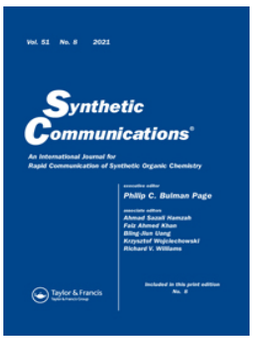

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Synthesis and anticancer assessment of some new 2-amino-3-cyanopyridine derivatives

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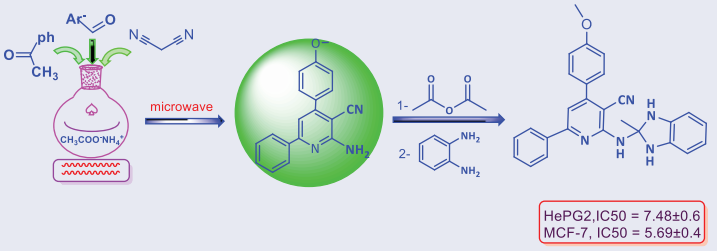
ABSTRACT

The 2-Aminonicotinonitrile derivative was reacted with different bifunctional reagents such as formamide, thiourea, acetic anhydride, and phthalic anhydride under optimized conditions to give pyrimidine, thiourea, acetamide, and isoindoline derivatives, respectively, When it was treated with active methylene reagents as malononitrile, phenacyl bromide, and ethyl bromoacetate under varied experimental modulation, it afforded 1, 8-naphthyridine, ethyl, and methylamino nicotinonitrile derivatives, respectively. Also, it was reacted with p-toluene sulfonyl chloride, chloroacetyl chloride, and benzoyl chloride to give sulfonamide, 2-chloro-N-acetamide, and benzamide derivatives, respectively. Likewise, it was reacted with diethyl malonate, ethyl cyanoacetate, and cyano acetic acid to give ethylpropanoate, naphthyridine, and cyano acetamide derivatives, respectively. However, treatment of ethylpropanoate and cyano acetamide derivatives with hydrazine hydrate gave pyrazole and 5-amino-pyrazole nicotinonitrile derivatives, respectively. In addition, it was reacted with p-anisaldehyde, phenyl isocyanate, and triethyl orthoformate to give benzylamino nicotinonitrile, phenyl urea, and *N*-formamide derivatives, respectively. Furthermore, it was reacted with nitrous acid then coupled with aniline; it was also reacted with isatine and 1,3- dibromo propane to give oxoindoline derivative, and the dimer. Elemental analyses, together with spectroscopic data including IR, ^{1}H-NMR in addition to ^{13}C-NMR and mass spectra submit proofs for the chemical structures for all compounds.

GRAPHICAL ABSTRACT



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KEYWORDS
Acetophenone; anisaldehyde; malononitrile; microwave; pyridine

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

This article has been corrected with minor changes. These changes do not impact the academic content of the article.

Introduction

Studying cyano and/or amino pyridine heterocyclic derivatives as a six-member ring containing nitrogen has attraced great attention because of its superior biological activities particularly in the medicinal field as antimicrobial active agents,[1–5] antiviral,[6] antidiabetic,[4,6] antituberculosis,[7] antitumor drugs activity,[8–10] antiinflammatory,[11] antioxidant,[12] proton pump inhibitors,[13] treatment of cardiovascular diseases as antihypertensive agents.[14] Also, derivatives containing substituted phenyl moiety sitting at positions 4- and 6- are of great importance as multiskilled scaffolds are used to construct a diversity of heterocyclic compounds that have pronounced biological effects and pharmaceutical applications.

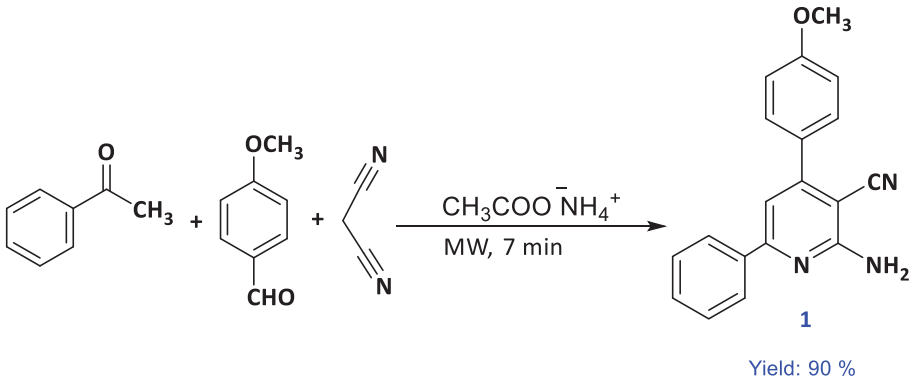
The above-mentioned screening of biological activity facts motivates our concern[14–17] for the preparation of various new heterocyclic products that comprise pyridine moiety and were tested as anticancer agents against hepatocellular carcinoma (liver) HepG2 and mammary gland breast MCF-7 cancer and as antimicrobial agents against Gram-positive bacteria (*Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli*). The antifungal activities of the compounds were tested against two fungi (*Candida albicans*, *Aspergillus flavus*).

Result and discussion

The one-pot synthesis is a specific research methodology (multicomponent reactions) in which three or more reactants are mixed in one flask, reacted with one another depending on their reactivity to produce the required product.[18,19] The one-pot (multicomponent) approach presents a higher yield with less reaction time.

The reaction of acetophenone, anisaldehyde, and malononitrile in the presence of ammonium acetate under microwave conditions using one-pot reaction produced 2-amino-4-(4-methoxyphenyl)-6-phenylnicotinonitrile (**1**) in an excellent yield[20] (Scheme 1).

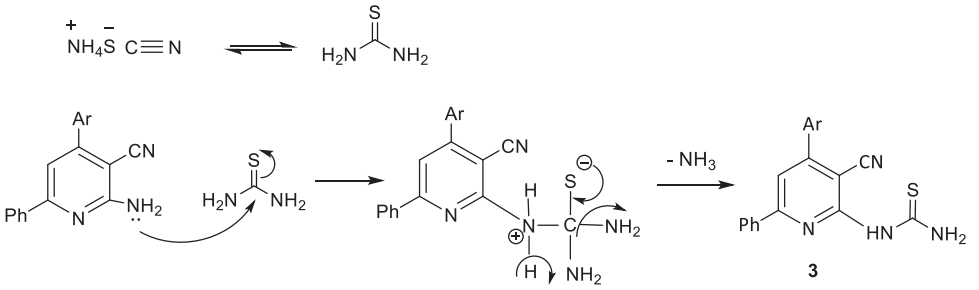
Compound **1** was reacted with formamide by different procedures; reflux and by irradiating in the microwave for 4 min., producing pyrido pyrimidinone derivative **2**. The second procedure gave a higher yield. The IR spectrum of compound **2** showed bands at 3292 and 1695 cm^{-1} for NH and C=O. The ^{1}H-NMR spectrum showed singlet for NH at 7.34 ppm.



Scheme 1. Formation of compound 1.

Starting compound **1** was interacted with thiourea *via* losing of ammonia molecule producing *3*-cyano-pyridin-thiourea derivative **3.** Compound **3** was alternatively prepared through the reaction of compound **1** with ammonium thiocyanate to give the same product (higher yield, shorter reaction time), the obtained products are identical in all aspects (IR spectra, m.p and mixed m.p), the last reaction probably proceeds through the following mechanism. Ammonium thiocyanate is stable in air, nevertheless, upon heating, it isomerizes to thiourea. Then, the reaction proceeds *via* the attack of the amino group on the C = S group followed by the elimination of ammonia.

The suggested mechanism for the formation of compound 3



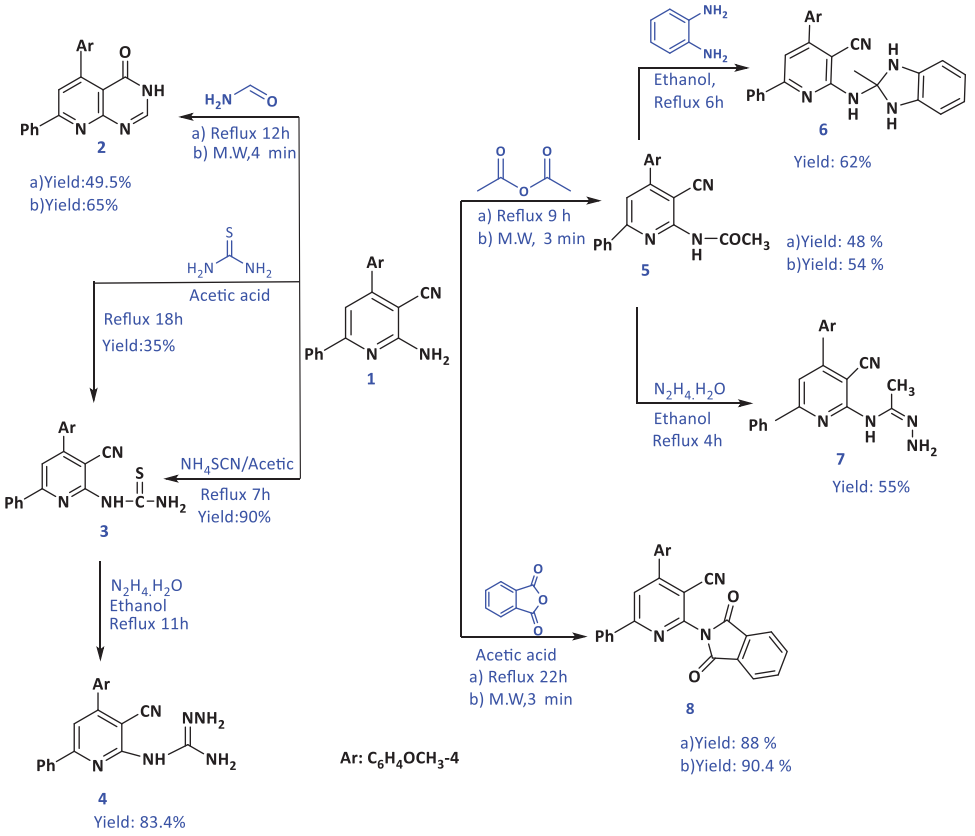
The thiourea derivative **3** underwent reaction with hydrazine hydrate/EtOH, giving rise to nicotinonitrile derivative **4**. Its infrared spectrum showed absorption bands at 3465, 3307, 3183, 2205, and 1639 cm^{-1} for NH_2, NH, C≡N, and C=N, respectively. However, its ^{1}H-NMR spectrum showed correctly the characteristic exchangeable singlet at δ 6.91 and 7.22 ppm for (4H, $2NH_2$) and (1H, NH), respectively.

2-Amino-nicotinonitrile derivative **1** was reacted with acetic anhydride, giving the monoacylated product **5** which when subjected to react with *o*-phenylene diamine, imidazolo nicotinonitrile derivative **6** was obtained. The ^{1}H-NMR spectrum of compound **6** showed singlet at 10.82 ppm for 3H, 3NH (D_2O exchangeable). Thereafter, product **5** was reacted with hydrazine hydrate, gave the acetohydrazonamide derivative **7.**

The reaction of compound **1** with phthalic anhydride yielded the 1, 3-dioxoisoindoline product **8**. The disappearance of the NH_2 group from IR and ^{1}H-NMR spectra of **8**, besides the appearance of the two absorption bands at 1792 and 1734 cm^{-1} for two carbonyl groups establish evidences for the structure of the product **8** (Scheme 2).

The reaction of compound **1** with malononitrile in the presence of drops of piperidine in boiling butanol produced 2, 4-diamino-5-(4-methoxyphenyl)-7-phenyl-1, 8-naphthyridine-3-carbonitrile (**9**). Its ^{1}H-NMR spectrum figures out one singlet signal at 4. 32, and broad singlet one at 6.05 due to 4H of two NH_2 groups (D_2O exchangeable).

The reaction of compound **1** with phenacyl bromide in butanol yielded 4-(4-methoxyphenyl)-2-((2-oxo-2-phenylethyl) amino)-6-phenylnicotinonitrile (**10**), whereas its reaction with ethyl bromoacetate in refluxing butanol and/or under microwave irradiation yielded 2-(methyl amino)-nicotinonitrile derivative **11**, the latter procedure offered higher yield with short reaction time. The reaction proceeded through the following

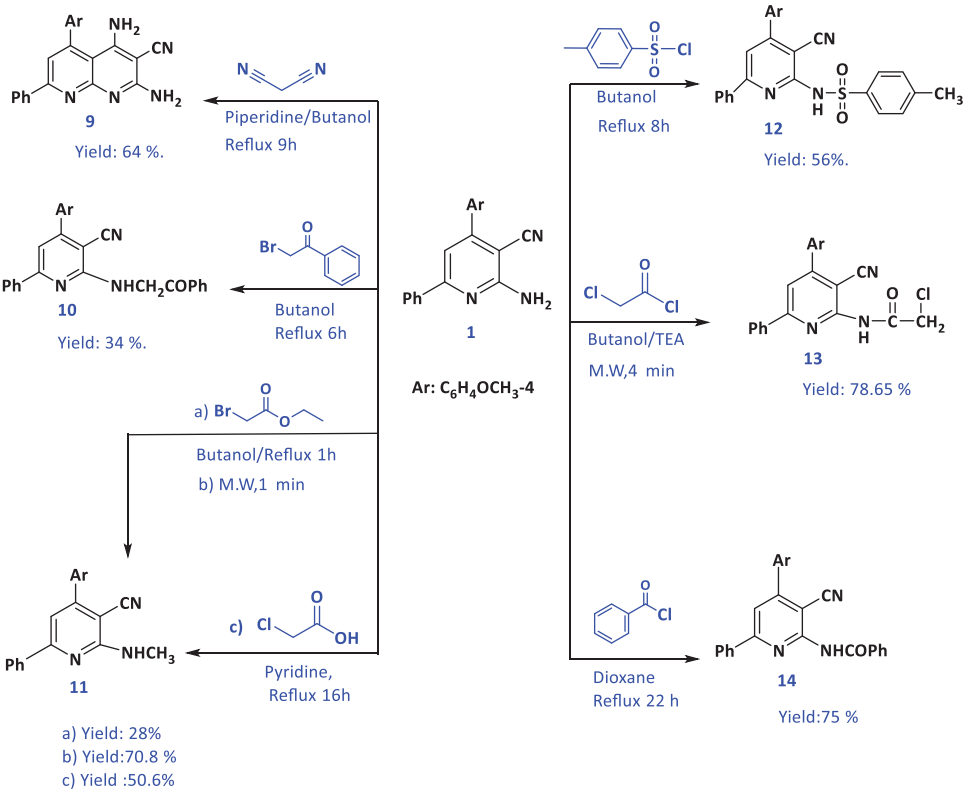


Scheme 2. Formation of compounds 2–8.

sequence; elimination of HBr, hydrolysis, and decarboxylation. Chemical evidence for the proposed structure of derivative **11** was received throughout the production of the authentic sample from the reaction of compound **1** with chloroacetic acid in refluxing pyridine by the elimination of HCl and decarboxylation. It was a matching pair in, mmp, mp as well as TLC.

In addition, 2-amino-6-phenylnicotinonitrile **1** was reacted with *p*-toluene sulfonyl chloride/butanol, chloroacetyl chloride/butanol plus drops of triethylamine, and benzoyl chloride/dioxane to give *N*-4-methylbenzene-sulfonamide derivative **12**, 2-chloro-*N*-acetamide derivative **13**, and *N*-benzamide derivative **14,** respectively. Three absorption bands were detected in their infrared spectra at 3339, 3378, and 3374 cm^{-1}, respectively, for NH group. Also, the ^{1}H-NMR characterize NH proton as singlet signals at 7.25, 9.88, and 8.23 ppm (D_2O exchangeable), respectively (Scheme 3).

When the starting material **1** was interacted with diethyl malonate, ethyl cyanoacetate, as well as cyanoacetic acid, it produced the ethyl3-((3-cyano-4-(4-methoxyphenyl)-6-phenylpyridin-2-yl)amino)-3-oxopropanoate (**15**),4-amino-5-(4-methoxy phenyl)-2-oxo-7-phenyl-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (**18**) along with 2-cyano-*N*-(3-cyano-4-(4-methoxyphenyl)-6-phenylpyridin-2-yl)acetamide (**19**).The infrared spectra of derivatives **15** and **19** lost the characteristic bands of the amino group. The ^{1}H-NMR spectrum of derivative **18** presents singlet signal at δ 6.92 ppm



Scheme 3. Formation of compounds 9–14.

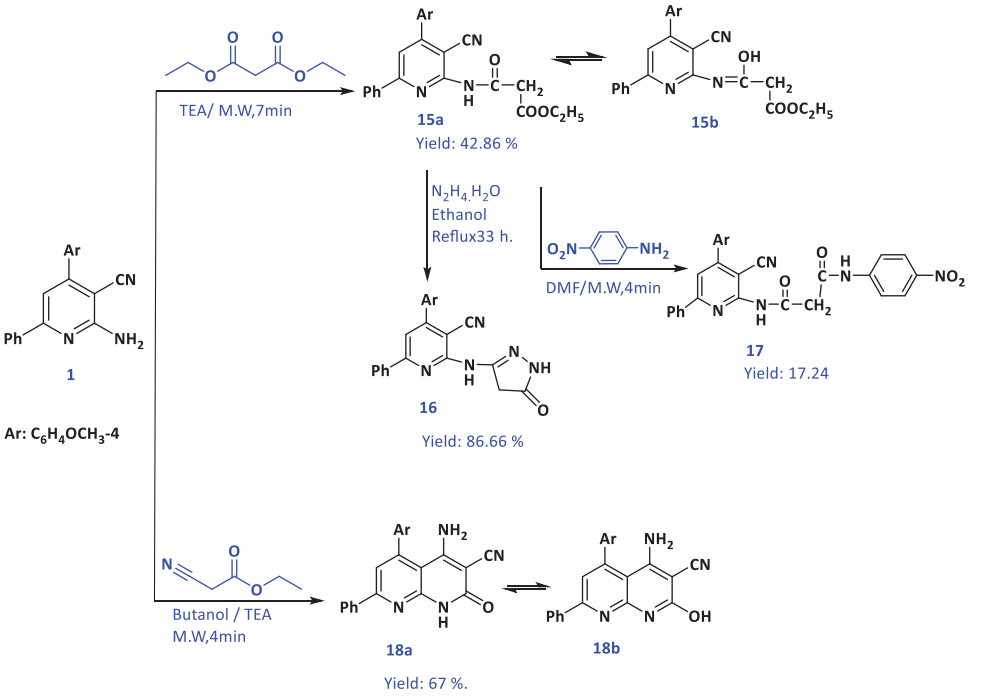
(s,2H, NH_2, D_2O exchangeable plus 2 singlet signals, exchangeable at δ 10.67, 11.27 ppm for OH and NH protons which were adequate affirmation for its existence as lactam lactim forms **18a**, **18 b**.

Afterward, propanoate derivative **15** was reacted with hydrazine hydrate and/or 4-nitro aniline, to produce pyrazolonicotinonitrile derivative ***16,*** *in addition to* malonamide derivative ***17,*** respectively**.**

In parallel acetamide derivative **19** underwent a similar reaction with hydrazine hydrate/ethanol to yield 2-((5-amino-4H-pyrazol-3-yl) amino)-4-(4-methoxyphenyl)-6-phenyl nicotinonitrile (**20**). The NH_2 and NH absorption bands with the 2 singlets at δ 6.91 and 10.19 ppm for 2H, $NH_{2,}$ and 1H, NH (D_2O exchangeable) was taken as evidence for the recommended structure of derivative **20** (Scheme 4).

Condensation of compound **1** with carbon electrophilic agents like anisaldehyde followed by reduction of the double bond gave nicotinonitrile derivative **21.** Although its reaction with phenyl isocyanate gave derivative **22**, the proposed structure of compound **22** got its approval from the existence of two exchangeable singlet signals at δ 6.92, 8.62 ppm due to 2H, 2NH protons.

Although compound **1** was reacted with triethyl orthoformate by different procedures, reflux, and by irradiating in the microwave for 3 min., gave the formamide derivative **23**, the latter procedure gave the higher yield. It was proved through its ^{1}H-NMR spectrum which defines exchangeable signals at δ 9.27 ppm (s, 1H, CHO),



Scheme 4. Formation of compounds 15–18.

10.94, and 10.96 (s, 1H, NH, D_2O exchangeable, the rate of NH exchange is slow and the proton couples with the nitrogen atom) (Scheme 5).

In addition to the above, since the starting compound, **1** possesses the primary NH_2 group, so it can interact with nitrous acid at 0-5 °C similar to ordinary aromatic amine and couple with aniline to offer 4-(4-methoxyphenyl)-6-phenyl-2-(3-phenyltriaz-1-en-1-yl) nicotinonitrile (**24**).

Further, the reaction of compound **1** with isatine gave the 2-oxoindolin-3-ylidene **25**.

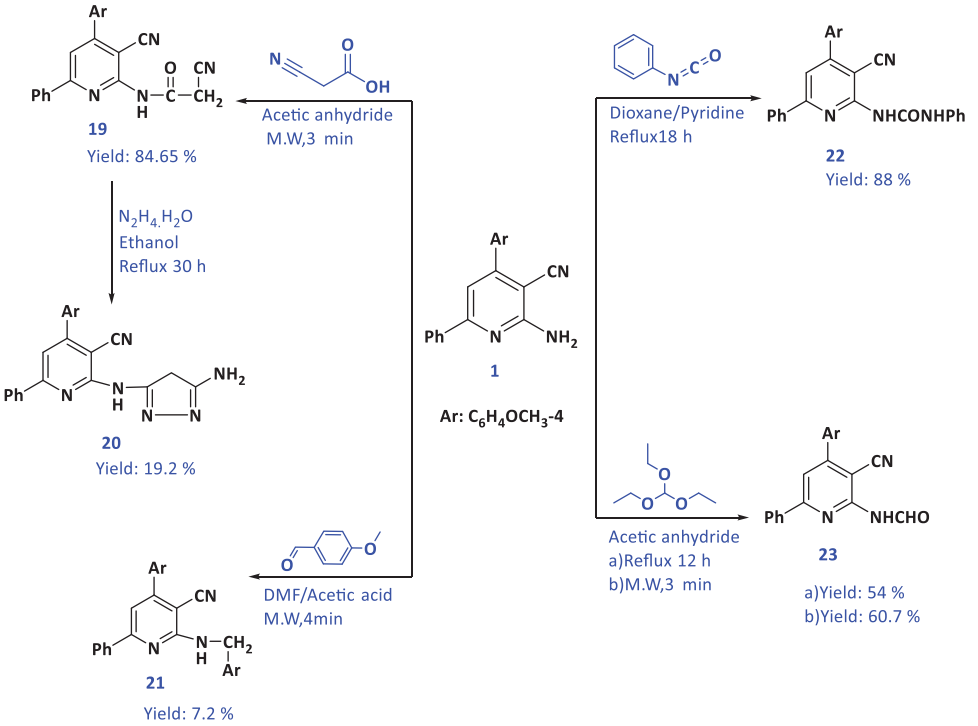
Also, compound **1** was allowed to undergo dimerization by reacting with 1,3- di bromopropane in 2:1 ratio to give the dimer **26** (Scheme 6).

Biological activity

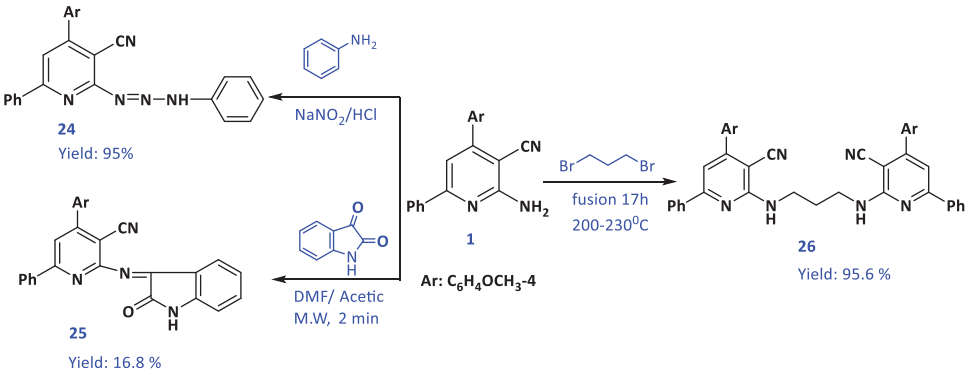
Cytotoxic activity

Cytotoxic activity utilizing an *in vitro* Ehrlich Ascites Assay, 21 derivatives out of all the newly synthesized compounds were elected to be evaluated for their *in vitro* cytotoxic effect against a panel of two cell lines (human tumor) namely: hepatocellular carcinoma (liver) HepG2 and mammary gland breast MCF-7 cancer cell lines (Table 1).

Generally, the activity detected by all the selected compounds ranged from very strong to a noncytotoxic effect. In general, compounds **1**, **5**, **6**, **12**, **15**, **16,** and **25** were found to be the most potent derivatives against the two cell lines. Compound **1** showed moderate activity against the cell line HePG-2 ($IC_{50} = 26.46 \pm 2.0$) and strong activity against the cell line MCF-7 ($IC_{50} = 18.02 \pm 1.5$). Compounds **5** and **6** showed very



Scheme 5. Formation of compounds 19–23.



Scheme 6. Formation of compounds 24–26.

strong cytotoxic activities against HePG-2 ($IC_{50} = 7.48 \pm 0.6$), ($IC_{50} = 9.63 \pm 0.8$) and MCF-7 ($IC_{50} = 5.69 \pm 0.4$), and ($IC_{50} = 10.66 \pm 0.9$), respectively. Compound **25** showed strong and very strong activity against the two cell lines HePG-2 ($IC_{50} = 12.77 \pm 1.0$) and MCF-7 ($IC_{50} = 8.31 \pm 0.6$), respectively. On the contrary, compound **15** displayed strong activity ($IC_{50} = 16.12 \pm 1.3$) and ($IC_{50} = 13.57 \pm 1.1$) against the two cell lines, respectively. While compound **12** showed strong activity against the cell line HePG-2 ($IC_{50} = 17.03 \pm 1.4$) and moderate activity against the cell line MCF-7 ($IC_{50} = 24.28 \pm 1.9$), respectively. Compound **16** offered strong activity against the two cell lines HePG-2 ($IC_{50} = 19.37 \pm 1.6$) and MCF-7 ($IC_{50} = 15.49 \pm 1.3$), respectively.

Table 1. Cytotoxicity (IC_{50}) of the evaluated compounds on various cell lines.

	IC_{50} (μg/mL)[a,b]	
Comp. no.	HePG2	MCF-7
DOX	4.50 ± 0.3	4.17 ± 0.2
1	26.46 ± 2.0	18.02 ± 1.5
2	71.08 ± 3.8	77.37 ± 4.3
4	36.85 ± 2.4	41.83 ± 3.1
5	9.63 ± 0.8	10.66 ± 0.9
6	7.48 ± 0.6	5.69 ± 0.4
7	83.17 ± 4.3	80.68 ± 4.5
8	>100	>100
9	59.26 ± 3.4	73.09 ± 4.0
12	17.03 ± 1.4	24.28 ± 1.9
13	48.82 ± 2.9	85.20 ± 4.7
14	76.51 ± 4.1	37.01 ± 2.8
15	16.12 ± 1.3	13.57 ± 1.1
16	19.37 ± 1.6	15.49 ± 1.3
17	39.12 ± 2.6	46.67 ± 3.3
18	52.60 ± 3.0	58.64 ± 3.7
19	45.23 ± 2.9	52.35 ± 3.6
22	88.42 ± 4.6	91.30 ± 5.1
23	31.29 ± 2.2	32.21 ± 2.5
24	23.89 ± 1.9	27.33 ± 2.2
25	12.77 ± 1.0	8.31 ± 0.6
26	54.71 ± 3.2	67.26 ± 3.9

[a]IC_{50} (μM): 1–10 (very strong). 11–20 (strong). 21–50 (moderate). 51–100 (weak) and above 100 (non-cytotoxic).
[b]DOX: doxorubicin

However, the rest of the compounds presented activity ranged from moderate to noncytotoxic effect toward the two cell lines HePG-2 and MCF-7.

Structure–activity relationship (SAR)

Inserting different groups and rings to the nicotinonitrile derivative **1** which has strong and moderate reactivity change its reactivity toward the two cell lines:

- Presence of the acetamide group increases the cytotoxic effect of compound **5** due to the formation of a hydrogen bond with the C = O group.
- Compound **6** displayed very strong activity, this may be attributed to the presence of three NH groups which may be added to any unsaturated moiety in DNA (aza Michael addition) or hydrogen bond formation with either one of the nucleobases of the DNA and causes its damage.
- Compound **12** showed strong activity against the cell line HePG-2 because the presence of the NH group available to form a hydrogen bond with the nucleobases of the DNA and lead to its damage. Also, introducing the SO_2Ph group as a strong electron attracting group creates a positively charged molecule, generates electrostatic attraction with the DNA nucleobases. Moreover, the SO_2 group acts on the mitoticspindle.[21]
- Presence of the ester group increases the cytotoxic effect of compound **15**.
- Presence of pyrazolyl ring in compound **16** showed strong activity.
- Presence of oxoindolinylidene ring increases the cytotoxic effect of compound **25**.

Antimicrobial activity

The antimicrobial activity of 19 compounds was checked against Gram-positive bacteria (*B. subtilis*) and Gram-negative bacteria (*E. coli*). The antifungal activities of the compounds were tested against two fungi (*C. albicans*, *A. flavus*). Largely, the activity noticed by all these compounds ranged from very strong to no activity. Most of all compounds displayed good inhibition against Gram-positive strains and Gram-negative strains with respect to the reference drugs. In general, it is clear that all the compounds were more toxic with respect to Gram-positive strains than Gram-negative strains. This could be attributed to their cell wall structural differences,[22] whereas the walls of Gram-negative cells are more complex than those of Gram-positive species, therefore it might be a little complicated for these compounds to diffuse inside the Gram-negative cell. The data outlined in Table 2 clarified that most of the compounds have marked antifungal potency. The most active compounds against the Gram-positive strain, Gram-negative strain, and fungi were compounds **5**, **6**, **15**, and **25.**

Experimental

All melting points were decided on Gallenkamp electronic melting point equipment. The infrared (IR) spectra were recorded on a Mattson 5000 Fourier transform-IR (FT-IR) spectrophotometer (λ, cm^{-1}). The ^{1}H-NMR (DMSO-*d6*), and ^{13}C-NMR (DMSO-*d6*), spectra were determined on a Bruker AV 400 MHz, using TMS as an internal standard. Mass spectra were obtained on GCMS/QP1000 Ex mass spectrometer at 70 eV. Elemental analyses (C, H, and N) had been done at the Microanalytical Center of

Table 2. Results of antimicrobial activity of the synthesized compounds against different types of microorganisms.

	E. coli		*Bacillus subtilis*		*C. Albicans*		*A. flavus*	
Compound	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index
1	9	36	15	65.2	17	63	18	72
2	NA	–	4	17.4	4	14.8	6	24
4	8	32	12	52.2	10	37	14	56
5	15	60	19	82.6	20	74.1	20	80
6	17	68	22	95.6	21	77.8	23	92
7	NA	–	3	13	4	14.8	3	12
8	NA	–	NA	–	NA	–	NA	–
12	11	44	16	69.6	17	63	17	68
13	3	12	5	21.7	3	11.1	2	8
14	NA	–	NA	–	10	37	15	60
15	12	48	19	82.6	19	70.4	18	72
16	10	40	17	73.9	18	66.7	19	76
17	7	28	10	43.5	9	33.3	14	56
18	2	8	9	39.1	7	25.9	10	40
22	NA	–	2	8.7	2	7.4	NA	–
23	9	36	13	56.5	14	51.8	16	64
24	9	36	16	69.6	15	55.5	17	68
25	12	48	20	86.9	21	77.8	22	88
26	2	8	8	34.8	6	22.2	10	40
Ampicillin	25	100	23	100	NA	–	NA	–
Colitrimazole	NA	–	NA	–	27	100	25	100

Cairo University, Giza, Egypt. The biological evaluation of the products was carried out at the Department of Pharmacology, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.

Synthesis of 2-amino-4-(4-methoxyphenyl)-6-phenylnicotinonitrile (1)

A mixture of acetophenone (1.2 mL, 0.01 mol), anisaldehyde (1.4 mL, 0.01 mol), malononitrile (0.66 g, 0.01 mol), and ammonium acetate (2.3 g, 0.03 mol) was heated under microwave irradiation for 7 min at power 270 W. After cooling, the separated solid material was filtered off, washed with ethanol, dried and recrystallized from ethanol to afford **1** as yellow crystals, Yield: 90%, m.p.178-180 °C. Lit; [17] IR (KBr, ν/cm^{-1}) : 3307, 3182, 2205,1639 (NH_2, C≡N, C = N); ^{1}H- NMR (DMSO-*d6*), δ, ppm: 3.84 (s, 3H, OCH_3) , 7.08–8.23 (m, 10H,Ar-H), 10.07 (s, 2H, NH_2, D_2O exchangeable). ^{13}C-NMR (DMSO-*d6*): 55.81, 86.83, 100.59, 109.49, 114.61(2), 117.76, 127.66(2), 129.06(2), 129.53, 130.30, 130.46, 138.11, 154.91, 158.91, 160.88, 161.40. .MS m/z (%):301 $[M]^{\cdot+}$ (100), 286 (80), 270 (33), 257 (88),198 (62),77 (54). Found, %: C, 75.78; H, 4.98 N, 13.85%. For $C_{19}H_{15}N_3O$ (301). Calculated, %: C, 75.73; H, 5.02; N, 13.94%.

5-(4-Methoxyphenyl)-7-phenylpyrido [2, 3-d] pyrimidin-4(3H)-one (2)

Method 1: A mixture of nicotinonitrile derivative **1** (3.01 g, 0.01 mol) and formamide (15 mL) was refluxed for 12 h. The reaction mixture was concentrated, left to cool and the separated solid was filtered off, washed with ethanol, dried, and crystallized from methanol to afford **2** as green crystals. Yield: 49.5%.

Supporting information

Full experimental detail, ^{1}H-NMR and ^{13}C-NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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