Microwave-assisted rapid synthesis of sugar-based pyrazole derivatives with anticancer activity in water

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1. Experimental

1.1 Analytical TLC was performed on a Merck percolated TLC (Silica Gel 60 F254) plate. The microwave synthesis reactor, UWave-1000, (SHANGHAI, XINYI) was chosen in the reaction. The solvents were purified according to the standard methods. Melting points were recorded on an X_4-Data microscopic melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Equinox-55 spectrophotometer using KBr discs in the 4000–400 cm^{-1} region. ESI-MS were acquired on a Bruker Esquire 3000 plus spectrometer. ^1H and ^{13}C NMR were recorded on a Bruker Advance 500 spectrometer in DMSO using TMS as internal standard.

1.2 General procedure for the synthesis of compounds 1, 2, 3 and 4 was reported in our previous work [1].

1.3. General experimental procedure for sugar-modified pyrazole compounds 5a-5k.

The microwave synthesis reactor UWave-1000 (SHANGHAI XINYI) was chosen in the reaction. The reaction was conducted in the open reaction vessel. All the reaction parameters were programmed through temperature-time control (500 W) with optimized increased time (2 min), target temperature **1** (80℃), standing time (2 min), target temperature **2** (100℃)， standing time (10 min).

All the synthesis processes were performed in the open reaction vessels as follows: a homogenized mixture of sugar phenyl hydrazide compound **4** (1 mmol) and 2, 4-pentanedione analogues (1.5 mmol) were irradiated in the above reaction conditions. The resulting solution was evaporated and the residue was purified by column chromatography (silica gel, ethyl acetate: petroleum ether = 2:1) to afford white solid **5a-5k**.

1.3.1. (3,5-dimethyl-1*H*-pyrazol-1-yl)(4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)methanone（5a）

White crystal; M. p. 105-107℃; IR (KBr ν cm^{-1}): 3362, 2924, 1693, 1605, 1580, 1509, 1418, 1350, 1326, 1244, 1076; ^{1}H NMR (500 MHz, DMSO): δ= 7.93 (d, *J* = 8.8 Hz, 2H, ArH), 7.14 (d, *J* = 8.7 Hz, 2H, ArH), 6.27 (s, 1H, PyrH), 5.43 (d, *J* = 4.2 Hz, 1H, H-1), 5.17 (d, *J* = 3.4 Hz, 1H, OH), 5.10 (d, *J* = 5.1 Hz, 1H, OH), 5.03 (t, *J* = 9.7 Hz, 1H, OH), 4.62 (t, *J* = 5.6 Hz, 1H, OH), 3.73-3.70 (m, 1H, H-6a), 3.51-3.47 (m, 1H, H-3), 3.42-3.34 (m, 4H, H-2, H-4, H-5, H-6b), 2.54 (s, 3H, CH_3), 2.17 (s, 3H, CH_3); ^{13}C NMR (126 MHz, DMSO): δ= 167.32, 161.13, 151.75, 144.86, 133.75, 126.55, 115.75, 111.49, 100.32, 77.59, 77.00, 73.60, 70.02, 61.05, 14.37, 13.97. HRMS (ESI^+): found $[M+H]^+$ 379.1489 $C_{18}H_{23}N_2O_7$ requires $[M+H]^+$ 379.1500

1.3.2. (3,5-diethyl-1*H*-pyrazol-1-yl)(4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)methanone (5b)

White crystal; M. p. 125-127℃; IR (KBr ν cm^{-1}): 3330, 2969, 1694, 1604, 1575, 1506,

1457, 1359,1320, 1248, 1066; ^{1}H NMR (500 MHz, DMSO): δ= 7.93 (d, J = 8.8 Hz, 2H , ArH), 7.15 (d, J = 8.8 Hz, 2H, ArH), 6.35 (s, 1H, PyrH), 5.44 (d, J = 4.0 Hz, 1H, H-1), 5.18 (s, 1H, OH), 5.10 (d, J = 4.9 Hz, 1H, OH), 5.05 (d, J = 7.0 Hz, 1H, OH), 4.64-4.63 (m, 1H, OH), 3.72-3.68 (m, 1H, H-6a), 3.52-3.49(m, 1H, H-3), 3.46 – 3.36 (m, 4H, H-2, H-4, H-5, H-6b), 2.98 (q, J = 7.3 Hz, 2H, CH_2), 2.55 (q, J = 7.6 Hz, 2H, CH_2), 1.23 (t, J = 7.3 Hz, 3H, CH_3), 1.17 (t, J = 7.6 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO): δ= 167.39, 161.12, 157.25, 151.07, 133.80, 126.67, 115.73, 108.31, 100.28, 77.57, 76.99, 73.61, 70.02, 61.05, 21.49, 13.40, 13.20. HRMS (ESI^{+}): found $[M+H]^{+}$ 407.1812 $C_{20}H_{27}N_2O_7$ requires $[M+H]^{+}$ 407.1813

1.3.3. (3-ethyl-5-methyl-1*H*-pyrazol-1-yl)(4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)methanone (5c)

White crystal; M. p. 95-97℃; IR (KBr ν cm^{-1}): 3329, 2963, 1698, 1604, 1580, 1505, 1416, 1349, 1320, 1250, 1066; ^{1}H NMR (500 MHz, DMSO): δ= 7.92 (d, J = 11.2 Hz, 2H, ArH), 7.14 (d, J = 8.8Hz, 2H, ArH), 6.29 (s,1H,PyrH), 5.40 (d, J = 4.7 Hz,, 1H, H-1), 5.18 (s, 1H, OH), 5.13 (d, J = 4.3 Hz, 1H, OH), 5.07-5.03 (m, 1H, OH), 4.59-4.57 (m, 1H, OH), 3.76 – 3.68 (m, 1H, H-6a), 3.54 – 3.45 (m, 1H, H-3), 3.44 – 3.35 (m, 4H, H-2, H-4, H-5, H-6b), 2.98 (q, J = 7.4 Hz, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.24 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, DMSO): δ= 167.36, 161.13, 151.78, 151.11, 133.70, 126.74, 115.79, 109.76, 100.40, 77.62, 77.04, 73.64, 70.09, 61.11, 21.32, 14.00, 13.23. HRMS (ESI^{+}): found $[M+H]^{+}$ 393.1631 $C_{19}H_{25}N_2O_7$ requires $[M+H]^{+}$ 393.1656.

1.3.4. (5-ethyl-3-methyl-1*H*-pyrazol-1-yl)(4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)methanone (5d)

White crystal; M. p. 96-98℃; IR (KBr ν cm^{-1}): 3329, 2963, 1698, 1604, 1575, 1505, 1416, 1349, 1315, 1250, 1066; ^{1}H NMR (500 MHz, DMSO): δ= 7.94 (d, *J* = 8.9 Hz, 2H, ArH), 7.14 (d, J = 8.8Hz, 2H, ArH), 6.31 (s,1H, PyrH), 5.40 (d, J = 4.7 Hz, 1H, H-1), 5.18 (s, 1H, OH),5.13 (d, J = 4.3 Hz, 1H, OH), 5.07-5.03 (m, 1H, OH), 4.60-4.59 (m, 1H, OH), 3.76 – 3.68 (m, 1H, H-6a), 3.54 – 3.45 (m, 1H, H-3), 3.44 – 3.35

(m, 4H, H-2, H-4, H-5, H-6b), 2.98 (q, J = 7.4 Hz, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.18 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, DMSO): δ= 167.36, 161.13, 151.78, 151.11, 133.70, 126.74, 115.79, 109.76, 100.40, 77.62, 77.04, 73.64, 70.09, 61.11, 21.47, 14.43, 13.39. HRMS (ESI^+): found $[M+H]^+$ 393.1631 $C_{19}H_{25}N_2O_7$ requires $[M+H]^+$ 393.1656.

1.3.5. (4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)(3,4,5-trimethyl-1*H*-pyrazol-1-yl)methanone (5e)

White crystal; M. p. 163-165℃; IR (KBr ν cm^{-1}): 3355, 2919, 1695, 1606, 1585, 1510, 1426, 1350, 1325, 1250, 1075; ^1H NMR (500 MHz, DMSO): δ= 7.92 (d, J = 11.2, 4.2 Hz, 2H, ArH), 7.14 (d, J =8.8 Hz, 2H, ArH), 5.38 (d, J = 4.7 Hz, 1H, H-1), 5.18 (s, 1H, OH),5.13 (d, J = 4.3 Hz, 1H, OH), 5.08-5.01 (m, 1H, OH), 4.59 (t, J = 5.7 Hz, 1H,OH), 3.76 – 3.68 (m, 1H, H-6a), 3.54 – 3.45 (m, 1H, H-3), 3.44 – 3.35 (m, 4H, H-2, H-4, H-5, H-6b), 2.46 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 1.93 (d, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO): δ= 167.23, 160.98, 152.10, 140.21, 133.57, 126.95, 117.60, 115.73, 100.42, 77.61, 77.04, 73.64, 70.09, 61.11, 12.63, 12.45, 7.79. HRMS (ESI^+): found $[M+H]^+$ 393.1648 $C_{19}H_{25}N_2O_7$ requires $[M+H]^+$ 393.1656

1.3.6. (4-chloro-3,5-dimethyl-1*H*-pyrazol-1-yl)(4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-tri hydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)methanone (5f)

White crystal; M. p. 115-117℃; IR (KBr ν cm^{-1}): 3373, 2925, 1699, 1605, 1585, 1507, 1417, 1343, 1320, 1247, 1076; ^1H NMR (500 MHz, DMSO): δ= 7.91 (d, J = 8.7 Hz, 2H ArH), 7.16 (d, J = 8.7 Hz, 2H, ArH), 5.40 (d, J = 4.2 Hz, 1H, H-1), 5.06-5.01 (m, 3H, OH), 4.56 (s, 1H, OH), 3.74-3.72 (m, 1H, H-6a), 3.50-3.49 (m, 1H, H-3), 3.43-3.36(m, 4H, H-2, H-4, H-5, H-6b), 2.55 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO): δ= 166.93, 161.45, 148.70, 140.40, 133.90, 125.61, 115.90, 113.74, 100.36, 77.63, 77.02, 73.62, 70.07, 61.09, 12.39, 11.86. HRMS (ESI^+): found $[M+K]^+$ 451.0662 $C_{18}H_{21}ClN_2O_7$ requires $[M+K]^+$ 451.0669.

1.3.7.(3-isobutyl-5-methyl-1*H*-pyrazol-1-yl)(4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)methanone (5g)

White crystal; M. p. 96-98℃; IR (KBr ν cm^{-1}): 3383, 2956, 1694, 1604, 1575, 1506, 1417, 1345, 1320, 1248, 1075; ^1H NMR (500 MHz, DMSO): δ= 7.89 (d, J = 8.8 Hz, 2H, ArH), 7.14 (d, J = 8.8 Hz, 2H, ArH), 6.28 (s, 1H, PyrH), 5.38 (d, J = 4.0 Hz, 1H, H-1), 5.18 (s, 1H, OH),5.13 (d, J = 4.3 Hz, 1H ,OH), 5.08-5.01 (m, 1H, OH), 4.59 (t, J = 5.7 Hz, 1H, OH), 3.76 – 3.68 (m, 1H, H-6a), 3.54 – 3.45 (m, 1H, H-3), 3.44 – 3.35 (m, 4H, H-2, H-4, H-5, H-6b), 2.86 (d, J = 7.0 Hz, 2H, CH_2), 2.19 (s, 3H, CH_3), 2.00 – 1.89 (m, 1H, CH), 0.92 (d, J = 6.7 Hz, 6H, CH_3); ^{13}C NMR (126 MHz, DMSO): δ= 167.56, 161.23, 151.53 , 148.20 , 133.69 , 126.79 , 115.87 , 111.43, 100.45 , 77.65 , 77.06, 73.65 , 70.13, 61.14, 36.19 , 27.91, 22.68, 13.95. HRMS (ESI^+): found $[M+H]^+$ 421.1969 $C_{21}H_{29}N_2O_7$ requires $[M+H]^+$ 421.1969

1.3.8.(5-isobutyl-3-methyl-1*H*-pyrazol-1-yl)(4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)methanone (5h)

White crystal; M. p. 98-100 ℃; IR (KBr ν cm^{-1}): 3383, 2956, 1694, 1604, 1580, 1506, 1417, 1345, 1315, 1248, 1075; ^1H NMR (500 MHz, DMSO): δ= 7.93 (d, J = 8.8 Hz, 2H, Ar-H), 7.14 (d, J = 8.8 Hz, 2H, Ar-H), 6.32 (s, 1H, Pyr-H), 5.38 (d, J = 4.3 Hz, 1H, H-1), 5.18 (s, 1H, OH), 5.13 (d, J = 4.3 Hz, 1H ,OH), 5.08-5.01 (m, 1H, OH), 4.59 (t, J = 5.7 Hz, 1H, OH), 3.76 – 3.68 (m, 1H, H-6a), 3.54 – 3.45 (m, 1H, H-3), 3.44 – 3.35 (m, 4H, H-2, H-4, H-5, H-6b), 2.86 (d, J = 7.0 Hz, 2H, CH_2), 2.19 (s, 3H, CH_3), 2.00 – 1.89 (m, 1H, CH), 0.94 (d, J = 6.7 Hz, 6H, CH_3); ^{13}C NMR (126 MHz, DMSO): δ= 167.56, 161.23, 151.53 , 148.20 , 134.13 , 126.79 , 115.87 , 111.43, 100.45 , 77.65 , 77.06, 73.65 , 70.13, 61.14, 36.53 , 27.98, 22.82, 14.10. HRMS (ESI^+): found $[M+H]^+$ 421.1969 $C_{21}H_{29}N_2O_7$ requires $[M+H]^+$ 421.1969

1.3.9. (4-butyl-3,5-dimethyl-1*H*-pyrazol-1-yl)(4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydr-oxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)methanone (5i)

White crystal; M. p. 106-108℃; IR (KBr ν cm^{-1}): 3405, 2926, 1693, 1604, 1580, 1506, 1435, 1342, 1320, 1245, 1075; ^{1}H NMR (500 MHz, DMSO): δ= 7.90 (d, J = 8.8 Hz, 2H, ArH), 7.14 (d, J = 8.8 Hz, 2H, ArH), 5.36 (d, J =4.2 Hz, 1H, H-1), 5.32 – 4.60 (m, 4H, OH), 3.77 – 3.67 (m, 1H, H-6a), 3.50-3.49 (m, 1H, H-3), 3.44 – 3.35 (m, 4H, H-2, H-4, H-5, H-6b), 2.47 (s, 3H, CH_3), 2.42 – 2.32 (m, 2H, CH_2), 2.15 (s, 3H, CH_3), 1.47 – 1.38 (m, 2H, CH_2), 1.36 – 1.27 (m, 2H, CH_2), 0.95 – 0.86 (m, 3H, CH_3); ^{13}C NMR (126 MHz, DMSO): δ= 167.30, 161.01, 151.68, 140.35, 133.57, 126.97, 122.26, 115.76, 100.47, 77.63, 77.07, 73.66, 70.13, 61.14, 32.26, 22.29, 14.22, 12.54. HRMS (ESI^+): found $[M+H]^+$ 435.2108 $C_{22}H_{31}N_2O_7$ requires $[M+H]^+$ 435.2126.

1.3.10.(4-ethyl-3,5-dimethyl-1*H*-pyrazol-1-yl)(4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)methanone (5j)

White crystal; M. p. 109-111℃;IR (KBr ν cm^{-1}): 3329, 2926, 1690, 1603, 1575,1507, 1342, 1315, 1248, 1067; ^{1}H NMR (500 MHz, DMSO): δ= 7.90 (d, J = 7.7 Hz, 2H, ArH), 7.14 (d, J = 7.6 Hz, 2H, ArH), 5.44 (d, J = 4.7 Hz, 1H, H-1), 5.34 – 4.68 (m, 4H, OH), 3.72-3.68 (m, 1H, H-6a), 3.56 – 3.45 (m, 1H, H-3), 3.40-3.34 (m, 4H, H-2, H-4, H-5, H-6b), 2.48 (s, 3H, CH_3), 2.40 (d, J = 6.8 Hz, 2H, CH_2), 2.16 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); ^{13}C NMR (126 MHz, DMSO): δ= 167.32, 161.01, 151.51, 140.03, 133.57, 126.97, 123.72, 115.77, 100.48, 77.63, 77.07, 73.67, 70.14, 61.14, 15.95, 15.01, 12.41. HRMS (ESI^+): found $[M+H]^+$ 407.1790. $C_{20}H_{27}N_2O_7$ requires $[M+H]^+$ 407.1813.

1.3.11. (3,5-diisopropyl-1*H*-pyrazol-1-yl)(4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)methanone (5k)

White crystal; M. p. 173-175℃； IR (KBr ν cm^{-1}): 3329, 2926, 1690, 1603, 1580, 1506, 1350, 1320, 1248, 1070； ^{1}H NMR (500 MHz, DMSO): δ= 7.92 (d, J = 8.9 Hz, 2H, ArH), 7.15 (d, J = 8.9 Hz, 2H, ArH), 6.40 (s, 1H, Pyrazole-H), 5.36 (d, J = 4.7 Hz, 1H, H-1), 5.07-4.84 (m, 4H, OH), 3.73 – 3.70 (m, 1H, H-6a), 3.68-3.62 (m, 1H, H-3), 3.51-3.36 (m, 4H, H-2, H-4, H-5, H-6b), 2.88 (dt, J = 13.8, 6.9 Hz, 1H, CH), 1.26 (dd,

J = 6.8, 1.8 Hz, 6H, CH_3), 1.20 (d, J = 6.9 Hz, 6H, CH_3); ^{13}C NMR (126 MHz, DMSO) ppm δ 167.58, 161.21, 161.15, 155.90, 133.86, 126.87, 115.78, 105.38, 100.34, 77.61, 77.04, 73.66, 70.12, 61.13, 27.89, 26.71, 22.91, 22.87, 22.31. HRMS (ESI^+): found $[M+H]^+$ 435.2123. $C_{22}H_{31}N_2O_7$ requires $[M+H]^+$ 435.2126.

1.4 Antiproliferation assay

Antiproliferative activities of **5a-k** and 5-Fluorouracil against HepG2 cell lines, A549 cell lines and normal RTE cells were evaluated using MTS assay method [2, 3].

1.4.1 Antiproliferation assay against HepG2 cell lines

The test compounds **5a-5k** and 5-Fluorouracil were prepared in DMSO and to the desired concentrations prior to the experiment. The HepG2 cells (1 x 10^4 cells per well) were incubated in 96-well plates in which each cell well contained 99 µl of the Cell dilutions. After 4 h of incubation, 1 µl of the drugs was added into the well with the final concentrations (0.001-100 µM). The samples were incubated for 24 h at 37 ^oC. After incubation, 20 µl of the medium containing MTS was added into the wells and then incubated at 37 ºC for 1 h. After 1h of incubation, the absorbencies of the samples were measured at 490 nm using Microplate reader. The percentage of growth inhibition was calculated as (1-(Net A_{490} (testing drug)/Net A_{490} (control)) x 100%. The IC_{50} values of the screened sugar-based pyrazole derivatives were calculated from the dose-response curve through non-linear regression analysis by using the data analysis software from three independent experiments.

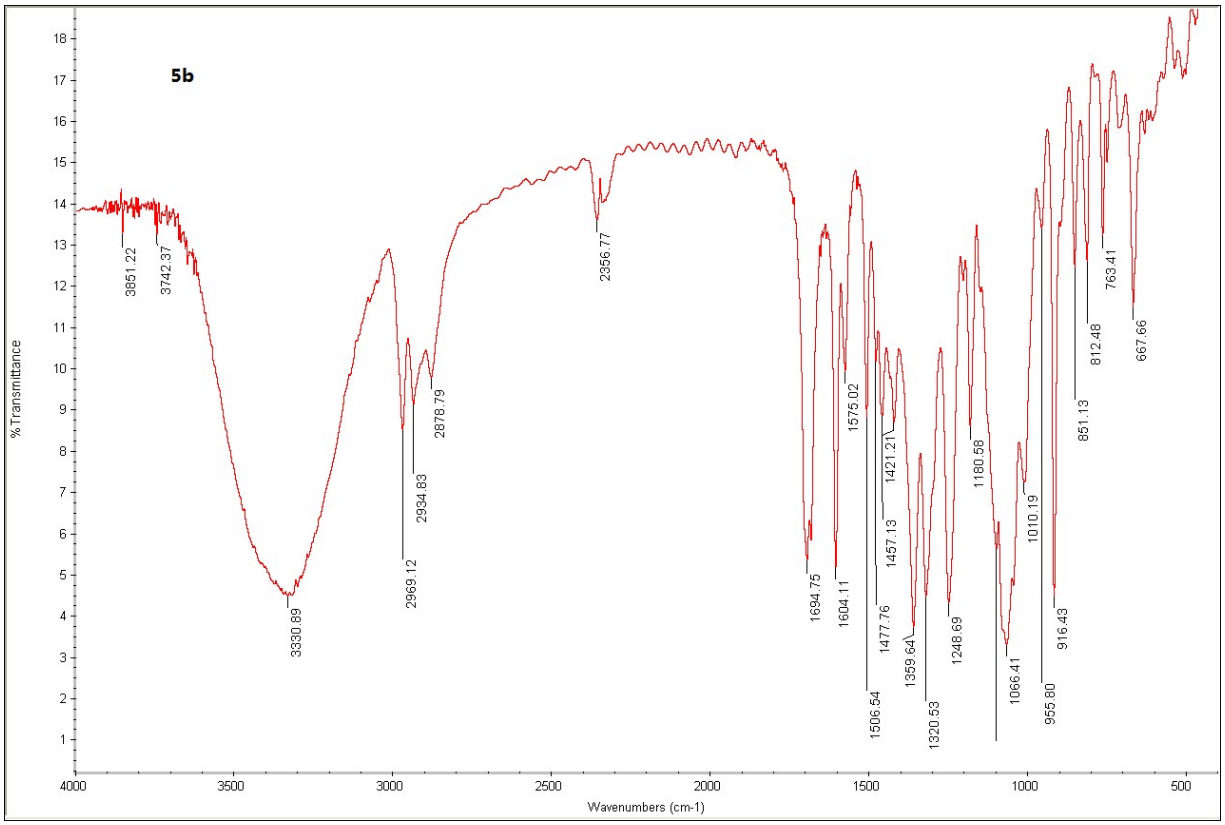
1.4.2 Antiproliferation assay against A549 cell lines

The test compounds **5a-5k** and 5-Fluorouracil in DMSO and to the desired concentrations prior to the experiment. The A549 cells (1 x 10^4 cells per well) were incubated in 96-well plates in which each cell well contained 99 µl of the Cell dilutions. After 4 h of incubation, 1 µl of the drugs was added into the well with the final concentrations (0.001-100 µM). The samples were incubated for 24 h at 37 ^oC. After incubation, 20 µl of the medium containing MTS was added into the wells and

then incubated at 37 ºC for 1 h. After 1h of incubation, the absorbencies of the samples were measured at 490 nm using Microplate reader. The percentage of growth inhibition was calculated as (1-(Net A_{490} (testing drug)/Net A_{490} (control)) x 100%. The IC_{50} values of the screened sugar-based pyrazole derivatives were calculated from the dose-response curve through non-linear regression analysis by using the data analysis software from three independent experiments.

1.4.3 Antiproliferation assay against normal RTE cells.

The test compounds **5a-5k** and 5-Fluorouracil in DMSO and to the desired concentrations prior to the experiment. The normal RTE cells (1 x 10^4 cells per well) were incubated in 96-well plates in which each cell well contained 99 µl of the Cell dilutions. After 4 h of incubation, 1 µl of the drugs was added into the well with the final concentrations (0.001-100 µM). The samples were incubated for 24 h at 37 ^oC. After incubation, 20 µl of the medium containing MTS was added into the wells and then incubated at 37 ºC for 1 h. After 1h of incubation, the absorbencies of the samples were measured at 490 nm using Microplate reader. The percentage of growth inhibition was calculated as (1-(Net A_{490} (testing drug)/Net A_{490} (control)) x 100%.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1575.02
1506.54
1477.76
1457.13
1421.21
1359.64
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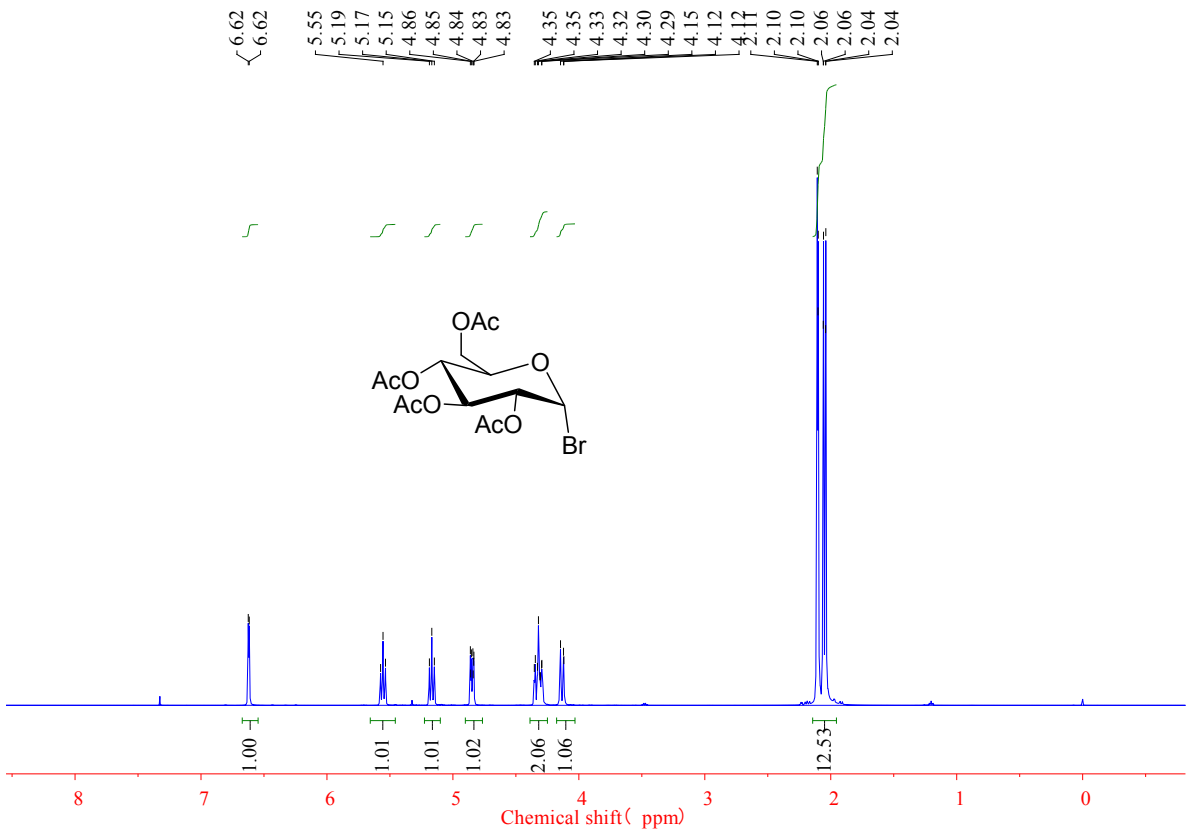
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4.32
4.30
4.29
4.15
4.12
2.10
2.10
2.06
2.06
2.04
2.04
OAc
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1.06
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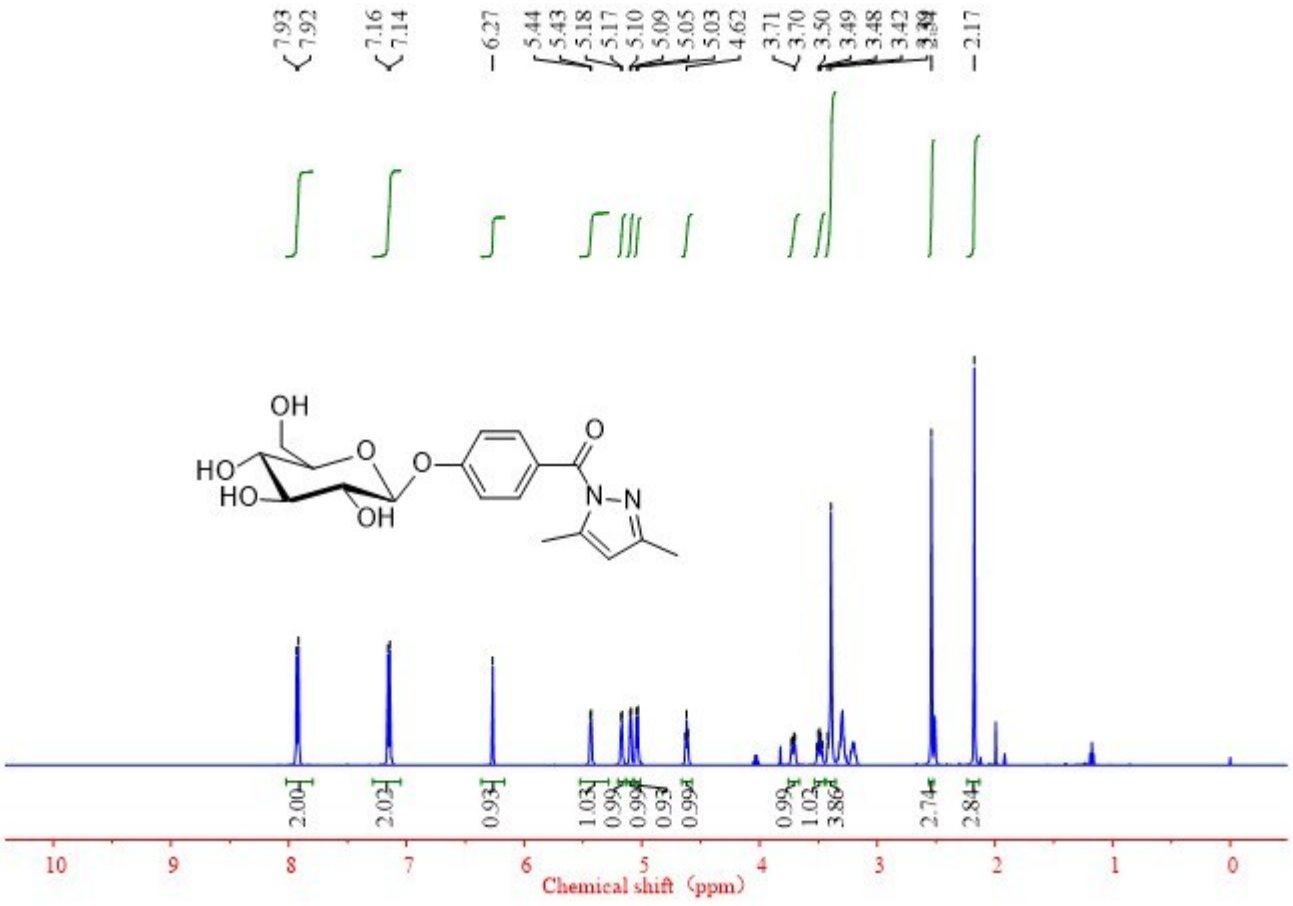
Chemical shift（ ppm）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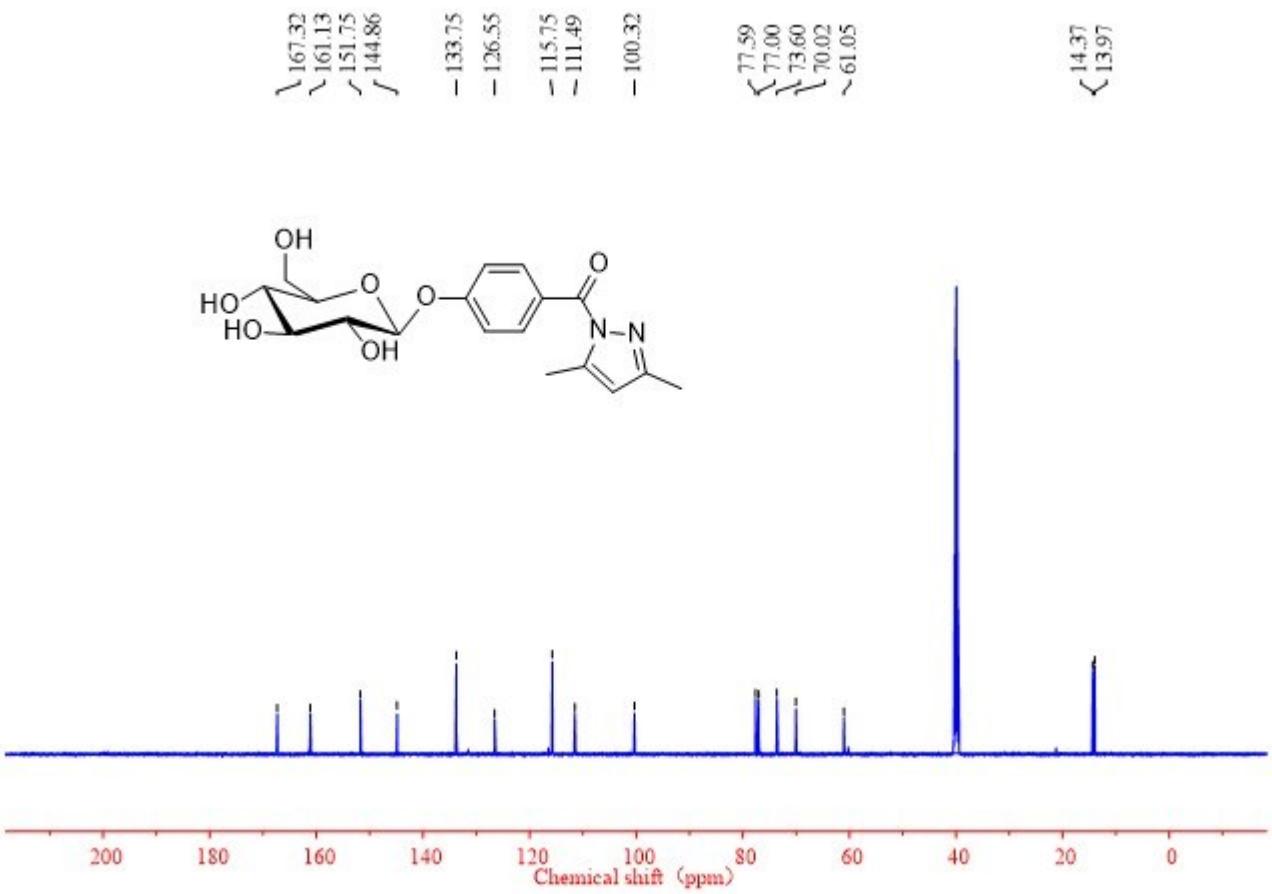
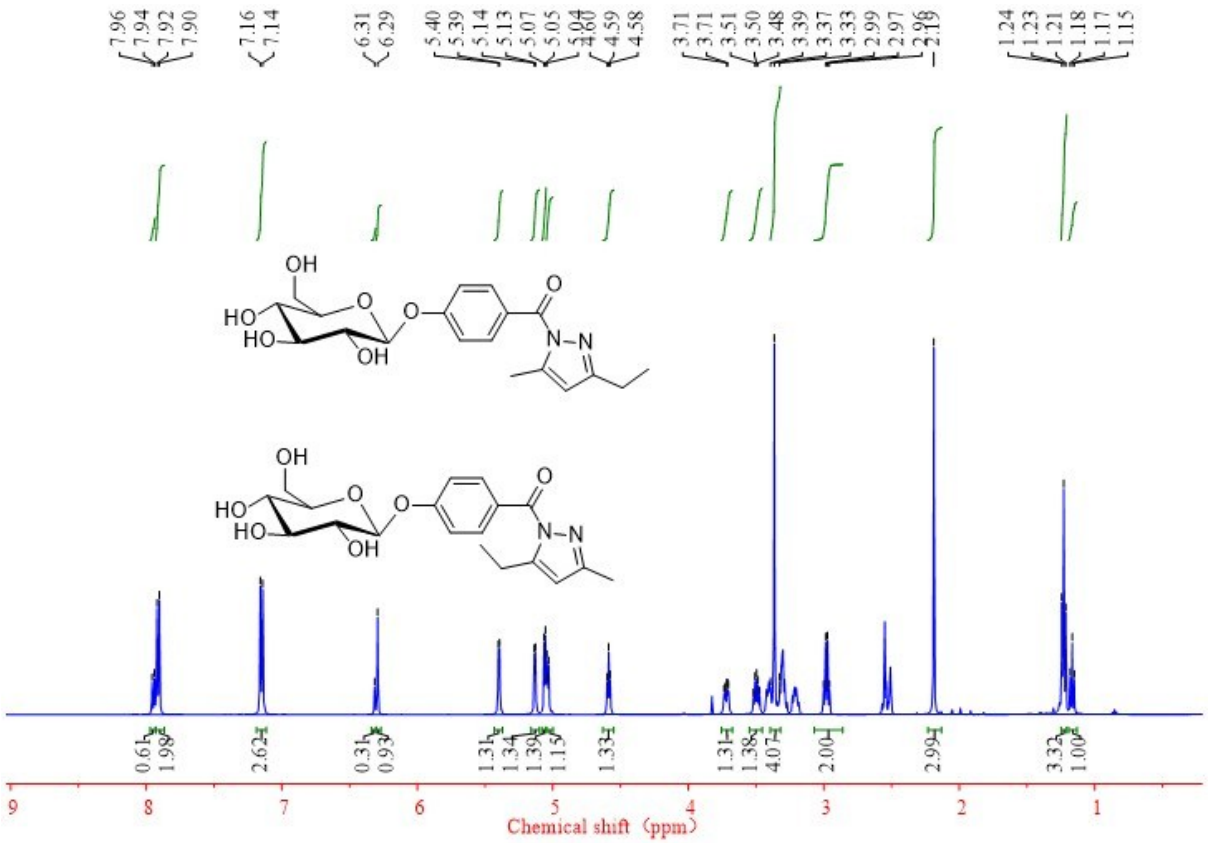
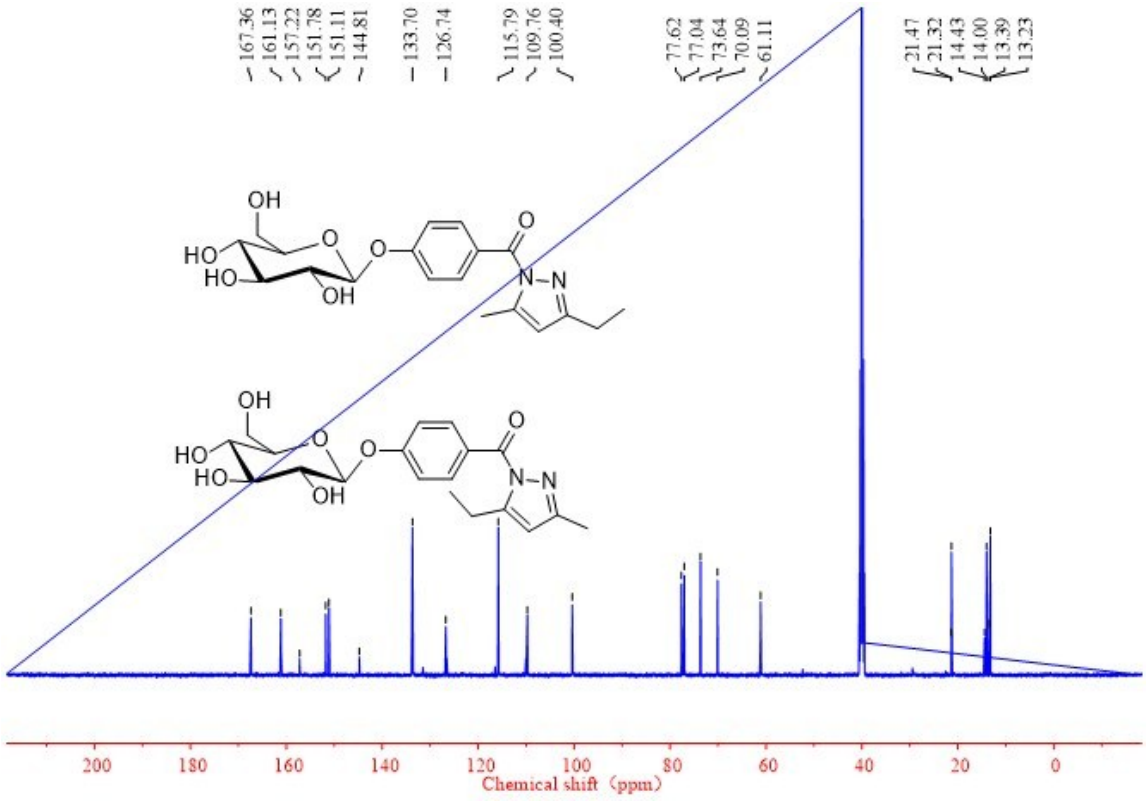
HO
HO
OH
O
O
N-N
2.00
2.02
0.93
1.03
0.99
0.99
0.93
0.99
0.99
1.02
3.86
2.74
2.84
10
9
8
7
6
5
4
3
2
1
0
Chemical shift (ppm)


167.32
161.13
151.75
144.86
133.75
126.55
115.75
111.49
100.32
77.59
77.00
73.60
70.02
61.05
14.37
13.97
OH
HO
HO
OH
O
O
N-N
200
180
160
140
120
100
80
60
40
20
0
Chemical shift (ppm)


7.96
7.94
7.92
7.90
7.16
7.14
6.31
6.29
5.40
5.39
5.14
5.13
5.07
5.05
5.04
4.60
4.59
4.58
3.71
3.71
3.51
3.50
3.48
3.39
3.37
3.33
2.99
2.97
2.96
2.19
1.24
1.23
1.21
1.18
1.17
1.15
OH
HO
HO
OH
O
O
N–N
0.61
1.98
2.62
0.31
0.93
1.31
1.34
1.39
1.15
1.33
1.31
1.38
4.07
2.00
2.99
3.32
1.00
9
8
7
6
5
4
3
2
1
Chemical shift (ppm)


167.36
161.13
157.22
151.78
151.11
144.81
133.70
126.74
115.79
109.76
100.40
77.62
77.04
73.64
70.09
61.11
21.47
21.32
14.43
14.00
13.39
13.23
OH
HO
HO
OH
O
O
N–N
200
180
160
140
120
100
80
60
40
20
0
Chemical shift (ppm)

References

1. Du, K.; Cao, X. T.; Zhang, P. F.; Zheng, H. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5318.
2. Panda, P.; Appalashetti, M.; Natarajan, M.; Chan-Park, M.; Venkatraman, S.S.; Judeh, Z.M.A. *Eur. J. Med. Chem.*, **2012**, *53*, 1.
3. Panda, P.; Appalashetti, M.; Natarajan, M.; Chan-Park, M.; Venkatraman, S.S.; Judeh, Z.M.A. *Eur. J. Med. Chem.*, **2012**, *58*, 418.