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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of arylfuran derivatives as potential antibacterial agents

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Abstract

Bacterial infections represent a serious health care problem mainly due to the misuse and overuse of antibiotics, with consequent emergence of multidrug resistant bacterial strains. Then, because the urgent need to find novel and alternative antibacterial agents, the present work focuses on the synthesis of arylfuran derivatives with potential antimicrobial activity. Eighteen arylfuran derivatives were synthesized and evaluated for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. Among them, seven compounds containing an amino group in their structure showed activity, with compound **24** being the most effective against both Gram-negative (*E. coli*, MIC = 49 μM) and Gram-positive (*S. aureus*, MIC = 98 μM) bacteria, besides having exhibited a modest activity against *P. aeruginosa* (MIC = 770 μM). In addition, based on in silico studies, this is a druglike compound since it does not violate any rules for predicting oral bioavailability. In this context, the significant antibacterial potential and the low similarity with known antibiotics indicate the innovative aspect of compound **24**.

Keywords Arylfuran derivatives · Antibacterial agents · Oral bioavailability · Innovative compound

Introduction

Bacteria are present everywhere and can cause a variety of infections that, if untreated, it can develop into much more serious consequences [1–3]. Currently, the increasing emergence of multidrug resistant (MDR) bacteria limits the effectiveness of therapeutic options, representing a serious public health problem [4–6].

Based on this the World Health Organization (WHO) declared the antimicrobial resistance (AMR), mainly the antibiotic (antibacterial) resistance (AR), as a major global public health problem of the 21st century, and requested the intervention of the scientific community to the research, discovery, and development of new innovative antibiotics [7]. In fact, although there has been an increase in the number of the FDA approved antibacterial agents in 2018–2019, the number and efficacy of these new drugs is far from sufficient [8].

As example of this worrying scenario related to the incidence of infections caused by MDR pathogens, it can mention the quinolones and fluoroquinolones whose use and rate of resistance have been increasing around the world [9], and the significant toxicity (nephrotoxicity) of the polymyxin B and colistin, considered the last-line options for the treatment of infections caused by MDR Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* [10]. Therefore, it is urgent and necessary that new approaches to treat bacterial infections are found.

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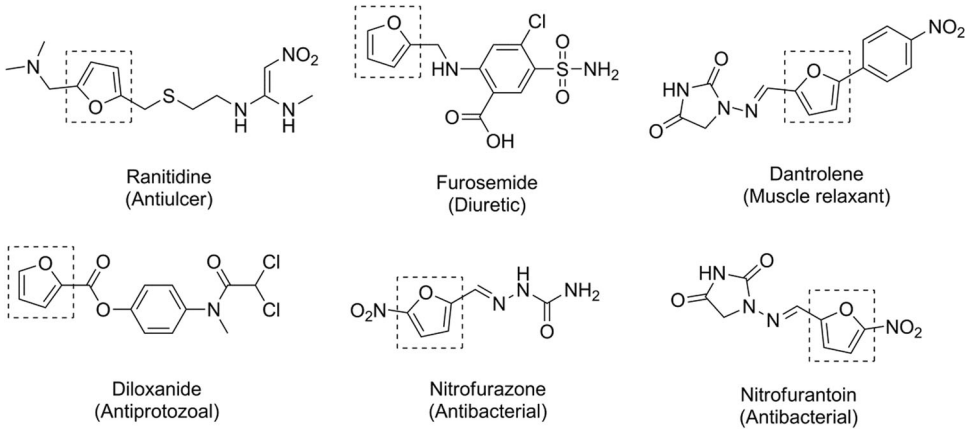


Fig. 1 Examples of furan derivatives with biological activity

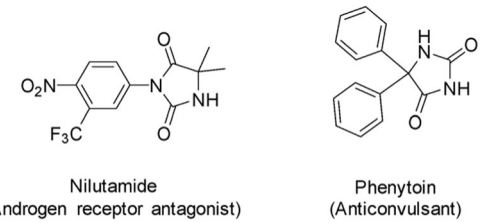


Fig. 2 Examples of hydantoin derivatives with biological activity

To overcome these limitations, mainly the AMR, natural products, combinatorial chemistry and synthetic approaches have been applied to face these challenges. In this context, furan derivatives represent an important class of compounds due to their diversified biological activities and the common presence of the furan moiety in the structure of several drugs, e.g., antiulcer ranitidine [11], diuretic furosemide [12], muscle relaxant dantrolene [13], anti-protozoal diloxanide [14] and antibacterial nitrofurazone [15] and nitrofurantoin [16] (Fig. 1).

Dantrolene and nitrofurantoin are synthetic drugs derived from furan by the addition of a side chain containing a hydantoin ring. Clinically approved drugs such as anticonvulsant phenytoin and androgen receptor antagonist nilutamide are also representative of compounds for therapeutic use that present the hydantoin moiety in their structure (Fig. 2). This other class of heterocycles also plays an important and significant role in the field of medicinal chemistry, especially because of its application as key pharmacophoric moieties or skeletal components. Besides that, hydantoin provides two hydrogen-bond acceptors and two hydrogen-bond donors, which are relevant for interaction with molecular targets [17]. The importance of the hydantoin scaffold in drug discovery has been supported by several pharmacological and biological activities associated with this group, mainly in antibiotic agents' development due to its low rate of bacterial resistance [18]. The old nitrofurantoin, for example, has been used to treat resistant urinary tract infections since many MDR microorganisms preserve their susceptibility to this antibiotic [19].

In general, heterocycles are considered a privileged scaffold in medicinal chemistry and triazoles are other representatives of this class. Due to the strong moment dipole, triazole can be used as an effective amide surrogate and as a linker in bioactive molecules. These motifs show bioisosteric relationship with peptide linkage, aromatic ring, double bonds and an imidazole ring. Triazoles can also be used to improve the solubility of compounds because of their ability to form hydrogen bonds [20]. The 1,2,3-triazole heterocycle has been included as a main moiety of many pharmaceutical drugs, such as anticancer carboxyamidotriazole and antibacterials cefatrizine and tazobactam (Fig. 3). In a recent research, El Malah and collaborators reported a series of 1,2,3-triazole glucosides as antimicrobial agents, especially against *Staphylococcus aureus*, which was found sensitive to all the tested compounds [21].

With this context in mind, we decided to synthesize and evaluate a series of arylfuran derivatives linked, or not, to other heterocycles (triazole or hydantoin) for their antibacterial property.

Material and methods

Chemistry

All melting points were determined on a Microquímica MQAPF 301 apparatus. The infrared (IR) spectra were recorded using a Perkin Elmer Spectrum One IR spectrometer and absorptions were reported as wave numbers (cm^{-1}). The nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE DRX200 or Bruker AVANCE DRX400 instrument, using tetramethylsilane as the internal standard. Chemical shifts were given in δ (ppm) scale and J values were given in Hz. Splitting patterns are designed as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), qt

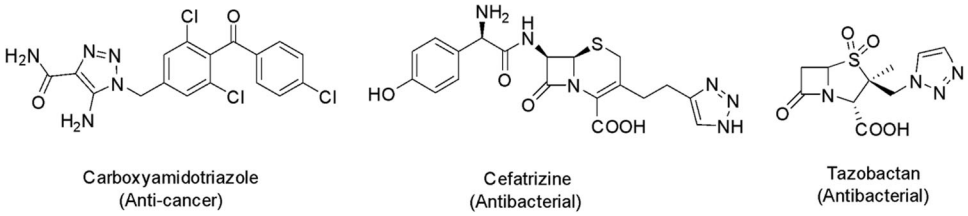


Fig. 3 Examples of triazole derivatives with biological activity

(quintet) or m (multiplet). High resolution mass spectra (HRMS) analyses were conducted on Agilent 1290 Infinity LC system and Agilent 6540 UHD Accurate-Mass Q-TOF mass spectrometer, equipped with an electrospray ion source in the positive mode. The aldehydes 5-(4-Bromophenyl) furan-2-carboxaldehyde 1 and 5-(4-chlorophenyl)furan-2-carboxaldehyde 2 [22], the morpholine derivatives 9 and 10 [23, 24], and the glycosyl derivatives 11 and 12 [25, 26] were synthesized according to the published procedures.

5-(4-bromophenyl)furan-2-carboxylic acid (3) and 5-(4-chlorophenyl)furan-2-carboxylic acid (4)

In a round-bottom flask containing $AgNO_3$ solubilized in distilled water, 1 M NaOH solution was added, obtaining a brown solid. After that, the aldehyde **1** or **2** (1 eq.) solubilized in ethanol was added to this suspension. The reaction mixture was refluxed under magnetic stirring for 2 h. The completion of the reaction was observed by thin layer chromatography (TLC) and precipitate was filtered and washed with hot water. Then, the filtered was acidified with 3 M HCl solution and extracted with EtOAc as solvent. The organic layers were dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure, obtaining a green solid as the product, 93% yield for both acids; mp 199.6–200.1 °C (compound **3**), lit.: 198.0–200.0 °C [22]; mp 189.0–190.0 °C (compound **4**), lit.: 197.0–198.0 °C [27]; (Compound **3**) ^{1}H NMR (200 MHz, acetone-*d6*) δ 7.79 (d, 2H, $J = 8.6$, H-7), 7.66 (d, 2H, $J = 8.6$, H-8), 7.32 (d, 1H, $J = 3.5$, H-3), 7.10 (d, 1H, $J = 3.5$, H-4); ^{13}C NMR (50 MHz, acetone-*d6*) δ 159.3 (C-10), 156.7 (C-5), 145.3 (C-2), 132.9 (C-8), 129.7 (C-6), 127.2 (C-7), 123.2 (C-9), 120.7 (C-3), 108.8 (C-4). (Compound **4**) ^{1}H NMR (400 MHz, acetone-*d6*) δ 7.84 (d, 2H, $J = 8.6$, H-7), 7.50 (d, 2H, $J = 8.6$, H-8), 7.31 (d, 1H, $J = 3.5$, H-3), 7.06 (d, 1H, $J = 3.5$, H-4); ^{13}C NMR (100 MHz, acetone-*d6*) δ 159.3 (C-10), 156.7 (C-5), 145.3 (C-2), 135.0 (C-9), 129.9 (C-8), 129.3 (C-6), 126.9 (C-7), 120.7 (C-3), 108.8 (C-4).

General procedure for the preparation of amides 5-8

In a round-bottom flask the acid derivative **3** or **4** (1 eq.) solubilized in dichloromethane was added. Then, *N*-hydroxysuccinimide (1 eq.) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (1.1 eq.) were put into the reaction mixture. The reaction was stirred at room temperature for 5 h. In the sequence, the corresponding amine (1.5 eq) was added and the reaction continued for more 24 h. The completion of the reaction was observed by TLC. Posteriorly, the flask contents were washed with 3 M HCl solution, sodium bicarbonate 10% solution and, finally, distilled water. The organic layers were dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure, obtaining the corresponding product.

5-(4-bromophenyl)-N-(2-hydroxyethyl)furan-2-carboxamide (5)

This compound was prepared from 5-(4-bromophenyl) furan-2-carboxylic acid **3** (500 mg, 1.9 mmol) in 20 mL of dichloromethane and obtained from the general procedure as a yellow solid (497 mg, 86% yield); mp 164.6–165.8 °C; IR (neat, cm^{-1}) 3435, 3335, 1626; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.49 (t, $J = 5.4$, 1H, NH), 7.86 (d, 2H, $J = 8.5$, H-7), 7.66 (d, 2H, $J = 8.5$, H-8), 7.15 (d,1H, $J = 3.5$, H-4), 7.13 (d, 1H, $J = 3.5$, H-3), 4.76 (t, 1H, $J = 5.2$, OH), 3.52 (q, 2H, $J = 5.7$, H-12), 3.34-3.30 (m, 2H, H-11); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 157.6 (C-10), 153.1 (C-5), 147.5 (C-2), 131.8 (C-8), 128.6 (C-6), 126.2 (C-7), 121.5 (C-9), 115.4 (C-4), 108.2 (C-3), 59.7 (C-12), 41.4 (C-11); HRMS (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{13}BrNO_3^+$ 310.0073, found 310.0077.

5-(4-bromophenyl)-N-(3-hydroxypropyl)furan-2-carboxamide (6)

This compound was prepared from 5-(4-bromophenyl) furan-2-carboxylic acid **3** (200 mg, 0.7 mmol) in 10 mL of dichloromethane and obtained from the general procedure as a brown solid (157 mg, 66% yield); mp 109.0–110.0 °C; IR (neat, cm^{-1}) 3396, 3309, 1622; ^{1}H NMR (200 MHz, DMSO-*d6*) δ 8.54 (t, NH, $J = 5.4$), 7.85 (d, 2H, $J = 8.5$, H-7), 7.65 (d, 2H, $J = 8.5$, H-8), 7.14–7.12 (m, 2H, H-3, H-4), 4.51 (t, 1H, $J = 4.9$, OH), 3.46 (q, 2H, $J = 5.8$, H-13), 3.34–3.26 (m, 2H, H-11), 1.67 (qt, 2H, $J = 6.5$, H-12); ^{13}C NMR (50 MHz, DMSO-*d6*) δ 157.5 (C-10), 153.1 (C-5), 147.5 (C-2), 131.8 (C-8), 128.6 (C-6), 126.2 (C-7), 121.5 (C-9), 115.3 (C-4), 108.2 (C-3), 58.5 (C-13), 35.9 (C-11), 32.5 (C-12); HRMS (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{15}BrNO_3^+$ 326.0230, found 326.0220.

5-(4-bromophenyl)-N-(prop-2-yn-1-yl)furan-2-carboxamide (7)

This compound was prepared from 5-(4-bromophenyl) furan-2-carboxylic acid **3** (200 mg, 0.7 mmol) in 10 mL of dichloromethane and obtained from the general procedure as an orange solid (154 mg, 68% yield); mp 129.4–130.4 °C; IR (neat, cm^{-1}) 3250, 2935, 2119, 1632; ^1H NMR (400 MHz, DMSO-*d6*) δ 9.00 (t, NH, $J = 5.6$), 7.87 (d, 2H, $J = 8.6$, H-7), 7.67 (d, 2H, $J = 8.6$, H-8), 7.20 (d, 1H, $J = 3.6$, H-4), 7.15 (d, 1H, $J = 3.6$, H-3), 4.6 (dd, 2H, $J = 5.6$, 2.4, H-11), 3.14 (t, 1H, $J = 2.4$, H-13); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 157.2 (C-10), 153.5 (C-5), 143.8 (C-2), 131.8 (C-8), 128.5 (C-6), 126.3 (C-7), 121.7 (C-9), 116.0 (C-4), 108.3 (C-3), 81.0 (C-12), 72.9 (C-13), 27.7 (C-11); HRMS (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{11}BrNO_2^+$ 305.9968, found 305.9953.

5-(4-chlorophenyl)furan-2-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone (8)

This compound was prepared from 5-(4-chlorophenyl) furan-2-carboxylic acid **4** (50 mg, 0.22 mmol) in 15 mL of dichloromethane and obtained from the general procedure as an yellow solid (56 mg, 74% yield); mp 100.0–103.0 °C; IR (neat, cm^{-1}) 3390, 2924, 2814, 1610; ^1H NMR (400 MHz, acetone-*d6*) δ 7.81 (d, 2H, $J = 8.7$, H-7), 7.49 (d, 2H, $J = 8.7$, H-8), 7.07 (d, 1H, $J = 3.6$, H-4), 7.03 (d, 1H, $J = 3.6$, H-3), 3.90–3.70 (m, 4H, H-11, H-13), 3.68–3.63 (m, 2H, H-16), 2.61–2.58 (m, 4H, H-12, H-14), 2.57–2.53 (m, 2H, H-15); ^{13}C NMR (100 MHz, Acetone-*d6*) δ 158.2 (C-10), 153.5 (C-5), 147.7 (C-2), 133.5 (C-9), 129.0 (C-8), 128.8 (C-6), 125.8 (C-7), 117.7 (C-4), 107.2 (C-3), 60.1 (C-12, C-14), 58.7 (C-11, C-13), 53.4 (C-15, C-16); HRMS (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{20}ClN_2O_3^+$ 335.1157, found 335.1149.

General procedure for the preparation of furan triazoles 13 and 14

In a round-bottom flask the alkyne **7** (1 eq.) and the corresponding azide **10** or **12** (1 eq.) were added and solubilized in tetrahydrofuran (THF). Then, sodium ascorbate (0.8 eq.) and a 10% aqueous solution of $CuSO_4.5H_2O$ (0.4 eq.) were put into the reaction mixture. The reaction mixture was maintained under magnetic stirring at room temperature for about 4 h. After confirming the completion of the reaction by TLC, ethanol was added and the precipitate formed was filtered, washed with ethanol and the filtrate was evaporated under reduced pressure.

5-(4-bromophenyl)-N-((1-(2-morpholino-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl) furan-2-carboxamide (13)

This compound was prepared from alkene 5-(4-bromophenyl)-*N*-(prop-2-yn-1-yl)furan-2-carboxamide **7** (350 mg, 1.15 mmol) in 4 mL of THF and obtained from the general procedure. A solution of ethanol/water (1:1, *v/v*) was added to the obtained residue and the precipitate formed was filtered. The filtrate volume was reduced by ~50% and the solid formed was isolated by filtration, obtaining a beige solid as the product (317 mg, 58% yield); mp 94.0–96.0 °C; IR (neat, cm^{-1}); 3287, 2968, 2859, 1644; ^1H NMR (400 MHz, DMSO-*d6*) δ 9.16 (broad s, NH), 7.90–7.87 (m, 3H, H-13 and H-7), 7.67 (d, 2H, $J = 8.4$, H-8), 7.20 (d, 1H, $J = 3.3$, H-4), 7.15 (d, 1H, $J = 3.3$, H-3), 5.43 (s, 2H, H-14), 4.53 (d, 2H, $J = 4.6$, H-11), 3.65–3.58 (m, 4H, H-17), 3.52–3.44 (m, 4H, H-16); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 164.5 (C-15), 157.5 (C-10), 153.4 (C-5), 147.1 (C-2), 131.8 (C-8), 128.6 (C-6), 126.3 (C-7), 124.7 (C-13), 121.6 (C-9), 115.8 (C-3), 108.3 (C-4), 65.9 (C-17), 65.8 (C-17‘), 50.5 (C-14), 44.7 (C-16‘), 41.9 (C-16), 34.1 (C-11); HRMS (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{21}BrN_5O_4^+$ 474.0771, found 474.0777.

5-(4-bromophenyl)-[(1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methyl]furan-2-carboxamide (14)

This compound was prepared from alkene 5-(4-bromophenyl)-*N*-(prop-2-yn-1-yl)furan-2-carboxamide **7** (100 mg, 0.3 mmol) in 4 mL of THF and obtained from the general procedure. The obtained residue was purified by column chromatography (Hexane/EtOAc 8:2), obtaining the product as a white solid (100 mg, 44% yield); mp 135.8–136.6 °C; IR (neat, cm^{-1}); 3348, 2959, 1747, 1651, 1215; ^1H NMR (400 MHz, DMSO-*d6*) δ 9.15 (t, NH, $J = 5.8$), 8.29 (s, 1H, H-13), 7.88 (d, 2H, $J = 8.5$, H-7), 7.67 (d, 2H, $J = 8.5$, H-8), 7.20 (d, 1H, $J = 3.5$, H-4), 7.15 (d, 1H, $J = 3.5$, H-3), 6.31 (d, 1H, $J = 9.3$, H-14), 5.67 (t, 1H, $J = 9.3$, H-15), 5.52 (t, 1H, $J = 9.3$, H-16), 5.17 (t, 1H, $J = 9.3$, H-17), 4.56–4.47 (m, 2H, H-11), 4.36–4.32 (m, 1H, H-18), 4.14–4.05 (m, 2H, H-19), 2.02 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$), 1.95 (s, 3H, $COCH_3$), 1.79 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 169.9 ($COCH_3$), 169.5 ($COCH_3$), 169.3 ($COCH_3$). 168.4 ($COCH_3$), 157.5 (C-10), 153.4 (C-5), 147.0 (C-2), 145.7 (C-12), 131.8 (C-8), 128.5 (C-6), 126.2 (C-7), 122.0 (C-13), 121.6 (C-9), 115.9 (C-4), 108.3 (C-3), 83.8 (C-14), 73.2 (C-18), 72.2 (C-16), 70.0 (C-15), 67.5 (C-17), 61.8 (C-19), 33.9 (C-11), 20.4 ($COCH_3$), 20.3 ($COCH_3$), 20.2 ($COCH_3$), 19.8 ($COCH_3$); HRMS (*m/z*) $[M + H]^+$ calcd for $C_{28}H_{30}BrN_4O_{11}^+$ 677.1089, found 677.1089.

((5-(4-chlorophenyl)furan-2-yl)methylene)amino) imidazolidine-2,4-dione (15)

In a round-bottom flask, immersed in an ice bath, 1-aminohydantoin (80.7 mg, 0.5 mmol) solubilized in 5 mL of 0.67 M HCl solution was added. Then, the aldehyde **2** (100 mg, 0.5 mmol) and 2.2 mL of *N*,*N*-dimethylformamide (DMF) were put into the reaction mixture. The reaction was maintained under magnetic stirring at room temperature for 3 h. After the end of the reaction, the precipitate formed was filtered and washed with cold water, obtaining a brown solid as the product (122 mg, 83% yield); mp 257–259 °C; IR (neat, cm^{-1}); 3287, 1774, 1764, 1726; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.28 (s, 1H, NH), 7.77 (d, 2H, J = 8.6, H-7), 7.72 (s, 1H, H-10), 7.51 (d, 2H, J = 8.6, H-8), 7.15 (d, 1H, J = 3.6, H-4), 6.95 (d, 1H, J = 3.6, H-3), 4.34 (s, 2H, H-11); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 168.9 (C-12), 153.3 (C-14 or C-5), 153.2 (C-5 or C-14), 149.4 (C-2), 132.9 (C-9), 132.6 (C-8), 129.0 (C-6), 128.4 (C-10), 125.4 (C-7), 115.4 (C-4) 108.9 (C-3) 48.9 (C-11); HRMS (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{11}ClN_3O_3^+$ 304.0483, found 304.0476.

General procedure for the preparation of amines 16-24

In a round-bottom flask the aldehyde **2** (1 eq.) and the corresponding amine (1-10 eq.) solubilized in chloroform were added. Then, Na_2SO_4 (1 eq.) was put into the reaction and the mixture was maintaining under magnetic stirring at room temperature overnight. In the sequence, under ice bath, methanol and $NaBH_4$ (6 eq) were added and the reaction was maintaining under magnetic stirring at room temperature for about 3 h. The completion of the reaction was observed by TLC and then distilled water was added and the mixture was extract with dichloromethane. After that, the organic phase was washed with 3 M HCl solution. The resulting aqueous phase of this last extraction was alkalized with 4 M NaOH solution and extracted with dichloromethane (3 × 20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure, obtaining the corresponding product.

N-((5-(4-chlorophenyl)furan-2-yl)methyl)propan-2-amine hydrochloride (16)

This compound was prepared from aldehyde 5-(4-chlorophenyl)furan-2-carboxaldehyde **2** (200 mg, 0.96 mmol) and isopropylamine (0.83 mL, 571.7 mg, 9.69 mmol) in 15 mL of chloroform. Compound **16** was obtained from the general procedure as a hydrochloride salt, white solid (186 mg, 67% yield); mp 215.5–216.7 °C; IR (neat, cm^{-1}) 2948, 2692, 1574-1544; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.65 (s, 2H, NH_2^+), 7.79 (d, 2H, J = 8.0, H-7), 7.50 (d, 2H, J = 8.0, H-8), 7.02 (d, 1H, J = 4.0, H-4), 6.78 (d, 1H, J = 4.0, H-3), 4.24 (s, 2H, H-10), 3.29–3.24 (m, 1H, H-11), 1.31 (d, 6H, J = 8.0, H12, H-13); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 152.6 (C-5), 146.2 (C-2), 132.2 (C-9), 128.9 (C-8), 128.7 (C-6), 125.4 (C-7), 114.1 (C-4), 107.5 (C-3), 49.1 (C-11), 39.6 (C-10), 18.5 (C-12, C-13); HRMS (*m/z*) $[M\text{-}Cl]^+$ calcd for $C_{14}H_{17}ClNO^+$ 250.0993, found 250.0991.

N-((5-(4-chlorophenyl)furan-2-yl)methyl)propan-1-amine (17)

This compound was prepared from aldehyde 5-(4-chlorophenyl)furan-2-carboxaldehyde **2** (400 mg, 1.93 mmol) and propylamine (1.6 mL, 1.14 g, 19.37 mmol) in 20 mL of chloroform. Compound **17** was obtained from the general procedure as a brown oil (263 mg, 55% yield); IR (neat, cm^{-1}) 2959, 2874, 1572-1481; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57 (d, 2H, J = 8.6, H-7), 7.32 (d, 2H, J = 8.6, H-8), 6.56 (d, 1H, J = 3.2, H-4), 6.28 (d, 1H, J = 3.2, H-3), 3.85 (s, 2H, H-10), 2.68–2.60 (m, 2H, H-11), 1.55 (qt, 2H, J = 7.3, H-12), 0.93 (t, 3H, J = 7.3, H-13); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.4 (C-5), 152.1 (C-2), 132.6 (C-9), 129.3 (C-6), 128.7 (C-8), 124.7 (C-7), 109.4 (C-4), 106.0 (C-3), 50.7 (C-10), 45.9 (C-11), 22.7 (C-12), 11.6 (C-13). HRMS (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{17}ClNO^+$ 250.0993, found 250.0980.

2-(((5-(4-chlorophenyl)furan-2-yl)methyl)amino)ethanol (18)

This compound was prepared from aldehyde 5-(4-chlorophenyl)furan-2-carboxaldehyde **2** (100 mg, 0.48 mmol) and ethanolamine (0.29 mL, 295.8 mg, 4.84 mmol) in 10 mL of chloroform. Compound **18** was obtained from the general procedure as a brown oil (73 mg, 60% yield); IR (neat, cm^{-1}) 3285, 3109, 2924, 2861, 1537-1479; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 2H, J = 8.6, H-7), 7.34 (d, 2H, J = 8.6, H-8), 6.57 (d, 1H, J = 3.2, H-4), 6.28 (d, 1H, J = 3.2, H-3), 3.86 (s, 2H, H-10), 3.69 (t, 2H, J = 5.1, H-12), 2.84 (t, 2H, J = 5.1, H-11); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4 (C-5), 152.4 (C-2), 132.9 (C-9), 129.3 (C-6), 128.9 (C-8), 124.8 (C-7), 109.5 (C-4), 106.1 (C-3), 60.8 (C-12), 50.3 (C-10), 45.3 (C-11); HRMS (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{15}ClNO_2^+$ 252.0786, found 252.0788.

3-(((5-(4-chlorophenyl)furan-2-yl)methyl)amino)propan-1-ol (19)

This compound was prepared from aldehyde 5-(4-chlorophenyl)furan-2-carboxaldehyde **2** (100 mg, 0.48 mmol) and 3-aminopropanol (0.37 mL, 363.4 mg, 4.84 mmol) in 10 mL of chloroform. Compound **19** was obtained from the

general procedure as a brown oil (87 mg, 68% yield); IR (neat, cm^{-1}) 3298, 2926, 2841, 1542–1481; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 2H, $J = 8.6$, H-7), 7.34 (d, 2H, $J = 8.6$, H-8), 6.57 (d, 1H, $J = 3.2$, H-4), 6.31 (d, 1H, $J = 3.2$, H-3), 3.88 (s, 2H, H-10), 3.82 (t, 2H, $J = 5.2$, H-13), 2.94 (t, 2H, $J = 5.2$, H-11), 1.79–1.74 (m, 2H, H-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6 (C-5), 152.2 (C-2), 132.9 (C-9), 129.2 (C-6), 128.9 (C-8), 124.9 (C-7), 109.9 (C-4), 106.1 (C-3), 63.6 (C-13), 48.4 (C-10), 45.8 (C-11), 30.6 (C-12); HRMS (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{17}ClNO_2^+$ 266.0942, found 266.0932.

2-(4-((5-(4-chlorophenyl)furan-2-yl)methyl)piperazin-1-yl) ethanol (20)

This compound was prepared from aldehyde 5-(4-chlorophenyl)furan-2-carboxaldehyde **2** (100 mg, 0.48 mmol) and 1-(2-hydroxyethyl)piperazine (0.1 mL, 124.0 mg, 0.96 mmol) in 10 mL of chloroform. Compound **20** was obtained from the general procedure as a yellow oil (57 mg, 37% yield); IR (neat, cm^{-1}) 3351, 2938, 2815, 1542-1481; ^1H NMR (400 MHz, acetone-*d6*) δ 7.71 (d, 2H, $J = 8.6$, H-7), 7.43 (d, 2H, $J = 8.6$, H-8), 6.83 (d, 1H, $J = 3.3$, H-4), 6.37 (d, 1H, $J = 3.3$, H-3), 3.60–3.55 (m, 4H, H-10 and H-16), 2.52–2.44 (m, 10H, H-11, H-12, H-13, H-14, H-15); ^{13}C NMR (100 MHz, acetone-*d6*) δ 152.7 (C-5), 151.9 (C-2), 132.2 (C-9), 129.8 (C-6), 128.8 (C-8), 124.9 (C-7), 110.8 (C-4), 106.7 (C-3), 60.2 (C-16), 58.5 (C-15), 54.4 (C-10), 53.3 (C12, C-14), 52.7 (C-11, C-13); HRMS (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{22}ClN_2O_2^+$ 321.1364, found 321.1356.

N-((5-(4-chlorophenyl)furan-2-yl)methyl)-3-morpholinopropan-1-amine (21)

This compound was prepared from aldehyde 5-(4-chlorophenyl)furan-2-carboxaldehyde **2** (100 mg, 0.48 mmol) and 3-morpholinopropylamine (0.07 mL, 69.2 mg, 0.48 mmol) in 10 mL of chloroform. Compound **21** was obtained from the general procedure as a yellow oil (105 mg, 65% yield); IR (neat, cm^{-1}) 3299, 2948, 2812, 1584-1481; ^1H NMR (400 MHz, acetone-*d6*) δ 7.68 (d, 2H, $J = 8.7$, H-7), 7.40 (d, 2H, $J = 8.7$, H-8), 6.79 (d, 1H, $J = 3.3$, H-4), 6.32 (d, 1H, $J = 3.3$, H-3), 3.78 (s, 2H, H-10), 3.55 (t, 4H, $J = 4.6$, H-15, H-17), 2.67 (t, 2H, $J = 6.8$, H-11), 2.31-2.38 (m, 6H, H-13, H-14, H-16), 1.63 (qt, 2H, $J = 6.8$, H-12); ^{13}C NMR (100 MHz, acetone-*d6*) δ 155.5 (C-5), 151.4 (C-2), 132.0 (C-9), 129.9 (C-6), 128.8 (C-8), 124.8 (C-7), 108.7 (C-4), 106.7 (C-3), 66.6 (C-15, C-17), 57.0 (C-13), 53.8 (C-14, C-16), 47.3 (C-10), 46.0 (C-11), 26.5 (C-12); HRMS (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{24}ClN_2O_2^+$ 335.1521, found 335.1516.

N-benzyl-1-(5-(4-chlorophenyl)furan-2-yl)methanamine hydrochloride (22)

This compound was prepared from aldehyde 5-(4-chlorophenyl)furan-2-carboxaldehyde **2** (100 mg, 0.48 mmol) and benzylamine (0.15 mL, 154.3 mg, 1.44 mmol) in 10 mL of chloroform. Compound **22** was obtained from the general procedure as a hydrochloride, white solid (130 mg, 81% yield); mp 248.0–250.0 °C; IR (neat, cm^{-1}) 2921, 2727, 2593, 1575-1438; ^1H NMR (400 MHz, DMSO-*d6*) δ 10.04 (broad s, 2H, NH_2^+), 7.79 (d, 2H, $J = 8.6$, H-7), 7.62–7.56 (m, 2H, H-14, H-16), 7.52 (d, 2H, $J = 8.6$, H-8), 7.45–7.40 (m, 3H, H-13, H-15, H-17), 7.04 (d, 1H, $J = 3.4$, H-4), 6.77 (d, 1H, $J = 3.4$, H-3), 4.25 (s, 2H, H-10), 4.18 (s, 2H, H-11); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 153.2 (C-5), 146.3 (C-2), 132.7 (C-19 or C-12), 132.2 (C-12 or C-9), 130.7 (C-8), 129.4 (C-13, C-17), 129.1 (C-7), 129.0 (C-14, C-16), 125.9 (C-15), 114.9 (C-4), 108.01 (C-3), 49.9 (C-11), 42.5 (C-10); HRMS (*m/z*) $[M\text{-}Cl]^+$ calcd for $C_{18}H_{17}ClNO^+$ 298.0993, found 298.0983.

1-(5-(4-chlorophenyl)furan-2-yl)-N-(furan-2-ylmethyl) methanamine (23)

This compound was prepared from aldehyde 5-(4-chlorophenyl)furan-2-carboxaldehyde **2** (100 mg, 0.48 mmol) and furfurylamine (0.14 mL, 139.8 mg, 1.44 mmol) in 10 mL of chloroform. Compound **23** was obtained from the general procedure as a yellow solid (92 mg, 66% yield); mp 197.0–200.0 °C; IR (neat, cm^{-1}) 2925, 2731, 1580–1439; ^1H NMR (400 MHz, DMSO-*d6*) δ 7.77 (d, 2H, $J = 8.6$, H-7), 7.75 (d, 1H, $J = 1.2$, H-15), 7.51 (d, 2H, $J = 8.6$,H-8), 7.02 (d, 1H, $J = 3.4$, H-4), 6.72 (d, 1H, $J = 3.4$, H-3), 6.65 (d, 1H, $J = 3.1$, H-13), 6.52–6.51 (m, 1H, H-14), 4.20 (s, 4H, H-10, H-11); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 153.1 (C-5), 146.9 (C-2 or C-12), 146.8 (C-12 or C-2), 144.4 (C-15), 132.7 (C-9), 129.4 (C-6), 129.2 (C-8), 125.8 (C-7), 114.5 (C-14), 112.5 (C-13), 111.5 (C-4), 107.9 (C-3), 42.5 (C-10 or C-11), 42.4 (C-11 or C-10). HRMS (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{15}ClNO_2^+$ 288.0786, found 288.0779.

N-((5-(4-chlorophenyl)furan-2-yl)methyl)-3-phenylpropan-1-amine hydrochloride (24)

This compound was prepared from aldehyde 5-(4-chlorophenyl)furan-2-carboxaldehyde **2** (100 mg, 0.48 mmol) and 3-phenyl-1-propylamine (0.2 mL, 194.7 mg, 1.44 mmol) in 10 mL of chloroform. Compound **24** was obtained from the general procedure as a white solid (80 mg, 46%); mp 203.0–204.0 °C; IR (neat, cm^{-1}) 2927, 2752, 1605-1451; ^1H NMR (400 MHz, DMSO-*d6*) δ 9.69 (s, 2H, NH_2^+), 7.76 (d, 2H, $J = 8.6$, H-7), 7.51 (d, 2H, $J = 8.6$, H-8), 7.29–7.13 (m, 5H, H-15, H-16, H-17, H-18, H-

19), 7.01 (d, 1H, $J = 3.4$, H-4), 6.74 (d, 1H, $J = 3.4$, H-3), 4.25 (s, 2H, H-10), 2.90 (t, 2H, $J = 7.8$, H-11), 2.65 (t, 2H, $J = 7.8$, H-13), 1.98 (qt, 2H, $J = 7.8$, H-12); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 153.2 (C-5), 146.5 (C-2), 141.1 (C-14), 132.8 (C-9), 129.4 (C-6), 129.2 (C-8), 128.9 (C-16, C-18), 128.7 (C-15, C-19), 126.5 (C-7), 114.9 (C-4), 107.9 (C-3), 46.1 (C-10), 42.6 (C-11), 32.4 (C-13), 27.4 (C-12); HRMS (*m/z*) $[M\text{-}Cl]^+$ calcd for $C_{20}H_{21}ClNO^+$ 326.1306, found 326.1303.

In vitro antibacterial activity

Bacterial strains and culture conditions

To carry out the in vitro antibacterial activity assays, three American Type Culture Collection (ATCC®) strains were selected according to the WHO priority group [7] and tested. *Staphylococcus aureus* subsp. *aureus* (ATCC® 29213™) [methicillin sensitive *S. aureus* (MSSA)], *Escherichia coli* (ATCC® 25922™) (fermentative Gram-negative bacteria) and *Pseudomonas aeruginosa* (ATCC® 27853™) (non-fermentative Gram-negative bacteria), in the second passage, were obtained from the Instituto Nacional de Controle de Qualidade em Saúde, Fundação Oswaldo Cruz, Rio de Janeiro city, Rio de Janeiro state, Brazil. These strains were maintained as suspensions in 10% (*w/v*) skim milk solution containing 10% (*v/v*) glycerol at −20 °C. Before use, these cultures were transferred to Müller-Hinton agar (MHA) (Difco Laboratories, Detroit, MI, USA) at 35 ± 2 °C for 18–24 h under aerobic conditions.

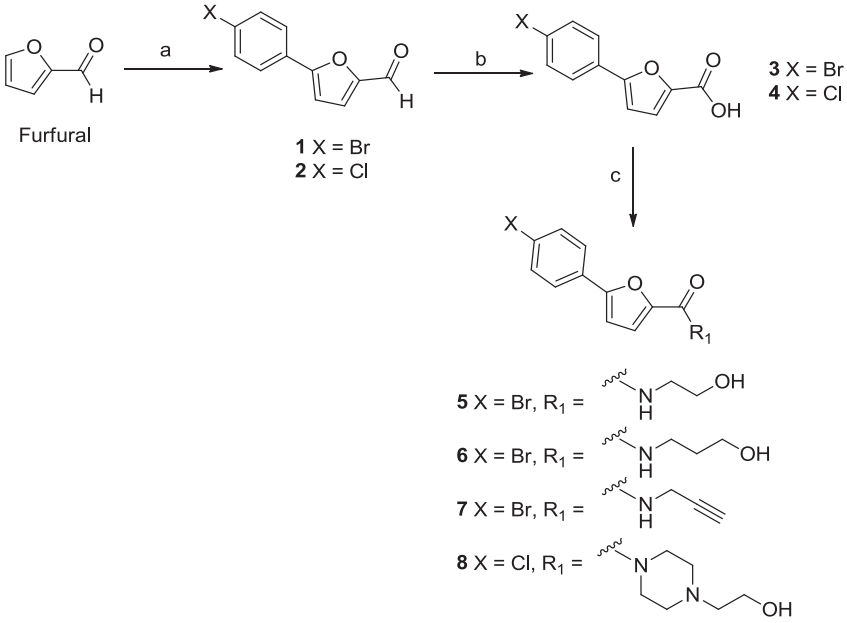
Determination of minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC)

The broth micro-dilution method was performed according to the Clinical and Laboratory Standards Institute (CLSI) guideline M07-A9 [28], with little adjustments, using Müeller-Hinton broth (MHB) (Difco Laboratories, Detroit, MI, USA) to determine MIC values of 18 arylfuran derivatives and ampicillin (AMP), chloramphenicol (CHL) and levofloxacin (LEVO) (Sigma-Aldrich, St Louis, MO, USA) against the three selected ATCC® strains aforementioned. Arylfuran derivative and antibiotic stock-solutions were prepared in dimethylsulfoxide (DMSO) and sterilized distilled water at the concentration of 1 mg/mL (*w/v*), respecting the limit of 1% in the first microplate well [29]. In a sterile polystyrene 96-well microplate, twofold serial dilutions of arylfuran derivatives (quadruplicate) and antibiotics (triplicate) were prepared in MHB at concentrations ranging from 4 to 250 µg/mL. MIC values above 250 µg/mL were not determined. Subsequently, 10 µL of standardized bacteria suspension according to 0.5 McFarland scale were added. After incubation at 35 ± 2 °C for 16–20 h under aerobic conditions, 20 µL of 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyl-2H-tetrazolium chloride (INT) solution (1 mg/mL) were added and used as an indicator of bacterial growth (any color change from purple to pink was recorded as bacterial growth). Posteriorly, the system was incubated for further 30 min, and the MIC was determined. When necessary, other biological indicator such as resazurin was used and the protocol was properly adjusted. The appropriate controls were performed. After determination of MIC values, MBC was established according to Andrews' method [30] by spreading of 10 µL of suspensions from wells that did not received INT and corresponding to the concentrations that showed no visible bacterial growth on MHA Petri dishes. After incubation at 35 ± 2 °C for 16–20 h under aerobic conditions, MBC was determined as the lowest concentration of dilutions that prevented the visible bacterial growth after subculture on MHA Petri dishes. Bacterial growth or absence of bacterial growth on MHA revealed a bacteriostatic or bactericidal effect, respectively.

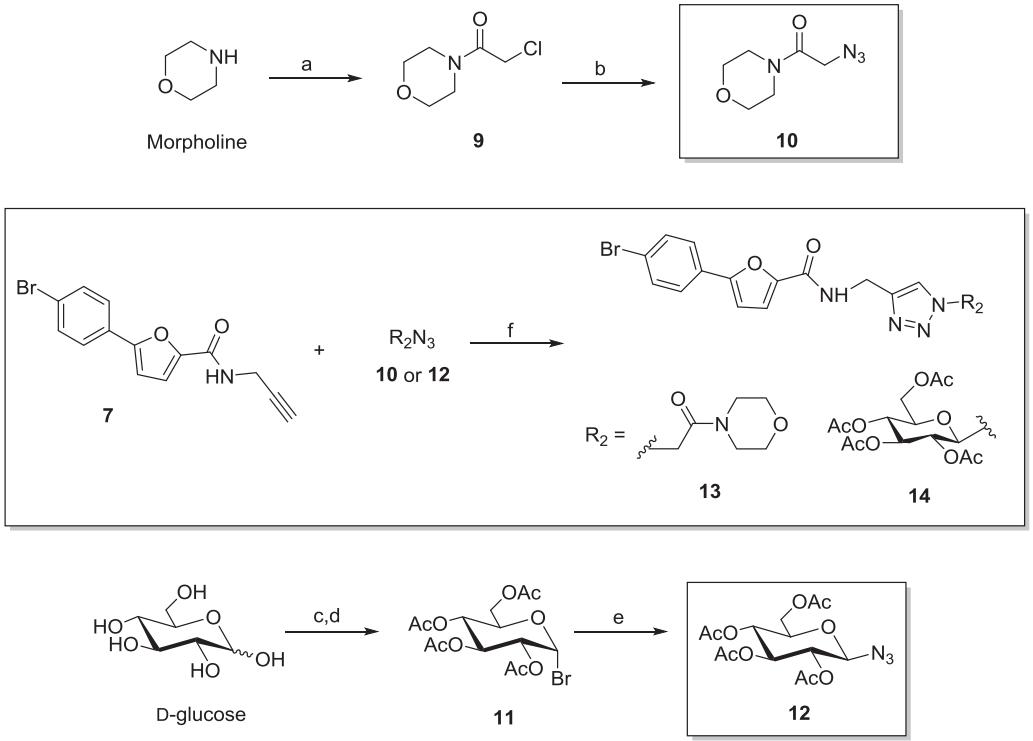
Computational studies

Semi-empirical calculations employing PM3 method [31, 32] implemented on MOPAC [33] interface implemented on Sybyl X 2.1 platform [34] were carried out in order to minimize the structure of selected compounds and calculate their molecular properties. Electrostatic potential surfaces were generated using MOLCAD module of Sybyl X 2.1. In addition, 30 lowest energy conformers of compounds **5** and **24** were generated using OMEGA 3.1.2.2 [35] ([36]) followed by molecular alignment of benzene and furan ring using ROCS 3.3.2.2 [37] ([38]) aiming to compare molecular flexibility of those compounds.

Compound **24** was employed in several predictions because it was the active compound found in this study. First, we used a target prediction approach reported by Serafim et al. [39]. to suggest a potential molecular target and guide a future search for its mechanism of action. In this step, we retrieved experimentally known active compounds against *S. aureus* and *E. coli* (MIC < 50 µM) from ChEMBL database [40] and calculated the 3D similarity of compound **24** against all obtained compounds after structures preparation (calculation of most stable conformer with OMEGA 3.1.2.2 [35] ([36]) and ionization states with [41]). The tridimensional similarities were calculated using ROCS 3.3.2.2 [37] ([38]) considering molecular shape and chemical functions and were expressed as Tanimoto coefficient (Tc). Posteriorly, the most similar compounds were used to suggest a possible action target for compound **24**. Finally, we also calculated physicochemical properties related to pharmacokinetics parameters with SwissADME [42], MarvinSketch 19.2 (ChemAxon, https://www.chemaxon.com) and pkCSM [43] webservers to evaluate its druglikeness.



Scheme 1 General scheme for the preparation of arylfurans **1**–**8**. **a** HCl, $NaNO_2$, 4-bromoaniline or 4-chloroaniline $CuCl_2.2H_2O$ (45%; 25%); **b** $AgNO_3$, NaOH, EtOH, 80 °C (93%); **c** (1) EDAC, NHS; CH_2Cl_2; (2) corresponding amine (ethanolamine, propanolamine, propargylamine or 1-(2-hydroxyethyl) piperazine) (66–86%)

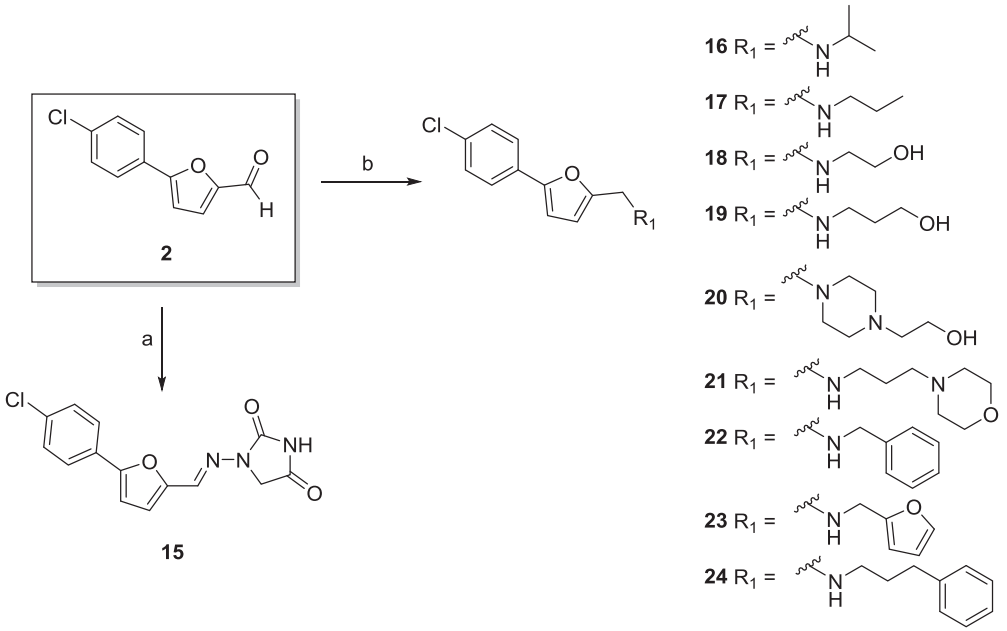


Scheme 2 General scheme for the preparation of azides **10** and **12** and furan-triazole derivatives **13** and **14**. **a** $CHCl_3$, chloroacetic anhydride (75%); **b** THF/H_2O, NaN_3, 60 °C (60%); **c** Ac_2O, I_2, r.t (99%); **d** HBr/AcOH 12% *v/v*, 0 °C-r.t. (90%); **e** NaN_3, acetone/H_2O, r.t. (80%); **f** Amide **7**, azide derivative **10** or **12**, THF, $CuSO_4.5H_2O$, sodium ascorbate (44%;58%)

Results and discussion

Synthesis

The first step for the synthesis of arylfurans involved direct furfural arylation with the haloarenediazonium salt using copper (II) chloride as a catalyst (Meerwein arylation) [44, 45]. Oxidation of 5-arylfurfural derivatives **1** or **2** in the presence of silver nitrate resulted in the formation of the corresponding carboxylic acid **3** or **4**, respectively, which was converted to amides **5**-**8** via carbodiimide/*N*-hydroxysuccinimide coupling (Scheme 1).



Scheme 3 General scheme for the preparation of hydantoin derivative **15** and amines **16–24**. **a** DMF, 1-aminohydantoin, HCl (83%); **b** (1) $CHCl_3$, corresponding amine, Na_2SO_4; (2) Methanol, $NaBH_4$ (37–81%)

The furan-triazole derivatives **13** and **14** were synthesized using click reaction of the propargyl amide **7** and the azide derivatives **10** and **12**. The azide derivative **10** was synthesized in two steps using chloroacetic anhydride and morpholine as starting material. The peracetylated glycosyl azide **12** was obtained from glycosyl halide **11** [25, 26] by reaction with NaN_3 in acetone/H_2O at room temperature [25, 46] (Scheme 2).

The arylfuran (**2**) was used as starting material for the synthesis of hydantoin derivative **15** and amines **16–24** (Scheme 3). We hypothesized that the presence of an additional heterocyclic ring in the compounds **13, 14** (triazole), **8**, **20** (piperazine), **13**, **21** (morpholine) and **23** (furan) or the attachment of a sugar moiety (compound **14**) could contribute favorably to the activity due to the possibility of further interactions with the possible molecular target. In addition, the presence of one or more basic nitrogen atoms in the compounds **16–24** may be important to modulate pKa and improve both the physicochemical and pharmacological properties of the molecules.

In vitro antibacterial activity

Eighteen arylfuran derivatives were tested to establish their in vitro antibacterial activity against *S. aureus* (ATCC® 29213™), *E. coli* (ATCC® 25922™) and *P. aeruginosa* (ATCC® 27853™). Among them, eight arylfuran derivatives (compounds **6**, **16**, **18**, **19**, and **21–24**) demonstrated the most interesting results (Table 1).

Compounds **21** and **24** were active for both Gram-negative (*P. aeruginosa*, ATCC® 27853™ and/or *E. coli*, ATCC® 25922™) and Gram-positive (*S. aureus*, ATCC® 29213™) bacteria, suggesting that these compounds may exhibit a broad spectrum of action. The amines **16**, **22** and **23** were only active against *E. coli* (ATCC® 25922™) (MIC values range from 125 to 250 μg/mL), while **18** and **19** exhibited activity against *S. aureus* (ATCC® 29213™) (MIC = 250 μg/mL). None of the tested amides (compounds **5–8** and **13** and **14**) showed antibacterial activity. These results indicate that the presence of an ionizable amino group is essential for activity. The presence of an ionizable nitrogen in amines can contribute for the solubility and penetration into microorganism. In line with our results, Parker et al. [47]. also obtained a new broad-spectrum antibiotic compound after the introduction of an ionizable amino group in its structure. The size of the side chain also plays a significant role in the activity, since compounds with a chain of three carbon atoms separating the nitrogen atom from the substituent at the end of the chain (morpholine (compound **21**) or phenyl (compound **24**) groups) were the most active. In addition, comparing the substituent on these two compounds and their MIC values, it is possible to infer the importance of the phenyl group for the activity of compound **24**. In this case, it is assumed that this group may be important for an interaction in a possible hydrophobic pocket on the target. It is worth mentioning that compound **24** was the only one that showed activity, even if modest, against *P. aeruginosa* (ATCC® 27853™), demonstrating the potential of this compound as a candidate for antibacterial drug.

Table 1 Minimal Inhibitory Concentration (MIC) and Minimal Bactericidal Concentration (MBC) values obtained with arylfuran derivatives, ampicillin (AMP), chloramphenicol (CHL) and levofloxacin (LEVO) against the three selected ATCC® bacterial strains

Compound	MIC			MBC		
	E. coli (ATCC® 25922™) μg/mL (μM)	*P. aeruginosa* (ATCC® 27853™) μg/mL (μM)	*S. aureus* (ATCC® 29213™) μg/mL (μM)	*E. coli* (ATCC® 25922™) μg/mL (μM)	*P. aeruginosa* (ATCC® 27853™) μg/mL (μM)	*S. aureus* (ATCC® 29213™) μg/mL (μM)
1	>250	>250	>250	>250	>250	>250
3	>250	>250	>250	>250	>250	>250
5	>250	>250	>250	>250	>250	>250
6	>250	ND	ND	>250	>250	>250
7	>250	>250	>250	>250	>250	>250
8	>250	>250	>250	>250	>250	>250
13	>250	>250	>250	>250	>250	>250
14	>250	>250	>250	>250	>250	>250
15	>250	>250	>250	>250	>250	>250
16	**125[f] (500)**	>250	>250	**250 (1000)**	>250	>250
17	>250	>250	>250	>250	>250	>250
18	>250	>250	**250[e] (990)**	>250	>250	**250 (990)**
19	>250	>250	**250[e] (940)**	>250	>250	**250 (940)**
20	>250	>250	>250	>250	>250	>250
21	**250[f] (750)**	>250	**250[f] (750)**	>250	>250	>250
22	**250[e] (840)**	>250	>250	**250 (840)**	>250	>250
23	**250[e] (870)**	>250	>250	**250 (870)**	>250	>250
24	**31[e] (98)**	**250[e] (770)**	**16[f] (49)**	**31 (98)**	**250 (770)**	**31 (98)**
AMP	<4[a] (<16)	>250	<4[b] (<16)	ND	ND	ND
CHL	<4[c] (<16)	125	16[c] (50)	ND	ND	ND
LEVO	<4[d] (<16)	<4[d] (<15)	ND	ND	ND	ND

ND not determined; Note: activity results for active compounds are highlighted in bold

[a]MIC values for AMP, CHL and LEVO are within the ranges described by the Clinical and Laboratory Standards Institute (CLSI), document M100-S24: MIC for AMP (Penicillin) (a) ≤8, 16 and ≥32 μg/mL classify the bacteria as sensitive, intermediate and resistant, respectively, and (b) ≤0.12 and ≥0.25 μg/mL as sensitive and resistant, in this order; MIC for CHL (c) ≤8, 16 and ≥32 μg/mL classify the bacteria as sensitive, intermediate and resistant, respectively; MIC for LEVO (d) ≤2, 4 and ≥8 μg/mL classify the bacteria as sensitive, intermediate and resistant, in this order. The experiments were performed in quadruplicate and in triplicate for compounds and antibiotics, respectively

[b]MBC values >250 μg/mL were not determined because they were above the established gradient. The antibacterial effect was classified as bactericidal (e) or bacteriostatic (f)

Despite the potential activity of triazole heterocycles, in the present work the introduction of a triazole ring was unfavorable for the activity. As already mentioned, it can be speculated that the presence of the amide group in compounds **13** and **14** may have been responsible for this low activity, since all active arylfuran derivatives have an amino group in that position. The same can be hypothesized for hydantoin derivative **15**, which has no ionizable amino groups. The pKa of compound **15** was predicted using MarvinSketch to be 8.23 (pKa referring to the acidic hydantoin NH).

Computational studies

From target prediction approach, no active compounds retrieved from ChEMBL are more than 50% similar to compound **24**. Therefore, we could not explore a molecular target by similarity and, then, the molecular docking studies were not carried out. On the other hand, the low similarity with known antibacterial agents indicates the innovative aspect of this compound. We also searched the DrugBank repository [48] for FDA approved drugs with more than 50% structural similarity and no results were found corroborating our previous finding.

In addition, in silico studies were performed to investigate the druglike properties and toxicity profile of the active arylfurans (**16**, **19**, **21**–**24**).

These six compounds were predicted to exhibit druglike profile since they do not violate any of Lipinski [49], Veber [50], Ghose [51], Egan [52] and Muegge [53] rules for predicting oral bioavailability (Table 2). Furthermore, the

Table 2 Physicochemical properties and prediction of absorption-related parameters

Compound	HBA[a]	HBD[a]	MW (da)[a]	ClogP[a]	rtB[a]	PSA (Å^2)[a]	pKa[b]	GI[a]	HIA (%)[c]
16	2	1	249.74	3.49	4	25.17	8.85	High	90.82
19	3	2	265.74	2.59	6	45.40	8.47	High	89.89
21	4	1	334.64	2.97	7	37.64	8.62	High	92.11
22	2	1	297.78	4.14	5	25.17	7.88	High	91.07
23	3	1	287.74	3.46	5	38.31	7.03	High	92.50
24	2	1	325.83	4.73	7	25.17	8.98	High	90.95

HBA hydrogen-bond acceptor, *HBD* hydrogen-bond donor, *MW* molecular weight, *ClogP* consensus prediction of the logarithm of n-octanol/water partition, *rtB* rotatable bonds, *PSA* polar surface area, *pKa* log of acidity constant, *GI* gastrointestinal absorption, *HIA* human intestinal absorption

[a]Calculated using SwissADME webserver

[b]Calculated using MarvinSketch

[c]Calculated using pkCSM

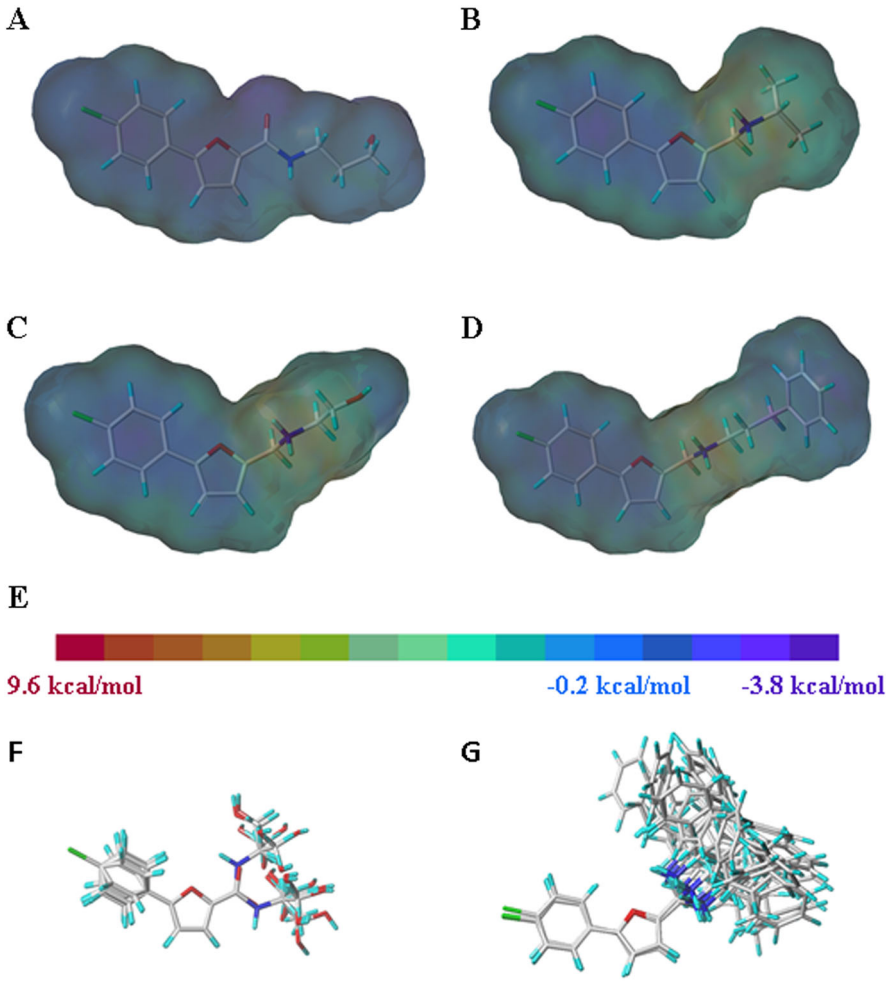


Fig. 4 Electrostatic potential surface of compounds **5** (**A**), **16** (**B**), **18** (**C**), and **24** (**D**) as well as the color scale of charge distribution (**E**) ranging from most positive regions (red) to most negative regions (purple). The superposition of 30 lowest energy conformers of the amide **5** (**F**) and amine **24** (**G**)

predictions of gastrointestinal absorption from SwissADME and human intestinal absorption from pkCSM corroborate the calculated druglikeness of compounds **16**, **19**, **21**–**24**.

For comparison, the main difference between compound **24** (most active) and compounds **16**, **19**, and **21**–**23** is the lipophilia (at least 0.7 logarithmic unity higher) indicating a better ability to permeate membranes. Furthermore, the nitrogen atom attached to furan of compound **24** is slightly more basic than other compounds. But, clearly, the ClogP difference could explain the activity profile of compounds with similar structure.

In addition, there is a major difference between charge distributions at molecular surface of amide (Fig. 4A) and amino derivatives (Fig. 4B–D). This result corroborates the

importance of ionization for biological activity because the presence of carbonyl of amide derivatives like compound **5** provides a negative electron density at the same regions which is positively charged at amino derivatives. Furthermore, we also compared the flexibility of and amide (**5**) and amino derivative (**24**) by superimposing the rigid part of molecules composed by benzene and furan rings (Fig. 4F, G). Then, the amide derivatives have a less flexible side chain (Fig. 4F) than amino derivatives (Fig. 4G) indicating that amino derivatives have more ability to acquire a suitable conformation for interaction with the molecular target binding site. Last but not least, the amides **5**–**7** have a bromide as substituent at benzene rings while amino derivatives possess a chloride and, therefore, the higher volume of bromide may cause a steric hindrance at a potential binding site, disfavoring the biological activities of these amides.

Conclusion

In the present work, 18 arylfuran derivatives were synthesized and evaluated for their antibacterial activity. The arylfuran derivative **24** was found to possess considerable activity against both Gram-negative and Gram-positive bacteria, indicating a broad spectrum of action of this novel compound. It is worth mentioning that compound **24** showed potency similar (MIC = 49 μM) to that of CHL (MIC = 50 μM), antibiotic used in the clinical practice, against *S. aureus* (ATCC® 29213™).

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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