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Synthesis and Anticancer Evaluation of Novel Nicotinamide Derivatives Containing Sugars

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Research Article

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Abstract

A series of nicotinamide derivatives tailed with monosaccharides via hydrazones linkage have been synthesized and evaluated for their anticancer activity against the NCI tumor panel. These conjugates were synthesized by acid catalyzed condensation of N-(4-(hydrazinecarbonyl) phenyl) nicotinamide with corresponding monosaccharides. The newly synthesized compounds were characterized by 1H-NMR, 13C-NMR, IR and elemental analysis. Weak anticancer activity was observed against the NCI 60 cell line screening.

Keywords: Nicotinamide; Monosaccharides; Anticancer; Hydrazones; NCI 60 cell line

Abbreviations: TMS: Tetramethylsilane; TLC: Thin Layer Chromatography; TCA: Tricarboxylic Acid; SRB: Sulforhodamine B; Tz: time zero; TGI: Total Growth Inhibition.

Introduction

Cancer is the main health challenge in most regions of the world and the second leading cause of death world-wide [1]. Currently, the main approaches used to treat cancers are surgery, radiotherapy, chemotherapy, and hormone therapy. Although these methods can have certain therapeutic effects on early tumors, they are often ineffective for patients with advanced and metastatic tumors. However, in many cases, they also have serious side effects. For example, chemotherapy drugs can also damage and even kill normal cells, causing serious side effects, such as hematology, gastrointestinal tract, and epithelial reactions [2]. Therefore, there is an urgent need for development of new lead structure for the synthesis of new, potent, and less toxic agents with short duration of therapy against cancer [3].

Benzamides containing drugs such as Entinostat, Mocetinostat and tacedinaline showed a good anti-tumor activity [4-8]. In addition, nicotinamide moiety is considered as bioisosteres of benzamide and has been found to exhibit good pharmacological activities such as anticancer [9-11], antioxidant [12], anti-inflammatory [13], and anti-bacterial ones [14]. On the other hand, Hydrazones containing an azometine -NHN=CH- group (Schiff base) are considered as an important class of compounds for drug discovery [15]. Such class of compounds have been reported to show anticancer [16,17], antitubercular [18,19], antimicrobial [20], antimalarial [21], antiviral [22], anti-inflammatory [23,24] antiplatelet [25], antifungal [26], analgesic [27], antibacterial [28], and anticonvulsant [29] activities.

Structurally modified nucleosides as acyclic and C-nucleoside analogues showed variety of biological

activities, including antiviral, antibiotic, and antitumor activities [30-35]. The promising strategy of combinations of different scaffolds in new hybrid structures for synthesis of new drugs promoted us to attach carbohydrate residues to nicotinamide in order to find new biologically active leads with good solubility in biological systems. Herein, we wish to report on the synthesis of nicotinamide conjugates with sugar (Figure 1) and their anticancer evaluations against different human cell lines.

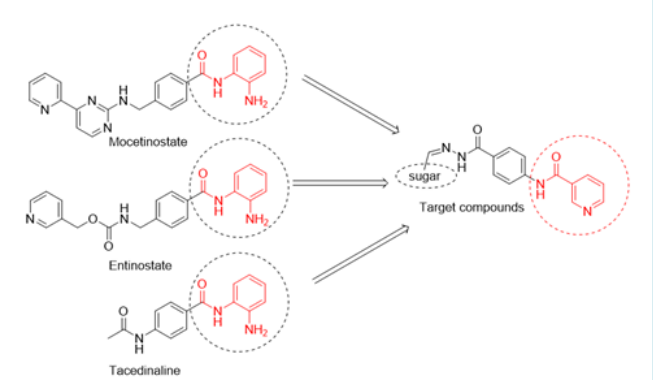


Figure 1: Structures of biologically active benzamides and compounds synthesized in this study.

Chemistry

All chemical reagents were purchased from common commercial sources with the high percent purity. The melting points (°C) of the synthesized compounds were determined in open capillaries using Stuart Melting Point Apparatus, and are uncorrected. NMR spectra, IR spectra and elemental analyses (C, H, N) were carried out at Applied Nucleic Acid Research Center, Faculty of Sciences, Zagazig University, Zagazig, Egypt. Mass spectra were carried out at the Regional center of Mycology and Biotechnology, Al-Azhar University, Nasr City, Egypt. The IR spectra (KBr, cm^{-1}) of compounds were recorded on Bruker Alpha FT-IR spectrometer. 1H-NMR and 13C APT NMR spectra were recorded on Bruker high performance Digital FT-NMR spectrometer advance III 400 MHz using dimethyl sulfoxide (DMSO)-d6 as solvent. Chemical shifts are reported in δ (ppm) relative to the internal tetramethylsilane (TMS) standard.

Mass spectra were obtained using a GC/MS Mat 112 S mass spectrometer under EI+ ionization technique/ mode. Elemental analyses were determined using the Vario MICRO cube (Elementar) CHNS analyzer. All reactions were monitored by thin layer chromatography (TLC) (Rf) on silica gel 60 GF245 (EMerck, Germany) using and UV lamp for visualization at a wavelength (λ) of 254 nm.

Experimental

Nicotinoylbenzotriazol (3)

To a solution of 1H-benzotriazole (4.76 g, 40mmol) in dichloromethane (100 mL), thionyl chlroide (1.48 mL, 20mmol) was added. The solution was allowed to be stirred at 25°C for 30min. After complete dissolving, nicoinic acid (1.23g, 10mmol) was added and the reaction was allowed to stir for additional 3hrs at 25°C. The reaction was diluted with dichloromethane (50mL) and the organic layer was washed with 1M sodium carbonate solution (3x 100ml) in a separating funnel. The organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure. The obtained white preciptate was crystallized from ethanol, yield 91%, m.p. = 101-102°C.

Ethyl 4-(nicotinamido) Benzoate (4)

To a solution of 1-nicotinoyl benzotriazole (3) (2.24 g, 10mmol) in THF (30 ml), ethyl 4-aminobenzoate (1.65g, 10mmol) was added. The mixture was refluxed for 8h. Then, the solvent was evaporated under reduced pressure. The residue was washed with petroleum ether, dried and crystallized from ethanol to give ethyl 4-(nicotinamido) benzoate (4) as white microcrystal in 86% yield (m.p. = 117-119°C) [36].

^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.75 (s, 1H, NH, exchangeable with D2O), 9.12 (d, *J*= 1.6 Hz, 1H, C2-H of pyridine), 8.78 (dd, *J* = 4.8, 1.6 Hz, 1H, C6-H of pyridine),8.31 (d, *J* = 8.0 Hz, 1H, C4-H of pyridine), 7.99-7.92 (m, 4H, Ar-H), 7.58 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H, C5-H of pyridine), 4.30 (q, *J* = 7.1 Hz, 2H, CH2), 1.32 (t, *J* = 7.1 Hz, 3H, CH3). ^{13}C APT NMR (100 MHz, DMSO-d6) δ ppm: 165.3 (CO), 164.6 (CO), 152.4 (CH pyridine), 148.8 (CH pyridine), 143.3 (Ar-C), 135.6 (CH pyridine), 130.3 (C pyridine), 130.1 (Ar-CH), 124.9 (Ar-C), 123.5 (CH pyridine), 119.6 (Ar-CH), 60.5 (CH2), 14.2 (CH3). IR (KBr, cm^{-1}): 3498, 3066, 2966, 1691, 1685, 1600, 1535. Analysis calcd. For $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.76; H, 5.29; N, 10.41.

N-(4-(hydrazinecarbonyl)phenyl)nicotinamide (5)

A mixture of compound (4) (0.54 g, 2mmol) and hydrazine hydrate (98%) (0.15 mL, 3mmol) in dioxane (20mL) was heated under reflux for 10h. Excess solvent was evaporated and the separated solid was filtered, washed with ethanol and crystallized from acetic acid to give the hydrazide (5) as pale yellow crystals in 65% yield (m.p., 296-

298 °C).

^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm: 10.62 (s, 1H, NH, exchangeable with D2O), 9.70 (s, 1H, NH, exchangeable with D2O), 9.12 (d, *J* =1.6 Hz, 1H, C2-H of pyridine), 8.77 (dd, *J* = 4.8, 1.6 Hz, 1H, C6-H of pyridine), 8.30 (d, *J* = 8.0 Hz, 1H, C4-H of pyridine), 7.89- 7.81 (m, 4H, Ar-H), 7.58 (dd, *J* = 8.0, 4.8 Hz, 1H, C5-H of pyridine), 4.46 (s, 2H, NH2, exchangeable with D2O). ^{13}C APT NMR (100 MHz, DMSO-d6) δ ppm: 165.5 (CO), 164.4 (CO), 152.3 (CH pyridine), 148.7 (CH pyridine), 141.3 (Ar-C), 135.6 (CH pyridine), 130.4 (C pyridine), 128.5 (Ar-C), 127.7 (Ar-CH), 123.5 (CH pyridine), 119.5 (Ar-CH). IR (KBr, cm^{-1}): 3350, 3300, 3076, 2986, 1674, 1665, 1597, 1531. MS, *m/z*: 256 (M+). Analysis calcd. For $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86. Found: C, 60.95; H, 4.92; N, 22.05.

General Procedure for the Preparation of N-(4 (sugarhydrazonecarbonyl) phenyl) nicotinamide (5a-d)

To a solution of the hydrazide 5 (0.512 g, 2mmol)) in ethanol (20 mL) containing few drops of glacial acetic acid, the respective sugar (2mmol) in water (1mL) was added. The reaction mixture was heated under reflux for 6 h and the solvent volume was concentrated under vacuum and left to cool at room temperature. After cooling, the formed precipitate was filtered, dried and recrystallized from ethanol-DMF mixture to give the corresponding sugar hydrazone.

N-(4-(D-(+)-Galactose Hydrazonecarbonyl) phenyl)nicotinamide (5a)

Yield 72%; white crystals, mp 228-229°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.53 (s, 1H, NH, Exchangeable with D_2O), 10.67 (s, 1H, NH, Exchangeable with D_2O), 9.12 9.12 (d, *J* = 1.7 Hz, 1H, C2-H of pyridine), 8.78 (dd, *J* = 4.7, 1.7 Hz, 1H, C6-H of pyridine), 8.31 (d, *J* = 8.1 Hz, 1H, C4-H of pyridine), 7.96-7.85 (m, 4H, Ar-H), 7.83 (d, *J* = 6.1 Hz, 1H, N=CH), 7.59 (dd, *J* = 8.1, 4.8 Hz, 1H, C_5-H of pyridine), 4.98 (d, *J* = 6.3 Hz 1H, OH, Exchangeable with D_2O), 4.56-4.50 (m, 1H, OH, Exchangeable with D_2O), 4.44 (t, *J* = 5.6 Hz, 1H, OH, Exchangeable with D_2O), 4.39 (t, *J* = 5.6 Hz, 1H, OH, Exchangeable with D2O), 4.23-4.19 (m, 1H, alditolyl 1H), (d, *J* = 6.5 Hz 1H, OH, Exchangeable with D2O), 3.73 (q, *J* = 6.5 Hz, 1H, alditolyl 1H), 3.59-3.50 (m, 2H, alditolyl 2H), 3.46-3.37 (m, 2H, alditolyl 2H). ^{13}C APT NMR(100 MHz, DMSO-d_6) δ ppm: 164.4 (CO), 162.4 (CO),153.7 (N=CH), 152.3 (CH, pyridine), 148.8 (CH, pyridine),141.8 (Ar-C), 135.6 (Ar-CH), 130.4 (C pyridine), 128.4 (CH, pyridine), 128.2 (Ar-C), 123.5 (Ar-CH), 119.5 (CH, pyridine), 72.4 (CH), 70.3 (CH), 69.8 (CH), 69.1 (CH), 63.1 (CH_2). IR (KBr, cm^{-1}): 3408, 3219, 3032, 2983, 1647, 1628, 1591; MS: *m/z*= 418.95 [M$^+$]. Anal. calcd. For $C_{19}H_{22}N_4O_7$: C, 54.54; H, 5.30; N, 13.39. Found: C, 54.67; H, 5.34; N, 13.53.

N-(4-(D-(+)-Mannose hydrazonecarbonyl) phenyl)nicotinamide (5b)

Yield 67%; white crystals, mp 220-221 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.51 (s, 1H, NH, Exchangeable with D_2O), 10.67 (s, 1H, NH, Exchangeable with D_2O), 9.14-9.10 (m, 1H, C_2-H of pyridine), 8.81- 8.76 (m, 1H, C_6-H of pyridine), 8.35-8.27 (m, 1H, C_4-H of pyridine), 7.98- 7.80 (m, 4H, Ar-H), 7.73 (d, *J* = 6.6 Hz, 1H, N=CH), 7.62-7.55 (m, 1H, C5-H of pyridine), 5.25 (d, *J* = 5.2 Hz, 1H, OH, Exchangeable with D_2O), 4.72 (t, *J* = 4.4 Hz, 1H, OH, Exchangeable with D_2O), 4.51-4.44 (m, 1H, OH, Exchangeable with D_2O), 4.37-4.27 (m, 2H, 2OH, Exchangeable with D_2O), 3.75-3.45 (m, 6H, alditolyl 6H). ^{13}C APT NMR(100 MHz, DMSO-d_6) δ ppm: 164.4 (CO), 162.4 (CO),152.9 (N=CH), 152.3 (CH, pyridine), 148.7 (CH, pyridine),141.8 (Ar-C), 135.6 (Ar-CH), 130.4 (C pyridine), 128.5 (CH, pyridine), 128.4 (Ar-C), 123.5 (Ar-CH), 119.5 (CH, pyridine), 71.1 (CH), 70.8 (CH), 70.5 (CH), 69.4 (CH), 63.8 (CH_2); IR (KBr, cm^{-1}): 3470, 3216, 3036, 2959, 1645, 1618, 1589; MS: *m/z* (%) =418.35[M$^+$]. Anal. calcd. for $C_{19}H_{22}N_4O_7$: C, 54.54; H, 5.30; N, 13.39. Found: C, 54.71; H, 5.36; N, 13.48.

N-(4-(D-(+)-Ribose hydrazonecarbonyl) phenyl)nicotinamide (5c)

Yield 73%; white crystals mp 220-221°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.50 (s, 1H, NH, Exchangeable with D_2O), 10.67 (s, 1H, NH, Exchangeable with D_2O), 9.12 (d, *J* = 1.5 Hz, 1H, C2-H of pyridine), 8.78 (dd, *J* = 4.6, 1.5 Hz, 1H, C6-H of pyridine), 8.31 (d, *J* = 8.0 Hz, 1H, C4-H of pyridine), 7.93-7.85 (m, 4H, Ar-H), 7.81 (d, *J* = 5.9 Hz, 1H, N=CH), 7.59 (dd, *J* = 8.0, 4.6 Hz, 1H, C_5-H of pyridine), 5.05 (d, 1H, *J* = 5.9 Hz, OH, Exchangeable with D_2O), 4.66- 4.53 (m, 2H, 2OH, Exchangeable with D_2O), 4.42-4.30 (m, 2H, alditolyl H and OH, Exchangeable with D_2O), 3.66-3.37 (m, 4H, alditolyl 4H). ^{13}C APT NMR(100 MHz, DMSO-d_6) δ ppm: 164.4 (CO), 162.4 (CO),153.3 (N=CH), 152.3 (CH, pyridine), 148.8 (CH, pyridine),141.9 (Ar-C), 135.6 (Ar-CH), 130.4 (C pyridine), 128.4 (CH, pyridine), 128.3 (Ar-C), 123.5 (Ar-CH), 119.5 (CH, pyridine), 73.6 (CH), 71.1 (CH), 70.3 (CH), 63.4 (CH_2); IR (KBr, cm^{-1}): 3490, 3226, 3057, 2945, 1644, 1634, 1593; MS: *m/z* (%) = 388.03[M$^+$]. Anal.calcd. for $C_{18}H_20N_4O_6$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.73; H, 5.25; N, 14.51.

N-(4-(D-(+)-Arabinose hydrazonecarbonyl) phenyl)nicotinamide (5d)

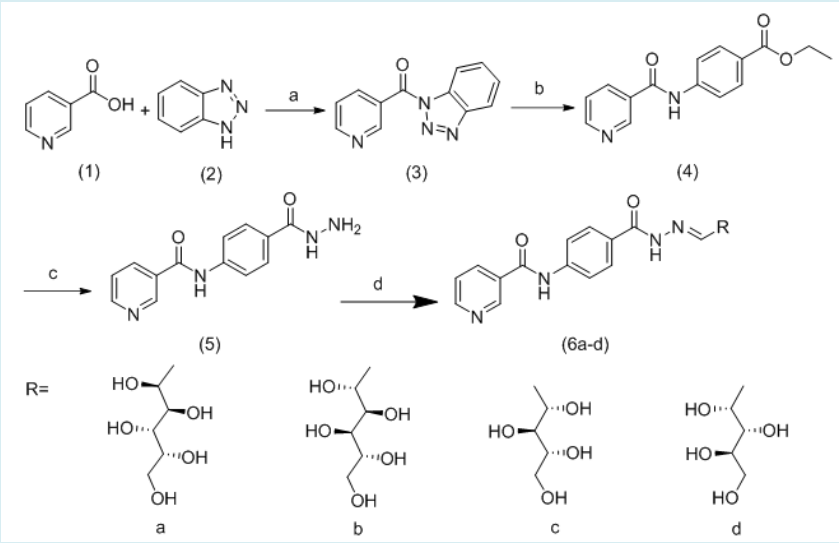
Yield 68%; white crystals mp 220-221°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.50 (s, 1H, NH, Exchangeable with D_2O), 10.67 (s, 1H, NH, Exchangeable with D_2O), 9.16-9.08 (m, 1H, C_2-H of pyridine), 8.82-8.75 (m, 1H, C_6-H of pyridine), 8.34-8.26 (m, 1H, C_4-H of pyridine), 7.93-7.84 (m, 4H, Ar-H), 7.81 (d, *J* = 6.0 Hz, 1H, N=CH), 7.62-7.55 (m, 1H, C_5-H of pyridine), 5.27-524 (m, 1H, OH, Exchangeable with D_2O), 5.04 (d, *J* = 6.0 Hz, 1H, OH, Exchangeable with D_2O), 4.65-

4.54 (m, 1H, OH, Exchangeable with D_2O), 4.40-4.31 (m, 1H, OH, Exchangeable with D_2O), 3.95-3.82 (m, 1H, alditolyl 1H), 3.70 – 3.35 (m, 4H, alditolyl 4H). ^{13}C APT NMR(100 MHz, DMSO-d_6) δ ppm: 164.4 (CO), 162.4 (CO),153.3 (N=CH), 152.3 (CH, pyridine), 148.8 (CH, pyridine),141.9 (Ar-C), 135.6 (Ar-CH), 130.4 (C pyridine), 128.4 (CH, pyridine), 128.3 (Ar-C), 123.5 (Ar-CH), 119.5 (CH, pyridine), 73.6 (CH), 71.0 (CH), 70.3 (CH), 63.4 (CH_2); IR (KBr, cm^{-1}): 3450, 3225, 3057, 2927, 1642, 1633, 1592; MS: *m/z* (%) = 388.23[M^+]; Anal.calcd. for $C_{18}H_20N_4O_6$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.81; H, 5.25; N, 14.51.

Results and Discussion

Chemistry

1H-benzo[d][1,2,3]triazol-1-yl)(pyridin-3-yl) methanone (3) was prepared according to the reported procedure by the reaction of nicotinic acid (1) With 1H-benzotriazole (2) (4 equiv.) and $SOCl_2$ (2 equiv.) in DCM at 25°C in a good yield (91%) [37]. Refluxing of 1-nicotinoylbenzotriazole (3) with ethyl 4-aminobenzoate in THF afford ester intermediate (4) in 86% yield. The ester (4) was then allowed to undergo hydrazinolysis reaction by refluxing with hydrazine hydrate in dioxane to give N-(4-(hydrazinecarbonyl)phenyl) nicotinamide (5) as reported. Thus, reaction of latter hydrazide (5) with equimolar amounts of a number of monosaccharides; namely D-galactose, D-mannose, D-ribose and D-arabinose was performed to afford the proposed sugar hydrazones (6a-d) by heating in an aqueous ethanolic solution and a catalytic amount of acetic acid, respectively in 67-73% yields (Scheme 1). The ^1H-NMR spectra of the afforded sugar hydrazones demonstrated the absence of the two proton signals of the NH_2 group and existence of the attributed signals to the hydroxyl protons as well as the alditol chain protons. The resulting chemical shift of the methine proton (i.e., H-1) and existence of a signal assigned to the NH confirmed the acyclic form feature of the sugar part in the resulting sugar hydrazones. The IR spectra of sugar hydrazones (6a-d) showed the presence of characteristic absorption bands corresponding to the hydroxyl groups in the region 3200-3500 cm^{-1}.



Scheme 1: Reagents and conditions: a) DCM, $SOCL^2$, 25°C, 3.5h. b) THF, ethyl 4-aminobenzoate, reflux, 8h. c) NH_2NH_2, dioxane, reflux, 10h. d) Appropriate aldoses, ethanol, acetic acid, reflux, 6h.

Anticancer Activity

Pharmacological evaluation of the anticancer activity was achieved on the compounds inconvertibly selected by National Institute of Health, Bethesda, USA, under the drug discovery program of NCI. All the finally synthesized 4 compounds have been registered on its website and all compounds have been selected and granted NSC codes: 821079, 821080, 821082 and 821081and screened for anticancer activity at a single high dose (10^{-5} M) in full NCI 60 cell lines.

Methodology of the in Vitro Cancer Screening

The human tumor cell lines of the cancer screening panel are grown in RPMI 1640 medium containing 5% fetal bovine serum and 2μL glutamine. The cells are inoculated into 96-well microtiter plates in 100 μL at plating densities ranging from 5000 to 40,000 cells/ well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37°C in the presence of 5% CO_2, 95% air, and 100% relative humidity for 24 h prior to addition of experimental drugs.

After 24h, two plates of each cell line are fixed in situ with TCA (Tricarboxylic Acid), to represent a measurement of the cell population for each cell line at the time of drug addiction (Tz). Experimental drugs are solubilized in dimethyl sulfoxide at desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50μg/mL gentamicin. Additional four, 10-fold or ½ log serial dilutions are made to provide a total of five drug concentrations plus control. Aliquots of 100 μL of these different drug dilutions are added to the appropriate microtiter wells already containing 100μL of medium, resulting in the required final drug concentrations.

After the following drug addition, the plates are incubated for an additional 48 h at 37°C, 5% CO2, 95% air, and 100% relative humidity. For adherent cells, the assay is terminated by the addition of cold TCA. Cells are fixed in situ by the gentle addition of 50 μL of cold 50% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 min at 4°C. The supernatant is discarded, and the plates are washed 5 times with tap water and air dried. Sulforhodamine B (SRB) solution (100 μL) at 0.4 % (w/v) in 1 % acetic acid is added to each well, and plates are incubated for 10 min at room temperature. After staining, unbound dye is removed by washing 5 times with 1% acetic acid and the plates are air dried. Bound stain is subsequently solubilized with 10 mM Trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm.

For suspension cells, the methodology is the same except that the assay is terminated by fixing settled cells at the bottom of the wells by gently adding 50 μL of 80% TCA (final concentration, 16% TCA). Using the 7 absorbance measurements [time zero, (Tz), control growth (C), and test growth in the presence of drug at the 5 concentration levels (Ti)], the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition is calculated as:

[(Ti-Tz)/(C-Tz)] × 100 for concentrations for which Ti ≥ Tz

[(Ti-Tz)/Tz] × 100 for concentrations for which Ti < Tz.

Three dose response parameters are calculated for each experimental agent. Growth inhibition of 50% (GI50) is calculated from [(Ti-Tz)/(C-Tz)] × 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) is calculated from Ti=Tz. The LC50 (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment is calculated from [(Ti-Tz)/Tz] × 100 = -50. Values are calculated for each of these three parameters if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter is expressed as greater or less than the maximum or minimum concentration tested. The compounds that reduce the growth of any one of the cell lines by 32% or less are passed on for further evaluation in the full panel of 60 cell lines [38]. The growth percent (GP [%]) for tested compounds (Samples) against selected NCI-60 cancer cell lines at single concentration 10^{-5} M were shown in Table 1.

Panel	Cell Line	GP [%] of Compound			
		5a	5b	5c	5d
Leukemia	CCRF-CEM	102.91	102.62	99.16	98.48
	HL-60(TB)	101.19	99.89	100.4	99.4
	K-562	110.39	102.07	104.51	103.15
	MOLT-4	114.04	106.93	108.59	113.3
	SR	103.45	99.94	99.9	95.7
Non-Small Cell Lung Cancer	A549/ATCC	101.72	107.47	99.79	101.09
	EKVX	106.84	107.78	104.8	100.47
	HOP-62	112.6	105.39	97.55	101.62
	HOP-92	111.03	106.12	102.6	103.36
	NCI-H226	105.59	107.69	104.91	99.93
	NCI-H23	109.66	109.09	100.52	107.39
	NCI-H322M	103.34	106.49	104.7	104.22
	NCI-H460	108.19	106.59	104.23	107.89
	NCI-H522	96.16	100.05	92.69	99.27

Colon Cancer	COLO 205	109.86	109.82	112.3	106.6
	HCC-2998	116.58	118.83	110.39	116.96
	HCT-116	107.54	102.78	104.63	102.78
	HCT-15	105.22	105.05	105.62	102.71
	HT29	110.82	107.58	103.8	105.19
	KM12	106.13	103.21	102.63	101.9
	SW-620	107.65	101.52	102.51	98.89
CNS Cancer	SF-268	102.76	104.88	98.59	98.5
	SF-295	101.92	105.04	101.02	100.53
	SF-539	106.08	101.45	98.54	103.01
	SNB-19	97.41	102.03	97.71	98.71
	SNB-75	**92.58**	**95.95**	**97.44**	**90.34**
	U251	102.02	102.74	104.68	101.37
Melanoma	LOX IMVI	104.01	99.19	99.05	101.27
	MALME-3M	108.26	102.76	107.7	110.42
	M14	114.38	97.83	102.3	105.75
	MDA-MB-435	106.09	104.11	103.5	103.55
	SK-MEL-2	108.95	112.39	118.4	119.52
	SK-MEL-28	111.3	107.51	111.91	102.93
	SK-MEL-5	104.48	104.32	104.27	106.18
	UACC-257	102.09	97.7	99.76	99.98
	UACC-62	95.54	99.69	96.17	99.49
Ovarian Cancer	IGROV1	110.47	105.59	107.16	109.13
	OVCAR-3	120.37	130.22	118.4	112.18
	OVCAR-4	102.07	108.31	110.34	114.26
	OVCAR-5	106.27	99.89	101.91	102.84
	OVCAR-8	104.93	111.33	102.12	104.57
	NCI/ADR-RES	106.34	109.29	109.18	112.26
	SK-OV-3	107.53	106.01	109.81	99.1
Renal Cancer	786-0	112.59	109.71	104.99	105.58
	A498	107.49	91.56	99.3	101.89
	ACHN	102.74	105.27	109.08	100.76
	CAKI-1	101.17	96.91	94.13	96.13
	RXF 393	120.62	119.48	106.6	109.09
	SN12C	99.45	100.95	94.49	97.15
	TK-10	105.52	98.06	104.43	105.52
	UO-31	**92.52**	**91.19**	**83.73**	**82.93**
Prostate Cancer	PC-3	102.48	100.64	96.27	101.36
	DU-145	119.09	119.4	111.41	111.78
Breast Cancer	MCF7	**94.84**	**97.31**	**91.97**	**92.63**
	MDA-MB-231/ATCC	100.01	95.18	94.49	102.35
	HS 578T	108.48	108.28	98.42	103.7
	BT-549	105.72	107.53	101.88	99.02
	T-47D	100.11	102.21	99.18	96.11
	MDA-MB-468	104.54	111.43	113.34	100.71

Table 1: Growth percent (GP [%]) for tested compounds (Samples) against selected NCI-60 cancer cell lines at single concentration 10^{-5} M.

Conclusion

All the compounds submitted to the NCI 60 cell screen have been tested initially at a single high dose (10^{-5} M) in the full NCI 60 cell panel. The operation of this screen utilizes 60 different human tumor cell lines, representing leukemia, melanoma, and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. Among all synthesized derivatives, analogues (5d) N-(4-(D-(+)-Arabinose hydrazonecarbonyl) phenyl) nicotinamide and (5c) N-(4-(D-(+)-Ribose hydrazonecarbonyl)phenyl) nicotinamide which coupled with pentoses sugars were found to exhibit good anticancer activity as compare to the others (5a) and (5b) which coupled with hexoses sugars against Renal Cancer (UO-31) cell line. The mean growth percentage, range of growth percentage, and growth inhibition percentage relative to Renal Cancer (UO-31) cell line are depicted in Table 2.

Compound no.	Mean growth percentage	Range of growth percentage	Most sensitive cell line	GI of most sensitive cell line percentage
5a	105.83	- 7.48 To 28.10	Renal Cancer (UO-31)	7.48
5b	104.75	-8.81 To 39.03	Renal Cancer (UO-31)	8.81
5c	102.88	- 16.27 To 34.67	Renal Cancer (UO-31)	16.27
5d	102.93	-17.07 To 36.59	Renal Cancer (UO-31)	17.07

Table 2: Anticancer screening data of synthesized compounds against Renal Cancer (UO-31) cell line.

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