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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antibacterial activity of new lactone 1,4-dihydroquinoline derivatives

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Abstract

In this work, a series of lactone 1,4-dihydroquinoline derivatives **4** were efficiently synthesized and characterized by ^{1}H and ^{13}C NMR. The synthesized compounds were evaluated for their in vitro antibacterial activity against the bacterial strains *Porphyromonas gingivalis*, *Prevotella nigrescens*, *Streptococcus mitis*, and *Streptococcus sanguinis* and against *Mycobacterium tuberculosis, Mycobacterium avium* and *Mycobacterium kansasii*. The results revealed that the evaluated compounds were more active against Gram negative bacteria. Compounds **4ba**, **4bb**, **4bg**, **4bi**, **4bn**, **4ch**, and **4ci** displayed moderate antibacterial activity against *P. gingivalis*. **4bi** was the most active compound against the three strains of *Mycobacterium*. Based on structure–activity relationship studies, we observed that the presence of a nitro group on the benzylic ring and a methylenedioxy group on the dihydroquinoline ring enhanced the antibacterial activity of the derivatives.

Keywords Azo-heterocyclic compounds · quinoline derivatives · antibacterial activity

Introduction

The combination of pharmacophoric moieties of different bioactive substances can produce a new hybrid molecule with improved biological efficacy and affinity, a modified selectivity profile, and different and/or dual modes of action, and may reduce undesired side effects (Viegas-Junior et al. 2007). The combination of lactone and 1,4-dihydroquinoline rings provides 7-azo synthetic analogs of aryltetralin lignan lactones. Aryltetralin lignan lactones are among the various classes of naturally occurring bioactive molecules that have aroused interest in the area of medicinal chemistry due to their structural diversity and biological properties (Teponno et al. 2016). Several studies have shown that the biological properties of these lignans are closely related to the nature of ring A, their stereochemistry, and substituents on the aromatic rings (Antunez-Mojica et al. 2016). However, little is known about how modifications in the chemical skeleton of ring B can affect these properties. The replacement of C7 with nitrogen can greatly alter these properties, creating new analogs with biological properties that have not yet been described for this class of compounds (Fig. 1). These derivatives present two important pharmacophoric groups, the lactone and dihydroquinoline rings. The lactone ring is present in many compounds with biological properties (Qiu et al. 2016) including antimicrobials (Grabarczyk et al. 2013; Mazur et al. 2016), along with quinoline and dihydroquinoline rings (Meléndez-Gómez and Kouznetsov 2013; Kharb and Kaur 2013; Desai et al. 2017).

New quinoline derivatives have been synthesized and investigated for several biological properties. The position and type of the substituents on the quinoline and dihydroquinoline rings are responsible for the variety of pharmacological activities that these compounds present, including antibacterial (El-Essawy and El-Sayed 2013; Desai et al. 2017), antiplasmodial (Vandekerckhove et al. 2015), antituberculosis (Keri and Patil 2014), antimalarial (Vandekerckhove and D'hooghe 2015) and anticancer

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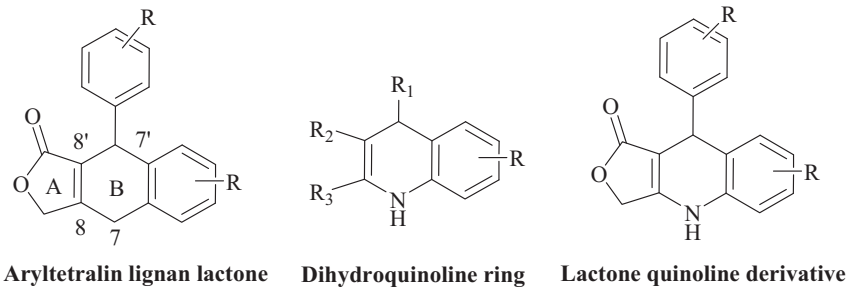
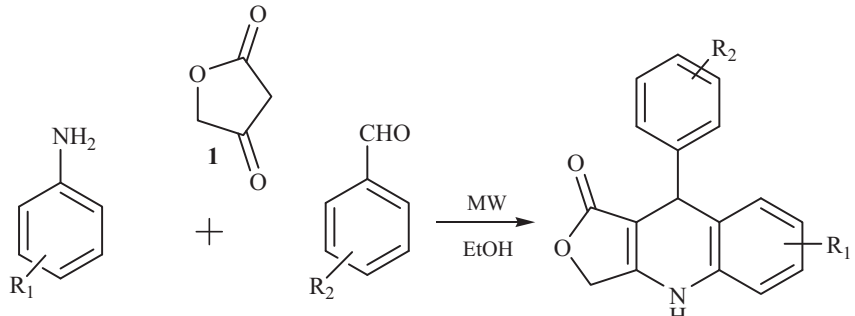


Fig. 1 General structure of dihydroquinoline ring, aryltetralin lignan lactone and lactone quinoline derivative



Scheme 1 Reaction conditions for obtaining derivatives **4**

R_1= 3,4,5-OCH_3 **2a**
3,4 OCH_2O **2b**
3,4- OCH_3 **2c**

R_2= 3,4-(OCH_2O) **3a,** 3,4-(OCH_3) **3b**
3,4,5-(OCH_3) **3c**, 4-Cl **3d**
3-(OCH_3)-4OBn **3e**, 4-F **3f**
4-SCH_3 **3g**; 4-CF_3 **3h**
3,4-(OCH_3)$_2$-6-NO_2 **3i**
3-(OCH_3)-4-(OH) **3j**, 3-(OH) **3k**
3-(OCH_3) **2l,** 3,4-(OH) **3m**
3,4-OCH_2O-6-NO_2 **3n**

(Spanò et al. 2015). However, there are no reports in the literature on the antimicrobial activity of lactone dihydroquinoline derivatives; therefore we decided to synthesize these compounds and evaluate their antibacterial activities.

Result and Discussion

Chemistry

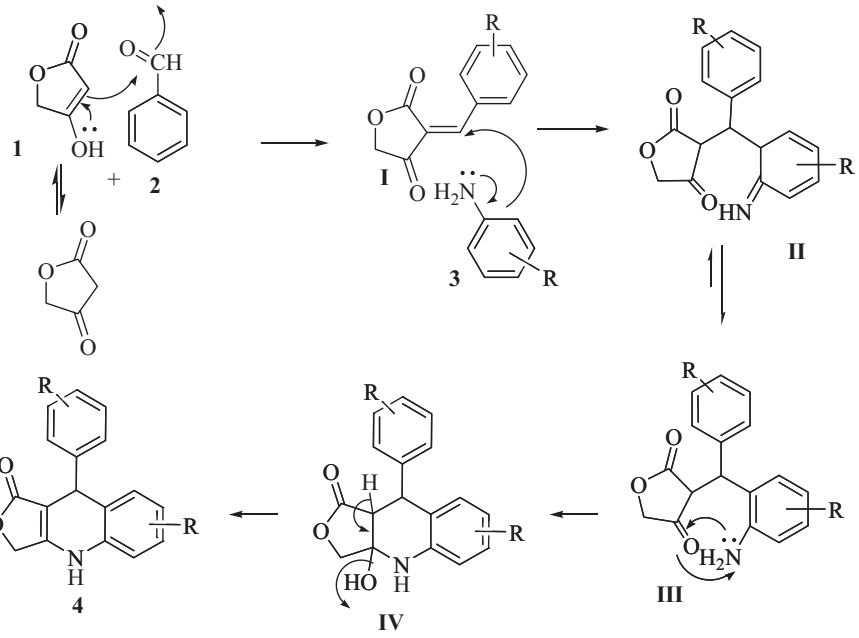
The lactone dihydroquinoline derivatives **4** presented in this paper were prepared via a microwave-assisted reaction between tetronic acid **1**, aniline **2** and aromatic aldehyde **3** in EtOH (Scheme 1). The use of a microwave furnished the derivatives **4** in high yield and with a shorter reaction time than the traditional methodology (Frackenpohl et al. 2009). The reaction was realized with anilines **2a-c** and aromatic aldehydes **3b-n** with electron-withdrawing, as well as electron-donating substituents in different positions on the aromatic ring (Scheme 1).

Substitution of aldehydes with a nitro group (*ortho* position) furnished the derivatives **4** in lower yields, due to the steric hindrance that the nitro group causes on the carbonyl. More pronounced effects on the reaction were observed depending on the substituent present in the aniline. Anilines with electron-withdrawing substituents or without electron-donating substituents in the *meta* position did not react in these conditions. According to the reactional mechanism proposed herein (Scheme 2), the reaction might proceed via sequential condensation, addition, cyclization, and elimination. First, condensation takes place between the tetronic acid **1** with aromatic aldehydes **3** to afford the intermediate **I**. The Michael addition of aniline **2** in **I** then furnishes the intermediate product **II**, which isomerizes to **III**.

In the intermediate **III**, the nucleophilic addition of the nitrogen in the carbonyl leads to the formation of the intermediate **IV**, which then undergoes dehydration to generate the target derivative **4**. In this proposed mechanism, the donating group in the *meta* position in the aniline activates the aromatic ring (*ortho* position at NH_2 group) to attack at intermediate **I**. The proposed mechanism explains the low reactivity of anilines with electron-withdrawing, as well as weakly electron-donating substituents in the *para* or *ortho* positions.

The combination of several anilines and aldehydes furnished 39 lactone dihydroquinoline derivatives, whose structures were confirmed by ^{1}H and ^{13}C NMR spectra. The

Scheme 2 Mechanistic proposal for the formation of **4**



spectral analyses were consistent with the structures proposed and are listed in the supplementary material.

Antibacterial activity

The 39 compounds synthesized were evaluated in vitro for antibacterial activity against Gram negative bacteria, Gram positive bacteria and mycobacterium strains by the microplate microdilution method using resazurin as an indicator of microbial activity. The minimum inhibitory concentration (MIC) values of antibacterial activity are shown in Table 1. The evaluated compounds were most active against Gram negative bacteria. *P. gingivalis* was more sensitive to the compounds evaluated than *P. nigrescence*. The substituents of aniline and aldehyde, such as halogen, methoxy, trifluormethyl, hydroxy, nitro, and methylthio were varied to explore the structure–activity relationships between the lactone dihydroquinoline derivatives. The results of the evaluation indicated that in the dihydroquinoline ring methylenedioxy and dimethoxy substituents were more favorable for antibacterial activity than trimethoxy substituents. In the benzylic ring, methylenedioxy, dimethoxy, methylthio, trifluormethyl, and nitro substituents favored antibacterial activity. Compounds **4ba**, **4bb**, **4bg**, **4bi**, **4bn**, **4ch**, and **4ci** showed good antibacterial activity against *P. gingivalis*. Only compounds **4ab**, **4ae** were active against *P. nigrescence*. None of the compounds evaluated were active against Gram positive bacteria. Compound **4bi** was the most active against the three strains of *Mycobacterium*. Overall, the most active compounds were **4bi** and **4bn**, which possess nitro and electron-donating groups attached to the benzylic ring and a methylenedioxy group attached to the dihydroquinoline ring. Nitro-organic compounds are reduced by microbial systems and reduced derivatives were shown to be reactive and to bind to DNA and to proteins (Shahid et al. 2016). However, the antibacterial effect of compounds **4bi** and **4bn** depend not only on the nitro group, but also on their overall structure and the type of bacteria evaluated.

Conclusion

Thirty-nine lactone dihydroquinoline derivatives were synthesized and their antibacterial activities against anaerobic bacteria, aerobic bacteria, and mycobacterium were assayed using the microplate microdilution method. The presence of halogen or hydroxyl groups did not enhance their antibacterial activity. The most active compounds were **4bi** and **4bn**, which possess nitro and electron-donating groups attached to the benzylic ring and a methylenedioxy group attached to the dihydroquinoline ring. Therefore, for this class of compounds the presence of these substituents was essential for antibacterial activity against *P. gingivalis* and *Mycobacterium*.

Materials and Methods

Chemistry

All chemicals and solvents were purchased from commercial sources and were used as received without further purification. Microwave irradiation was carried out with a

Table 1 In vitro antibacterial activity (MIC μg/mL)

Compounds	G-negative		G-positive		*Mycobacterium*		
	P. gingivalis	*P. nigrescens*	*S. mitis*	*S. sanguinis*	*Tuberculosis*	*Avium*	*kansasii*
4aa	>200	>200	>200	>200	>2000	>2000	>2000
4ab	200	100	>200	>200	>2000	>2000	>2000
4ac	>200	200	>200	>200	500	>2000	>2000
4ad	>200	>200	>200	>200	>2000	>2000	>2000
4ae	>200	100	200	>200	>2000	>2000	500
4af	200	>200	>200	>200	>2000	>2000	>2000
4ag	>200	>200	>200	>200	>2000	>2000	>2000
4ah	>200	>200	>200	>200	>2000	>2000	>2000
4ai	>200	>200	>200	>200	>2000	>2000	>2000
4aj	>200	>200	>200	>200	>2000	>2000	>2000
4am	>200	>200	>200	>200	>2000	>2000	>2000
4an	>200	>200	>200	>200	>2000	>2000	>2000
4ba	100	>200	200	200	2000	2000	1000
4bb	50	>200	>200	>200	>2000	>2000	>2000
4bc	200	>200	>200	>200	>2000	>2000	>2000
4bd	200	>200	>200	>200	>2000	>2000	>2000
4be	>200	>200	>200	>200	>2000	>2000	>2000
4bf	>200	>200	200	>200	>2000	>2000	>2000
4bg	100	>200	>200	>200	>2000	>2000	>2000
4bh	>200	>200	>200	>200	>2000	>2000	>2000
4bi	25	>200	>200	200	250	250	125
4bj	>200	>200	>200	>200	>2000	>2000	>2000
4bn	12,5	>200	>200	>200	>2000	>2000	>2000
4ca	>200	>200	>200	>200	>2000	>2000	>2000
4cb	>200	>200	>200	>200	>2000	>2000	>2000
4cc	>200	>200	>200	>200	>2000	>2000	>2000
4cd	>200	>200	>200	>200	>2000	>2000	>2000
4ce	200	>200	>200	>200	>2000	>2000	>2000
4cf	>200	>200	>200	>200	>2000	>2000	500
4cg	>200	>200	>200	>200	>2000	>2000	>2000
4ch	25	>200	>200	>200	>2000	>2000	>2000
4ci	100	>200	>200	>200	>2000	>2000	>2000
4cn	>200	>200	>200	>200	>2000	>2000	>2000
4cm	>200	>200	>200	>200	>2000	>2000	>2000
Isoniazid	—	—	—	—	0.06	>1	1
Chlorhexidine	0.922	0.922	3.68	3.68	—	—	—

—: not tested

Reactor Discover Reflux (CEM Corporation, 300 W). Reactions were monitored using thin-layer chromatography (TLC) plates coated with 0.2 mm silica gel 60 F254 (Merck, Germany). TLC plates were visualized using ultraviolet (UV) irradiation (254 nm). The products were washed with hexane:ethyl acetate (8:2) for purification. Both ^{1}H and ^{13}C NMR spectra were determined on a Bruker ARX 400 spectrometer in DMSO-d_6. Proton chemical shifts in DMSO-d_6 are related to the middle of the residual multiplet ($\delta = 2.50$). Carbon chemical shifts were reported in parts per million (δ) relative to DMSO- d_6 (39.5 p.p.m.), and J (coupling constant) values were reported in hertz. The splitting patterns of protons are described as s (singlet), d (doublet), dd (doublet of doublets), t (triplet) and m (multiplet). All melting points were determined on Melting Point B-540 Buchi apparatus and are uncorrected. The high-resolution mass spectral data for new compounds were obtained using Bruker Daltonics—micrOTOF-Q, fitted with an ESI operating in the positive ion mode.

General experimental procedure and characterization of synthesized derivatives 4

The mixture of tetronic acid **1** (1.0 mmol), aldehyde **2** (1.0 mmol), and aniline **3** (1.0 mmol) in 2 mL of EtOH was irradiated at a power of 200 W in an open vessel in a microwave reactor (reflux temperature of the solvent). The reaction was monitored using TLC every 3 min and after 15 min the reaction was cooled, the solvent was removed under vacuum and the solid obtained was washed with hexane-acetate (8:2).

9-(benzo[d][1,3]dioxol-5-yl)-6,7,8-trimethoxy-4,9-dihydrofuro[3,4-b]quinolin-1(3H)-one (4aa)

Yellow solid, yield 92%, mp 271–273 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.93 (s, 1H, NH), 6.77 (d, 1H, $J = 7.9$ Hz), 6.63 (d, 1H, $J = 1.7$ Hz), 6.54 (dd, 1H, $J = 7.9$ and 1.7 Hz), 6.38 (s, 1H), 5.94 (d, 1H, $J = 0.9$ Hz), 5.93 (d, 1H,, $J = 0.9$ Hz), 4.90 (d, 1H, $J = 15.7$ Hz), 4.88 (s, 1H), 4.79 (d, 1H, $J = 15.7$ Hz), 3.79 (s, 3H), 3.64 (s, 3H), 3.42 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.94, 157.59, 152.77, 151.66, 146.84, 145.27, 141.11, 137.47, 132.99, 120.37, 110.05, 108.00, 107.69, 95.92, 95.48, 64.84, 60.31, 60.013, 55.64, 34.92.

9-(3,4-dimethoxyphenyl)-6,7,8-trimethoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(*3H*)-one (4ab)

White solid, yield 91%, mp 258–260 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.89 (s, 1H, NH), 6.80 (d, 1H, $J = 8.2$ Hz), 6.80 (d, 1H, $J = 1.8$ Hz), 6.51 (dd, 1H, $J = 1.8$ and 8.2 Hz), 6.38 (s, 1H), 4.90 (s, 1H), 4.88 (d, 1H, $J = 15.7$ Hz), 4.78 (d, 1H, $J = 15.7$ Hz), 3.78 (s, 3H), 3.68 (s, 3H), 3.67 (s, 3H), 3.63 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.12, 157.58, 152.70, 151.67, 148.10, 147.08, 139.68, 137.52, 133.02, 119.42, 111.76, 111.66, 10.13, 99.11, 95.53, 64.87, 64.83, 60.32, 59.98, 55.69, 55.46, 34.70.

6,7,8-trimethoxy-9-(3,4,5-trimethoxyphenyl)-4,9-dihydrofuro[3,4-b]quinolin-1(3H)-one (4ac)

Yellow solid, yield 89%, mp 229–231 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.91 (s, 1H, NH), 6.40 (s, 3H), 4.97 (s, 1H), 4.92 (d, 1H, $J = 15.6$ Hz), 4.79 (d, 1H, $J = 15.6$ Hz), 3.80 (s, 3H), 3.67 (s, 3H), 3.65 (s, 3H), 3.60 (s, 3H), 3.47 (s, 3H), 3.46 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.06, 157.87, 152.78, 152.40, 151.73, 142.48, 136.45, 135.88, 133.15, 109.53, 104.85, 95.72, 95.50, 64.83, 60.32, 60.02, 59.91, 55.74, 55.66, 35.33.

9-(4-chlorophenyl)-6,7,8-trimethoxy-4,9-dihydrofuro[3,4-b]quinolin-1(3*H*)-one (4ad)

Yellow solid, yield 81%, mp > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.99 (s, 1H, NH), 7.31 (d, 2H, $J = 8.4$ Hz), 7.13 (d, 2H, $J = 8.4$ Hz), 6.39 (s, 1H), 4.96 (s, 1H), 4.90 (d, 1H, $J = 15.7$ Hz), 4.81 (d, 1H, $J = 15.7$ Hz), 3.79 (s, 3H), 3.63 (s, 3H), 3.38 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.86, 157.79, 152.97, 151.66, 145.76, 137.46, 132.97, 130.46, 129.34, 127.91, 109.47, 95.51, 95.37, 64.92, 60.30, 59.94, 55.63, 34.95. HRMS (ESI$^+$): m/z $[M + Na]^+$ calculated for $C_{20}H_{18}ClNO_5Na$: 410.0764; found: 410.0755.

9-(4-(benzyloxy)-3-methoxyphenyl)-6,7,8-trimethoxy-4,9-dihydrofuro[3,4-b]quinolin-1(3*H*)-one (4ae)

White solid, yield 85%, mp > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.89 (s, 1H, NH), 7.43–7.28 (m, 5H), 6.88 (d, 1H, $J = 8.3$ Hz), 6.83 (d, 1H, $J = 2.0$ Hz), 6.49 (dd, 1H, $J = 8.3$ and 2.0 Hz), 6.38 (s, 1H), 5.00 (s, 1H), 4.89 (d, 1H, $J = 16.0$ Hz), 4.79 (s, 1H, $J = 16.0$ Hz), 3.79 (s, 3H), 3.71 (s, 3H, 3.64 (s, 3H), 3.38 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.03, 157.55, 152.70, 151.69, 148.53, 146.01, 140.18, 137.48, 137.23, 133.06, 128.31, 127.70, 119.38, 113.56, 112.01, 110.07, 96.03, 95.47, 69.97, 64.81, 60.30, 59.94, 55.65, 55.53, 34.78. HRMS (ESI$^+$): m/z $[M + H]^+$ calculated for $C_{28}H_{28}NO_7$: 490.1857; found: 490.1849.

9-(4-fluorophenyl)-6,7,8-trimethoxy-4,9-dihydrofuro[3,4-b]quinolin-1(3*H*)-one (4af)

White solid, yield 82%, mp > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.96 (s, 1H, NH), 7.17–7.11 (m, 2H), 7.10–7.03 (m, 2H), 6.39 (s, 1H), 4.96 (s, 1H), 4.89 (d, 1H, $J = 15.7$ Hz), 4.81 (d, 1H, $J = 15.7$ Hz), 3.79 (s, 3H), 3.63 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.93, 161.69, 159.28, 157.70, 152.89, 151.66, 143.11, 143.08, 137.49, 132.95, 129.26, 129.18, 114.71, 114.50, 109.82, 95.67, 95.51, 64.89, 60.29, 59.91, 55.65, 34.71. HRMS (ESI$^+$): m/z $[M + H]^+$ calculated for $C_{20}H_{19}FNO_5$: 372.1241; found: 372.1244.

6,7,8-trimethoxy-9-(4-(methylthio)phenyl)-4,9-dihydrofuro[3,4-b]quinolin-1(3*H*)-one (4ag)

White solid, yield 81%, mp 221–223 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.94 (s, 1H, NH), 7.14 (d, 2H, $J = 8.4$ Hz), 7.06 (d, 2H, $J = 8.4$ Hz), 6.39 (s, 1H), 4.91 (s, 1H), 4.89 (d, 1H, $J = 15.8$ Hz), 4.80 (d, 1H, $J = 15.8$ Hz), 3.79 (s, 3H), 3.63 (s, 3H), 3.39 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.91, 157.64,

152.81, 151.67, 143.76, 137.46, 135.24, 133.02, 128.09, 125.75, 109.88, 95.75, 95.49, 64.86, 60.30, 59.96, 55.64, 34.87, 14.81. HRMS (ESI^+): m/z $[M + H]^+$ calculated for $C_{21}H_{22}SNO_5$: 400.1211; found: 400.1182.

6,7,8-trimethoxy-9-(4-(trifluoromethyl)phenyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(*3H*)-one (4ah)

White solid, yield 84%, mp > 300 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 10.05 (s, 1H, NH), 7.63 (d, 1H, J = 8.2 Hz), 7.34 (d, 1H, J = 8.2 Hz), 6.41 (s, 1H), 5.07 (s, 1H), 4.91 (d, 1H, J = 15.8 Hz), 4.83 (d, 1H, J = 15.8 Hz), 3.80 (s, 3H), 3.62 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.82, 157.99, 153.12, 151.65, 151.13, 137.46, 133.01, 128.31, 124.96, 124.93, 109.07, 95.57, 95.02, 64.98, 60.31, 59.89, 55.67, 35.54. HRMS (ESI^+): m/z $[M + H]^+$ calculated for $C_{21}H_{19}F_3NO_5$: 422.1209; found: 422.1208.

9-(4,5-dimethoxy-2-nitrophenyl)-6,7,8-trimethoxy-4,9-dihydrofuro[3,4-b]quinolin-1(3*H*)-one (4ai)

Yellow solid, yield 76%, mp 284–286 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.99 (s, 1H, NH), 7.45 (s, 1H), 6.57 (s, 1H), 6.37 (s, 1H), 6.00 (s, 1H), 4.92 (d, 1H, J = 15.8 Hz), 4.83 (d, 1H, J = 15.8 Hz), 3.81 (s, 3H), 3.78 (s, 3H), 3.65 (s, 3H), 3.60 (s, 3H), 3.40 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.50, 158.33, 153.13, 152.42, 151.63, 146.65, 140.13, 137.32, 135.28, 132.87, 112.495, 109.25, 107.24, 95.63, 94.65, 64.96, 60.34, 59.91, 55.92, 55.72, 55.68, 30.00. HRMS (ESI^+): m/z $[M+H–H_2O]^+$ calculated for $C_{22}H_{21}N_2O_8$: 441.1290; found: 441,1283

9-(4-hydroxy-3-methoxyphenyl)-6,7,8-trimethoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(3*H*)-one (4aj)

White solid, yield 80%, mp 216–218 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.86 (s, 1H, NH), 8.72 (brs, 1H, OH), 6.77 (d, 1H, J = 1.9 Hz), 6.62 (d, 1H, J = 8.1 Hz), 6.41 (dd, 1H, J = 8.1 and 1.9 Hz), 6.37 (s, 1H), 4.89 (d, 1H, J = 15.7 Hz), 4.87 (s, 1H), 4.78 (d, 1H, J = 15.7 Hz), 3.79 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.06, 157.44, 152.61, 151.70, 146.90, 144.71, 138.25, 137.50, 133.05, 119.75, 115.09, 112.12, 110.39, 96.29, 95.48, 64.78, .28, 59.95, 55.66, 55.63, 34.67. HRMS (ESI^+): m/z $[M + Na]^+$ calculated for $C_{21}H_{21}NO_7Na$: 422.1208; found: 422.1212.

9-(3-hydroxyphenyl)-6,7,8-trimethoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(*3H*)-one (4ak)

White solid, yield 81%, mp 263–265 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.90 (s, 1H, NH), 9.19 (s, 1H, OH), 7.01 (t, 1H, J = 7.6 Hz), 6.56 (d, 1H, J = 7.6 Hz), 6.54–6.48 (m, 2H), 6.38 (s, 1H), 4.88 (d, 1H, J = 15.7 Hz), 4.86 (s, 1H), 4.79 (d, 1H, J = 15.7 Hz), 3.79 (s, 3H), 3.64 (s, 3H), 3.37 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.88, 157.58, 156.98, 152.72, 151.70, 148.25, 137.53, 133.13, 128.71, 118.31, 114.56, 112.95, 110.14, 96.00, 95.52, 64.79, 60.30, 59.88, 55.68, 35.22. HRMS (ESI^+): m/z $[M + H]^+$ calculated for $C_{20}H_{20}NO_6$: 370.1284; found: 370.1286.

6,7,8-trimethoxy-9-(3-methoxyphenyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1(*3H*)-one (4al)

White solid, yield 92.0%, mp 231–233 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.93 (s, 1H, NH), 7.15 (t, 1H, J = 8.2 Hz), 6.73–6.69 (m, 1H), 6.67 (brd, 1H, J = 1.4 Hz), 6.68–6.65 (m, 2H), 6.39 (s, 1H), 4.93 (s, 1H), 4.89 (d, 1H, J = 15.8 Hz), 4.79 (d, 1H, J = 15.8 Hz), 3.79 (s, 3H), 3.69 (s, 3H), 3.36 (s, 3H), 3.38 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.89, 158.92, 157.73, 152.80, 151.67, 148.35, 137.50, 133.12, 128.95, 119.82, 113.85, 110.67, 109.84, 95.81, 95.54, 64.83, 60.31, 59.91, 55.68, 54.83, 35.26. HRMS (ESI^+): m/z $[M + H]^+$ calculated for $C_{21}H_{22}NO_6$: 384.1440; found: 384.1441.

9-(3,4-dihydroxyphenyl)-6,7,8-trimethoxy-4,9-dihydrofuro[3,4-*b*]quinolin-1(*3H*)-one (4am)

White solid, yield 83%, mp 272–274 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.84 (s, 1H, NH), 8.70 (s, 1H, OH), 8.59 (s, 1H, OH), 6.57 (d, 1H, J = 8.0 Hz), 6.50 (d, 1H, J = 2.1 Hz), 6.38 (dd, 1H, J = 8,0 and 2.1 Hz), 6.36 (s, 1H), 4.86 (d, 1H, J = 15.8 Hz), 4.77 (d, 1H, J = 15.8 Hz), 4.77 (s, 1H), 3.78 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.97, 157.24, 152.53, 151.72, 144.58, 143.38, 138.27, 137.54, 133.04, 118.25, 115.11, 114.91, 110.72, 96.48, 95.47, 64.72, 60.28, 59.94, 55.67, 34.48. HRMS (ESI^+): m/z $[M + H]^+$ calculated for $C_{20}H_{20}NO_7$: 386.1233; found: 386.1221.

6,7,8-trimethoxy-9-(6-nitrobenzo[d][1,3]dioxol-5-yl)-4,9-dihydrofuro[3,4-b]quinolin-1(*3H*)-one (4an)

Orange solid, yield 70%, mp 265–266 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 10.03 (s, 1H, NH), 7.48 (s, 1H), 6.57 (s, 1H), 6.37 (s, 1H), 6.12 (d, 2H, J = 4.7 Hz), 5.94 (s, 1H), 4.93 (d, 1H, J = 15.7), 4.83 (d, 1H, J = 15.7), 3.79 (s, 3H), 3.61 (s, 3H), 3.44 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.35, 158.42, 153.24, 151.58, 151.21, 145.75, 141.38, 137.74, 137.28, 132.76, 109.18, 109.18, 104.17, 103.00, 95.71, 94.48, 65.00, 60.35, 59.92, 30.11. HRMS (ESI^+): m/z $[M+H-H_2O]^+$ calculated for $C_{21}H_{17}N_2O_8$: 425.0977: found: 425.0953.

9-(benzo[d][1,3]dioxol-5-yl)-6,9-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-b]quinolin-8(5*H*)-one (4ba)

White solid, yield 86%, mp 288–289 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.87 (s, 1H, NH), 6.78 (d, 1H, $J = 8.0$ Hz), 6.73 (s, 1H), 6.65 (d, 1H, $J = 8.0$ Hz), 5.95 (brs, 1H), 5.94 (brs, 1H), 5.93 (brs, 1H), 5.89 (brs, 1H), 4.94 (d, 1H, $J = 15.76$ Hz), 4.83 (d, 1H, $J = 15.7$ Hz), 4.83 (s, 1H) ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.56, 158.70, 147.82, 147.00, 146.17, 143.80, 141.75, 130.94, 120.92, 117.27, 110.03, 108.51, 108.40, 101.68, 101.29, 97.79, 94.94, 65.43, 40.09.

9-(3,4-dimethoxyphenyl)-6,9-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-b]quinolin-8(5H)-one (4bb)

White solid, yield 86%, mp 289–291 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.84 (s, 1H, NH), 6.88 (s, 1H), 6.82 (d, 1H, $J = 8.5$ Hz), 6.62 (brd, 1H), 6.62 (s, 1H), 6.52 (s, 1H), 5.91 (brs, 1H), 5.90 (brs, 1H), 4.96 (d, 1H, $J = 15.7$ Hz), 4.85 (s, 1H), 4,84 (d, 1H, $J = 15.7$ Hz), 3.71 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.11, 158.12, 148.44, 147.25, 146.34, 143.16, 139,78, 130.30, 119.41, 116.88, 111.86, 111.47, 109,58, 101.10, 97.19, 94.41, 64.85, 55.47, 55.44, 39.10.

9-(3,4,5-triimethoxy)-6,9-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-b]quinolin-8(5*H*)-one (4bc)

White solid, yield 90%, mp 271–274 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.86 (s, 1H, NH), 6.67 (s, 1H), 6.53 (s, 1H), 6.48 (s, 2H), 5.95 (d, 1H, $J = 0.7$ Hz), 5.90 (d, 1H, $J = 0.7$ Hz), 4.98 (s, 1H, $J = 15.7$ Hz), 4.85 (s, 1H), 4.84 (d, 1H, $J = 15.7$ Hz), 3.70 (s, 6H), 3.60 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.18, 158.41, 152.74, 146.44, 143.22, 142.68, 136.04, 130.25, 116.50, 109.49, 104.82, 101.24, 101.14, 97.28, 94.14, 64.92, 59.86, 55.82, 39.76.

9-(4-chlorophenyl)-6,9-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-*b*]quinolin-8(*5H*)-one (4bd)

White solid, yield 80%, mp 290–292 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.93 (s, 1H, NH), 7.33 (d, 2H, $J = 8.4$ Hz), 7.22 (d, 2H, $J = 8.4$ Hz), 6.58 (s, 1H), 6.54 (s, 1H), 5.97 (brs, 1H), 5.91 (brs, 1H), 4.96 (s, 1H), 4.96 (d, 1H, $J = 15.7$ Hz), 4.86 (d, 1H, $J = 15.7$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.98, 158.37, 146.61, 145.72, 143.36, 130.90, 130.48, 129.34, 128.24, 116.05, 109.53, 101.22, 97.35, 93.92, 64.97, 38.95.

9-(4-(benzyloxy)-3-methoxyphenyl)- 6,9-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-*b*]quinolin-8(*5H*)-one (4be)

White solid, yield 84%, mp > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.85 (s, 1H, NH), 7.45–7.29 (m, 5H), 6.92 (d, 1H, $J = 1.9$ Hz), 6.90 (d, 1H, $J = 8.4$ Hz), 6.63 (s, 1H), 6.59 (dd, 1H, $J = 8.4$ and 1.9 Hz), 6.52 (s, 1H), 5.96 (brs, 1H), 5.90 (brs, 1H), 5.01 (s, 2H), 4.96 (d, 1H, $J = 15.7$ Hz), 4.85 (d, 1H, $J = 15.7$ Hz), 4.86 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.12, 158.16, 148.76, 146.36, 146,29, 143.18, 140.17, 137.26, 130.31, 128.36, 127.75, 127.66, 119.36, 116.82, 113.52, 111.73, 109.58, 101.11, 97.20, 94.38, 69.908, 64.86, 55.53, 39.11. HRMS (ESI$^+$): m/z $[M + H]^+$ calculated for $C_{26}H_{22}NO_6$: 444.1440; found: 444.1444.

9-(4-fluorphenyl)-6,9-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-*b*]quinolin-8(*5H*)-one (4bf)

White solid, yield 81%, mp > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.90 (s, 1H, NH), 7.24–7.19 (m, 2H), 7.11–7.04 (m, 2H), 6.56 (s, 1H), 6.53 (s, 1H), 5.95 (brs, 1H), 5.90 (brs, 1H), 4.95 (s, 1H), 4.94 (d, 1H, $J = 15.6$ Hz), 4.85 (d, 1H, $J = 15.6$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.99, 158.24, 146.55, 143.33, 143.08, 143.05, 130.49, 129.29, 129.21, 116.35, 115.04, 114.83, 109.54, 101.19, 97.31, 94.23, 64.93, 38.81. HRMS (ESI$^+$): m/z $[M + H]^+$ calculated for $C_{18}H_{13}FNO_4$: 326.0824; found: 326.0828.

9-(4-(methylthio)phenyl)-6,9-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-b]quinolin-8(5*H*)-one (4bg)

White solid, yield 81%, mp 277–280 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.89 (s, 1H, NH), 7.18–7.12 (m, 4H), 6.56 (s, 1H), 6.53 (s, 1H), 5.96 (brs, 1H), 5.90 (brs, 1H), 4.94 (d, 1H, $J = 15.6$ Hz), 4.89 (s, 1H), 4.85 (d, 1H, $J = 15.6$ Hz), 2.43 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.02, 158.22, 146.47, 143.75, 143.27, 135.71, 130.42, 128.08, 126.08, 116.48, 109.56, 101.16, 97.27, 94.18, 64.91. HRMS (ESI$^+$): m/z $[M + K + H_2O - 2H]^+$ calculated for $C_{19}H_{16}NO_5S$: 408.0307; found: 408.0324.

9-(4-(trifluoromethyl)phenyl)-6,9-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-b]quinolin-8(5*H*)-one (4bh)

White solid, yield 88%, mp > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.98 (s, 1H, NH), 7.64 (d, 2H, $J = 8.2$ Hz), 7.43 (d, 2H, $J = 8.2$ Hz), 6.58 (s, 1H), 6.57 (s, 1H), 5.97 (brs, 1H), 5.91 (brs, 1H), 5.08 (s, 1H), 4.96 (d, 1H, $J = 15.7$ Hz), 4.88 (d, 1H, $J = 15.7$ Hz). ^{13}C NMR (100

MHz, DMSO-d_6): δ (p.p.m.) 171.95, 158.54, 146.75, 143.45, 130.57, 128.35, 125.29, 125.26, 115.53, 109.54, 101.27, 97.45, 93.70, 65.05, 39.47. HRMS (ESI^+): m/z $[M + Na]^+$ calculated for $C_{19}H_{13}F_3NO_4Na$: 398.0611; found: 398.0609.

9-(4,5-dimethoxy-2-nitrophenyl)-6,9-dihydro-[1,3]dioxolo [4,5-g]furo[3,4-b]quinolin-8(5*H*)-one (4bi)

Yellow solid, yield 69%, mp 243–244 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.96 (s, 1H, NH), 7.43 (s, 1H), 6.71 (s, 1H), 6.57 (s, 1H), 5.97 (brs, 1H), 5.94 (brs, 1H), 5.69 (s, 1H), 4.93 (d, 1H, $J = 15.6$ Hz), 4,84 (d, 1H, $J = 15.6$ Hz), 3.83 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.65, 158.39, 152.68, 147.14, 146.87, 143.56, 140.69, 134.45, 130.86, 115.11, 112.95, 108.86, 107,10, 101.34, 97.63, 93.76, 64.99, 56.01, 55.89, 34.32. HRMS (ESI^+): m/z $[M + H - H_2O]^+$ calculated for $C_{20}H_{15}N_2O_7$: 395.0872; found: 395.0869.

9-(4-hydroxy-3-methoxyphenyl)-6,9-dihydro-[1,3]dioxolo [4,5-g]furo[3,4-b]quinolin-8(5*H*)-one (4bj)

White solid, yield 81%, mp 279–281 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.80 (s, 1H, NH), 8.76 (s, 1H, OH), 6.84 (d, 1H, $J = 1.8$ Hz), 6.64 (d, 1H, $J = 8.0$ Hz), 6.61 (s, 1H), 6.51 (s, 1H), 6.49 (dd, 1H, $J = 1.8$ and 8.0 Hz), 5.95 (brs, 1H), 5.90 (brs, 1H), 4.94 (d, 1H, $J = 15.6$ Hz), 4.83 (d, 1H, $J = 15.6$ Hz), 4.79 (s, 1H), 3.3 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.12, 158.02, 147.24, 146.28, 144.97, 143.14, 38.31, 130.30, 119.72, 117.14, 115.33, 111.89, 109.57, 101.06, 97.15, 94.61, 64.81, 55.63, 39.12. HRMS (ESI^+): m/z $[M + Na]^+$ calculated for $C_{19}H_{15}NO_6Na$: 376.0791; found 376.0792

9-(6-nitrobenzo[d][1,3]dioxol-5-yl)-6,9-dihydro-[1,3]dioxolo [4,5-g]furo[3,4-b]quinolin-8(5*H*)-one (4bn)

Yellow solid, yield 71%, mp 225–227 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 10.00 (s, 1H, NH), 7.47 (s, 1H), 6.71 (s, 1H), 6.58 (s, 2H), 6.16 (d, 1H, $J = 0.8$ Hz), 6.14 (d, 1H, $J = 0.8$ Hz), 5.98 (d, 1H, $J = 0.7$ Hz), 5.94 (d, 1H, $J = 0.7$ Hz), 5.62 (s, 1H), 4.92 (d, 1H, $J = 15.5$ Hz), 4.85 (d, 1H, $J = 15.5$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.62, 158.38, 151.50, 147.00, 146.18, 143.66, 141.87, 136.94, 130.84, 114.89, 109.64, 108.85, 103.84, 103.16, 101.39, 97.68, 93.72, 68.08, 34.15. HRMS (ESI^+): m/z $[M + H - H_2O]^+$ calculated for $C_{19}H_{11}N_2O_7$: 379.0560; found: 379.0558

9-(benzo[d][1,3]dioxol-5-yl)-6,7-dimethoxy-4,9-dihydrofuro [3,4-b]quinolin-1(3*H*)-one (4ca)

White solid, yield 91%, mp 287–289 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.85 (s, 1H, NH), 6.79 (d, 1H, $J = 7.9$ Hz), 6.73 (d, 1H, $J = 1.6$ Hz), 6.66 (dd, 1H, $J = 7.9$ and 1.6 Hz), 6.62 (s, 1H), 6.51 (s, 1H), 5.95 (brs, 1H), 5.94 (brs, 1H), 4.95 (d, 1H, $J = 15.5$ Hz), 4.87 (s, 1H), 4.84 (d, 1H, $J = 15.5$ Hz), 3.73 (s, 3H), 3.60 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.15, 158.20, 148.16, 147.19, 145.51, 144.92, 141.15, 129.63, 120.35, 115.44, 113.71, 107.97, 107.85, 100.72, 100.34, 99.46, 64.92, 55.84, 55.43, 38.86.

9-(3,4-dimethoxyphenyl)-6,7-dimethoxy-4,9-dihydrofuro [3,4-b]quinolin-1(3*H*)-one (4cb)

Yellow solid, yield 90%, mp 228–230 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.82 (s, 1H, NH), 6.89 (d, 1H, $J = 1.9$ Hz), 6.1 (d, 1H, $J = 8.6$ Hz), 6.66 (s, 1H), 6.60 (dd, 1H, $J = 8.3$ and 1.9 Hz), 6.56 (s, 1H), 4.95 (d, 1H, $J = 15.6$ Hz), 4.88 (s, 1H), 4.84 (d, 1H, $J = 15.6$ Hz), 3.73 (s, 3H), 3.71 (s, 3H), 3.69 (s, 3H), 3.60 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.22, 158.18, 148.40, 148.07, 147.16, 144.85, 139.59, 29.62, 119.35, 115.56, 113.78, 111.71, 111.49, 100.29, 94.48, 64.88, 55.83, 55.44, 55.42, 38.74.

6,7-dimethoxy-9-(3,4,5-trimethoxyphenyl)-4,9-dihydrofuro [3,4-b]quinolin-1(3*H*)-one (4cc)

White solid, yield 92%, mp 236–238 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.83 (s, 1H, NH), 6.85 (s, 1H), 6.73 (s, 1H), 6.52 (s, 1H), 6.50 (s, 1H), 5.00 (d, 1H, $J =$ 15.5 Hz), 4.89 (s, 1H), 4.85 (d, 1H, $J = 15.5$ Hz), 3.73 (s, 3H), 3.70 (s, 3H), 3.62 (s, 3H), 3.61 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 17.22, 158.51, 15.70, 148.20, 144.87, 142.49, 135.95, 129.63, 115.17, 113.83, 107.62, 104.78, 100.78, 94.11, 64.94, 59.85, 56.08, 55.99, 55.93, 55.8, 55.45, 18.52.

9-(4-chlorophenyl)-6,7-dimethoxy-4,9-dihydrofuro[3,4-b] quinolin-1(3*H*)-one (4 cd)

White solid, yield 81%, mp 265–267 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.88 (s, 1H, NH), 7.31 (d, 2H, $J = 8.4$ Hz), 7.21 (d, 2H, $J = 8.4$ Hz), 6.58 (s, 1H), 6.52 (s, 1H), 4.97 (s, 1H), 4.94 (d, 1H, $J = 15.7$ Hz), 4.85 (d, 1H, $J = 15.7$ Hz), 3.73 (s, 3H), 3.57 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.04, 158.34, 148.37, 145.63, 145.08, 130.78, 129.79, 129.35, 128.18, 114.78, 113.83,

100.52, 94.09, 64.99, 55.89, 55.48, 38.66. HRMS (ESI^+): m/z $[M + Na]^+$ calculated for $C_{19}H_{17}ClNO_4Na$: 380.0659: found: 380.0661.

9-(4-(benzyloxy)-3-methoxyphenyl)-6,7-dimethoxy-4,9-dihydrofuro[3,4-b]quinolin-1(3*H*)-one (4ce)

White solid, yield 92%, mp 232–234 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.80 (s, 1H, NH), 7.44–7.28 (m, 5H), 6.92 (d, 1H, $J = 1.9$ Hz), 6.89 (d, 1H, $J = 8.3$ Hz), 6.66 (s, 1H), 6.56 (dd, 1H, $J = 8.3$ and 1.9 Hz), 6.50 (s, 1H), 4.99 (s, 1H), 4.94 (d, 1H, $J = 15.6$ Hz), 4.87 (s, 1H), 4.83 (d, 1H, $J = 15.6$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.95, 158.19, 148.81, 148.16, 146.27, 144.92, 140.02, 137.27, 129.70, 128.34, 127.73, 127.68, 119.36, 115.56, 113.93, 113.56, 111.89, 100.41, 94.50, 69.98, 64.89, 55.91, 55.61, 55.48, 38.76. HRMS (ESI^+): m/z $[M + Na]^+$ calculated for $C_{27}H_{25}NO_6Na$: 482.1571; found: 482.1578.

9-(4-fluorophenyl)-6,7-dimethoxy-4,9-dihydrofuro[3,4-b]quinolin-1(3*H*)-one (4cf)

White solid, yield 79%, mp 257–258 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.87 (s, 1H, NH), 7.24–7.20 (m, 2H), 7.11–7.06 (m, 2H), 6.59 (s, 1H), 6.53 (s, 1H), 4.98 (s, 1H), 4.94 (d, 1H, $J = 15.6$ Hz), 4.85 (d, 1H, $J = 15.6$ Hz), 3.73 (s, 3H), 3.58 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.08, 158.24, 1478.31, 145.05, 14.98, 142.95, 129.79, 129.28, 129.20, 115.98, 114.98, 114.77, 113.90, 100.50, 94.35, 64.95, 55.90, 55.49, 38.50. HRMS (ESI^+): m/z $[M + H]^+$ calculated for $C_{19}H_{17}FNO_4$: 342.1136; found: 342.1133.

6,7,8-trimethoxy-9-(4-(methylthio)phenyl)-4,9-dihydrofuro[3,4-b]quinolin-1(3*H*)-one (4cg)

White solid, yield 81%, mp 286–287 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.85 (s, 1H, NH), 7.17–7.12 (m, 4H), 6.58 (s, 1H), 6.52 (s, 1H), 4.93 (d, 1H, $J = 15.7$ Hz), 4.91 (s, 1H), 4.84 (d, 1H, $J = 15.7$ Hz), 3.73 (s, 3H), 3.58 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.13, 158.22, 148.25, 145.01, 143.65, 135.55, 129.74, 128.08, 126.03, 115.25, 113.86, 100.47, 94.37, 64.94, 55.89, 55.44, 55.49, 38.74, 14.78. HRMS (ESI^+): m/z $[M + H]^+$ calculated for $C_{20}H_{20}NO_4S$: 370.1106; found: 370.1109.

6,7-dimethoxy-9-(4-(trifluoromethyl)phenyl)-4,9-dihydrofuro[3,4-b]quinolin-1(3*H*)-one (4ch)

White solid, yield 82%, mp 255–256 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.95 (s, 1H, NH), 7.64 (d, 2H, $J = 8.1$ Hz), 7.43 (d, 2H, $J = 8.1$ Hz), 6.60 (s, 1H), 6.56 (s, 1H), 5.10 (s, 1H), 4.97 (d, 1H, $J = 15.7$ Hz), 4.87 (d, 1H, $J = 15.7$ Hz), 3.75 (s, 3H), 3.58 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.02, 158.53, 150.96, 148.49, 145.16, 130.67, 129.88, 128.33, 125.21, 125.18, 114.30, 113.83, 100.61, 93.85, 65.07, 55.88, 55.48, 39.15. HRMS (ESI^+): m/z $[M + H]^+$ calculated for $C_{20}H_{17}F_3NO_4$: 392.1104; found: 392.1105.

9-(4,5-dimethoxy-2-nitrophenyl)-6,7-dimethoxy-4,9-dihydrofuro[3,4-b]quinolin-1(3*H*)-one (4ci)

Yellow solid, yield 77%, mp 249–251 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.94 (s, 1H, NH), 7.45 (s, 1H), 6.68 (s, 1H), 6.65 (s, 1H), 6.57 (s, 1H), 5.73 (s, 1H), 4.95 (d, 1H, $J = 15.6$ Hz), 4.85 (d, 1H, $J = 15.6$ Hz), 3.83 (s, 3H), 3.76 (s, 3H), 3.70 (s, 3H), 3.57 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.77, 158.48, 152.61, 148.53, 147.01, 145.11, 140.69, 134.52, 130.04, 113.93, 112.98, 112.75, 107.00, 100.63, 93.87, 65.04, 55.95, 55.83, 55.69, 55.42, 33.81. HRMS (ESI^+): m/z $[M + H]^+$ calculated for $C_{21}H_{21}N_2O_8$: 429.1290: found: 429.1297.

9-(3,4-dihydroxyphenyl)-6,7-dimethoxy-4,9-dihydrofuro[3,4-b]quinolin-1(3*H*)-one (4 cm)

White solid, yield 80%, mp 244–246 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.75 (s, 1H, NH), 8.70 (s, 1H, OH), 8.64 (s, 1H, OH), 6.58 (d, 1H, $J = 8.0$ HZ), 6.55 (s, 1H), 6.50 (d, 1H, $J = 2.0$ Hz), 6.49 (s, 1H), 6.46 (dd, 1H, $J = 8.0$ and 2.0 Hz), 4.89 (d, 1H, $J = 15.7$ Hz), 4.81 (d, 1H, $J = 15.7$ Hz), 4.71 (s, 1H), 3.72 (s, 3H), 3.58 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 172.14, 157.76, 148.06, 144.92, 144.89, 143.63, 138.27, 129.70, 118.19, 116.06, 115.10, 115.03, 113.95, 100.35, 94.98, 64.73, 55.87, 55.49, 38.67. HRMS (ESI^+): m/z $[M + H + K]^+$ calculated for $C_{19}H_{18}NO_6K$: 395.0765; found: 395.0761

6,7-dimethoxy-9-(6-nitrobenzo[d][1,3]dioxol-5-yl)-4,9-dihydrofuro[3,4-b]quinolin-1(3*H*)-one (4cn)

Yellow solid, yield 70%, mp 245–246 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (p.p.m.) 9.98 (s, 1H, NH), 6.67 (s, 1H), 6.65 (s, 1H), 6.56 (s, 1H), 6.15 (s, 1H), 6.14 (s, 1H), 5.64 (s, 1H), 4.94 (d, 1H, $J = 15.6$ Hz), 4.87 (d, 1H, $J = 15.6$ Hz), 3.75 (s, 3H), 3.58(s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (p.p.m.) 171.74, 158.50, 141.45, 148.63, 146.08, 145.21, 141.84, 137.00, 129.97, 113.75, 112.95, 109.53, 103.88, 103.14, 100.71, 93.78, 65.13, 55.69, 55.45, 33.73. HRMS (ESI^+): m/z $[M + H - H_2O]^+$ calculated for $C_{20}H_{15}N_2O_7$: 395.0878; found: 395.0872.

Biological activity

The antibacterial activity of the derivatives **4** was assessed against *Porphyromonas gingivalis* (ATCC 33277), *Prevotella nigrescens* (ATCC 33563), *Streptococcus mitis* (ATCC 49456), *Streptococcus sanguinis* (ATCC 10556), *Mycobacterium tuberculosis* (ATCC 27294), *Mycobacterium avium* (ATCC 25291), and *Mycobacterium kansasii* (ATCC 12478).

The minimal inhibitory concentration (MIC) of the derivatives **4** was determined using the microdilution broth method in 96-well microplates (Sousa et al. 2015). Samples were dissolved in dimethyl sulfoxide (DMSO) to a concentration of 8000 µg/mL, followed by dilution in tryptic soy broth (TSB) for aerobic microorganisms and Schaedler broth (Difco) supplemented which hemin (5.0 g/mL), and menadione (10.0 g/mL) for anaerobic microorganisms; the sample concentrations tested ranged from 200 to 0.195 µg/mL. The final DMSO content was 4% (v/v), and this solution was used as a negative control. The inoculum was adjusted for each organism to yield a cell concentration of 5×10^5 colony forming units per mL (CFU/mL), according to the Clinical and Laboratory Standards Institute (CLSI 2012a) guidelines (CLSI 2012b). The 96-well microplates containing the aerobic microorganisms were closed with a sterile plate sealer and incubated aerobically at 37 °C for 24 h. The plates containing the anaerobic microorganisms were closed with a sterile plate sealer and incubated for 72 h in an anaerobic chamber, in 5–10% H_2, 10% CO_2, 80–85% N_2 atmosphere, at 36 °C. After that, resazurin (30 µL) in aqueous solution (0.01%) was added to the microplates to indicate microorganism viability for MIC determination. Chlorhexidine dihydrochloride (CHD) was used as a positive control, and the concentrations ranged from 0.115 to 59 µg/mL. Controls were also performed to determine the sterility of the TSB and Schaedler broths, control culture (inoculum), CHD, the derivatives **4**, and control DMSO. The MIC values were determined as the lowest concentration of derivatives **4** capable of inhibiting the growth of the microorganisms.

For *Mycobacterium* spp. the antimicrobial activity of the derivatives **4** was evaluated in vitro using the microplate microdilution technique (Palomino et al. 2002), using resazurin as an indicator of microbial activity (REMA-Resazurin Microtiter Assay), which allowed the determination of the minimum inhibitory concentration (MIC) against the microorganisms evaluated. The compounds were dissolved in dimethyl sulfoxide (DMSO) and serially diluted in Middlebrook 7H9 broth prior to inoculation, the final concentration of DMSO being <0.3%. The inoculum was adjusted to each organism to produce a cellular concentration of 10^8 colony forming units (CFU/mL). The concentrations of the compounds tested ranged from 0.195 to 200 µg/mL for the bacteria and from 31.5 to 2000 µg/mL for *Mycobacterium*. Microplates (96 wells) were incubated at 37 °C for 24 h. Thereafter, 30 µL of aqueous resazurin solution (0.01%) was added to indicate the viability of the microorganisms. The MIC was determined as the lowest concentration of the compound capable of inhibiting the growth of the microorganism. Chlorhexidine was used as the reference antibiotic at concentrations of 0.115–59.0 µg/mL in the bioassays for bacteria and isoniazid at concentrations of 0.015–1.0 µg/mL for *Mycobacterium*. Middlebrook 7H9 broth containing 0.2% DMSO was used as a negative control.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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