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ORIGINAL PAPER

C-Furyl glycosides, II: synthesis and antimicrobial evaluation of *C*-furyl glycosides bearing pyrazolines, isoxazolines, and 5,6-dihydropyrimidine-2(1*H*)-thiones

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Abstract New *C*-furyl glycosides bearing pyrazolines, isoxazolines, and dihydropyrimidine-2(1*H*)-thiones were synthesized in order to increase the number of tested compounds screened for antimicrobial activity. The antimicrobial activity screening showed that the pyrazoline derivatives were the most active compounds.

Keywords *C*-Furyl glycosides · Pyrazolines · Isoxazolines · Antimicrobial activity

Introduction

Carbohydrates exist on cell surfaces as glycoproteins or glycolipid conjugates and are engaged in important structural functions in various biological recognition processes, such as cancer metastasis, inflammatory response, innate and adaptive immunity, viral and bacterial infections, and many other receptor-mediated signaling processes [1–6]. Moreover, a large number of natural products require glycosylation in order to show proper biological performance [7–9]. Interest continues to rise in new applications of natural and synthetic *C*-glycoside to basic research and medicine owing to their potential therapeutic applications and synthetic utility [10–16]. *C*-Glycosyl derivatives habitually exist in a variety of biologically important natural products as papulacandins, pluramycins, vineomycin, gilvocarcin V, and urdamycin A, which are recognized for their various biological activities, including antibiotic, antitumoral, and antiplatelet aggregation activities [17–21]. Furthermore, they have become increasingly useful as building blocks for the synthesis of various types of natural products and as potential enzyme inhibitors [22–24]. It has been found that the tetrahydrofuran moiety is a basic structural constituent of a large number of *C*-glycosides [25–30] of considerable biological and chemical interest. *C*-Furyl glycosides are useful precursors for the synthesis of many *C*-glycosyl antibiotics [31]. The synthesis of arylpyrazolines is of major interest [32, 33]. Functionalized isoxazoline and isoxazole derivatives are active pharmacophores in several pharmacologically important molecules [34–36], and are also useful intermediates for the synthesis of a wide variety of bioactive natural products [37–39]. Thioxopyrimidine is an essential structural unit of several heterocycles that display a wide range of interesting biological and pharmacological properties, such as anticancer and antimicrobial activities [40, 41]. Our interest in the synthesis of such compounds was focused on biological studies of them as antimicrobial agents as a part of our program aimed at the development of a new heterocyclic compounds with potential biological activities [42–44].

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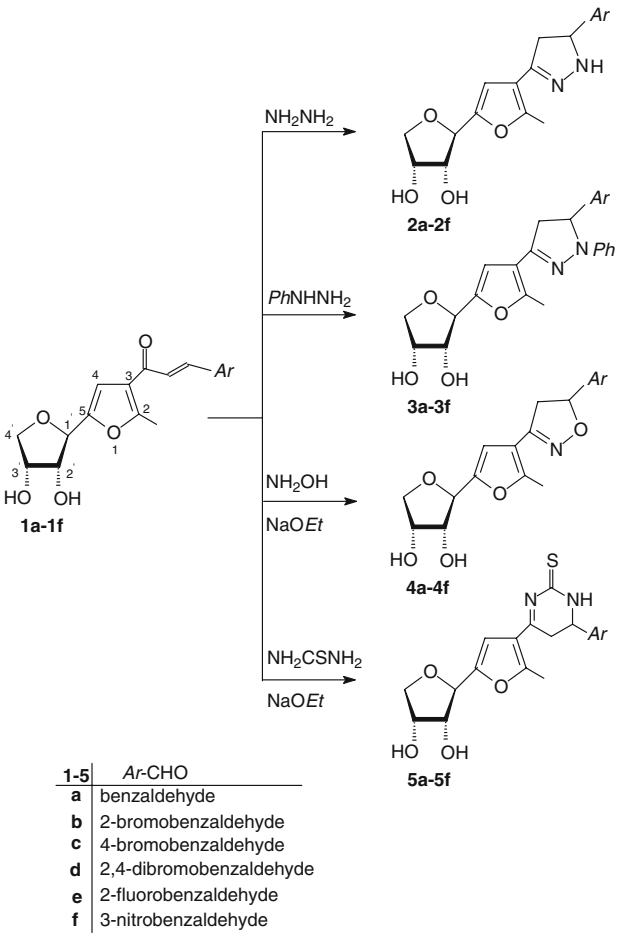
Results and discussion

Synthesis

It has been reported that α,β-unsaturated ketones can react with hydrazine hydrate or phenyl hydrazine to give the

corresponding pyrazolines [45, 46]. So, **1a–1f** [49] were treated with hydrazine hydrate or phenyl hydrazine in ethanol to afford the Δ^2-pyrazolines **2a–2f** in 70–74% yields, and *N*-phenyl-Δ^2-pyrazolines **3a–3f** in 75–80% yields. The ^{1}H NMR spectra of **2a–2f** showed two doublets at δ 3.00–3.04 and 3.45–3.53 for the pyrazoline-H-4, while pyrazoline-H-5 appeared as a triplet at δ 4.90–5.03 ppm. The ^{1}H NMR spectra of **3a–3f** showed two doublets at δ 3.00–3.02 and 3.44–3.50 for the pyrazoline-H-4 and a triplet at δ 4.92–5.04 ppm for the pyrazoline-H-5. Condensation of **1a–1f** with hydroxylamine hydrochloride or thiourea in ethanolic sodium hydroxide solution gave 4,5-dihydroisoxazoles **4a–4f** in 78–82% yields, and 5,6-dihydropyrimidine-2-(1*H*)-thiones **5a–5f** in 72–75% yields. The ^{1}H NMR spectra of **4a–4f** showed a multiplet at δ 3.53–3.80 for the isoxazoline-H-4, H-3′, and H-4′$_a$, and a triplet at δ 5.90–5.98 ppm for the isoxazoline-H-5. The ^{1}H NMR spectra of **5a–5f** showed a multiplet at δ 5.07–5.29 for the dihydro-2-thioxopyrimidine-H-5 and 2xOH, and a triplet at δ 5.39–5.55 for the dihydro-2-thioxopyrimidine-H-6, and a broad singlet at δ 12.69–12.74 ppm for the NH group (Scheme 1).



Scheme 1

Antimicrobial activity

The newly synthesized compounds were tested for their antimicrobial action [47, 48] against four different bacterial species, namely *Pseudomonas* sp. (Gram-negative bacterium), *Bacillus subtilis* (Gram-positive bacterium), *Bacillus cereus* (Gram-positive bacterium), and *Streptomyces* sp. (one of the important actinomycetes). All of the tested compounds exhibited different degrees of antibacterial activity or inhibitory action. The most susceptible organisms were the two Gram-positive bacteria (*Bacillus subtilis* and *Bacillus cereus*), followed by *Streptomyces* sp., while the lowest inhibitory effect was encountered in the case of *Pseudomonas* sp. The highest degrees of inhibition were recorded for compounds **2a–2f** and **3a–3c** followed by **3d–3f**, **4a–4f**, and **5a–5f** (Table 1). The results were compared to amoxicillin (penicillin) as a reference drug.

Experimental

Melting points were determined using a Kofler block instrument. ^{1}H NMR spectra were recorded with Bruker (Rheinstetten, Germany) AC 250 FT NMR spectrometer at 250 MHz with *TMS* as an internal standard. MALDI-MS were measured with a Kratos Analytical (Manchester, UK) Compact, using 2,5-dihydroxybenzoic acid (*DHB*) as matrix. The $(M + Na)^+$ ions were peak-matched using ions derived from the 2,5-dihydroxybenzoic acid matrix. The microanalyses were performed at the microanalytical unit, Cairo University, Egypt, and were found to agree favorably with the calculated values. The antimicrobial activities of the synthesized compounds were evaluated at the Botany Department, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt.

*General procedure for the preparation of pyrazolines **2a–2f** and N-phenylpyrazolines **3a–3f***

A mixture of **1a–1f** [49] (5 mmol), 0.13 cm^3 $N_2H_4{\cdot}H_2O$ (5 mmol) and/or 0.27 cm^3 phenylhydrazine (5 mmol) in 25 cm^3 ethanol was refluxed for 8 h (TLC). The reaction mixture was cooled; the precipitate was filtered off and recrystallized from ethanol to give **2a–2f** in 70–74% yields, and **3a–3f** in 75–80% yields.

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-phenyl-4,5-dihydro-1H-pyrazole (**2a**; $C_{18}H_{20}N_2O_4$)

White powder (74%); $R_f = 0.30$ (petroleum ether/*Et*OAc, 2:1). M.p.: 120–122 °C; ^{1}H NMR (*DMSO*-d$_6$, δ,

Table 1 Antimicrobial activity of the newly synthesized compounds **2–5**

Compound no.	*Pseudomonas* sp.	*Bacillus subtilis*	*Bacillus cereus*	*Streptomyces*
Amoxicillin (penicillin)	–	++	+++	+
2a	+	++++	++++	++
2b	+	++++	++++	++
2c	+	++++	++++	++
2d	+	++++	++++	+
2e	+	++++	+++	+
2f	+	++++	++++	+
3a	+	+++	+++	+
3b	+	+++	+++	++
3c	+	+++	+++	+
3d	+	++	++	+
3e	+	++	++	+
3f	+	++	++	+
4a	+	++	++	++
4b	+	++	++	+
4c	+	++	++	+
4d	+	++	++	+
4e	+	++	++	+
4f	+	++	++	+
5a	+	++	++	+
5b	+	++	++	+
5c	+	++	++	+
5d	+	++	++	++
5e	+	++	++	+
5f	+	++	++	+

– No antimicrobial effect

+ Low antimicrobial effect (4 mm)

++ Moderate antimicrobial effect (8–10 mm)

+++ High antimicrobial effect (15–18 mm)

++++ Complete antimicrobial effect (20–22 mm)

250 MHz): 2.22 (s, CH_3), 3.03, 3.49 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 3.60 (m, H-3′), 3.70 (m, H-4′$_a$), 4.00 (m, H-4′$_b$), 4.12 (m, H-2′), 4.80 (br, s, 2×OH), 4.90 (t, $J = 3.6$ Hz, pyrazoline-H-5), 5.33 (d, $J = 6.4$ Hz, H-1′), 6.40 (s, H-4), 7.00 (br, s, NH), 7.12–7.23 (m, Ar-H), 7.25–7.34 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 351 [$(M + Na)^+$, 22].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(2-bromophenyl)-4,5-dihydro-1H-pyrazole (**2b**; $C_{18}H_{19}BrN_2O_4$)

Pale yellow powder (73%); $R_f = 0.37$ (petroleum ether/*Et*OA*c*, 2:1). M.p.: 178–180 °C; ^{1}H NMR (*DMSO*-d$_6$, δ, 250 MHz): 2.20 (s, CH_3), 3.04, 3.45 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 3.62 (m, H-3′), 3.69 (m, H-4′$_a$), 4.04 (m, H-4′$_b$), 4.15 (m, H-2′), 4.87 (br, s, 2×OH), 4.92 (t, $J = 3.6$ Hz, pyrazoline-H-5), 5.30 (d, $J = 6.4$ Hz, H-1′), 6.44 (s, H-4), 7.06 (br, s, NH), 7.06–7.13 (m, Ar-H), 7.34–7.38 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 429 [$(M + Na)^+$, 17].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(4-bromophenyl)-4,5-dihydro-1H-pyrazole (**2c**; $C_{18}H_{19}BrN_2O_4$)

Pale yellow powder (74%); $R_f = 0.37$ (petroleum ether/*Et*OA*c*, 2:1). M.p.: 163–165 °C; ^{1}H NMR (*DMSO*-d$_6$, δ, 250 MHz): 2.26 (s, CH_3), 3.02, 3.52 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 3.67 (m, H-3′), 3.71 (m, H-4′$_a$), 4.07 (m, H-4′$_b$), 4.18 (m, H-2′), 4.89 (br, s, 2×OH), 4.99 (t, $J = 3.6$ Hz, pyrazoline-H-5), 5.37 (d, $J = 6.4$ Hz, H-1′), 6.44 (s, H-4), 7.03 (br, s, NH), 7.11–7.18 (m, Ar-H), 7.30–7.32 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 429 [$(M + Na)^+$, 39].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(2,4-dibromophenyl)-4,5-dihydro-1H-pyrazole (**2d**; $C_{18}H_{18}Br_2N_2O_4$)

Yellow powder (71%); $R_f = 0.39$ (petroleum ether/*Et*OA*c*, 2:1). M.p.: 196–198 °C; ^{1}H NMR (*DMSO*-d$_6$, δ, 250 MHz): 2.24 (s, CH_3), 3.02, 3.53 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 3.65 (m, H-3′), 3.70 (m, H-4′$_a$), 4.09 (m, H-4′$_b$), 4.22 (m, H-2′), 4.88 (br, s, 2×OH), 4.90 (t, $J = 3.6$ Hz, pyrazoline-H-5), 5.33 (d, $J = 6.4$ Hz, H-1′), 6.49 (s, H-4), 7.02 (br, s, NH), 7.37–7.52 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 509 [$(M + Na)^+$, 13].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(2-fluorophenyl)-4,5-dihydro-1H-pyrazole (**2e**; $C_{18}H_{19}FN_2O_4$)

White powder (70%); $R_f = 0.36$ (petroleum ether/*Et*OA*c*, 2:1). M.p.: 138–140 °C; ^{1}H NMR (*DMSO*-d$_6$, δ, 250 MHz): 2.22 (s, CH_3), 3.00, 3.47 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 3.65 (m, H-3′), 3.71 (m, H-4′$_a$), 4.00 (m, H-4′$_b$), 4.13 (m, H-2′), 4.81 (br, s, 2×OH), 4.95 (t, $J = 3.6$ Hz, pyrazoline-H-5), 5.32 (d, $J = 6.4$ Hz, H-1′), 6.47 (s, H-4), 7.01 (br, s, NH), 7.07–7.15 (m, Ar-H), 7.40–7.50 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 369 [$(M + Na)^+$, 44].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(3-nitrophenyl)-4,5-dihydro-1H-pyrazole (**2f**; $C_{18}H_{19}N_3O_6$)

Yellow powder (7o%); $R_f = 0.40$ (petroleum ether/*Et*OA*c*, 2:1). M.p.: 158–160 °C; ^{1}H NMR (*DMSO*-d$_6$, δ, 250 MHz): 2.23 (s, CH_3), 3.02, 3.49 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H–4), 3.62 (m, H-3′), 3.77 (m, H-4′$_a$), 4.05 (m, H-4′$_b$), 4.14 (m, H-2′), 4.88 (br, s, 2×OH), 5.03 (t, $J = 3.6$ Hz, pyrazoline-H-5), 5.35 (d, $J = 6.4$ Hz, H-1′), 6.48 (s, H-4), 7.00 (br, s, NH), 7.39–7.52 (m, Ar-H),

8.05–8.15 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 396 [(M + Na)$^+$, 53].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-1,5-diphenyl-4,5-dihydro-1H-pyrazole (**3a**; $C_{24}H_{24}N_2O_4$)
White powder (79%); $R_f = 0.40$ (petroleum ether/*Et*OAc, 2:1). M.p.: 180–182 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.21 (s, CH_3), 3.02, 3.44 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 3.62 (m, H-3′), 3.74 (m, H-4′$_a$), 4.02 (m, H-4′$_b$), 4.13 (m, H-2′), 4.84 (br, s, 2×OH), 4.92 (t, $J = 3.6$ Hz, pyrazoline-H-5), 5.39 (d, $J = 6.4$ Hz, H-1′), 6.48 (s, H-4), 7.07–7.23 (m, Ar-H), 7.30–7.44 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 427 [(M + Na)$^+$, 28].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(2-bromophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**3b**; $C_{24}H_{23}BrN_2O_4$)
Pale yellow powder (80%); $R_f = 0.44$ (petroleum ether/*Et*OAc, 2:1). M.p.: 190–192 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.21 (s, CH_3), 3.00, 3.48 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 3.63 (m, H-3′), 3.70 (m, H-4′$_a$), 4.00 (m, H-4′$_b$), 4.12 (m, H-2′), 4.91 (br, s, 2×OH), 5.03 (t, *J*= 3.6 Hz, pyrazoline-H-5), 5.39 (d, $J = 6.4$ Hz, H-1′), 6.40 (s, H-4), 7.19–7.30 (m, Ar-H), 7.33–7.39 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 505 [(M + Na)$^+$, 22].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(4-bromophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**3c**; $C_{24}H_{23}BrN_2O_4$)
Pale yellow powder (78%); $R_f = 0.47$ (petroleum ether/*Et*OAc, 2:1). M.p.: 212–214 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.25 (s, CH_3), 3.02, 3.44 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 3.63 (m, H-3′), 3.68 (m, H-4′$_a$), 4.01 (m, H-4′$_b$), 4.13 (m, H-2′), 4.86 (br, s, 2×OH), 4.96 (t, $J = 3.6$ Hz, pyrazoline-H-5), 5.33 (d, $J = 6.4$ Hz, H-1′), 6.39 (s, H-4), 7.03–7.15 (m, Ar-H), 7.26–7.37 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 505 [(M + Na)$^+$, 31].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(2,4-dibromophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**3d**; $C_{24}H_{22}Br_2N_2O_4$)
Yellow powder (75%); $R_f = 0.48$ (petroleum ether/*Et*OAc, 2:1). M.p.: 236–238 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.24 (s, CH_3), 3.00, 3.45 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 3.62 (m, H-3′), 3.67 (m, H-4′$_a$), 4.02 (m, H-4′$_b$), 4.19 (m, H-2′), 4.88 (br, s, 2×OH), 4.99 (t, $J = 3.6$ Hz, pyrazoline-H-5), 5.35 (d, $J = 6.4$ Hz, H-1′), 6.43 (s, H-4), 7.11–7.23 (m, Ar-H), 7.39–7.50 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 585 [(M + Na)$^+$, 14].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(2-fluorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**3e**; $C_{24}H_{23}FN_2O_4$)
White powder (76%); $R_f = 0.48$ (petroleum ether/*Et*OAc, 2:1). M.p.: 211–213 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.26 (s, CH_3), 3.00, 3.48 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 3.66 (m, H-3′), 3.71 (m, H-4′$_a$), 4.05 (m, H-4′$_b$), 4.18 (m, H-2′), 4.89 (br, s, 2×OH), 4.97 (t, $J = 3.6$ Hz, pyrazoline-H-5), 5.30 (d, $J = 6.4$ Hz, H-1′), 6.39 (s, H-4), 7.08–7.24 (m, Ar-H), 7.40–7.55 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 445 [(M + Na)$^+$, 27].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(3-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**3f**; $C_{24}H_{23}N_3O_6$)
Pale yellow powder (75%); $R_f = 0.49$ (petroleum ether/*Et*OAc, 2:1). M.p.: 225–227 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.22 (s, CH_3), 3.02, 3.50 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 3.62 (m, H-3′), 3.71 (m, H-4′$_a$), 4.00 (m, H-4′$_b$), 4.12 (m, H-2′), 4.94 (br, s, 2×OH), 5.04 (t, $J = 3.6$ Hz, pyrazoline-H-5), 5.33 (d, $J = 6.4$ Hz, H-1′), 6.40 (s, H-4), 7.17–7.28 (m, Ar-H), 7.30–7.32 (m, Ar-H), 8.03–8.15 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 472 [(M + Na)$^+$, 26].

General procedure for the preparation of isoxazolines ***4a–4f***

A mixture of **1a–1f** [49] (5 mmol), 0.16 g $HONH_2$·HCl (5 mmol), and 0.5 g NaOH (12 mmol) in 60 cm^3 ethanol was refluxed for 8 h (TLC). The reaction mixture was cooled and poured onto crushed ice. The precipitate was filtered, washed with H_2O, and purified on silica gel column chromatography using CH_2Cl_2 in petroleum ether (3:7 v/v) to give **4a–4f** in 78–82% yields.

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-phenyl-4,5-dihydroisoxazole (**4a**; $C_{18}H_{19}NO_5$)
White powder (81%); $R_f = 0.41$ (petroleum ether/*Et*OAc, 2:1). M.p.: 139–141 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.20 (s, CH_3), 3.58–3.80 (m, isoxazoline-H-4, H-3′, H-4′$_a$), 4.09 (m, H-4′$_b$), 4.21 (m, H-2′), 5.09 (br, s, 2×OH), 5.39 (d, $J = 6.4$ Hz, H-1′), 5.95 (t, $J = 3.5$ Hz, isoxazoline-H-5), 6.47 (s, H-4), 7.19–7.40 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 352 [(M + Na)$^+$, 33].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(2-bromophenyl)-4,5-dihydroisoxazole (**4b**; $C_{18}H_{18}BrNO_5$)
Yellow powder (82%); $R_f = 0.46$ (petroleum ether/*Et*OAc, 2:1). M.p.: 166–168 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.23 (s, CH_3), 3.55-3.77 (m, isoxazoline-H-4, H-3′, H-4′$_a$), 4.08 (m, H-4′$_b$), 4.24 (m, H-2′), 5.11 (br, s, 2×OH), 5.36 (d, $J = 6.4$ Hz, H-1′), 5.94 (t, $J = 3.5$ Hz, isoxazoline-H-5), 6.45 (s, H-4), 7.11–7.23 (m, Ar-H), 7.29–7.36 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 430 [(M + Na)$^+$, 17].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(4-bromophenyl)-4,5-dihydroisoxazole (**4c**; $C_{18}H_{18}BrNO_5$)
Yellow powder (80%); $R_f = 0.48$ (petroleum ether/*Et*OAc, 2:1). M.p.: 149–151 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.22 (s, CH_3), 3.58–3.78 (m, isoxazoline-H-4, H-3′, H-4′$_a$), 4.03 (m, H-4′$_b$), 4.27 (m, H-2′), 5.06 (br, s, 2×OH), 5.43 (d, $J = 6.4$ Hz, H-1′), 5.90 (t, $J = 3.5$ Hz, isoxazoline-H-5), 6.49 (s, H-4), 7.09–7.23 (m, Ar-H), 7.28–7.33 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 430 [(M + Na)$^+$, 23].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(2,4-dibromophenyl)-4,5-dihydroisoxazole (**4d**; $C_{18}H_{17}Br_2NO_5$)
Yellow powder (79%); $R_f = 0.48$ (petroleum ether/*Et*OAc, 2:1). M.p.: 177–179 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.24 (s, CH_3), 3.55–3.74 (m, isoxazoline-H-4, H-3′, H-4′$_a$), 4.03 (m, H-4′$_b$), 4.24 (m, H-2′), 5.12 (br, s, 2×OH), 5.43 (d, $J = 6.4$ Hz, H-1′), 5.92 (t, $J = 3.5$ Hz, isoxazoline-H-5), 6.43 (s, H-4), 7.10–7.24 (m, Ar-H), 7.44–7.50 (m, Ar-H ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 510 [(M + Na)$^+$, 12].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)–2-methylfuran]–5-(2-fluorophenyl)-4,5-dihydroisoxazole (**4e**; $C_{18}H_{18}FNO_5$)
White powder (78%); $R_f = 0.41$ (petroleum ether/*Et*OAc, 2:1). M.p.: 160–162 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.27 (s, CH_3), 3.53–3.77 (m, isoxazoline-H-4, H-3′, H-4′$_a$), 4.06 (m, H-4′$_b$), 4.20 (m, H-2′), 5.07 (br, s, 2×OH), 5.33 (d, $J = 6.4$ Hz, H-1′), 5.98 (t, $J = 3.5$ Hz, isoxazoline-H-5), 6.44 (s, H-4), 7.09–7.20 (m, Ar-H), 7.66–7.73 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 370 [(M + Na)$^+$, 41].

3-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-5-(3-nitrophenyl)-4,5-dihydroisoxazole (**4f**; $C_{18}H_{18}N_2O_7$)
Yellow powder (78%); $R_f = 0.41$ (petroleum ether/*Et*OAc, 2:1). M.p.: 169–171 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.25 (s, CH_3), 3.58–3.74 (m, isoxazoline-H-4, H-3′, H-4′$_a$), 4.02 (m, H-4′$_b$), 4.20 (m, H-2′), 5.03 (br, s, 2×OH), 5.30 (d, $J = 6.4$ Hz, H-1′), 5.90 (t, $J = 3.5$ Hz, isoxazoline-H-5), 6.40 (s, H-4), 7.49–7.64 (m, Ar-H), 8.20–8.33 (m, Ar-H) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 397 [(M + Na)$^+$, 18].

General procedure for the preparation of 5,6-dihydropyrimidine-2-(1H)-thiones ***5a–5f***

A mixture of **1a–1f** [49] (10 mmol), 0.1 g thiourea (14 mmol), and 1.0 g NaOH (25 mmol) in 30 cm^3 ethanol was refluxed for 6 h. The reaction mixture was concentrated, cooled, and filtered. The precipitate was recrystallized from ethanol to give **5a–5f** in 72–75% yields.

4-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-6-phenyl-5,6-dihydropyrimidine-2(1H)-thione (**5a**; $C_{19}H_{20}N_2O_4S$)
Yellow powder (74%); $R_f = 0.51$ (petroleum ether/*Et*OAc, 2:1). M.p.: 205–207 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.27 (s, CH_3), 3.44–3.70 (m, H-3′, H-4′$_a$), 4.06 (m, H-4′$_b$), 4.20 (m, H-2′), 5.10–5.25 (m, 2×OH, dihydro-2-thioxopyrimidine-H-5), 5.43–5.55 (m, dihydro-2-thioxopyrimidine-H-6, H-1′), 6.44 (s, H-4), 7.10–7.20 (m, Ar-H), 7.30–7.39 (m, Ar-H), 12.70 (br, s, NH) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 395 [(M + Na)$^+$, 23].

4-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-6-(2-bromophenyl)-5,6-dihydropyrimidine-2(1H)-thione (**5b**; $C_{19}H_{19}BrN_2O_4S$)
Yellow powder (75%); $R_f = 0.53$ (petroleum ether/*Et*OAc, 2:1). M.p.: 237–239 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.25 (s, CH_3), 3.40–3.70 (m, H-3′, H-4′$_a$), 4.00 (m, H-4′$_b$), 4.27 (m, H-2′), 5.10–5.29 (m, 2×OH, dihydro-2-thioxopyrimidine-H-5), 5.40–5.52 (m, dihydro-2-thioxopyrimidine-H-6, H-1′), 6.40 (s, H-4), 7.00–7.17 (m, Ar-H), 7.29–7.38 (m, Ar-H), 12.71 (br, s, NH) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 475 [(M + Na)$^+$, 16].

4-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-6-(4-bromophenyl)-5,6-dihydropyrimidine-2(1H)-thione (**5c**; $C_{19}H_{19}BrN_2O_4S$)
Yellow powder (73%); $R_f = 0.54$ (petroleum ether/*Et*OAc, 2:1). M.p.: 271–273 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.23 (s, CH_3), 3.40–3.66 (m, H-3′, H-4′$_a$), 4.07 (m, H-4′$_b$), 4.22 (m, H-2′), 5.07–5.27 (m, 2×OH, dihydro-2-thioxopyrimidine-H-5), 5.40–5.55 (m, dihydro-2-thioxopyrimidine-H-6, H-1′), 6.46 (s, H-4), 7.05–7.20 (m, Ar-H), 7.30–7.37 (m, Ar-H), 12.74 (br, s, NH) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 475 [(M + Na)$^+$, 20].

4-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-6-(2,4-dibromophenyl)-5,6-dihydropyrimidine-2(1H)-thione (**5d**; $C_{19}H_{18}Br_2N_2O_4S$)
Yellow powder (74%); $R_f = 0.57$ (petroleum ether/*Et*OA*c*, 2:1). M.p.: 266–268 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.23 (s, CH_3), 3.39–3.69 (m, H-3′, H-4′$_a$), 4.09 (m, H-4′$_b$), 4.27 (m, H-2′), 5.10–5.29 (m, 2×OH, dihydro-2-thioxopyrimidine-H-5), 5.43–5.53 (m, dihydro-2-thioxopyrimidine-H-6, H-1′), 6.41 (s, H-4), 7.16–7.29 (m, Ar-H), 7.39–7.55 (m, Ar-H), 12.72 (br, s, NH) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 553 [(M + Na)$^+$, 13].

4-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-6-(2-fluorophenyl)-5,6-dihydropyrimidine-2(1H)-thione (**5e**; $C_{19}H_{19}FN_2O_4S$)
Yellow powder (72%); $R_f = 0.56$ (petroleum ether/*Et*OA*c*, 2:1). M.p.: 259–261 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.20 (s, CH_3), 3.40–3.63 (m, H-3′, H-4′$_a$), 4.09 (m, H-4′$_b$), 4.28 (m, H-2′), 5.12–5.27 (m, 2×OH, dihydro-2-thioxopyrimidine-H-5), 5.41–5.52 (m, dihydro-2-thioxopyrimidine-H-6, H-1′), 6.38 (s, H-4), 7.00–7.16 (m, Ar-H), 7.40–7.60 (m, Ar-H), 12.69 (br, s, NH) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 413 [(M + Na)$^+$, 22].

4-[5-C-(1,4-Anhydro-β-D-erythro-tetrofuranosyl)-2-methylfuran]-6-(3-nitrophenyl)-5,6-dihydropyrimidine-2(1H)-thione (**5f**; $C_{19}H_{19}N_3O_6S$)
Yellow powder (742%); $R_f = 0.59$ (petroleum ether/*Et*OA*c*, 2:1). M.p.: 247–249 °C; ^{1}H NMR (*DMSO*-d_6, δ, 250 MHz): 2.24 (s, CH_3), 3.38–3.68 (m, H-3′, H-4′$_a$), 4.08 (m, H-4′$_b$), 4.18 (m, H-2′), 5.12-5.28 (m, 2×OH, dihydro-2-thioxopyrimidine-H-5), 5.39–5.49 (m, dihydro-2-thioxopyrimidine-H-6, H-1′), 6.41 (s, H-4), 7.40–7.50 (m, Ar-H), 8.05–8.15 (m, Ar-H), 12.73 (br, s, NH) ppm; (MALDI, positive mode, matrix: DHB): *m/z* (%) = 440 [(M + Na)$^+$, 28].

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