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Synthesis and Anticancer Activity of Some Novel Fused Nicotinonitrile Derivatives

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Abstract

A series of fused nicotinonitrile derivatives was synthesized by reaction of 2,6-dioxonicotinonitrile derivative 1 with different electrophilic reagents. Reaction of pyridone 1 with benzyledine derivative 2, 3 and 7 afforded pyrano[2,3-b] pyridine 4 and 11 derivatives, respectively. Upon reaction of pyridone 1 with α,β-unsaturated carbonyl compounds and benzoyl isothiocyanate gave the corresponding pyridine derivatives 11-13 and 16, respectively, Morevere sulfurization and selenation of pyridone 1 with sulfur and selenium in the presence of triethyl amine afforded the fused pyridine 14 and 15, respectively. The structure of the new synthesized compounds was elucidated by IR, NMR and elemental analysis. Some of new synthesized pyridines were screnned for anticancer activity.

Keywords: 2,6-Dioxonicotinonitrile; Pyrano[2,3-b]pyridine; Synthesis; Dihydropyridine; Anticancer activity

Introduction

Pyridine nucleus and their fused heterocyclic systems have attracted a great deal of interest over the years [1]. Furthermore, pyridine is one of the most popular N-heteroaromatics incorporated into the structure of many pharmaceuticals. Among these, cyanopyridines (nicotinonitriles) with different alkyl and aryl groups were found to have antihypertensive [2,3] antiinflammatory, analgesic, antipyretic properties [4,5] antimicrobial [6], cardiotonic [7], anticancer activity [8] as well as 1KK-b inhibitor properties [9]. Additionally, there is much interest in the anticancer activity of these compounds owing to different types of biological targets they might interfere with for this effect to occur e.g., PDE3, PIM1 Kinase, and Survivin protein. In view of the previous applications and continuation of our previous work on chemistry and pharmaceutical activity on nicotinonitrile derivatives [10-12] we aim to use 4-methyl-2,6-dioxo-1-phenyl-1,2,5,6-tetrahydropyridine-3-carbonitrile (1) as building blocks for the synthesis of some new family of fused heterocyclic compounds incorporating pyridine moiety with the hope to possess better anticancer activity.

Experimental

All melting points are uncorrected and were measured using an Electro thermal IA 9100 apparatus. TLC was performed on Merck Silica Gel 60F254 with detection by UV light. The IR spectra (KBr disc) were recorded on a Pye Unicam Sp-3-300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer. The ^{1}H and ^{13}C NMR spectra were determined with JEOL-JNM-LA 400 and 500 MHz spectrometer. The chemical shifts are expressed on the δ (ppm) scale using TMS as the standard reference. Elemental analysis determined on a Perkin Elmer 240 (microanalysis), Micro analytical Center, Cairo University, Cairo, Egypt. The anticancer screening was carried at Micro analytical Center, Cairo University, Cairo, Egypt.

4-(4-Fluorophenyl)-2-hydroxy-5-methyl-7-oxo-8-phenyl-7,8-dihydro-4H-pyrano[2,3-b]pyridine-3,6-dicarbonitrile (4)

A mixture of pyridine-3-carbonitrile 1(0.01 mol) and benzylidene 2 or/ 3 (0.01 mol) in ethanol (50 mL) and triethylamine (0.5 mL) was refluxed for 6 h, the ewaction mixture was cooled, poured into cold water and neutralized with HCl. The solid formed was filtered off, washed with water then dried and recrystallized from ethanol to give 4 as pale yellow crystals, Yield: 76%; mp >360°C. IR (KBr): 3432 cm^{-1} (OH), 2217 cm^{-1} (C≡N) and 1657 cm^{-1} (C=O). ^{1}H NMR (DMSO-d$_6$): δ=2.27 (s, 3H, CH$_3$), 4.53 (s, 1H, OH), 5.66 (s, 1H, pyran-H), 7.19-7.49 (m, 9H, Ar-H). ^{13}C NMR (DMSO-d$_6$): δ=20.9 (CH$_3$), 56.19, (pyran-C-4), 88.08, 92.86, 116.3, 116.8, 117.8, 128.4, 128.5, 129.08, 135.5, 139.3, 143.2, 145.9, 146.2, 159.2, 160.9, 161.2, 176.8 (Ar-C, olefenic carbons, 2C≡N and C=O). MS :m/z (%): 399 (1.26), 371 (1.65), 226 (65.21), 119 (100), 91 (45.44), 77 (51.93). Analytical Calculated for $C_{23}H_{14}FN_3O_3$ (399.37): C, 69.17; H, 3.53; N, 10.52. Found: C, 69.28; H, 3.45; N, 10.43.

6-Cyano-4-(4-fluorophenyl)-2-imino-5-methyl-7-oxo-N,8-diphenyl-7,8-dihydro-2H-pyrano[2,3-b]pyridine-3-carboxamide (10)

A mixture of pyridine-3-carbonitrile 1 (0.01 mol) and amide 7 (0.01 mol) in ethanol (50 mL) and triethylamine (0.5 mL) was refluxed for 6 h, the reaction mixture was cooled, poured onto cold water and neutralized with HCl. The solid formed was filtered off, washed with water then dried and recrystallized from ethanol to give 10 as pale yellow crystals, Yiled: 71%; mp=260-262°C. IR (KBr): 3317 (anilide NH), 3049 (imine-NH), 2221 cm^{-1} (C≡N), 1674 and 1622 cm^{-1} (2C=O) cm^{-1}. ^{1}H NMR (DMSO-d$_6$): δ=2.94 (s, 3H, CH$_3$), 7.11-8.10 (m, 14H, Ar-H), 8.27 (s, 1H, anilide-H), 10.36 (s, 1H, C=NH). ^{13}C NMR (DMSO-d$_6$): δ=22.7 (CH$_3$), 90.6, 107.07, 107.09, 116.2, 116.5, 116.7, 120.7, 124.56, 128.64, 128.68, 128.9, 132.8, 132.9, 138.2, 145.6, 149.7, 160.5, 162.9, 156.4, 173.8, 175.9, 177.4. Analytical Calculated for $C_{29}H_{19}FN_4O_3$ (490.48): C, 71.01; H, 3.90; N, 11.42. Found: C, 70.92; H, 3.84; N, 11.50.

2-Amino-5-methyl-7-oxo-2,4,8-triphenyl-7,8-dihydro-2H-pyrano[2,3-b]pyridine-6-carbonitrile (11)

A mixture of compound 1 (0.01 mol), benzalacetophenone (0.01

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mol) and ammonium acetate (0.02 mol) in acetic acid (30 mL) was refluxed for 6 h, cooled, added few of water. The precipitate was filtered off, dried and recrystalized from ethanol to give 11 as pale yellow crystals. Yield: 65%; mp=326-328°C. IR (KBr): 3424 cm^{-1} (NH_2), 2216 cm^{-1} (C≡N) and 1660 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ=2.25 (s, 3H, CH_3), 4.53 (s, 2H, NH_2), 5.62 (s, 1H, olefenic-H), 7.18-7.48 (m, 15H, Ar-H). Analytical Calculated for $C_{28}H_{21}N_3O_2$ (431.49): C, 77.94; H, 4.91; N, 9.74. Found: C, 77.85; H, 4.98; N, 9.67.

4-Methyl-2-oxo-1,5-diphenyl-7-styryl-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (12)

A mixture of compund 1 (0.01 mol), dibenzalacetone (0.01 mol) and ammonium acetate (0.02 mol) in acetic acid (30 mL) was refluxed for 6 h, cooled, added few of water. The precipitate was filtered off, dried and recrystalized from ethanol to give 12 as yellow crystals. Yield: 55%; mp=180-182°C. IR (KBr): 2186 cm^{-1} (C≡N), 1627 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ=2.36 (s, 3H, CH_3), 7.00-7.41 (m, 18H, Ar-H and olefenic protons). MS: m/z (%): 439 (4.38), 131 (65.95), 103 (48.11), 91 (100), 77 (44.47). Analytical Calculated for $C_{30}H_{21}N_3O$ (439.51): C, 81.98; H, 4.82; N, 9.56. Found: C, 82.09; H, 4.76; N, 9.48.

5,5'-dimethyl-7,7'-dioxo-4,4',8,8'-tetraphenyl-7,7',8,8'-tetrahydro-2,2'-spirobi[pyrano[2,3-b]pyridine]-6,6'-dicarbonitrile (13)

A mixture of pyridone 1 (0.01 mol) and dibenzalacetone (0.01 mol) in ethanol (50 mL) containing triethylamine (0.5 mL) was refluxed for 8 h. The reaction mixture was cooled, poured onto cold water and neutralized with HCl. The precipitate was filtered off, washed with water, dried and recrystalized from acetic acid to give 13 as white crystals. Yield: 67%; mp=348-350°C. IR (KBr): 2221 cm^{-1} (CN), 1674 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ=2.26 (s, 6H, CH_3), 5.64 (s, 2H, olefenic-H), 7.19-7.48 (m, 20H, Ar-H). MS: m/z (%): 666 (33.19), 226 (67.35), 119 (100), 91 (43.51), 80 (2.75), 64 (56.06). Analytical Calculated for $C_{43}H_{28}N_4O_4$ (664.71): C, 77.70; H, 4.25; N, 8.43. Found: C, 77.59; H, 4.32; N, 8.35.

7-hydroxy-5-oxo-6-phenyl-5,6-dihydro-3H-[1,2]dithiolo[3,4-c]pyridine-4-carbonitrile (14)

A mixture of pyridone 1 (0.01 mol), sulfur (0.01 mol) and triethylamine (0.5 mL) in ethanol (30 mL) was refluxed for 8 h, cooled, poured onto cold water neutralized with HCl. The solid formed was filtered off, washed with water then dried and recrystalized from acetic acid to give 14 as yellow crystals. Yield: 79%; mp=326-328°C. IR (KBr): 3437 cm^{-1} (OH), 2215 cm^{-1} (C≡N), 1658 cm^{-1} (C=O), 512 cm^{-1} (S-S). ^1H NMR (DMSO-d_6): δ=3.18 (s, 2H, CH_2), 4.05 (s, 1H, OH), 7.17-7.47 (m, 5H, Ar-H). Analytical Calculated for $C_{13}H_8N_2O_2S_2$ (288.34): C, 54.15; H, 2.80; N, 9.72. Found: C, 54.06; H, 2.85; N, 9.66.

7-hydroxy-5-oxo-6-phenyl-5,6-dihydro-3H-[1,2]diselenolo[3,4-c]pyridine-4-carbonitrile (15)

A mixture of pyridone 1 (0.01 mol), selenium (0.01 mol) and triethylamine (0.5 mL) in ethanol (30 mL) was refluxed for 8 h, cooled, poured onto cold water neutralized with HCl. The solid formed was filtered off, washed with water then dried and recrystalized from petroleum ether to give 15 as gray crystals. Yield: 60%; mp=358-360°C. IR (KBr): 3422 cm^{-1} (OH), 2216 cm^{-1} (C≡N), 1659 cm^{-1} (C=O), 700 cm^{-1} (Se-Se). ^1H NMR (DMSO-d_6): δ=3.15 (s, 2H, CH_2), 5.23 (s, 1H, OH), 7.19-7.48 (m, 5H, Ar-H). Analytical Calculated for $C_{13}H_8N_2O_2Se_2$ (382.13): C, 40.86; H, 2.11; N, 7.33. Found: C, 40.93; H, 2.06; N, 7.39.

N-(5-Cyano-2-hydroxy-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridine-3carbonothioyl)benzimidic acid (16)

A mixture of pyridone 1 (0.01 mol) and benzoyl isothiocyanate (0.01 mol) in dry acetone (30 mL) and containing triethylamine (0.5 mL) was refluxed for 3 h, the reaction mixture was cooled, the solid formed was filtered off, dried and recrystalized from acetic acid to give 16 as orange crystals. Yield: 79%; mp=304-306°C. IR (KBr): 3427 cm^{-1} (2OH), 2215 cm^{-1} (CN), 1655 cm^{-1} (C=O), 1256 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6): δ=2.25 (s, 3H, CH_3), 4.27 (s, 1H, OH), 5.61 (s, 1H, OH), 7.12-7.97 (m, 10 H, Ar-H). MS :m/z (%): 388 (0.19), 226 (67.83),119 (100), 107 (38.19), 91 (34.31),77 (37.12). Analytical Calculated for $C_{21}H_{15}N_3O_3S$ (389.43): C, 64.77; H, 3.88; N, 10.79. Found: C, 64.69; H, 3.93; N, 10.86.

Results and Discussion

Chemistry

4-Methyl-2,6-dioxo-1-phenyl-1,2,5,6-tetrahydropyridine-3-carbonitrile (1) in general contain free fifth position that act as active nucleophilic center. This nucleophilic center reacts with the electrophilic reagents affording new condensed pyridine derivatives at positions 5 and 6 or at 4 and 5 (Figure 1).

2,6-Dioxonicotinonitrile derivative 1 was synthesized according to the reported method [13] via condensation of 2-cyano-N-phenylacetamide with ethyl acetoacetate. The synthesis of condensed pyran derivative 4 was performed via one pot reaction of pyridine derivative 1 and benzylidene 2 in the presence of triethyl amine as basic catalyst (Scheme 1). The target compound 4 was also obtained by the base induced of pyridone 1 and benzylidene derivative 3 through the formation of iminopyran derivative 5 and subsequent hydrolysis and [1,3-H] shift (Scheme 1).

The IR spectrum of pyran derivative 4 indicated the presence of OH group (a medium absorption band) in the region 3432 cm^{-1} and CN function (a sharp medium absorption band) at 2217 cm^{-1} in addition to the amide carbonyl absorption band at 1657 cm^{-1}.

Its ^1H NMR showed a deshielded multiplet at 7.19-7.49 ppm for aromatic protons, the pyran-4-H proton appeared as a singlet at 5.66 ppm in addition to OH broad signal at 4.53 ppm. The ^{13}C NMR was also participate in the detection of the structure of the compound 4 (see the experimental section). The novel condensed pyridine 10 was obtained as a result of addition of activated heterocyclic methylene of compound 1 to bezylidene 7 via the formation of non-isolable Micheal type product 8 followed by the attack of nucleophilic OH to the cyano group producing iminopyran and subsequent oxidation (Scheme 2).

The IR spectrum of pyranopyridine 10 reveal all the expected frequency region of NH, C≡N, and C=O, the band at 3049 cm^{-1}

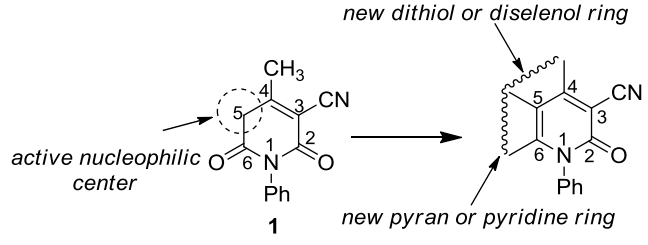


Figure 1: The pyridine 1 as a key for heterocyclic synthesis.

represent stretching vibration of NH in the imine group that involved in intramolecular hydrogen bond, the anilide NH band is clearly observed at 3317 cm^{-1}, the cyano function frequency was located at 2221 cm^{-1}, in addition to, the two electronically different carbonyl stretching vibration was observed at 1674 cm^{-1} for the exocyclic one, while that appeared at 1622 cm^{-1} for the anilide carbonyl, which might related to the resonance affected with the imino-NH and existence of intramolecular hydrogen bonding with NH. The ^{1}H and ^{13}C NMR spectra of compound 10 were agreement with its structure.

Base mediated reaction of pyridone 1 with α,β-unsaturated carbonyl compounds (namely, 1,3-diphenylprop-1-en-3-one and 1,5-diphenylpenta-1,4-dien-3-one) in the presence of ammonium acetate afforded pyranopyridine 11 and styryl naphthyridine 12 derivatives, respectively, while its reaction with 1,5-diphenylpenta-1,4-dien-3-one in the presence of triethyl amine afforded the unexcpected spiro compound 13 (Scheme 3). The spectral data of compounds 11-13 were agreement with their structure (see the experimental section).

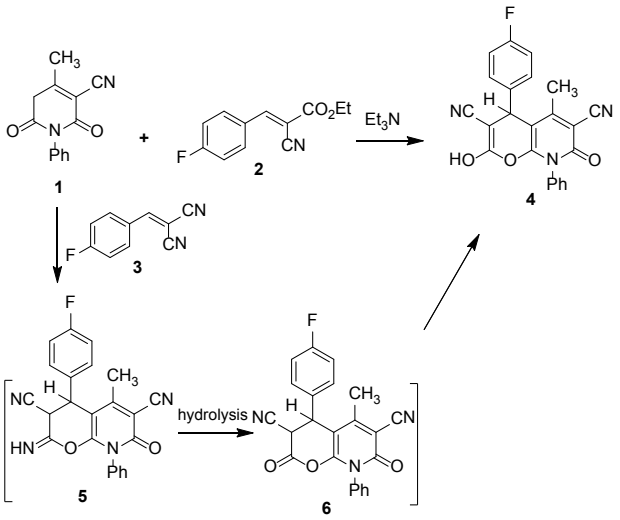
The sulfurization and selenation of pyridone 1 with sulfur and selenium elements in the presence of triethyl amine in ethanol gave 1,2-dithiolo[3,4-c]pyridine 14 and 1,2-Diseleno[3.4-c]pyridine-4-carbonitrile 15 derivatives, respectively (Scheme 3). Finally, the nucleophilic addition reaction of pyridone 1 with benzoyl isothiocyanate in the presence of triethyl amine gave the benzimidic acid derivative 16 (Scheme 3). The structure of condensed system 14 was elucidated from the spectral data, thus in its IR bands were observed at 3437 cm^{-1}, 2215 cm^{-1} and 1658 cm^{-1} corresponding to the stretching frequency of OH, CN and C=O respectively, in addition to the disulphide stretching frequency that detected at 512 cm^{-1}. The ^{1}HNMR spectrum of compound 14 was also participate in the elucidation of its chemical structure, thus the aromatic multiplicity was observed at 7.17-7.47 ppm, the OH singlet signal was observed at 4.05 ppm in addition to the CH_2 protons at 3.18 ppm as singlet. The spectral data of compound 15 and 16 was agreement with their structure (see the experimental section).

Anticancer activity

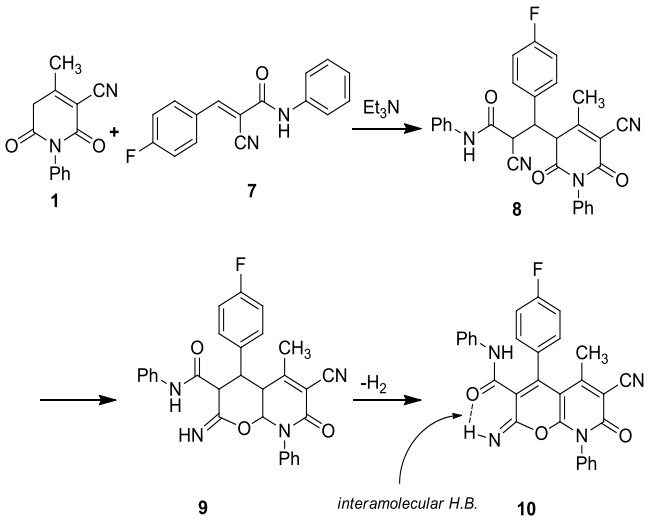
Reagents: Fetal bovine serum (FBS) and L-glutamine were from Gibco Invitrogen Co. (Scotland, UK). RPMI-1640 medium was from Cambrex (New Jersey, USA). Doxorubicin, dimethyl sulfoxide (DMSO), penicillin, streptomycin and sulforhodamine B (SRB) were from Sigma Chemical Co. (Saint Louis, USA).

Cell cultures: Three human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), and SF-268 (CNS cancer) were used. MCF-7 was obtained from the European Collection of Cell Cultures (ECACC, Salisbury, UK) and NCI-H460 and SF-268 were kindly provided by the National Cancer Institute (NCI, Cairo, Egypt). They grow as monolayer and routinely maintained in RPMI-1640 medium supplemented with 5% heat inactivated FBS, 2 mM glutamine and antibiotics (penicillin 100 U/mL, streptomycin 100 µg/mL) at 37°C in a humidified atmosphere containing 5% CO_2. Exponentially growing cells were produced by plating 1.5×10^5 cells/mL for MCF-7, SF-268 and 0.75×10^4 cells mL^{-1} for NCI-H460, followed by 24 h of incubation. The effect of the vehicle solvent (DMSO) on the growth of cell lines which it was evaluated in all experimental by exposing untreated control cells to the maximum concentration (0.5%) of DMSO used in each assay.

Tumor cell growth assay: The effects of some newly synthesized compounds 4 and 10-16 on the *in vitro* growth of human tumor



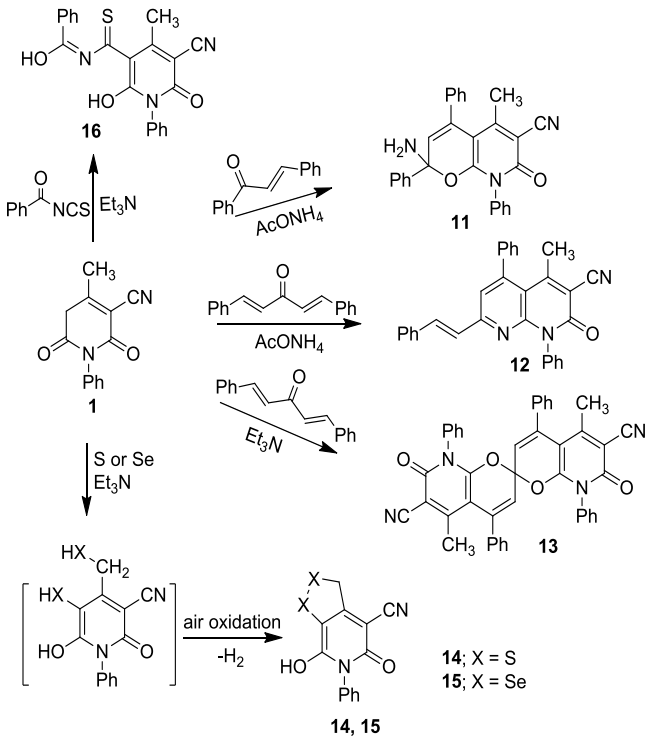
Scheme 1: Reaction of pyridone 1 with benzylidine derivatives 2 and 3.



Scheme 2: Synthetic approach of pyrano[2,3-b]pyridine 10.

cell lines were evaluated according to the procedure adopted by the National Cancer Institute (NCI, USA) in the '*In vitro* Anticancer Drug Discovery Screen' that uses the protein-binding dye sulforhodamine B to assess cell growth [11-13]. Briefly, exponentially cells growing in 96-well plates were then exposed for 48 h to five serial concentrations of each compound starting from a maximum concentration of 150 µM. Following this exposure period adherent cells were fixed, washed and stained. The bound stain was solubilized and the absorbance was measured at 492 nm in a plate reader. For each test compound and cell line, a dose response curve was obtained and the growth inhibition of 50% (GI_{50}), corresponding to the concentration of the compounds that inhibited 50% of the net cell growth was calculated as described elsewhere. Doxorubicin was used as a positive control and tested in the same manner.

The results of antitumor activity are given in concentrations that were able to cause 50% of cell growth inhibition (GI_{50}) after a continuous exposure of 48 h and show means ± SEM of three independent



Scheme 3: Reaction of pyridone 1 with α,β-unsaturated carbonyl compounds.

Compound	GI_{50}, µmol L^{-1}		
	NCI-H460	MCF-7	SF-268
4	46.4	38.4	45.5
10	0.21	0.18	0.11
11	40.1	21.2	33.4
12	19.3	10.1	30.3
13	33.8	18.9	38.4
14	0.15	0.23	0.36
15	0.84	0.50	0.45
16	0.78	0.29	0.51
Doxorubicin	0.09 ± 0.008	0.04 ± 0.008	0.09 ± 0.007

Table 1: Effect of compounds 4 and 10-16 on the growth of three human tumor cell lines.

experiments performed in duplicate (Table 1). Where compounds 10 and 14 showed the highest inhibitory effects against all three tumor cell lines. Such activity is not higher than the corresponding reference Doxorubicin, while compounds 15 and 16 showed moderate inhibitory effects against the tree cell lines. Compounds 4 and 11-13 showed lower inhibitory effect comparing to Doxorubicin. The structure-activity relationship studies revealed that the presence of amide grroup (NHC=O) as a side chain in pyrano[2,3-b]pyridine derivative 10 and dithiol ring fused with compound 1 at positions 4 and 5 in compound 14 is responsible for their reactivity over the other compounds, Morever, presense of diselenol ring in compound 15 and thioamide group as a side chain in compound 16 may be rise the inhibitory effects of these compounds.

Conclusion

In summary, we synthesized here a series of fused 2-oxonicotinonitrile derivatives using 4-methyl-2,6-dioxo-1-phenyl-1,2,5,6-tetrahydropyridine-3-carbonitrile as a starting material. The newly synthesized compounds have low anticancer activity against NCI-H460, MCF-7 and SF-268 cell lines. Compound 10 have the higher activity among the other compounds; on the other hand, none of the synthesized compounds have activity higher than Doxorubicin. The structural modification to improve the potency of this class of compounds will be reported in due course.

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