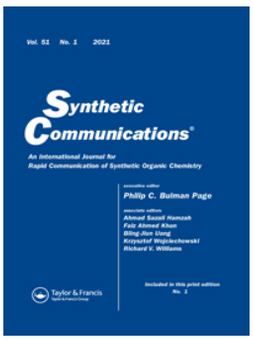

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Synthesis, characterization, antimicrobial activities, anticancer of some new pyridines from 2, 3-dihydro-2-oxo-4-phenyl-6-(thien-2-yl) pyridine-3-carbonitrile

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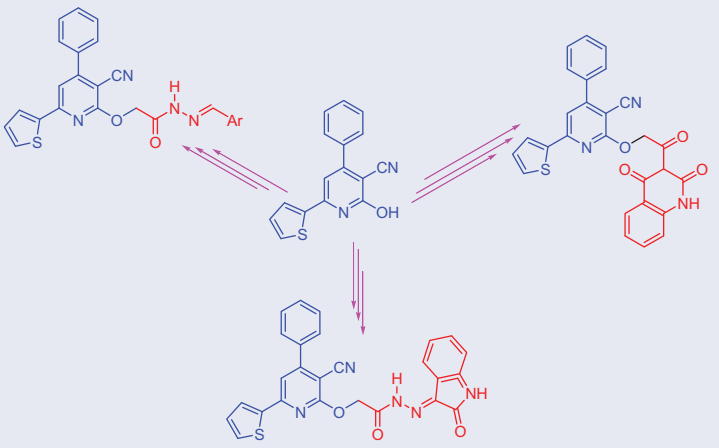
ABSTRACT

2,3-Dihydro-2-oxo-4-phenyl-6-(thien-2-yl)pyridine-3-carbonitrile **(4)** was synthesized *via* reaction of four compounds (benzaldehyde, 2-acetylthiophene, ethyl cyanoacetate and ammonium acetate) in one step reaction. 2-((Hydrazinocarbonyl)methyloxy)-4-phenyl-6-(2-thienyl)pyridine-3-carbonitrile was obtained by reaction of **5** with hydrazine hydrate. Schiff's bases, pyrazole derivatives, urea derivatives, and carbamates were also synthesized. Based on the spectral facts and elemental analysis, structures of the newly synthesized compounds were elucidated. Also, the new compounds were evaluated for their antibacterial and antitumor activities.

GRAPHICAL ABSTRACT



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KEYWORDS
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Supplemental data for this article can be accessed on the publisher's website.

Introduction

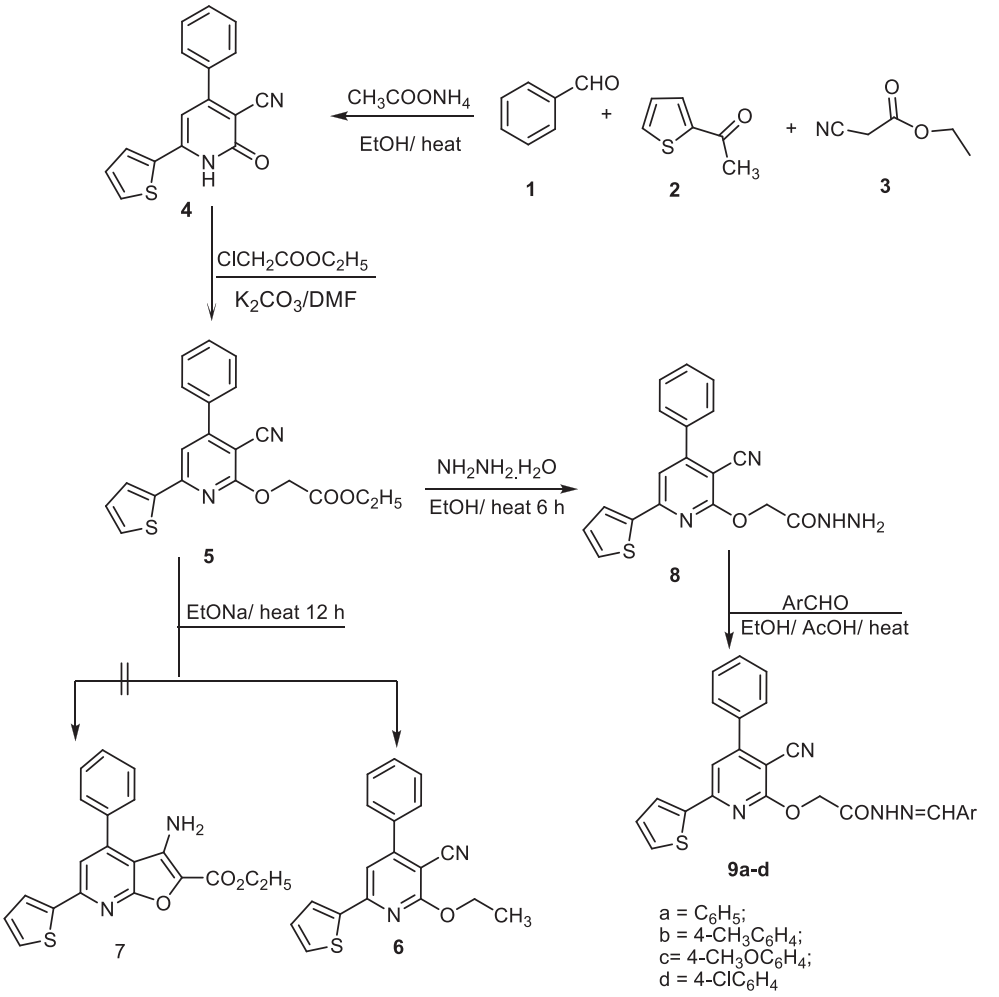
Breast cancer is a complex disease that comprises heterogeneous tumors associated with distinctive histological patterns and different clinical characteristics.[1] An estimated 1.7 million women will be diagnosed with breast cancer in 2020, a 26% increase from current levels.[2] Approximately 30% of the women diagnosed with early-stage disease subsequently progress to metastatic breast cancer (MBC), for which few therapeutic regimens exist.[3] Despite the advances in therapeutic modalities, MBC remains incurable, with an estimated survival rate of about 23% over 5 years.[4] Chemotherapy resistance is also a consistent obstacle in the management of breast cancer, where many of the initially responsive tumors relapse and develop resistance to diverse chemotherapeutic agents.[5] Consequently, new agents with low susceptibility to common drug resistance mechanisms are urgently needed for the management and treatment of various forms of breast cancer.

Pyridine derivatives are very essential chemical compounds with the tremendous biological applications. In medicinal applications, these compounds share a necessary part. The activities of pyridine derivatives vary from moderate to excellent against a number of biological targets such as anti-microbial, anti-viral, antioxidant, anti-diabetic, anticancer activities, antimalarial agents, and anti-amoebic agents.[6–26] With altering substituents on the pyridine nucleus, the biological targets differ from microbial diseased to viral problems and a variety of cancerous cells. These derivatives target exclusive biological problems by interacting with enzymes, proteins and DNA. From the above facts, and our interest in designing new heterocyclic compounds that have pharmaceutical properties.[27–34]

Results and discussion

Pyridine-3-carbonitrile derivative **(4)** was synthesized by the condensation reaction of a mixture of benzaldehyde **(1)**, 2-acetylthiophene **(2)**, and ethyl cyanoacetate **(3)** in boiling ethanol in presence of ammonium acetate. 2-((ethoxycarbonyl)methyloxy)-4-phenyl-6-(2-thienyl)pyridine-3-carbonitrile **(5)** was obtained by the reaction of **4** with ethyl chloroacetate in ethanol. Compound **5** reacted with sodium ethoxide in boiling ethanol afforded one isolable product **(6)** according to TLC. The IR of the product revealed bands at (KBr, ν, cm^{-1}): 3109, 3092 (CH), 2217 (CN), 1584 (C=C), 1445 (CH_2), 1355 (CH_3). H^1-NMR spectra of the synthesized compound **(6)** revealed a triplet-quartet pattern of ethyl protons at 1.46–1.50 and 4.55–4.61 ppm and singlet signal at 7.06 for pyridine H. Meanwhile, the reaction of compound **5** with hydrazine hydrate gave pyridine-3-carbonitrilederivative **(8)**. Schiff's bases (**9a–d**) were obtained from reaction of compound **5** with the appropriate benzaldehyde,4-methoxybenzaldehyde,4-methylbenzaldehyde and 4-chlorobenzaldehyde in ethanol, respectively, in the presence of a few drops of acetic acid (Scheme 1).The structures of **8** and **9a–d** were established on the foundation of elemental analysis and spectral results (*cf.* Section "Experimental").

Also, thienylpyridine-3-carbonitrile derivative **10** was synthesized by the reaction of **8** with indoline-2,3-dione in methanol and the presence of catalytic amounts of acetic acid (Scheme 2).

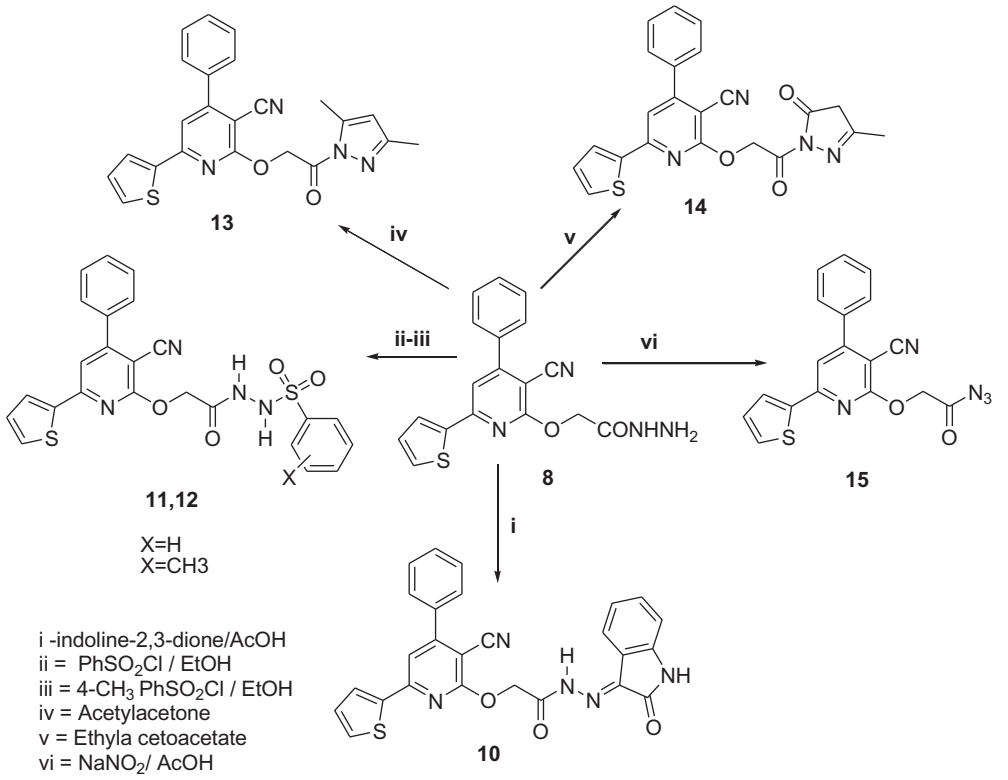


Scheme 1. 2-Ethoxy-4-phenyl-6-(thien-2-yl)nicotinonitrile.

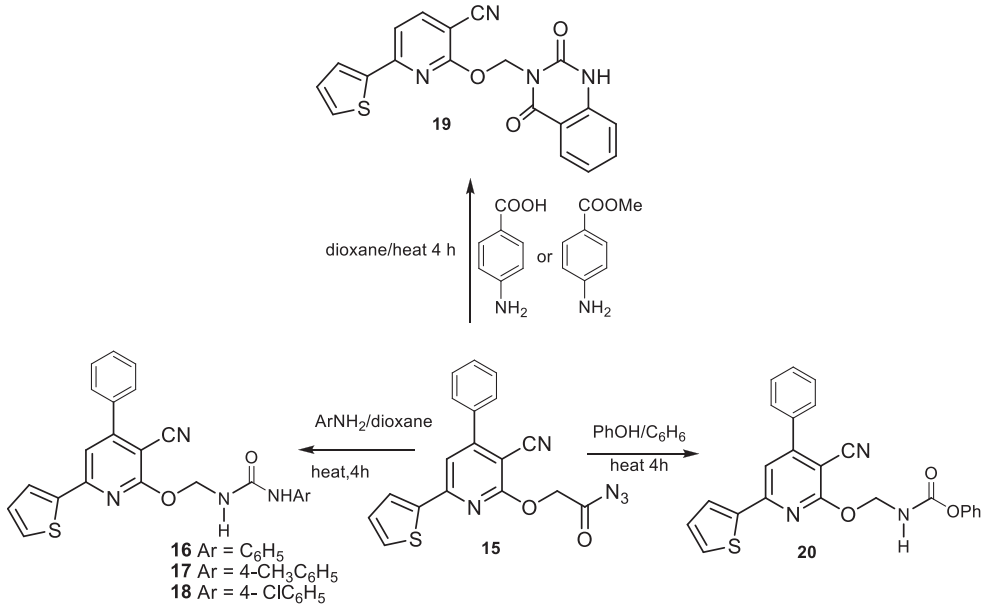
Treatment of compound **8** with the appropriate benzene sulfonyl chloride and p-toluene sulfonyl chloride in pyridine at room temperature afforded compound (**11**) and (**12**), respectively.

Thienylpyridine-3-carbonitrile **13** and nicotinonitrile derivatives **14** were obtained *via* the reaction of compound **8** with appropriate acetylacetone, ethyl acetoacetate in ethanol/glacial acetic acid mixture (30 mL) (2:1) (*cf.* Scheme 2 and Section "Experimental").

Furthermore, Compound **8** was reacted with nitrous acid to give nicotinonitrile derivative **15**. Based on the elemental analysis, spectral records, and chemical transformation, the structure of **15** was confirmed. Thus, compound **15** can be transformed into urea derivatives, **16–18**, and **19** from the suitable aromatic amines, or anthranilic acid (or methyl anthrarnelate) in boiling dry dioxane, respectively. Pyridine-3-carbonitrile derivative **20** can also be formed by boiling phenol in dry benzene with azido **15** (Scheme 3).



Scheme 2. Synthesis of pyrazole and azide.



Scheme 3. Synthesis of urea, quinoxaline and carbamate derivatives.

Antimicrobial activity

Recently, Antimicrobial resistance becomes one of the biggest threats to humanity.[40] It can affect any person at any age, in any country. Antimicrobial resistance usually happens when humans misuse antibiotics and several pathogenic infections, such as tuberculosis, gonorrhea, pneumonia, and salmonellosis—are becoming harder to treat as the antibiotics used to treat them become less effective. In our effort to evaluate the inhibitory activities of the synthesized compounds, the antibacterial potential against *S. aureus, B. subtilis, E. coli,* and *P. aruginosa* were measured. Compounds **11** and **15** displayed a pronounced antibacterial activity against Gram-positive *S. aureus* with 59.54% and 55.84% of inhibition respectively, followed by compounds **9a, 10**, **13, 18, 20**. While compounds **9b** and **9c** showed a mild to moderate inhibitory activity against Gram-positive *B. subtilis* with % of inhibition ranged from 45.09% to 48.01%. Both compounds **9a** and **9c** showed potent to moderate inhibitory activity against Gram-negative ***E. coli*** with inhibition ratio of 64.81% and 64.61%, followed by **15**, **18b**, and **11**. Compound **13** showed moderate antibacterial activity against Gram-negative *P. aruginosa* with an inhibition ratio 53.10% (Figure 1).

Antibiofilm activity

Bacterial biofilm formation has been found to play a critical role in the persistence of bacterial infections[36,37] This phenomenon helps bacteria to maintain their attachment on living or no living surface in close proximity to each other.[38] Thus, biofilms are recognized as a remarkable source of bacterial infectious diseases such as peridontitis, osteomyelitis, dental caries, otitis media.[39] The antibiofilm activity of the synthesized compounds has been measured against four clinical microbes (*P. aeruginosa*, *S. aureus*,

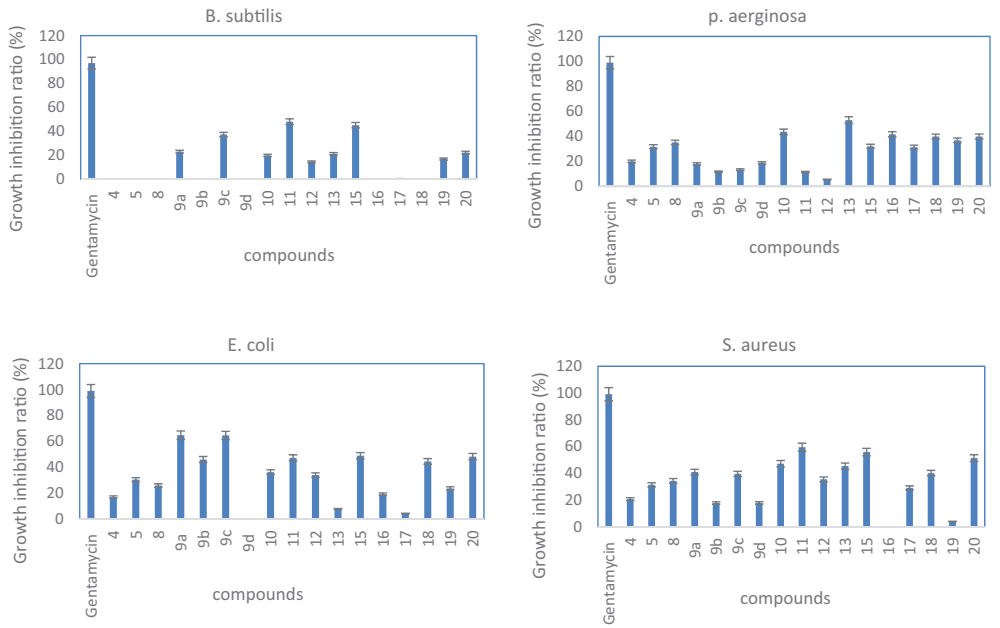


Figure 1. Antibacterial activity as % of inhibition (**4**, **5**, **8**, **9a**, **9 b**, **9c**, **9d**, **10**, **11**, **12**, **13**, **15**, **16**, **17**, **18**, **19** and **20**) against different bacterial strains.

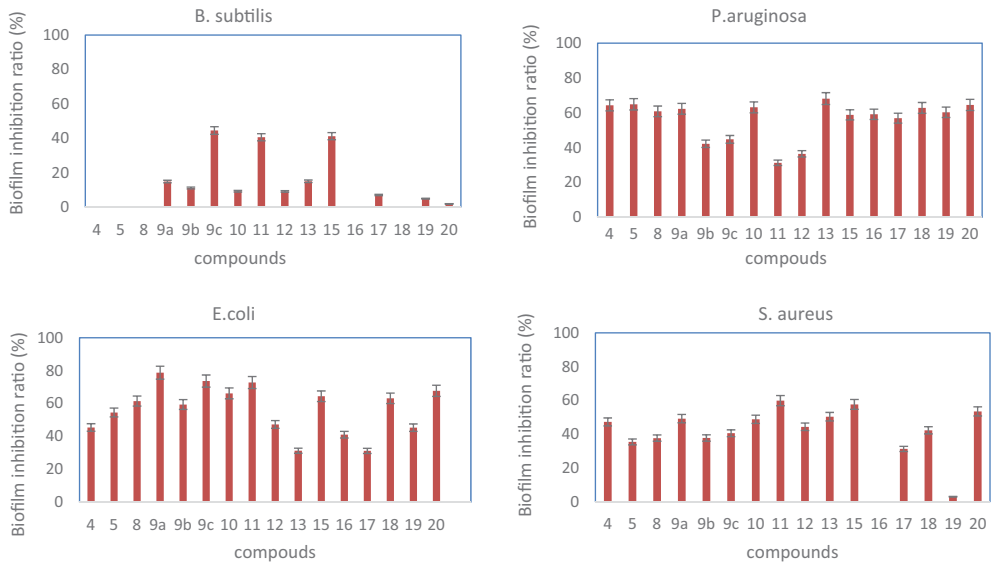


Figure 2. Anti-biofilm activity of compounds (**4**, **5**, **8**, **9a**, **9 b**, **9c**, **9d**, **10**, **11**, **12**, **13**, **15**, **16**, **17**, **18**, **19** and **20**) on different strains of microorganisms.

E. coli and *B. subtilis*) (Figure 2). Compounds **15** and **11** reduced the biofilm formation of the strain *S. aureus* up to 57.61% and 59.84%, respectively followed by compounds **4**, **13**, **10**, **9a** with inhibition ratio ranged from 47.23% to 50.33%. While in the case of *B. subtilis* biofilm inhibition, only three compounds **15**, **9c**, **11** showed a moderate to low biofilm inhibition activity 41.19%, 44.46% and 40.56%. On the other hand, compounds **9a**, **9c**, **11** displayed a potent anti-biofilm activity with inhibition ratio 78.75, 73.67, and 72.78%, followed by compounds **8**, **10**, **15**, **20**, **18** with inhibition activity ranged from 61.49 to 67.70. *P. aruginosa* was more susceptible bacteria to the synthesized compounds. While, compounds **4**, **5**, **8**, **13**, **10**, **20**, **18**, **19**, and **9a** showed biofilm inhibitory activity ranged from 60.29 to 68.14%, followed by compounds **15**, **16**, **17**, **9d**, **9b** and **9c** with inhibition ratio ranged from 42.17 to 59.13 (Figure 2).

In vitro cytotoxicity

As there is a matching correlation between the antimicrobial activity of the synthesized compounds and their cytotoxicity. Three compounds **15**, **9a**, and **9c** were accordingly selected based on antimicrobial and anti-biofilm results to investigate their efficiency as anti-cancer agents. So, they were studied against liver (HePG-2), breast (MCF-7), colon (HCT-116) cancer cell lines, in comparison with doxorubicin as a reference control. Accordingly, compounds **9c**, **9a** and **15** showed moderate cytotoxic activity against HCT116 and MCF7cell lines (IC_{50}: 23.09–39.70 µg/mL), meanwhile, compound **15** showed a strong cytotoxicity (IC_{50}:19.85 µg/mL) against HePG-2 followed by **9a** and **9c** with (Table 1).

Structure activity relationship

Recent reports demonstrated that the antibacterial mechanism of action generally involves regulation or inhibition of enzymes responsible for the cell wall biosynthesis,

Table 1.

	In vitro cytotoxicity IC50 (μg/ml)[a]			
Comp.	WI38	HCT116	HePG-2	MCF7
DOX	6.72 ± 0.5	5.23 ± 0.3	4.50 ± 0.2	4.17 ± 0.2
15	56.16 ± 3.5	29.17 ± 1.9	19.85 ± 1.4	23.09 ± 2.3
9a	39.26 ± 2.5	25.39 ± 0.8	36.84 ± 0.6	30.48 ± 1.0
9c	45.89 ± 2.9	34.10 ± 2.3	28.76 ± 2.1	39.70 ± 2.9

[a]IC50 (μg/ml): 1–10 (very strong); 11–20 (strong); 21–50 (moderate); 51–100 (weak) and above 100 (non-cytotoxic)
DOX: Doxorubicin.

protein synthesis, nucleic acid metabolism and repair and disruption of membrane structure.[40] The obtained biological activity results (antibacterial, anti-biofilm, and anticancer) declared that, compounds **15**, **11**, **9c**, **9d** and **9a** displayed pronounced antibacterial, and anti-biofilm activity. On the other hand, three compounds **15**, **9a**, and **9d** showed anti-proliferative activity toward liver (HePG-2), breast (MCF-7), colon (HCT-116) cancer cell lines. Based on the structure of the active compounds, the activity have resulted from the presence of thiophene group in combination with azide group in compound **15**, cyanide group in compound **11**, methoxy group in compound **9c**, chlorine element in compound **9d** and benzene ring in compound **9a**. These results confirmed that the presence of chemical groups such as (azide, methoxy, cyanide, benzene) and chlorine element may increase the activity of the synthesized compounds.

Conclusion

In our work, new pyridine-3-carbonitile derivatives were synthesized, and their structures were confirmed by different spectral data, also it was found that they are useful as a key precursor for the synthesis of different heterocyclic derivatives which have an interesting anti-proliferative activity such as Schiff's bases, azide, urea, quiazoline , and carbamate derivatives. Most of the synthesized compounds were investigated for their anticancer activity. The anticancer effects of some compounds showed moderate cytotoxic activity against HCT116 and MCF7cell lines, meanwhile, others showed strong cytotoxicity against HePG-2, in addition it was also compared with the standard anticancer drug doxorubicin.

Experimental

All melting points have been measured by the use of Reichert Thermovar equip-ment and are uncorrected. Listed yields are of isolated compounds. The IR spectra for the KBr disk was registered on a Perkin-Elmer spectrometer model 1720 FTIR.1H-NMR and ^{13}C-NMR spectra have been reported on a BrukerAC-400 or DPX-400 spectrometer in $CDCl_3$ and $(CD_3)_2SO$ solutions and chemical shifts are expressed in ppm units using tetramethylsilane as an internal reference and the *J* coupling constants are given in Hz. Once TLC followed the progress of the reactions using aluminum silica gel plates 60 with a Shimadzu GCMS–QP–1000 EX mass spectrometer in EI (70 eV) model F245. Elemental analyses were performed at the University of Cairo Microanalytical Center.

The Biological Activity of the compounds was carried out at National Research Center (NRC), Tahrir Street, Dokki, Cairo, Egypt.

2-Oxo-4-phenyl-6-(thienyl-2-yl)-1,2-dihydropyridine-3-carbonitrile (4)

A mixture of benzaldehyde **1** (1.06 g, 1.02 mL, 0.01 mol), 2-acetylthiophene **2** (1.26 g, 1.08 mL, 0.01 mol), ethyl cyanoacetate **3** (1.13 g, 1.09 mL, 0.01 mol) and ammonium acetate (7.71 g, 0.1 mol) in ethanol (50 mL) refluxed for 1 h. Filtered, treated with cold ethanol (50 mL), the precipitate was dried and crystallized with ethanol. Yield: 90%, yellowish-green crystal, m.p.: 340 − 342 °C. IR (KBr, ν, cm^{-1}): 3453 (NH), 2216 (CN), 1635 (C = O); ^{1}H NMR (DMSO-d_6, δ ppm), 7.08 (s, 1H, pyridinone-H-5) 7.27–7.22 (dd, $J = 4$ Hz, $J = 12$ Hz, 1H, thienyl H-4), 7.58–7.68 (m, 3H, thienyl and ArH), 7.69–7.71 (d, 2H, $J = 8$ Hz, ArH), 8.06–8.08 (d, 2H, $J = 8$ Hz, ArH), 12.77 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δppm): 39.37, 39.58, 39.79, 40.00, 40.20, 40.42, 40.62, 42.00, 116.73, 128.68, 129.29, 129.44, 130.04, 130.71, 132.92, 136.42; Anal. For $C_{16}H_{10}N_2OS$ (278.33), calcd (%): C, 69.04; H, 3.62; N, 10.06; Found: C, 69.29; H, 3.41; N, 9.86.

2-((Ethoxycarbonyl)methyloxy)-4-phenyl-6-(2-thienyl)pyridine-3-carbonitrile (5)

A mixture of **4** (2.78 g, 0.01 mol), ethyl chloroacetate (1.22 g, 1.06 mL 0.01 mol) and anhydrous potassium carbonate (4.5 g, 0.04 mol) in DMF (30 mL) was stirred at room temperature for 20 h. The reaction mixture was poured onto ice-cold water and the reaction left in a fridge for overnight. The resulting solid was filtered, washed with water, dried and recrystallized from ethanol (50 mL).Yield: 75%, paje crystal, m.p.: 130–132 °C. IR (KBr, ν, cm^{-1}): 2218 (CN), 1751 (CO), 1586 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 1.26 (t, 3H, $J = 4$ Hz, CH_3), 4.23–4.25 (q, 2H, $J = 8$ Hz, CH_2), 5.11 (s, 2H, CH_2), 7.27–7.22 (dd, 1H, $J = 4$, Hz, $J = 12$ Hz, thienyl H-4), 7.22–7.31 (m, 3H, thienyl and ArH), 7.61 (s, 1H, pyridinone-H-5), 7.71–7.73 (d, 2H, $J = 8$ Hz, ArH), 8.06–8.08 (d, 2H, $J = 8$ Hz, ArH); MS, m/z (%): 365 (M^{+1}, 20.53), 364 (M^+, 78.48), 291 (100), 279 (10.60), 261 (36.38), 190 (18.14), 127.20 (3.86), 102 (3.98), 77 (15.79); Anal. for $C_{20}H_{16}N_2O_3$ S (364.42), calcd (%): C, 65.92; H, 4.43; N, 7.69, S, 8.80; Found: C, 65.56; H, 4.50; N, 7.99, S, 8.72.

2-Ethoxy-4-phenyl-6-(thien-2-yl)nicotinonitrile (6)

In absolute ethanol (25 mL) a mixture of **5** (0.364 g, 0.001 mol) and sodium ethoxide (0.68 g sodium) was heated under reflux for 12 h, the reaction mixture was cooled up. The solid was obtained and crystallized from ethanol (50 mL) to give colorless needles m.p. 90–92 °C. IR (KBr, ν, cm^{-1}): 3109, 3092 (CH), 28,217 (CN), 1584 (C = C), 1445 (CH_2), 1355 (CH_3). ^{1}H NMR ($CDCl_3$, δ) showed signals at = 1.46–1.50 (t, 3H, $\underline{CH_3}CH_2O$), 4.55–4.61(q, 2H, $CH_3\underline{CH_2}O$), 7.06 (s, 1H, pyridine H-5),7.20–7.25 (m, 3H, thienyl and ArH), 7.26–7.30 (dd, 1H, $J = 4$, Hz, $J = 12$ Hz, thienyl H-4), 7.73–7.75 (d, 2H, $J = 8$ Hz, ArH), 7.94–7.96 (d, 2H, $J = 8$ Hz, ArH), Anal. for $C_{18}H_{14}N_2OS$ (306.38), calcd (%): C, 70.56; H, 4.61; N, 9.14; S, 10.47; Found: C, 70.64; H, 4.55; N, 9.00; S, 10.38.

2-((Hydrazinocarbonyl)methyloxy)-4-phenyl-6-(2-thienyl)pyridine-3-carbonitrile (8)

The hydrazine hydrate (5 g, 4.9 mL, 0.1 mol) was added once to a suspension of **5** (3.64 g, 0.01 mol) in absolute ethanol (50 mL). The mixture was heated under reflux for 6 h and cooled at room temperature. The precipitate was filtered, dried and crystallized from ethanol (50 mL). Yield: 68%, pale yellow needles, m.p.: 228–230 °C. IR (KBr, ν, cm^{-1}): 3329–3105 (NH_2, NH), 2222 (CN), 1678 (CO), ^{1}H NMR (DMSO-d_6, δ ppm): 5.09 (s, 2H, CH_2), 5.37 (s, br., 2H , NH_2, exchangeable), 7.08 (s, 1H, pyridinone-H-5), 7.26–7.30 (dd, $J = 4{,}12$ Hz, 1H, thienyl H-4), 7.60–7.62 (m, 3H, thienyl and ArH), 7.71–7.73 (d, 2H, $J = 8$ Hz, ArH), 8.06–8.08 (d, 2H, $J = 8$ Hz, ArH), 9.35 (s, 1H, NH exchangeable); ^{13}C NMR (DMSO-d_6, δppm): 39.37, 39.58, 39.79, 40.00, 40.20, 40.41, 40.42, 42.00, 116.73(2 C), 128.68, 129.29(2 C), 129.44, 130.04, 130.71, 132.92, 136.42;MS m/z (%): 352 (1.26 M^{+2}), 351 (4.17, M^{+1}), 350 (17.23, M^{+}), 320 (16.99), 319 (75.16), 292 (14.47), 291 (59.76), 280 (22.09), 279 (100), 278 (71.43), 262 (10.08); Anal. for $C_{18}H_{14}N_4O_2S$ (350.40), calcd (%): C, 61.70; H, 4.03; N, 15.99; S, 9.15; Found: C, 61.56; H, 4.11; N, 16.05; S, 9.20.

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