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One-Pot Microwave Synthesis of Pyrimido[4,5-*b*]quinoline and its *C*- and *S*-Glycosides with Anti-Inflammatory and Anticancer Activities

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Abstract: An efficient one-pot synthesis of 2-thioxopyrimido[4,5-*b*]quinoline **3a,b** has been accomplished from a three-component reaction of 6-aminothiouracil, cyclohexanone and aromatic aldehyde under microwave irradiation. Compound **3a,b** was used as a key intermediate for the synthesis of *S*- and *C*-nucleoside analogs of types, 5-(4-fluorophenyl / 4-anisyl)-2-*S*-(β-D-ribofuranosyl / arabinofuranosyl)-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*]quinolin-4-one (**6a–d**) and 5-(4-fluorophenyl / 4-anisyl)-2-*S*-(β-D-gluco / galactopyranosyl)-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*]quinolin-4-one (**8a–d**). Also. the 2-hydrazino compounds **9a,b** were used for the synthesis of 3-(glycosyl)-6-(4-substituted phenyl)-7,8,9,10-tetrahydro[1,2,4]triazolo[4',3':1,2]pyrimido[4,5-*b*]quinoline-5-(1*H*)-one (**11a–d** and **13a–d**). The title compounds were investigated for anti-inflammatory and anticancer activities. Compounds **11a** exhibited the comparable anti-inflammatory activity (83.4 %) to the standard drug Indomethacin (85.2 %). 5-(4-Fluorophenyl)-2-*S*-(β-D-ribofuranosyl)-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*]quinolin-4-one **6a** and 3-(ribosyl)-5-(4-fluorophenyl)-7,8,9,10-tetrahydro[1,2,4]triazolo[4',3':1,2]pyrimido[4,5-*b*]quinolin-5-one (**13a**) exhibited the maximum cytotoxic effect against the three human cancer cell lines with inhibitory effects higher than the reference doxorubicin.

Keywords: *C*-glycoside, *S*-glycoside of pyrimido[4,5-*b*]qinoline, anti-inflammatory and anticancer activities.

INTRODUCTION

CANCER disease is a major worldwide problem. In the new millennium, rapid progress has been made in the area of a cancer cell, it has become clear that inflammation has an essential role in increased cancer risk.[1,2] The process of development of cancers may be due to inflammatory cells, in addition to a variety of mediators, like cytokines, chemokines and enzymes.[3]

Oxidative stress is an important mechanism in the pathogenesis of many diseases including cancer. The generation of reactive oxygen species (ROS) with consecutive DNA damage is an initial step in carcinogenesis induced by inflammatory processes.[4] ROS is generated either *via* inflammatory cytokines or *via* cytochrome P-450 2E1 induction and may lead to lipid peroxidation. Chemokines and pro-inflammatory cytokines as interleukin(IL)-6 and IL-1α can favor the growth of tumor while the treatment with NSAIDS can minimize cancer incidence,[5] so there is a strong relation between cancer and inflammation.

Some of the pro-inflammatory factors such as reactive oxygen species, prostaglandin E2(PGE2) and tumor necrosis factor α (TNF α) are among molecules that play a major role in suppressing inflammation.[6] Nonsteroidal anti-inflammatory drugs (NSAIDS) have inhibitory activity toward cyclooxygenase-1(COX-1) and cyclooxygenase-2 (COX-2).[7] NSAIDS suppress transcription factor NF-kB which regulates COX-2 and inhibits the tumor cell.[8] Quinoline occupies the catalytic split of human DNA repair O^6-alkylguanine DNA alkyltransferase, by acting as analogs of the O^6-guanine moiety in the natural substrate, and reaching the catalytic residue Cys145.[9] Furthermore, pyrimidine and fused heterocyclic pyrimidine derivatives show anti-inflammatory and anticancer activities,[10] so the fused ring of quinoline and pyrimidine skeletons

pyrimidoquinolines are considered to be promising nuclei for anticancer drug development. In addition to the wide range of biological activity of quinoline and pyrimidoquinoline derivatives, these compounds have attracted a great deal of attention in the field of medicinal chemistry. Quinoline and pyrimidoquinoline derivatives are an important class of therapeutically useful antibacterial drugs,[11–14] anticancer,[15,16] antioxidant, analgesic and anti-inflammatory activities,[17–19] antiallergic,[20] microsomal prostaglandin *E* synthase-1 (mPGES-1) inhibitor.[21] Also, some of these derivatives showed antimalarial activity.[22]

Microwave mediated multi-component reactions constitute an especially attractive synthetic strategy for rapid and efficient library generation because products are formed in a single step and diversity can be achieved by varying the reacting components. In continuation of our efforts towards multi-component reactions,[12] we report herein a conventional and microwave rapid synthesis of pyrimido[4,5-*b*]quinoline from a three-component reaction.

EXPERIMENTAL

Melting points were determined on griffin apparatus. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL EX-300 and JEOL ECA-500 (Japan). Chemical shifts were expressed in ppm relative to $SiMe_4$ as internal standard in DMSO-d_6 as a solvent. IR spectra were recorded as KBr pellets on a spectrometer (Perkin-Elmer 1430, USA) (National Research Centre and Department of Chemistry, Cairo University). Mass spectra were run at 70 eV on HP- 5988A mass spectrometer (Micro-analytical Centre, Cairo University). Elemental analyses were done on a model 2400 CHNSO analyser (Perkin Elmer, USA). All the values were within ±0.4 % of the theoretical values. Thin layer chromatography (chloroform / methanol, 8 : 2) indicated the formation of pure compounds. Cyclohexanone, 6-aminothiouracil, aldehydes and 1-bromo-2,3,5-tri-*O*-acetyl-α-D-arabinofuranose, 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl bromide, 2,3,4,6-tetra-*O*-acetyl-α-D-gluco-, galactopyranosyl bromide, chemicals and solvents were purchased from Sigma-Aldrich (USA). The biological activities were screened in Pharmacological Unit, National Research Centre and National Cancer Institute (NCI), Cairo, Egypt.

Synthesis of Aryl-2-thioxo-3,6,7,8,9-pentahydro-1*H*-pyrimido[4,5-*b*]quinolin-4-ones (3a,b)

A mixture of cyclohexanone (0.01 mol), aryl aldehyde (0.01 mol) and 6-aminothiouracil (0.01 mol) was irradiated in a domestic microwave for 15 min. The reaction mixture was cooled, the precipitate was filtered off, washed with ethanol, dried and crystallized from DMF to produce **(3a,b)**.

5-(4-FLUOROPHENYL)-2-THIOXO-3,6,7,8,9-PENTAHYDRO-1*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (3a)

with *p*-florobenzaldehyde, as yellow powder in a 89 % yield, mp 315–317 °C. IR (KBr, cm^{-1}) 3345, 1687 ;^{1}H NMR (DMSO-d_6, ppm) δ: 1.50–1.60 (m, 2H, CH_2), 1.61–1.76 (m, 2H, CH_2), 2.18 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), 7.13 (d, 2H, phenyl, J = 8.6 Hz), 7.47 (d, 2H, phenyl, J = 8.6 Hz), and 8.21, 12.22 (2br s, 2NH, D_2O exchangeable); MS (m / z), 327 (M^+, 78 %); $C_{17}H_{14}FN_3OS$ (327.3) calcd. C: 62.30, H: 4.31, N: 12.83; found C 62.32, H: 4.29, N: 12.78.

5-(4-ANISYL)-2-THIOXO-3,6,7,8,9-PENTAHYDRO-1*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (3b)

With *p*-anisaldehyde, as white powder in a 86 % yield, mp 301–302 °C. IR (KBr, cm^{-1}) 3400, 1683; ^{1}H NMR (DMSO-d_6, ppm) δ: 1.52–1.61 (m, 2H, CH_2), 1.63–1.79 (m, 2H, CH_2), 2.23 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 3.89 (s, 3H, OCH_3), 7.23 (d, 2H, phenyl, J = 8.4 Hz), 7.50 (d, 2H, phenyl, J = 8.5 Hz), and 8.10, 11.30 (2br s, 2NH, D_2O exchangeable). ^{13}C.NMR: 22.29, 23.56, 23.90, 24.78 ($4CH_2$), 53.77 (OCH_3), 121.6–154.8 (11C-Ar), 167.6 (C-2-pyrimidine), 168.1 (CO); MS (m/z), 303 (M^+, 83 %); $C_{18}H_{17}N_3O_2S$ (303.3) calcd. C: 59.38, H: 5.64, N: 13.85; found C 59.36, H: 5.62, N: 13.81.

Synthesis of 5-Aryl-2-methylthio-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*]quinolin-4-one (4a,b)

To a warm ethanolic potassium hydroxide solution (prepared by dissolving 0.01 mol of potassium hydroxide in 30 mL absolute ethanol) was added compound **3a,b** (0.01 mol), the heating was continued for 30 min, the mixture was allowed to cool to room temperature and methyl iodide (0.12 mol) was added. The mixture was stirred under reflux for 3 h, cooled to room temperature, and poured onto cold water (100 mL). The solid precipitated was filtered off, washed with water and dried, crystallized from DMF.

5-(4-FLUOROPHENYL)-2-METHYLTHIO-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (**4a**)

Yellow crystals, in a 79 % yield; mp 264-266 °C. IR (KBr, cm^{-1}) 3354, 1687; ^{1}H NMR (DMSO-d_6, ppm) δ:1.49–1.57 (m, 2H, CH_2), 1.60–1.74 (m, 2H, CH_2), 2.17 (t, 2H, CH_2), 2.52 (s, 3H, S-CH_3), 2.84 (t, 2H, CH_2), 7.14 (d, 2H, phenyl), 7.46 (d, 2H, phenyl) and 9.45 (br s, NH, D_2O exchangeable). MS (m/z), 341 (M^+, 69 %); $C_{18}H_{17}N_3O_2S$ (303.3) calcd. C: 63.32, H: 4.72, N: 12.31; found C 63.29, H: 4.68, N: 12.27.

5-(4-ANISYL)-2-METHYLTHIO-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (**4b**)

Pale yellow crystals, in a 74 % yield; mp 243-245 °C. IR (KBr, cm^{-1}) 3354, 1687; ^{1}H NMR (DMSO-d_6, ppm) δ: 1.48–1.56 (m, 2H, CH_2), 1.56–1.70 (m, 2H, CH_2), 2.21 (t, 2H, CH_2), 2.51

(s, 3H, S-CH_3), 2.76 (t, 2H, CH_2), 3.78 (s, 3H, OCH_3), 7.11 (d, 2H, phenyl), 7.67 (d, 2H, phenyl) and 9.30 (br s, NH, D_2O exchangeable). MS (*m* / z), 337 (M^+, 56 %); $C_{19}H_{19}N_3OS$ (337.4) calcd. C: 67.62, H: 5.67, N: 12.45; found C 67.60, H: 5.63, N: 12.42.

Synthesis of Acetylated 2-S-Glycoosides of 5-Aryl-6,7,8,9-tetra-hydro-3*H*-pyrimido[4,5-*b*]-quinolin-4-one (5a–d and 7a–d)

To a solution of **3a,b** (0.01 mol) in aqueous potassium hydroxide (0.01 mol) in distilled water (5 mL) a solution of 1-bromo-2,3,5-tri-*O*-acetyl-α-D-arabinofuranose / 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl bromide or 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and galactopyranosyl bromide (0.015 mol) in acetone (40 mL) was added. The reaction mixture was stirred at room temperature for 15–24 h (under TLC control). The solvent was evaporated under reduced pressure at 40 °C, and the crude product was filtered off and washed with distilled water to remove KBr formed. The product was dried, and crystallized from the ethanol to produce **5a**–**d** and **7a**–**d**, respectively.

2-(S-2',3',5'-TRI-*O*-BENZOYL-β-D-RIBOFURANOSYL)-5-(4-FLUOROPHENYL)-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (5a)

It was obtained from **3a** and 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl bromide, as pale yellow powder in a 67 % yield; mp 289–291 °C. IR (KBr, cm^{-1}) 3379, 1730, 1689, ^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.50–1.58 (m, 2H, CH_2), 1.62–1.75 (m, 2H, CH_2), 2.25 (t, 2H, CH_2), 2.78 (t, 2H, CH_2), 4.09 (m, *H-4'*), 4.19 (m, *H-5'*, *H-5''*), 5.30 (m, *H-3'*), 5.38 (m, *H-2'*), 6.83 (d, *J* = 3.67 Hz, *H-1'*), 7.00-7.09 (m, 6H, phenyl), 7.17 (d, 2H, phenyl), 7.49–7.65 (m, 9H, phenyl), 8.00 (d, 2H, phenyl), and 9.80 (brs, NH, D_2O exchangeable). ^{13}C.NMR: 23.08, 23.11, 23.62, 24.51 ($4CH_2$), 61.40 (C-5'), 66.23(C-3'), 68.84 (C-2'), 70.19 (C-4'), 84.78 (C-1'), 121.3-155.6 (29 C-Ar), 159.5 (C-2-pyrimidine), 167.5 (CO), 169.9, 170.7, 173.4 (3CO). MS (*m* / z), 771 (M^+, 24 %); $C_{43}H_{34}FN_3O_8S$ (771.7) calcd. C: 66.91, H: 4.44, N: 5.44; found C 66.88, H: 4.42, N: 5.39.

2-(*S*-2',3',5'-TRI-*O*-BENZOYL-β-D-RIBOFURANOSYL)-5-(4-ANISYL)-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO-[4,5-*b*]QUINOLIN-4-ONE (5b)

It was obtained from **3b** and 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl bromide; as pale yellow powder. in a 70 % yield; mp 278–280 °C. IR (KBr, cm^{-1}) 3360, 1726, 1686, ^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.48–1.56 (m, 2H, CH_2), 1.60–1.73 (m, 2H, CH_2), 2.19 (t, 2H, CH_2), 2.76 (t, 2H, CH_2), 3.78 (s, 3H, OCH_3), 4.11 (m, H-4'), 4.18 (m, H-5', H-5''), 5.28 (m, H-3'), 5.36 (m, H-2'), 6.90 (d, *J* = 3.67 Hz, H-1'), 6.96–7.11 (m, 6H, phenyl), 7.18 (d, 2H, phenyl), 7.56–7.70 (m, 9H, phenyl), 8.04 (d, 2H, phenyl), and 9.55 (brs, NH). ^{13}C.NMR: 23.10, 23.14, 23.67, 24.59 ($4CH_2$), 55.09 (OCH_3), 60.56 (C-5'), 67.19 (C-3'), 69.04 (C-2'), 70.23 (C-4'), 85.67 (C-1'), 120.6-155.4 (29 C-Ar), 159.2 (C-2-pyrimidine), 165.8 (CO), 170.2, 171.3, 173.8 (3CO). MS (*m*/z), 783 (M^+, 15 %); $C_{44}H_{37}N_3O_9S$ (783.8) calcd. C: 67.42, H: 4.76, N: 5.36; found C 67.39, H: 4.78, N: 5.34.

2-(S-2',3',5'-TRI-*O*-ACETYL-β-D-ARABINOFURANOSYL)-5-(4-FLUOROPHENYL)-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (5c)

It was obtained from compound **3a** (0.01 mol) and 2,3,5-tri-*O*-acetyl-*α*-D-arabinofuranosyl bromide (0.01 mol) as yellow powder, in a 58 % yield; mp 217–219 °C. IR (KBr, cm^{-1}) 3320, 1710, 1689, ^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.51–1.59 (m, 2H, CH_2), 1.61–1.74 (m, 2H, CH_2), 2.16 (t, 2H, CH_2), 2.19–2.31 (3s, 9H, $3CH_3CO$), 2.81 (t, 2H, CH_2), 3.55 (m, 2H, H-5', H-5''), 3.71 (m, 1H, H-4'), 3.98 (m, 1H, H-3'), 4.21 (m, 1H, H-2'), 4.61 (d, 1H, *J* = 3.74 Hz, H-1'), 7.21 (d, 2H, phenyl), 8.07 (d, 2H, phenyl), and 9.70 (brs, NH, D_2O exchangeable). MS (*m*/z), 585 (M^+, 34 %); $C_{28}H_{28}FN_3O_8S$ (585.6) calcd. C: 57.42, H: 4.82, N: 7.17; found C 57.40, H: 4.79, N: 7.15.

2-(S-2',3',5'-TRI-*O*-ACETYL-β-D-ARABINOFURANOSYL)-5-(4-ANISYL)-6,7,8,9-TETRAHYDRO-3*H*-PYRIM-IDO[4,5-*b*]QUINOLIN-4-ONE (5d)

It was obtained from compound **3b** (0.01 mol) and 2,3,5-tri-*O*-acetyl-α-D-arabinofuranosyl bromide (0.01 mol) as yellow powder, in a 69 % yield; mp 199–201 °C. IR (KBr, cm^{-1}) 3360, 1720, 1686.^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.45–1.50 (m, 2H, CH_2), 1.57–1.65 (m, 2H, CH_2), 2.18 (t, 2H, CH_2), 2.22–2.35 (3s, 9H, $3CH_3CO$), 2.83 (t, 2H, CH_2), 3.52 (m, 2H, H-5', H-5''), 3.67 (m, 1H, H-4'), 3.78 (s, 3H, OCH_3), 3.96 (m, 1H, H-3'), 4.24 (m, 1H, H-2'), 4.63 (d, 1H, *J* = 3.71 Hz, H-1'), 7.23 (d, 2H, phenyl), 8.12 (d, 2H, phenyl), and 9.45 (brs, NH). ^{13}C.NMR: 22.89, 23.17, 23.91, 25.21 ($4CH_2$), 53.78 (OCH_3), 60.78 (C-5'), 66.45 (C-3'), 69.17 (C-2'), 70.35 (C-4'), 85.74 (C-1'), 120.4-155.8 (29 C-Ar), 158.7 (C-2-pyrimidine), 166.3 (CO), 170.3, 171.7, 174.3 (3CO). MS (*m* / z), 597 (M^+, 25 %); $C_{29}H_{31}N_3O_9S$ (597.6) calcd. C: 58.28, H: 3.23, N: 7.03; found C 49.27, H: 3.19, N: 6.98.

5-(4-FLUOROPHENYL)-6,7,8,9-TETRAHYDRO-2-(2',3',4',6'-TETRA-*O*-ACETYL-β-D-GLUCOPYRANOSYL-THIO)-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (7a)

It was obtained from compound **3a** (0.01 mol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.01 mol) as pale yellow powder, in a 73 % yield; mp 219–221 °C. IR (KBr, cm^{-1}) 3300, 1692,1720.^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.44–1.58 (m, 2H, CH_2), 1.55–1.63 (m, 2H, CH_2), 2.08 (t, 2H, CH_2), 2.15–2.29 (4s, 12H, $4CH_3CO$), 2.72 (t, 2H, CH_2), 3.92 (m, 1H, H-5'), 4.20 (m, 2H, H-6' , H-6''), 5.07 (t, 1H, H-4'), 5.11 (m, 1H, H-2'), 5.43 (t, 1H, *J* = 9.40 Hz, H-3'), 5.69 (d,1H, *J* = 10.8,

H-1'), 7.20 (d, 2H, *J* = 8.5 Hz, phenyl), 7.98 (d, 2H, *J* = 8.5 Hz, phenyl), 10.00 (br, NH, D_2O exchangeable). MS (*m*/z), 657 (M^+, 56 %); $C_{31}H_{32}FN_3O_{10}S$ (657.6) calcd. C: 56.61, H: 4.90, N: 6.39; found C 58.59, H: 4.87, N: 6.41.

5-(4-ANISYL)-6,7,8,9-TETRAHYDRO-2-(2',3',4',6'-TETRA-*O*-ACETYL-β-D-GLUCOPYRANOSYL-THIO)-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (7b)

It was obtained from compound 3b (0.01 mol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.01 mol) as pale yellow powder, in a 68 % yield; mp 236–238 °C. IR (KBr, cm^{-1}) 3320, 1687, 1727.^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.47–1.54 (m, 2H, CH_2), 1.58–1.67 (m, 2H, CH_2), 2.10 (t, 2H, CH_2), 2.16–2.32 (4s, 12H, $4CH_3CO$), 2.80 (t, 2H, CH_2), 3.83 (s, OCH_3), 3.92 (m, 1H, H-5'), 4.21 (m, 2H, H-6' , H-6''), 5.05 (t, 1H, H-4'), 5.14 (m, 1H, H-2'), 5.46 (t, 1H, *J* = 9.42 Hz, H-3'), 5.69 (d,1H, *J* =10.6, H-1'), 7.23 (d, 2H, *J* =8.5 Hz, phenyl), 7.88 (d, 2H, *J* = 8.5 Hz, phenyl), 10.15 (br, NH, D_2O exchangeable). MS (*m* / z), 669 (M^+, 49 %); $C_{32}H_{35}N_3O_{11}S$ (669.7) calcd. C: 57.38, H: 5.26, N: 6.27; found C 57.40, H: 5.24, N: 6.25.

5-(4-FLUOROPHENYL)-6,7,8,9-TETRAHYDRO-2-(2',3',4',6'-TETRA-*O*-ACETYL-β-D-GALACTOPYRANOSYL-THIO)-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (7c)

It was obtained from compound 3a (0.01 mol) and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (0.01 mol) as pale yellow powder, in a 70 % yield; mp 193–195 °C. IR (KBr, cm^{-1}) 3310, 1682, 1720.^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.50–1.57 (m, 2H, CH_2), 1.59–1.69 (m, 2H, CH_2), 2.12 (t, 2H, CH_2), 2.15–2.31 (4s, 12H, $4CH_3CO$), 2.85 (t, 2H, CH_2), 3.96 (m, 1H, H-5'), 4.22 (m, 2H, H-6', H-6''), 5.07 (t, 1H, H-4'), 5.16 (m, 1H, H-2'), 5.49 (t, 1H, *J* = 9.40 Hz, H-3'), 5.72 (d,1H, *J* = 9.8, H-1'), 7.23 (d, 2H, *J* = 8.6 Hz, phenyl), 7.90 (d, 2H, *J* = 8.6 Hz, phenyl), 9.70 (br, NH, D_2O exchangeable). MS (*m* / z), 657(M^+, 53 %); $C_{31}H_{32}FN_3O_{10}S$ (657.6) calcd. C: 56.61, H: 4.90, N: 6.39; found C 58.57, H: 4.92, N: 6.36.

5-ANISYL-6,7,8,9-TETRAHYDRO-2-(2',3',4',6'-TETRA-*O*-ACETYL-β-D-GALACTOPYRANOSYL-THIO)-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (7d)

It was obtained from compound **3b** (0.01 mol) and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (0.01 mol) as pale yellow powder, in a 71 % yield; mp 247-249 °C. IR (KBr, cm^{-1}) 3310, 1682, 1720.^{1}H NMR (DMSO-d_6, ppm) δ: 1.50–1.57 (m, 2H, CH_2), 1.59–1.69 (m, 2H, CH_2), 2.12 (t, 2H, CH_2), 2.15–2.31 (4s, 12H, $4CH_3CO$), 2.85 (t, 2H, CH_2), 3.96 (m, 1H, H-5'), 4.22 (m, 2H, H-6', H-6''), 5.07 (t, 1H, H-4'), 5.16 (m, 1H, H-2'), 5.49 (t, 1H, *J* = 9.40 Hz, H-3'), 5.72 (d,1H, *J* = 9.8, H-1'), 7.23 (d, 2H, *J* = 8.6 Hz, phenyl), 7.90 (d, 2H, *J* = 8.6 Hz, phenyl), 9.70 (br, NH, D_2O exchangeable). MS (*m*/z), 657 (M^+, 53 %); $C_{32}H_{35}N_3O_{11}S$ (669.7) calcd. C: 57.38, H: 5.26, N: 6.27; found C 57.36, H: 5.27, N: 6.24.

General Procedure of Deacetylated *S*-Glycosides of 5-Aryl-6,7,8,9-tetrahydro-3*H*-pyrimido-[4,5-*b*]quinolin-4-one (6a–d and 8a–d)

Dry gaseous ammonia was passed through a solution of acetylated compound **5a–d** or **7a–d** (1.0 mmol) in dry methanol (20 mL) at room temperature for 10 min. The mixture was stirred overnight (followed by TLC). The resulting mixture was then evaporated under reduced pressure to afford a solid residue that was crystallized from ethanol to afford 5-(4-flurophenyl / 4-anisyl)-2-*S*-(β-D-ribofuranosyl / arabinofuranosyl)-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*]quinolin-4-one (**6a–d**) and 5-(4-flurophenyl / 4-anisyl)-2-S-(β-D-gluco / galactopyranosyl)-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*]quinolin-4-one (**8a-d**), as a white powder, respectively.

5-(4-FLUOROPHENYL)-2-*S*-(β-D-RIBOFURANOSYL)-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]QUINO-LIN-4-ONE (6a)

Yield 52 %; mp 261–263 °C. IR (KBr, cm^{-1}) 3400, 3320, 1674. ^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.45–1.55 (m, 2H, C*H*$_2$), 1.56–1.63(m, 2H, C*H*$_2$), 2.18 (t, 2H, C*H*$_2$), 2.86 (t, 2H, C*H*$_2$), 3.87 (m, *H-5', H-5*''), 4.16 (m, *H-4'*), 4.83 (t, *H-2'*), 5.19 (t, *J* = 5.41 Hz, *J* = 4.94 Hz, OH-C(5'), 5.25 (d, *J* = 4.51 Hz, OH-C(3'), 5.46 (d, *J* = 5.90 Hz, OH-C(2'), 5.68 (t, *J* = 9.83 Hz, *H*-3'), 6.83 (d, *J* = 5.63 Hz, *H*-1'), 7.18 (d, 2H, phenyl), 8.11 (d, 2H, phenyl), 10.16 (br, N*H*, D_2O exchangeable). MS (*m*/z), 459 (M^+, 45 %); $C_{22}H_{22}FN_3O_5S$ (459.5) calcd. C: 57.50, H: 4.82, N: 9.14; found C 57.49, H: 4.79, N: 9.11.

5-(4-ANISYL)-2-*S*-(β-D-RIBOFURANOSYL)-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (6b)

Yield 59 %; mp 241–243 °C. IR (KBr, cm^{-1}) 3432, 3305, 1669. ^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.46–1.53 (m, 2H, CH_2), 1.59–1.68 (m, 2H, CH_2), 2.14 (t, 2H, CH_2), 2.83 (t, 2H, CH_2), 3.76 (s, OCH_3), 3.89 (m, H-5', H-5''), 4.17 (m, H-4''), 4.82 (t, H-2'), 5.19 (t, *J* = 5.43 Hz, *J* = 4.98 Hz, OH-C(5'), 5.24 (d, *J* = 4.47 Hz, OH-C(3'), 5.43 (d, *J* = 5.92 Hz, OH-C(2'), 5.69 (t, *J* = 9.80 Hz, H-3'), 6.85 (d, *J* = 5.60 Hz, H-1'), 7.22 (d, 2H, phenyl), 8.10 (d, 2H, phenyl), 10.26 (br, NH, D_2O exchangeable), ^{13}C NMR: 21.19, 22,75, 23.40, 24.53 ($4CH_2$), 56.09 (OCH_3), 60.86 (C-5'), 65.33 (C-3'), 67.58 (C-2'), 69.26 (C-4'), 87.71 (C-1'), 120.6-147.9 (11C- Ar), 166.7 (CO). MS (*m*/z), 471 (M^+, 53 %); $C_{23}H_{25}N_3O_6S$ (471.5) calcd. C: 58.58, H: 5.34, N: 8.91; found C 58.59, H: 5.31, N: 8.93.

5-(4-FLUOROPHENYL)-2-*S*-(β-D-ARABINOFURANOSYL)-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (6c)

Yield 55 %; mp 270–273 °C. IR (KBr, cm^{-1}) 3455, 3335, 1675. ^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.47–1.54 (m, 2H, CH_2), 1.58–1.67 (m, 2H, CH_2), 2.15 (t, 2H, CH_2), 2.79 (t, 2H, CH_2), 3.83 (m, H-5', H-5''), 4.12 (m, H-4'), 4.81 (t, H-2'), 5.12 (t, *J* = 5.41

Hz, *J* = 4.87 Hz, OH-C(5'), 5.22 (d, *J* = 4.64 Hz, OH-C(3'), 5.41 (d, *J* = 5.95 Hz, OH-C(2'), 5.66 (t, *J* = 9.80 Hz, H-3'), 6.81 (d, *J* = 5.60 Hz, H-1'), 7.28 (d, 2H, phenyl), 8.07 (d, 2H, phenyl), 10.15 (br, NH, D_2O exchangeable). MS (*m*/z), 459 (M^+, 38 %); $C_{22}H_{22}FN_3O_5S$ (459.5) calcd. C: 57.50, H: 4.82, N: 9.14; found C 57.51, H: 4.77, N: 9.10.

5-(4-ANISYL)-2-*S*-(β-D-ARABINOFURANOSYL)-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (6d)
Yield 51 %; mp 273–275 °C. IR (KBr, cm^{-1}) 3423, 3318, 1668. ^1H NMR (DMSO-d_6, ppm) *δ*: 1.46–1.53 (m, 2H, CH_2), 1.57–1.69 (m, 2H, CH_2), 2.12 (t, 2H, CH_2), 2.85 (t, 2H, CH_2), 3.70 (s, OCH_3), 3.82 (m, H-5', H-5''), 4.12 (m, H-4'), 4.80 (t, H-2'), 5.14 (t, *J* = 5.41 Hz, *J* = 4.97 Hz, OH-C(5'), 5.22 (d, *J* = 4.46 Hz, OH-C(3'), 5.41 (d, *J* = 5.92 Hz, OH-C(2'), 5.66 (t, *J* = 9.78 Hz, H-3'), 6.86 (d, *J* = 5.60 Hz, H-1'), 7.28 (d, 2H, phenyl), 8.18 (d, 2H, phenyl), 9.85 (br, NH, D_2O exchangeable), ^{13}C NMR: 21.21, 22,56, 23.48, 24.61 ($4CH_2$), 56.12 (OCH_3), 60.85 (C-5'), 65.36 (C-3'), 67.58 (C-2'), 69.68 (C-4'), 87.68 (C-1'), 121.2-148.9 (11C- Ar), 167.4 (CO). MS (*m*/z), 471 (M^+, 40 %); $C_{23}H_{25}N_3O_6S$ (471.5) calcd. C: 58.58, H: 5.34, N8.91; found C 58.56, H: 5.29, N: 8.90.

5-(4-FLUOROPHENYL)-2-*S*-(β-D-GLUCOPYRANOSYL)-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]QUINO-LIN-4-ONE (8a)
Yield 51 %; mp 259–261 °C. IR (KBr, cm^{-1}) 3420, 3260, 1675. ^1H NMR (DMSO-d_6, ppm) *δ*: 1.48–1.56 (m, 2H, CH_2), 1.59–1.68 (m, 2H, CH_2), 2.18 (t, 2H, CH_2), 2.83 (t, 2H, CH_2), 3.95 (m, H-5'), 4.05 (m, H-6', H-6''), 4.39 (m, H-4'), 4.98 (t, H-2'), 4.65 (br, D_2O-exchangeable OH), 5.08 (br, D_2O-exchangeable OH), 5.17 (d, *J* = 4.82 Hz, D_2O-exchangeable OH), 5.23 (t, *J* = 9.63 Hz, H-3'), 5.67 (br, D_2O-exchangeable OH), 6.25 (d, *J* = 10.64 Hz, H-1'), 7.25 (d, 2H, phenyl), 8.03 (d, 2H, phenyl), 10.35 (br, 1H, NH, D_2O exchangeable). MS (*m*/z), 489 (M^+, 59 %); $C_{23}H_{24}FN_3O_6S$ (489.5) calcd. C: 56.43, H: 4.94, N: 8.58; found C 56.39, H: 4.91, N: 8.56.

5-(4-ANISYL)-2-*S*-(β-D-GLUCOPYRANOSYL)-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (8b)
Yield 54 %; mp 276–278 °C. IR (KBr, cm^{-1}) 3430, 3278, 1682. ^1H NMR (DMSO-d_6, ppm) *δ*: 1.48–1.56 (m, 2H, CH_2), 1.61–1.69 (m, 2H, CH_2), 2.09 (t, 2H, CH_2), 2.75 (t, 2H, CH_2), 3.76 (s, OCH_3), 3.99 (m, H-5'), 4.09 (m, H-6', H-6''), 4.51 (m, H-4'), 4.70 (br, D_2O-exchangeable OH), 4.91 (t, H-2'), 5.12 (br, D_2O-exchangeable OH), 5.19 (d, *J* = 4.81 Hz, D_2O-exchangeable OH), 5.28 (t, *J* = 9.62 Hz, H-3'), 5.69 (br, D_2O-exchangeable OH), 6.23 (d, *J* = 10.61 Hz, H-1'), 7.28 (d, 2H, phenyl), 8.05 (d, 2H, phenyl), 10.15 (br, NH, D_2O exchangeable). ^{13}C NMR: 22.34, 23.81, 24.12, 25.08 ($4CH_2$), 56.03 (OCH_3), 61.45 (C-6'), 66.40 (C-3'), 67.89 (C-2'), 68.95 (C-4'), 77.82 (C-5'), 89.71 (C-1'), 120.8–148.4 (11C-Ar), 159.3 (C-2-pyrimidine), 165.9 (CO). MS (*m*/z), 485 (M^+, 56 %); $C_{24}H_{27}N_3O_6S$ (485.5) calcd. C: 59.36, H: 5.61, N: 8.65; found C 59.33, H: 5.59, N: 8.63.

5-(4-FLUOROPHENYL)-2-*S*-(β-D-GALACTOPYRANOSYL)-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (8c)
Yield 51 %; mp 245–247 °C. IR (KBr, cm^{-1}) 3425, 3310, 1672. ^1H NMR (DMSO-d_6, ppm) *δ*: 1.44–1.58 (m, 2H, CH_2), 1.60–1.72 (m, 2H, CH_2), 2.19 (t, 2H, CH_2), 2.79 (t, 2H, CH_2), 3.93 (m, H-5'), 4.07 (m, H-6', H-6''), 4.38 (m, H-4'), 4.98 (t, H-2'), 4.75 (br, D_2O-exchangeable OH), 5.08 (br, D_2O-exchangeable OH), 5.12 (d, *J* = 4.80 Hz, D_2O-exchangeable OH), 5.19 (t, *J* = 9.62 Hz, H-3'), 5.71 (br, D_2O-exchangeable OH), 6.29 (d, *J* = 10.62 Hz, H-1'), 7.26 (d, 2H, phenyl), 8.02 (d, 2H, phenyl), 9.95 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR: 22.32, 23.76, 24.19, 25.11 ($4CH_2$), 61.53 (C-6'), 66.38 (C-3'), 67.93 (C-2'), 70.05 (C-4'), 76.91 (C-5'), 89.67 (C-1'), 121.1–149.6 (11C-Ar), 159.1 (C-2-pyrimidine), 166.3 (CO). MS (*m*/z),) 489 (M^+, 62 %); $C_{23}H_{24}FN_3O_6S$ (489.5) calcd. C: 56.43, H: 4.94, N: 8.58; found C 56.41, H: 4.90, N: 8.54.

5-(4-ANISYL)-2-*S*-(β-D-GALACTOPYRANOSYL)-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]-QUINOLIN-4-ONE (8d)
Yield 50 %; mp 263–265 °C. IR (KBr, cm^{-1}) 3400, 3295, 1679. ^1H NMR (DMSO-d_6, ppm) *δ*: 1.49–1.59 (m, 2H, CH_2), 1.62–1.74 (m, 2H, CH_2), 2.21 (t, 2H, CH_2), 2.87 (t, 2H, CH_2), 3.86 (s, OCH_3), 3.99 (m, H-5'), 4.14 (m, H-6', H-6''), 4.50 (m, H-4'), 4.99 (t, H-2'), 4.73 (br, D_2O-exchangeable OH), 5.13 (br, D_2O-exchangeable OH), 5.18 (d, *J* = 4.83 Hz, D_2O-exchangeable OH), 5.25 (t, *J* = 9.65 Hz, H-3'), 5.75 (br, D_2O-exchangeable OH), 6.21 (d, *J* = 10.60 Hz, H-1'), 7.21 (d, 2H, phenyl), 8.11 (d, 2H, phenyl), 10.18 (br, 1H, NH, D_2O exchangeable). MS (*m* / z), 485 (M^+, 43 %); $C_{24}H_{27}N_3O_6S$ (485.5) calcd. C: 59.36, H: 5.61, N: 8.65; found C: 59.35, H: 5.58, N: 8.61.

Synthesis of 5-Aryl-2-hydrazino-6,7,8,9-tetraahydro-3*H*-pyrimido[4,5-*b*]quinolin-4-one (9a,b)

A suspension of compound **3** (10 m mol) in hydrazine hydrate (99 %, 20 mL) was stirred under reflux for 10 h. The reaction mixture was allowed to cool to room temperature. The solid precipitated was filtered off, washed with ethanol, dried and crystallized from dimethylformamide to produce 5-(4-flutophenyl)-2-hydrazino-6,7,8,9-tetrahydro-3*H*-pyrimido-[4,5-*b*]quinolin-4-one (**9a**) and 5-(4-anisyl)-2-hydrazino-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*]quinolin-4-one (**9b**), as white powder in good yields.

5-(4-FLUOROPHENYL)-2-HYDRAZINO-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (**9a**)
Yield 86 %; mp 319–321 °C. IR (KBr, cm^{-1}) 3455, 1685. ^1H NMR (DMSO-d_6, ppm) *δ*: 1.45–1.57 (m, 2H, CH_2), 1.59–1.66

(m, 2H, CH_2), 2.17 (t, 2H, CH_2), 2.80 (t, 2H, CH_2), 7.22 (d, 2H, phenyl, *J* = 8.4 Hz), 7.65 (d, 2H, phenyl, *J* = 8.5 Hz), and 9.20, 11.50 (2br s, 2NH, D_2O exchangeable). ^{13}C.NMR: 22.69, 23.21, 23.87, 24.59 ($4CH_2$), 121.3–155.5 (11 C-Ar), 156.9 (C-2-pyrimidine), 164.9 (CO). MS (*m* / z), 325 (M^+, 78 %); $C_{17}H_{16}FN_5O$ (325.3) calcd. C: 62.75, H: 4.96, N: 21.53; found C: 62.72, H: 4.93, N: 21.50.

5-(4-ANISYL)-2-HYDRAZINO-6,7,8,9-TETRAHYDRO-3*H*-PYRIMIDO[4,5-*b*]QUINOLIN-4-ONE (9b)

Yield 89 %; mp 307–309 °C. IR (KBr, cm^{-1}) 3450, 1678. ^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.51–1.61 (m, 2H, CH_2), 1.64-1.79 (m, 2H, CH_2), 2.23 (t, 2H, CH_2), 2.84 (t, 2H, CH_2), 7.27 (d, 2H, phenyl, *J* = 8.6 Hz), 7.68 (d, 2H, phenyl, *J* = 8.5 Hz), and 9.35, 11.78 (2brs, 2NH, D_2O exchangeable). ^{13}C.NMR: 22.19, 22.51, 23.89, 24.71 ($4CH_2$), 53.09 (OCH_3). 122.3–154.5 (11 C-Ar), 156.3 (C-2-pyrimidine), 165.6 (CO). MS (*m*/z), 337 (M^+, 86 %); $C_{18}H_{19}N_5O_2$ (337.4) calcd. C: 64.07, H: 5.67, N: 20.76; found C: 64.11, H: 5.63, N: 20.73.

Synthesis of 3-(Penta-*O*-acetyl/tetra-*O*-acetyl-glycosyl)-6-(4-substituted-phenyl)-7,8,9,10-tetrahydro[1,2,4]triazolo[4',3':1.2]pyrimido[4,5-*b*]qunioline-5-(1H)-one (10a–d and 12a–d)

A solution from each of **9a,b** (10 mmol) and aldopentose / aldohexose (10 mmol) in a mixture of acetic anhydride, acetic acid (1 : 1) (50 mL) was stirred under reflux for 3–5 h (under TLC control). The mixture was then extracted with chloroform several times (150–200 mL). After removal of chloroform under reduced pressure the residue (the intermediates **10a**–**d**, **12a**–**d**) was followed up in the next step without identification.

Synthesis of 3-(Glycosyl)-6-(4-substituted phenyl)-7,8,9,10-tetrahydro[1.2.4]triazolo[4',3'-:1,2]pyrimido[4,5-*b*]quinoline-5-(1*H*)-one (11a–d and 13a–d)

A solution from each of **10a**–**d** or **12a**–**d** (10 mmol) in solution of sodium methoxide (10 mmol) (sodium metal in methanol, 100 mL), was stirred at room temperature for 24 h, and then neutralized with hydrochloric acid solution (pH control). The precipitate formed was filtered off, washed with cold water, dried and crystallized from ethanol (60–100 mL) to obtain 3-(glucosyl/galactosyl)-6-(4-flurophenyl / 4-anisyl)-7,8,9,10 tetrahydro[1,2,4]triazolo [4',3':1,2] pyrimido[4,5-*b*]quinolin-5-one (**11a**–**d**) and 3-(ribosyl / arabinosyl)-6-(4-flurophenyl / 4-anisyl)-7,8,9,10-tetrahydro[1,2,4]triazolo[4',3':1,2]-pyrimido[4,5-*b*]quinolin-5-one (**13a**–**d**), in moderate yields, as a white powder, respectively.

3-(GLUCOSYL)-5-(4-FLUOROPHENYL)-7,8,9,10-TETRAHYDRO[1,2,4]TRIAZOLO[4',3':1,2]PYRIMIDO[4,5-*b*]-QUINOLIN-5-ONE (11a)

Yield 48 %; mp 269–271 °C. IR (KBr, cm^{-1}) 3450-3100, 1692. ^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.49–1.64 (m, 2H, CH_2), 1.68–1.79 (m, 2H, CH_2), 2.26 (t, 2H, CH_2), 2.90 (t, 2H, CH_2), 3.56 (m, 5OH, D_2O exchangeable), 3.95 (m, 1H, H-4'), 4.21 (m, 2H, H-5', H-5"), 4.53 (m, 1H, H-3'), 4.80 (m, 1H, H-2'), 5.69 (m, 1H, H-1'), 7.24 (d, 2H, *J* = 8.4 Hz, phenyl), 7.98 (d,2H, *J* = 8.5 Hz, phenyl), 10.15 (br, NH, D_2O exchangeable). ^{13}C NMR: 22.28, 23.73, 24.21, 25.85 ($4CH_2$), 41.35 (OCH_2), 67.70, 68.45, 69.24, 70.52 (4CH), 121.4–157.6 (13 Ar-C), 164.5 (CO). MS (*m*/z), 485 (M^+, 37 %); $C_{23}H_{24}FN_5O_6$ (485.5) calcd. C: 56.90, H: 4.98, N: 14.43; found C: 56.87, H: 4.96, N: 14.40.

3-(GLUCOSYL)-5-(4-ANISYL)-7,8,9,10-TETRAHYDRO[1,2,4]TRIAZOLO[4',3':1,2]PYRIMIDO[4,5-*b*]-QUINOLIN-5-ONE (11b)

Yield 51 %; mp 239–241 °C. IR (KBr, cm^{-1}) 3500–3150, 1692. ^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.51–1.62 (m, 2H, CH_2), 1.64–1.77 (m, 2H, CH_2), 2.23 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), 3.53 (m, 5OH, D_2O exchangeable), 3.68 (s, 3H, OCH_3), 3.89 (m, 1H, H-4'), 4.20 (m, 2H, H-5', H-5"), 4.53 (m, 1H, H-3'), 4.85 (m, 1H, H-2'), 5.70 (m, 1H, H-1'), 7.22 (d, 2H, *J* = 8.6 Hz, phenyl), 7.82 (d, 2H, *J* = 8.5 Hz, phenyl), 10.19 (br, 1H, NH, D_2O exchangeable). MS (*m*/z), 497 (M^+, 29 %); $C_{24}H_{24}N_5O_7$ (497.5) calcd. C: 57.94, H: 5.47, N: 14.07; found C: 57.89, H: 5.49, N: 14.03.

3-(GALACTOSYL)-5-(4-FLUOROPHENYL)-7,8,9,10-TETRAHYDRO[1,2,4]TRIAZOLO[4',3':1,2]PYRIMIDO[4,5-*b*]QUINOLIN-5-ONE (11c)

Yield 45 %; mp 253–255 °C. IR (KBr, cm^{-1}) 3480–3120, 1692. ^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.47–1.61 (m, 2H, CH_2), 1.65–1.73 (m, 2H, CH_2), 2.18 (t, 2H, CH_2), 2.90 (t, 2H, CH_2), 3.50 (m, 5OH, D_2O exchangeable), 3.87 (m, 1H, H-4'), 4.24 (m, 2H, H-5', H-5"), 4.49 (m, 1H, H-3'), 4.72 (m, 1H, H-2'), 5.68 (m, 1H, H-1'), 7.30 (d, 2H, *J* = 8.5 Hz, phenyl), 7.98 (d, 2H, *J* = 8.5 Hz, phenyl), 9.80 (br, NH, D_2O exchangeable). MS (*m*/z), 485 (M^+, 30 %); $C_{23}H_{24}FN_5O_6$ (485.5) calcd. C: 56.90, H: 4.98, N: 14.43; found C: 56.89, H: 4.94, N: 14.38.

3-(GALACTOSYL)-5-(4-ANISYL)-7,8,9,10-TETRAHYDRO[1,2,4]TRIAZOLO[4',3':1,2]PYRIMIDO[4,5-*b*]QUINOLIN-5-ONE (11d)

Yield 54 %; mp 247–249 °C. IR (KBr, cm^{-1}) 3440-3160, 1687. ^{1}H NMR (DMSO-d_6, ppm) *δ*: 1.50–1.66 (m, 2H, CH_2), 1.69–1.80 (m, 2H, CH_2), 2.28 (t, 2H, CH_2), 2.92 (t, 2H, CH_2), 3.55 (m, 5OH, D_2O exchangeable), 3.76 (s, 3H, OCH_3), 3.85 (m, 1H, H-4'), 4.24 (m, 2H, H-5', H-5"), 4.61 (m, 1H, H-3'), 4.75 (m, 1H, H-2'), 5.68 (m, 1H, H-1'), 7.34 (d, 2H, *J* = 8.5 Hz, phenyl), 7.87 (d,2H, *J* = 8.6 Hz, phenyl), 10.05 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR: 22.31, 23.65, 24.33, 25.91

($4CH_2$), 46.08 (OCH_2), 57.66 (OCH_3), 67.91, 68.67, 70.14, 71.23 (4CH), 121.6-157.2 (13 Ar-C), 165.6 (CO). MS (*m*/z), 497(M^+, 31 %); $C_{24}H_{24}N_5O_7$ (497.5) calcd. C: 57.94, H: 5.47, N: 14.07; found C: 57.90, H: 5.45, N: 13.98.

3-(RIBOSYL)-5-(4-FLUOROPHENYL)-7,8,9,10-TETRAHYDRO[1,2,4]TRIAZOLO[4',3':1,2]PYRIMIDO[4,5-*b*]-QUINOLIN-5-ONE (**13a**)

Yield 60 %; mp 262–264 °C. IR (KBr, cm^{-1}) 3480–3180, 1689. ^1H NMR (DMSO-d_6, ppm) δ: 1.51–1.63 (m, 2H, CH_2), 1.66–1.79 (m, 2H, CH_2), 2.23 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 3.80 (m, 4OH), 4.31 (m, 1H, H-3'), 4.62 (m, 2H, H-4', H-4''), 5.33 (t, 1H, H-2', *J* = 7.6 Hz), 5.67 (d, 1H, H-1', *J* = 7.8 Hz), 7.28 (d, 2H, *J* = 8.5 Hz, phenyl), 8.02 (d, 2H, *J* = 8.5 Hz, phenyl), 9.85 (br, 1H, NH, D_2O exchangeable). MS (*m*/z), 455 (M^+, 26 %); $C_{22}H_{22}FN_5O_5$ (455.4) calcd. C: 58.01, H: 4.87, N: 15.37; found C: 57.97, H: 4.88, N: 15.33.

3-(RIBOSYL)-5-(4-ANISYL)-7,8,9,10-TETRAHYDRO[1,2,4]TRIAZOLO[4',3':1,2]PYRIMIDO[4,5-*b*]-QUINOLIN-5-ONE (***13b***)

Yield 48 %; mp 251–253 °C. IR (KBr, cm^{-1}) 3490–3150, 1681. ^1H NMR (DMSO-d_6, ppm) δ: 1.48–1.62 (m, 2H, CH_2), 1.67–1.89 (m, 2H, CH_2), 2.19 (t, 2H, CH_2), 2.86 (t, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.87 (m, 4OH), 4.29 (m, 1H, H-3'), 4.61 (m, 2H, H-4', H-4''), 5.34 (t, 1H, H-2', *J* =7.6 Hz), 5.66 (d, 1H, H-1', *J* = 7.8 Hz), 7.28 (d, 2H, *J* = 8.4 Hz, phenyl), 7.96 (d, 2H, *J* = 8.5 Hz, phenyl), 9.95 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR: 22.31, 23.81, 24.56, 25.90 ($4CH_2$), 45.19 (OCH_2), 55.13 (OCH_3), 68.78, 70.34, 72.59 (3CH), 122.3–156.4 (13 Ar-C), 165.2 (CO). MS (*m*/z), 467 (M^+, 18 %); $C_{23}H_{25}N_5O_6$ (467.5) calcd. C: 59.09, H: 5.39, N: 14.98; found C: 59.11, H: 5.35, N: 14.93.

3-(ARABINOSYL)-5-(4-FLUOROPHENYL)-7,8,9,10-TETRAHYDRO[1,2,4]TRIAZOLO[4',3':1,2]PYRIMIDO-[4,5-*b*]QUINOLIN-5-ONE (**13c**)

Yield 58 %; mp 241–242 °C. IR (KBr, cm^{-1}) 3500–3120, 1685. ^1H NMR (DMSO-d_6, ppm) δ: 1.50–1.63 (m, 2H, CH_2), 1.65–1.83 (m, 2H, CH_2), 2.26 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 3.73 (m, 4OH), 4.27 (m, 1H, H-3'), 4.61 (m, 2H, H-4', H-4''), 5.31 (t, 1H, H-2', *J* = 7.5 Hz), 5.64 (d, 1H, H-1', *J* = 7.8 Hz), 7.25 (d, 2H, *J* = 8.4 Hz, phenyl), 7.86 (d, 2H, *J* = 8.5 Hz, phenyl), 10.35 (br, NH, D_2O exchangeable). MS (*m*/z), 455 (M^+, 21 %); $C_{22}H_{22}FN_5O_5$ (455.4) calcd. C: 58.01, H: 4.87, N: 15.37; found C: 58.02, H: 4.85, N: 15.39.

3-(ARABINOSYL)-5-(4-ANISYL)-7,8,9,10-TETRAHYDRO[1,2,4]TRIAZOLO[4',3':1,2]PYRIMIDO[4,5-*b*]-QUINOLIN-5-ONE (**13d**)

Yield 51 %; mp 239–241 °C. IR (KBr, cm^{-1}) 3470–3160, 1683. ^1H NMR (DMSO-d_6, ppm) δ: 1.51–1.62 (m, 2H, CH_2), 1.64–1.78 (m, 2H, CH_2), 2.21 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.75 (m, 4OH), 4.27 (m, 1H, H-3'), 4.58 (m, 2H, H-4', H-4''), 5.27 (t, 1H, H-2', *J* =7.4 Hz), 5.64 (d, 1H, H-1', *J* = 7.7 Hz), 7.20 (d, 2H, *J* = 8.5 Hz, phenyl), 7.36 (d, 2H, *J* = 8.6 Hz, phenyl), 9.85 (br, NH, D_2O exchangeable). MS (*m*/z), 467 (M^+, 22 %); $C_{23}H_{25}N_5O_6$ (467.5) calcd. C: 59.09, H: 5.39, N: 14.98; found C: 59.07, H: 5.37, N: 14.96.

Animals

Adult male albino rats (Harlan Sprague-Dawley), weighing 150–180 g, were used for the evaluation of anti-inflammatory activity. Animals were fasted for 12 hours before the assay. International principle and local regulations concerning the care of used laboratory animals was taken into account.[23] All animals were obtained from the animal house colony of the National Research Centre, Cairo, Egypt. The animals were acclimatized to the experimental room having temperature 22 ± 1 °C, controlled humidity conditions, and 14 : 10 h light and dark cycle. The rats were fed on autoclaved standard mice food pellets (Hindustan Lever Ltd., New Delhi) and water ad libitum.

Anti-Inflammatory Activity

Carrageenin-induced paw edema test was performed on male albino rats by using the method of Winter *et al.*[24] The animals were weighed, marked for identification and divided into 14 groups, each group containing 6 animals. 1 % carboxymethyl cellulose (CMC) was selected as vehicle to suspend the standard drug and test compounds. The 1st group was kept as control and was given the respective volume of vehicle (1 % CMC, oral) only. The 2nd to 13th groups were given a 100 mg kg^{-1} body mass oral dose of test compounds. One hour later, 0.2 mL of 1 % carrageenan suspension in 0.9 % NaCl solution was injected subcutaneously, into the subplantar tissue of the right hind paw of each mouse and the paw volume was measured with a plethysmometer (UGO Basile 7140, model-7141, Biological research apparatus, Italy) . The initial paw volume was measured within 30 s of the injection and remeasured again 1 h, 2 h, 3 h and 4 h after administration of Carrageenan. The last group was administered indomethacin in a dose of 10 mg kg^{-1} orally as a standard reference.[25] The mean increase in paw volume was compared with that of control group and percent inhibition values were calculated by the formula given below: % anti-inflammatory activity = ($V_c - V_t / V_c$) × 100. Where V_t represents the paw volume in drug treated animals and V_c represents the paw volume of control group of animals.

In vitro Anticancer Activity in Cultured Cells by MTT Assay

ANTITUMOR SCREENING

Dimethyl sulfoxide (DMSO), doxorubicin, penicillin, streptomycin and sulforhodamine B (SRB) were from Sigma

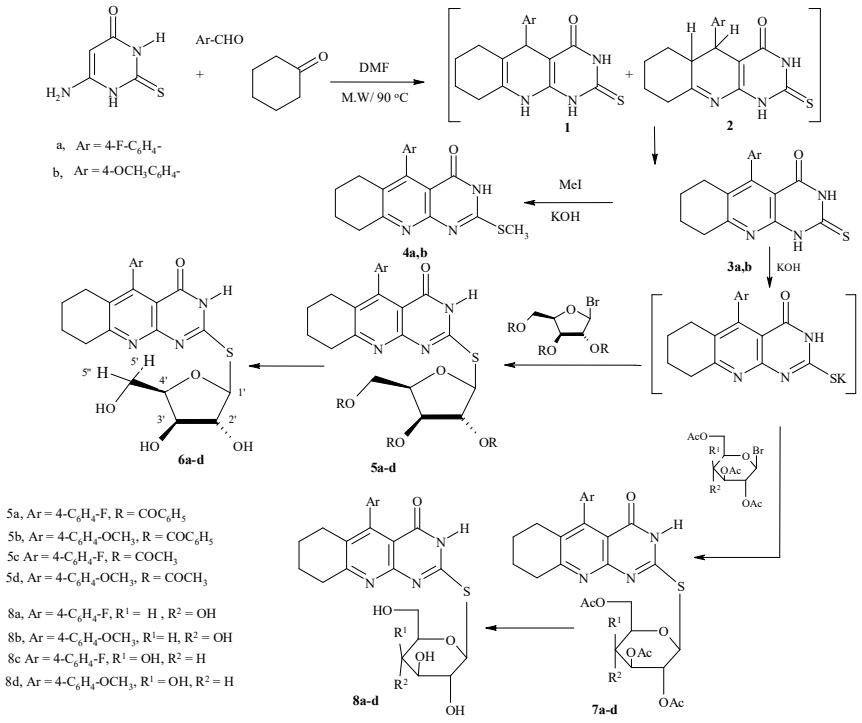
Chemical Co. (USA). RPMI-1640 medium was from Cambrex (USA). Fetal bovine serum (FBS) and L-glutamine were from Gibco Invitrogen Co. (UK).

CELL CULTURES

Some of the synthesized compounds (**3a**,**b**), (**6a**,**b**), (**8a**,**b**), (**9a**,**b**), (**11a**,**b**) and (**13a**,**b**) were tested for *in vitro* anticancer activity against three human tumor cell lines, HepG2 (human liver carcinoma), NCI-H460 (non-small cell lung cancer) and MCF-7 (breast adenocarcinoma) by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.[26] HepG2 and NCI-H460 were kindly provided by the National Cancer Institute (Cairo, Egypt) and MCF-7 was obtained from the European Collection of Cell Cultures (Salisbury, UK). They grew as monolayers and were routinely maintained in RPMI-1640 medium supplemented with 5 % heat inactivated FBS, 2 mmol L^{-1} glutamine and antibiotics (penicillin 100 U mL^{-1}, streptomycin 100 µg mL^{-1}), at 37 °C in a humidified atmosphere containing 5 % CO_2. Exponentially growing cells were obtained by plating 1.5×10^5 cells mL^{-1}, followed by 24 h incubation. The effect of the vehicle solvent DMSO on the growth of these cell lines was evaluated by exposing untreated control cells to the maximum concentration (0.5 %) of DMSO used in each assay. The effect of compounds on *in vitro* growth of human tumor cell lines was evaluated according to the procedure adopted by the national cancer institute (NCI, USA) by using sulforhodamine B as protein binding dye to assess cell growth.[27] Cells growing exponentially in 96-well plates were then exposed for 48 h to five different concentrations of each test compound (5, 12, 25, 50 and 100 µmol L^{-1}). After this exposure period, adherent cells were fixed, washed and stained. The bound stain was solubilized and the optical density (absorbance) was measured, and the growth inhibition of 50 % (GI_{50}) was calculated.[28] Doxorubicin was used as a reference compound (Table 2).

RESULTS AND DISCUSSION

In continuation of our drug research program, and on the basis of the above considerations, original nucleoside analogs directed upon reverse transcriptase still aroused considerable interest.[29] In this study the synthetic pathways depicted in Schemes 1 and 2 outlines the chemistry of the present study. Thus, pyrimido-[4,5-*b*]quinoline as the starting materials **3a,b** are easily prepared following the well established procedure reported in the literature.[12] Treatment of 6-aminothiouracil with cyclohexanone gave the corresponding 1,4-dihydropyridine derivatives as intermediates **1, 2** which in turn gave compounds **3a,b** upon microwave irradiation at 90 °C for 20 min in DMF with arylaldehyde (Scheme 1).



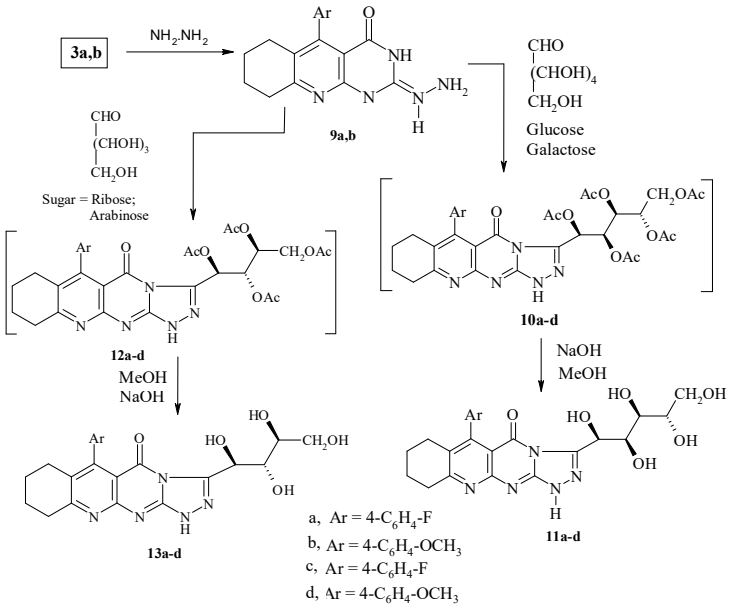
Scheme 1. Synthesis of Deacetylated *S*-Glycosides of 5-Aryl-6,7,8,9-tetrahydro-3*H*-pyrimido-[4,5-*b*]quinolin-4-one **6a–d** and **8a–d**.

Compounds **3a,b** was found to be useful for the syntheses of the interesting *S*-glycosides. As a model experiment the alkylation of **4a,b** was carried out by the reaction of one equivalent of methyl iodide with the potassium salt of **3a,b** (generated in situ by the reaction of **3a,b** with alcoholic potassium hydroxide). The structure of the new 2-methylthioquinoline **4a,b** was confirmed by all spectroscopic data. The ^{13}C NMR spectrum as an example revealed that the corresponding signal of the C-2 (C–SCH_3) appeared at $\delta \approx 159$ ppm. The chemical shifts in the ^{13}C NMR spectrum of the 2-thioxo- (**4a**) and 2-methylthio-pyrimidine in the literature[30] indicated that the site of the alkylation is the sulfur atom rather than the nitrogen atom (Scheme 1).

The synthetic route we used for the preparation of 2-*S*-(β-D-glycopyranosyl / or furanosyl)-pyrimido[4,5-*b*]quinoline is outlined in Scheme 1. The heterocycle pyrimido[4,5-*b*]quinolines **3a–d** was converted into its potassium salt with used of KOH in acetone and was stirred at room temperature for 15–20 hours with 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl bromide or 2,3,5-tri-*O*-acetyl-α-D-arabinofuranose-bromide afforded the *S*-glycosylated nucleosides **5a–d** in good yields. Thin layer chromatography (chloroform:methanol, 8:2) indicated the formation of the pure compounds. Also, the reaction of compounds **3a,b** with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and galactopyranosyl bromide under the same conditions gave the *S*-glycosides **7a–d**, respectively. The structures assignment of this product was based on their elemental analysis and the spectral data.

Deacetylation of *S*-nucleosides **5a–d** and **7a–d** proceeded smoothly *via* methanolic ammonia solution treatment to afford the free nucleoside mimetics **6a–d** and **8a–d** in moderate yields (Scheme 1). The ^{1}H NMR data of the compounds **6** and **8** revealed the absence of the acetyl protons and appearance of the D_2O exchangeable OH-protons at δ 5.19–5.46 ppm for compounds **6** and around δ 4.65–5.70 ppm for compounds **8**. The IR data of the compound **6a** as a typical example also showed the absence of the acetyl function and the appearance of the characteristic OH's band at 3400 (br) cm^{-1}.

Action of hydrazine hydrate on 2-thioxopyrimido[4,5-*b*]quinoline (**3a,b**) in ethanol afforded 5-aryl-2-hydrazino-2,3,6,7,8,9-hexahydro-1*H*-pyrimido[4,5-*b*]quinolin-4-one (**9a,b**). Structures of these compounds are supported by spectral data such as IR, NMR, Mass and Elemental analyses. The required hydrazone intermediates **10a–d** and **12a–d** were prepared by condensation of 2-hydrazino-pyrimidoquinoline **9** with the appropriate aldohexoses and aldopentoses sugar (Scheme 2). Thus, Stirring of aryl-2-hydrazino-2,3,6,7,8,9-hexahydro-1*H*-pyrimido[4,5-*b*]-quinolin-4-one derivatives (**9a,b**) with aldosugar at room temperature in a mixture of acetic anhydride-pyridine (1 : 1) afforded the respective hydrazone (**10a–d**, **12a–d**), respectively as intermediates. Deprotection of the acyclic *C*-nucleosides **10a–d** and **12a–d** could be achieved when they were stirred in methanolic sodium methoxide solution at room temperature to give a moderate yields of 3-(glycosyl)-6-(4-substitutedphenyl)-7,8,9,10-tetrahydro [1,2,4]triazolo-[4',3':1,2]pyrimido[4,5-*b*]quinoline-5-(1*H*)-one (**11a–d**, **13a–d**). Structures **11a–d** and **13a–d** were confirmed by spectral and elemental analyses. Their ^{1}H NMR spectra showed no absorption signals for the acetyl



Scheme 2. Synthesis of 3-(glycosyl)-6-(4-substitutedphenyl)-7,8,9,10-tetrahydro[1,2,4]triazolo[4',3'- :1,2]pyrimido[4,5-*b*]quinoline-5-(1*H*)-one **11a–d** and **13a–d**.

protons but showed the multiplet signal supported to the hydroxyl group protons in the region δ 3.55–3.80 (D_2O exchangeable), the signals due to the protons of the sugar moiety at δ 3.85–5.68. Also, the ^{13}C NMR spectrum for compound **11d** as an example showed eight lines around 22.31–71.23 corresponding to ten sp^3 carbon atoms, thirteen lines around 121.6–157.2 supported to the sp^2 carbon atoms and the absorption signal corresponds to the carbonyl group at 165.6.

The anti-inflammatory activity of newly synthesized compounds was evaluated by carrageenan-induced paw edema model in rats using indomethacin as a reference drug. Results are expressed as mean ±S.D. (Table 1). Differences between control and treatment groups evaluated for statistical significance using one way ANOVA followed by Tukey's test. The test compounds administered 1 h prior to carrageenan injection at a dose of 100 mg kg^{-1} body wt. caused significant inhibition of paw edema volume. Most of the tested compounds showed good anti-inflammatory activity after the 2nd hour of drug treatment comparable to the standard drug Indomethacin. Compound **6a** comprising *S*-ribofuranozyl moiety was found to be most potent, showing very high activity after 1st, 2nd, 3rd as well as 4th hour of drug, exhibited activity of 78.6 % in comparison with Indomethacin (92.8 %). Compounds **8a** (*S*-glucopyranozyl) and **13a** (1,2,4-triazoloribosyl), in addition to 4-fluorophenyl substitution on pyrimidoquinoline derivatives confer high anti-inflammatory activity in the range 58.7–76.5 % compared to Indomethacin. Compound **11a** (1,2,4-triazologlucosyl) showed excellent activity (83.4 %), comparable to the standard drug Indomethacin (85.2 %). Compound **3a** with pyrimidoquinoline-2-thion, hydrazino derivative of pyrimidoquinoline **11b** and **13b** exhibited excellent inhibition of paw edema volume. Among the tested compounds, incorporation of electron releasing *p*-methoxyphenyl on pyrimidoquinoline **3b, 6b, 8b** and **9b** resulted in a decrease of activity.

The effect of newly synthesized compounds was evaluated through the *in vitro* growth of three human tumor cell lines representing different tumor types, namely, human liver carcinoma (HepG2), non-small cell lung cancer (NCI-H460) and breast adenocarcinoma (MCF-7), after continuous exposure for 48 h. The results summarized in Table (2) showed that most of the tested compounds exhibited significant activity compared to doxorubicin. Compounds **6a** (GI_{50} = 0.01, 0.04 and 0.08 μmol L^{-1}), **13a** (GI_{50} = 0.01, 0.03 and 0.06 μmol L^{-1}) exhibited higher anticancer activity than that of doxorubicin (GI_{50} = 0.04, 0.05 and 0.09 μmol L^{-1}) against the three tumor cell line, respectively. Such high activity of both compounds is attributed to the insertion of ribofuranosyl moiety at position 2 of compound **3a** as in compound **6a**, and the presence of more hydroxyl group of ribosyl moiety attached to the triazolopyrimidoquinoline as in compound **13a**. In addition to this, the presence of fluorine atom in the

Table 1. Anti-inflammatory activity of tested compounds.

Compd.	1 h	2 h	3 h	4 h
3a	0.45 ± 0.03 (39.0)	0.47 ± 0.12[(b)] (62.9)	0.66 ± 0.14 (45.1)	0.59 ± 0.22[(a)] (53.8)
3b	0.55 ± 0.21 (23.5)	1.04 ± 0.20 (24.2)	0.76 ± 0.08 (40.2)	0.50 ± 0.12 (28.1)
6a	0.18 ± 0.03[(b)] (77.5)	0.28 ± 0.07[(b)] (78.6)	0.30 ± 0.05[(b)] (75.0)	0.48 ± 0.11[(b)] (61.5)
6b	0.33 ± 0.03 (57.7)	0.26 ± 0.05[(b)] (76.8)	0.57 ± 0.28[(b)] (59.8)	0.42 ± 0.10[(b)] (66.9)
8a	0.30 ± 0.04 (58.7)	0.28 ± 0.06[(b)] (76.5)	0.55 ± 0.29[(b)] (59.8)	1.03 ± 0.13 (17.8)
8b	0.47 ± 0.11[(b)] (62.9)	0.27 ± 0.08[(b)] (75.6)	0.58 ± 0.29[(b)] (58.8)	0.68 ± 0.16 (44.9)
9a	0.59 ± 0.21[(a)] (52.8)	0.69 ± 0.11[(a)] (49.2)	0.56 ± 0.29[(b)] (58.8)	0.76 ± 0.08 (39.2)
9b	0.43 ± 0.07 (23.4)	0.76 ± 0.11 (32.2)	0.76 ± 0.08 (39.4)	0.75 ± 0.14(35.4)
11a	0.50 ± 0.22[(b)] (58.6)	0.20 ± 0.07[(b)] (83.4)	0.89 ± 0.19 (34.5)	1.04 ± 0.13 (16.8)
11b	0.36 ± 0.09 (56.2)	0.50 ± 0.22[(b)] (58.6)	0.76 ± 0.08 (39.2)	0.69 ± 0.11[(a)] (49.2)
13a	0.40 ± 0.10[(b)] (67.9)	0.59 ± 0.21[(a)] (54.8)	0.52 ± 0.20[(b)] (61.7)	0.59 ± 0.21[(a)] (52.8)
13b	0.69 ± 0.11[(a)] (49.2)	0.56 ± 0.29[(b)] (58.8)	0.69 ± 0.11[(a)] (49.2)	0.48 ± 0.11[(b)] (61.6)
Control	–	–	–	–
Indomethacin	0.05 ± 0.02[(b)] (92.8)	0.18 ± 0.03[(b)] (85.2)	0.27 ± 0.02[(b)] (80.6)	0.16 ± 0.03[(b)] (87.4)

All values are expressed as mean ±SEM of six rats in each group.
Values in parenthesis represent % inhibition.

[(a)] Statistically significant $p > 0.05$ compared to control.

[(b)] Statistically significant $p < 0.01$ compared to control.

aromatic system attached to the tetrahydroquinoline moiety plays a significant role in the growth inhibition effect. Compound **11a** (GI_{50} = 0.3, 0.6 and 0.1 μmol L^{-1}) exhibited high inhibition activity on the three tumor cell lines, but still lower than that of doxorubicin. Compound **8a** shows good activity due to the presence of glucopyranozyl moiety. On the other hand, comparing the activity of compounds **8a**,**b**, **11a**,**b** and **13a**,**b** one can say that the presence of the electron withdrawing group (*p*-fluoro) **8a**, **11a** and **13a** is responsible for their higher activity while presence of the electron donating group attached to the phenyl group lowered activity in **8b**, **11b** and **13b**. 2-thioxo-pyrimido[4,5-*b*]quinolin-4-ones **3a**,**b** and 2-hydrazino pyrimido[4,5-*b*]quinolin-4-ones derivatives **9a**,**b** exhibited moderate antitumor activity on the three tumor cell lines. Furthermore, it is convenient to compare the activity of 3-(glucosyl)-5-(4-fluorophenyl)-7,8,9,10-tetrahydro[1,2,4] triazolo-[4',3':1,2]pyrimido[4,5-*b*]quinolin-5-one (**11a**) and 3-(ribosyl)-5-(4-fluorophenyl)-7,8,9,10-tetrahydro[1,2,4] triazolo[4',3':1,2]pyrimido[4,5-*b*]quinolin-5-one (**13a**). The former compound derived from aldopentose was more active than its derivative derived from aldohexose.

From the obtained results we can conclude that the synthesized compounds were evaluated for anti-inflammatory and anticancer activity. *In vivo* anti-inflammatory activity of *C*- and *S*-glycoside of pyrimido[4,5-*b*]quinoline derivatives on carrageenan-induced rat paw edema model identified compounds **6a** and **11a** as a potent antiinflammatory agents. The cytotoxicity of synthesized compounds was evaluated against human liver carcinoma (HepG2), non-small cell lung cancer (NCI-H460) and breast adenocarcinoma (MCF-7). Among the synthesized compounds, 5-(4-fluorophenyl)-2-*S*-(β-D-ribofuranosyl)-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*]quinolin-4-one **6a** and 3-(ribosyl)-5-(4-fluorophenyl)-7,8,9,10-tetrahydro [1,2,4]triazolo[4',3':1,2]pyrimido[4,5-*b*]quinolin-5-one **13a** exhibited the maximum growth inhibition activity toward the three human cancer cell lines, higher than that of the reference doxorubicin.

Table 2. Effects of synthesized compounds on the growth of the three human tumor cell lines.

Compd.	GI_{50} / μmol L^{-1}		
	HepG2	NCI-H460	MCF-7
3a	8.6 ± 1.5	8.2 ± 2.6	12.0 ± 4.4
3b	20.5 ± 3.6	20.0 ± 2.8	18.0 ± 4.6
6a	0.01 ± 0.006	0.04 ± 0.01	0.08 ± 0.08
6b	2.1 ± 0.6	1.8 ± 0.8	4.8 ± 0.2
8a	1.0 ± 0.2	2.8 ± 0.6	3.4 ± 0.6
8b	4.05 ± 0.2	3.8 ± 0.4	4.5 ± 0.2
9a	6. 8 ± 0.4	8.9 ± 0.8	6.0 ± 0.6
9b	12.2 ± 4.6	8.6 ± 2.6	8.2 ± 1.9
11a	0.3 ± 0.01	0.6 ± 0.02	0.1 ± 0.02
11b	2.5 ± 0.6	4.6 ± 0.4	4.01 ± 0.2
13a	0.01 ± 0.008	0.03 ± 0.006	0.06 ± 0.02
13b	2. 04 ± 0.4	1.06 ± 0.2	2.8 ± 0.6
Doxorubicin	0.04 ± 0.008	0.05 ± 0.007	0.09 ± 0.007

Results are given as concentrations that were able to cause 50 % cell growth inhibition (GI50) after continuous exposure for 48 h.
Mean ± SEM of three independent experiments performed in duplicate.

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