_1=F, R_2=H, 79%
23: X=S, R_1=Br, R_2=H, 92%
24: X=O, R_1=Br, R_2=H, 78%
25: X=S, R_1=NO_2, R_2=H, 75%
26: X=S, R_1=Ph, R_2=H, 99%
27: X=S, R_1=4-F-Ph, R_2=H, 92%

i) $H_2NNHC(NH)NH_2$·HCl, EtOH, $HCl_{(aq)}$, 90 °C

Scheme 3. Synthesis of guanylhydrazones **18**–**27**.

Antimicrobial activity

All synthesized guanylhydrazones were assessed for their antimicrobial activity against one Gram-negative strain (*Pseudomonas aeruginosa* PAO1, NCTC 10332), and three Gram-positive strains (*Staphylococcus aureus* ATCC 25923, *Micrococcus luteus* ATCC 379 and *Listeria monocytogenes* NCTC 11994) and

three fungal strains (*Candida albicans* ATCC 10231, *Issatchenkia orientalis* ATCC 6258 and *Candida parapsilosis* ATCC 22019). The minimum inhibitory concentration (*MIC*) values obtained by the standard broth dilution method were compared to those of clinically used antibiotics (kanamycin and nystatin).

Most of the tested compounds were found to display poor to moderate activities against the tested bacterial strains, with the exception of compound **22**, which displayed excellent antibacterial activity against *P. aeruginosa* PAO1, and compounds **26** and **27**, which exhibited excellent activities against *S. aureus* ATCC 25923 and *M. luteus* ATCC 379 (Table I). It is noteworthy that compounds **22**, **26** and **27** showed better antibacterial activities against these three bacterial strains in comparison to the control drug, kanamycin (Table I).

TABLE I. Minimal inhibitory concentrations, *MIC* / μg mL^{-1}

Compound	*P. aer*[a]	*S. aur*[b]	*M. lut*[c]	*L. mon*[d]	*C. alb*[e]	*I. ori*[f]	*C. par*[g]
18	150	62.5	62.5	125	50	62.5	31.2
19	200	125	31.2	500	250	125	62.5
20	125	62.5	125	250	200	125	62.5
21	>500	15.6	125	>500	31.2	62.5	31.2
22	4	62.5	62.5	125	125	100	62.5
23	>500	125	15.6	15.6	31.2	31.2	15.6
24	250	62.5	62.5	62.5	62.5	18.8	31.2
25	>500	>500	>500	>500	62.5	62.5	31.2
26	>500	4	4	>500	15.6	15.6	6
27	>500	4	4	>500	31.2	31.2	6
Kanamycin[h]	50	10	12.5	12.5	–	–	–
Nystatin[h]	–	–	–	–	1	7.8	2

[a]*Pseudomonas aeruginosa* PAO1 NCTC 10332; [b]*Staphylococcus aureus* ATCC 25923; [c]*Micrococcus luteus* ATCC 379; [d]*Listeria monocytogenes* NCTC 11994; [e]*Candida albicans* ATCC 10231; [f]*Issatchenkia orientalis* ATCC 6258; [g]*Candida parapsilosis* ATCC 22019; [h]control drug

From a perusal of the data, it could be seen that all the tested compounds showed moderate antifungal activity against all the tested fungal strains, while two compounds **26** and **27** exhibited the most promising activity against *C. parapsilosis* ATCC 22019 (Table I).

Overall, the minimal inhibitory concentrations (*MIC*) values lead to the conclusion that the additional aromatic ring on thiophene was beneficial to the antibacterial and antifungal activity of compounds **26** and **27**.

EXPERIMENTAL

Instrumentation

Dry-flash chromatography was performed on SiO_2 (0.018–0.032 mm). Melting points were determined on a Boetius PMHK apparatus and were not corrected. IR spectra were recorded on a Thermo-Scientific Nicolet 6700 FT-IR Diamond Crystal instrument. ^{1}H- and ^{13}C--NMR spectra were recorded on a Bruker Ultrashield Advance III spectrometer (at 500 and 125 MHz, respectively) using tetramethylsilane (TMS) as the internal standard. Chemical

shifts are expressed in ppm (δ) values and coupling constants (J) in Hz. ESI MS spectra of the synthesized compounds were recorded on an Agilent Technologies 6210 time-of-flight LC–MS instrument in the positive ion mode using MeOH/H_2O = 1/1 with 0.2 % HCOOH as the carrying solvent solution. The samples were dissolved in pure MeOH (HPLC grade). The selected settings were as follows: capillary voltage, 4 kV; gas temperature, 350 °C; drying gas, N_2, 12 L·min^{-1}; nebulizer pressure, 45 psig*; fragmentator voltage, 70–200 V. The GC–MS spectra of the synthesized compounds were acquired on an Agilent Technologies 7890A apparatus equipped with a DB-5 MS column (30 m×0.25 mm×0.25 μm), a 5975C MSD and FID detector. Selected settings were as follows: carrier gas He (1.0 mL min^{-1}), temperature linearly increased from 40–315 °C (10 °C min^{-1}), injection volume, 1 μL, temperature, 250 °C, temperature (FID detector), 300 °C, and EI mass spectra range: m/z 40–550. Thin-layer chromatography was performed on pre-coated Merck silica gel 60 F_{254} and Merck RP-18 F_{254} plates. All the reported yields refer to isolated yields. The compounds were analyzed for purity (HPLC) using a Agilent 1200 HPLC system equipped with Quat pump (G1311B), injector (G1329B) 1260 ALS, TCC 1260 (G1316A) and detector 1260 DAD VL + (G1315C) (other details are presented in the Supplementary material to this paper). All compounds were >95 % pure.

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

Chemistry

*General procedure. 5-(4-Methylphenyl)furan-2-carbaldehyde (**4**).*[6] In a dry glass flask purged with argon, $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) was dissolved in dry dimethoxyethane (DME) (2 mL) and PPh_3 (16.2 mg, 0.060 mmol) was added. The resultant solution was stirred at room temperature for 10 min and **3** (113.8 mg, 0.650 mmol) and Na_2CO_3 (aq.) (2M, 0.65 mL, 1.3 mmol) were added. After 5 min stirring at room temperature, a solution of (4-methylphenyl)boronic acid (111.5 mg, 0.820 mmol) was added and the reaction mixture was purged with argon and refluxed at 90 °C overnight under argon. The solution was cooled to room temperature and filtered through a Celite pad, washed with CH_2Cl_2 and dried with anh. Na_2SO_4. The organic solvent was removed under reduced pressure and the crude product was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 95/5 to 9/1) to afford the title compound **4** (113.6 mg, 94 %).

*5-(4-Bromophenyl)furan-2-carbaldehyde (**5**).*[7] To a glass flask, **3** (113.8 mg, 0.650 mmol), (4-bromophenyl)boronic acid (143.6 mg, 0.715 mmol), tetrabutylammonium bromide (209.6 mg, 0.650 mmol), $Pd(OAc)_2$ (2.9 mg, 0.013 mmol) and K_2CO_3 (224.6 mg, 1.63 mmol) were added and then dissolved in deionized water (3 mL). The reaction mixture was stirred vigorously for 5 h at room temperature. After the white reaction mixture had become yellow and non-homogeneous, the mixture was diluted with water (10 mL), and the product was extracted with EtOAc. The organics were separated, filtered through a Celite pad, and dried with $MgSO_4$. The organic solvent was removed under reduced pressure and the crude product was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 9/1 to 7/3) to afford the title compound **5** (11 mg, 7 %).

*5-(4-Fluorophenyl)furan-2-carbaldehyde (**6**).*[6] The general Suzuki coupling procedure was followed, except 4-fluorophenylboronic acid (114.7 mg) was used. The reaction mixture was refluxed for 12 h. The crude product was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 95/5 to 8/2) to afford the title compound **6** (108.3 mg, 88 %).

* 45 psig = 310.3 kPa

5-(4-Methoxyphenyl)furan-2-carbaldehyde (7).[6] The general Suzuki coupling procedure was followed, except 4-methoxyphenylboronic acid (124.6 mg) was used. The reaction mixture was refluxed for 12 h. The crude product was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 9/1 to 6/4) to afford the title compound **7** (118 mg, 90%).

*4-Bromo-5-phenylthiophene-2-carbaldehyde (**10**).*[5] To a solution of aldehyde **8** (76 mg, 0.40 mmol) in dry $CHCl_3$ (700 μL) was added a solution of bromine (33 μL, 0.64 mmol) in dry $CHCl_3$ (330 μL). The resulting solution was stirred at r.t. for 3 h. To the reaction mixture was added sat. $Na_2S_2O_3$ solution and the reaction mixture extracted with CH_2Cl_2 (2×10 mL). The organic layer was washed with sat. $NaHCO_3$ solution and brine and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 9/1) to yield **10** (81 mg, 75 %).

*4-Bromo-5-phenyl-2-furaldehyde (**11**).*[8] To a solution of aldehyde **9** (100 mg, 0.58 mmol) in MeCN (10 mL) was added NBS (114 mg, 0.64 mmol). The resulting solution was stirred at r.t. for 24 h. To the reaction mixture was added H_2O (10 mL) and the reaction mixture was extracted with CH_2Cl_2 (2×10 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 95/5) to yield **11** (72.9 mg, 50 %).

*4,5-Diphenylthiophene-2-carbaldehyde (**12**).*[6] The general Suzuki coupling procedure was followed, except phenylboronic acid (38.3 mg) was used. The reaction mixture was refluxed for 12 h. The crude product was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 9/1) to afford the title compound **12** (53 mg, 89 %).

*4-(4-Fluorophenyl)-5-phenylthiophene-2-carbaldehyde (**13**).* The general Suzuki coupling procedure was followed, except 4-fluorophenylboronic acid (36.6 mg) was used. The reaction mixture was refluxed for 12 h. The crude product was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 9/1) to afford the title compound **13** (42 mg, 77 %).

*2-(4-Bromo-5-phenyl-2-furyl)-1,3-dioxolane (**14**).* Aldehyde **11** (117 mg, 0.46 mmol), ethylene glycol (130 μL, 2.33 mmol), and *p*-toluenesulfonic acid monohydrate (1.8 mg, 9.32×10^{-3} mmol) were dissolved in PhMe (4 mL). Under Dean–Stark conditions, the reaction mixture was refluxed for 3h, and then washed sequentially three times with 3 M NaOH and water. The PhMe layer was dried, filtered, evaporated under vacuum and the crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 9/1) to yield acetal **14** (109 mg, 80 %).

4-*Fluoro-5-phenyl-2-furaldehyde (**15**)*. To a solution of acetal **14** (49 mg, 0.167 mmol) in dry THF (2.5 mL), *n*BuLi (1.6 M in hexane, 125 μL, 0.2 mmol) was added dropwise at a temperature below –60 °C under Ar. After stirring the mixture for 2 h, *N*-fluorobenzenesulfonimide (58 mg, 0.18 mmol) in THF (1 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature. H_2O was added to the reaction mixture, which was then extracted with CH_2Cl_2, washed with brine, dried with $MgSO_4$ and concentrated. To a stirred solution of crude residue in THF (2 mL) at 25 °C was added 2M HCl (0.6 mL), and the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was slowly quenched with sat. aq. $NaHCO_3$ (2 mL), the biphasic mixture was extracted with CH_2Cl_2 (2×10 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated. The crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 9/1) to yield **15** (9.4 mg, 30 % for 2 steps).

*(4-Nitro-5-phenyl-2-thienyl)methylene diacetate (**16**).* To a cold solution of aldehyde **8** (35 mg, 0.186 mmol) in Ac_2O (500 μL) was added a solution of HNO_3 (9.5 μL, 0.223 mmol)

in AcOH (190 μL). The resulting solution was stirred at r.t. for 2 h, and then ice was added and the reaction mixture was extracted with CH_2Cl_2 (2×10 mL). The organic layer was washed with sat. $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 8/2) to yield **14** (44 mg, 71 %).

*4-Nitro-5-phenylthiophene-2-carbaldehyde (**17**).* To a solution of diacetate **16** (17 mg, 0.05 mmol) in MeOH/H_2O (1/1volume ratio, 1 mL), was added H_2SO_4 (100 μL). The resulting solution was stirred at r.t. for 2 h, and then H_2O was added and the reaction mixture extracted with CH_2Cl_2 (2×10 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the crude product was used in the next step.

General procedure for the preparation of guanylhydrazones.[4] *(2*E*)-2-{[5-(4-Methylphenyl)furan-2-yl]methylidene}hydrazinecarboximidamide hydrochloride (**18**)*. To a solution of aldehyde **4** (86.2 mg, 0.463 mmol) in absolute ethanol (10 mL), aminoguanidine hydrochloride (51.2 mg, 0.463 mmol) was added. The resultant solution was stirred at room temperature for 5 min, and a solution of concentrated HCl (5 mol %) in absolute EtOH (50 μL, 1/25, v/v) was added. The reaction mixture was heated to 90 °C, refluxed for 18 h and allowed to cool to room temperature. The solvent was removed under reduced pressure, the crude product was washed with CH_2Cl_2 (1 mL) and then crystallized from EtOH/hexane (9/1) to provide the title compound **18** (127.8 mg, 99 %).

*(2*E*)-2-{[5-(4-Methoxyphenyl)furan-2-yl]methylidene}hydrazinecarboximidamide hydrochloride (**19**)*. Following the general procedure for guanylhydrazone formation, **19** (144 mg, 100 %) was obtained from **7**.

*(2*E*)-2-{[5-(4-Fluorophenyl)furan-2-yl]methylidene}hydrazinecarboximidamide hydrochloride (**20**)*. Following the general procedure for guanylhydrazone formation, **20** (93.2 mg, 100 %) was obtained from **6**.

*(2*E*)-2-{[5-(4-Bromophenyl)furan-2-yl]methylidene}hydrazinecarboximidamide hydrochloride (**21**)*. Following the general procedure for guanylhydrazone formation, **21** (17.2 mg, 100 %) was obtained from **5**.

*(2*E*)-2-[(4-Fluoro-5-phenyl-furan-2-yl)methylidene]hydrazinecarboximidamide hydrochloride (**22**)*. Following the general procedure for guanylhydrazone formation, **22** (7.1 mg, 79 %) was obtained from **15**.

*(2*E*)-2-[(4-Bromo-5-phenyl-2-thienyl)methylidene]hydrazinecarboximidamide hydrochloride (**23**)*. Following the general procedure for guanylhydrazone formation, **23** (41 mg, 92 %) was obtained from **10**.

*(2*E*)-2-[(4-Bromo-5-phenyl-furan-2-yl)methylidene]hydrazinecarboximidamide hydrochloride (**24**)*. Following the general procedure for guanylhydrazone formation, **24** (44 mg, 78 %) was obtained from **11**.

*(2*E*)-2-[(4-Nitro-5-phenyl-2-thienyl)methylidene]hydrazinecarboximidamide hydrochloride (**25**)*. Following the general procedure for guanylhydrazone formation, **25** (19.5 mg, 75 %) was obtained from **17**.

*(2*E*)-2-[(4,5-Diphenyl-2-thienyl)methylidene]hydrazinecarboximidamide hydrochloride (**26**)*. Following the general procedure for guanylhydrazone formation, **26** (51.9 mg, 99%) was obtained from **12**.

*(2*E*)-2-{[4-(4-Fluorophenyl)-5-phenyl-2-thienyl]methylidene}hydrazinecarboximidamide hydrochloride (**27**)*. Following the general procedure for guanylhydrazone formation, **27** (36.5 mg, 92%) was obtained from **13**.

Antimicrobial activity

Guanylhydrazones were dissolved in DMSO in stock concentrations of 50 mg mL^{-1} and used immediately for antimicrobial activity assessments. *MIC* concentrations (concentration value corresponding to the lowest concentration that inhibited the growth after 24 h at 37 °C) were determined according to the standard broth microdilution assays, recommended by the National Committee for Clinical Laboratory Standards (M07-A8) for bacteria in LB (Luria--Bertani) broth and Standards of European Committee on Antimicrobial Susceptibility Testing (EDef7.1.) in SAB (Sabouraud Dextrose) broth. The highest concentration used was 500 μg mL^{-1}. The test organisms included *Pseudomonas aeruginosa* PAO1 (NCTC 10332), *Staphylococcus aureus* (ATCC 25923), *Micrococcus luteus* (ATCC 379), *Listeria monocytogenes* (NCTC 11994) *Candida albicans* (ATCC 10231), *Issatchenkia orientalis* (ATCC 6258) and *Candida parapsilosis* (ATCC 22019). The inoculums were 10^5 colony forming units, CFU mL^{-1}, for the bacteria and 10^4 CFU mL^{-1} for the *Candida* strains.

CONCLUSIONS

In the present work, an efficient synthesis of novel guanylhydrazones was designed. The activity of these compounds against the panel of human pathogens consisting of one Gram-negative strain, three Gram-positive strains, and three fungal strains, was assessed. Noticeably, compounds **26** and **27** showed excellent antibacterial activities against Gram-positive *S. aureus* ATCC 25923 and *M. luteus* ATCC 379, even better than the control drug, kanamycin. Furthermore, compounds **26** and **27** displayed good antifungal activity against *C. parapsilosis* ATCC 22019. Altogether, the reported results indicate that the selected guanylhydrazones could form the basis for further development of new and effective antimicrobial agents.

SUPPLEMENTARY MATERIAL

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

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И З В О Д

АНТИБАКТЕРИЈСКА И АНТИФУНГАЛНА АКТИВНОСТ ГВАНИЛХИДРАЗОНСКИХ ДЕРИВАТА

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У овом раду приказана је синтеза серије гуванилхидразонских деривата. Добијеним дериватима испитана је антибактеријска и антифунгална активност. Утврђено је да једињења **26** и **27** показују изражену антибактеријску активност према *Staphylococcus aureus*

ATCC 25923 и *Micrococcus luteus* ATCC 379 сојевима. Истовремено, ова једињења показала су и изражену антифунгалну активност према *Candida parapsilosis* ATCC 22019 сој.

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