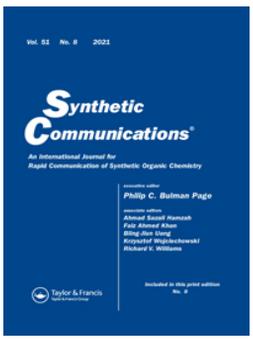

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Green synthesis of 2-amino-3-cyanopyridines via a cooperative vinylogous anomeric-based oxidation and their antiproliferative effects on liver, breast, and prostate cancer studies

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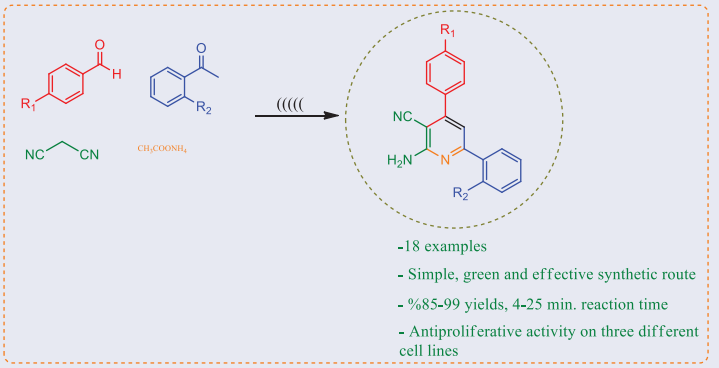
ABSTRACT

2-Amino-3-cyanopyridine derivatives were synthesized in an ultrasonic bath and one pot four-component reactions with high yields, in a short time, without solvent and catalyst, and anticancer activity studies on MCF7, DU145, and HepG2 cell lines were investigated. 18 compounds were synthesized in 4–25 min time interval and 85–99% yield. Among these compounds, the IC50 values in **7a**, **6a**, and **3a** on MCF7 breast cancer cell line was found to be 1.80, 1.95, and 2.50 μM, respectively, while the values in the HepG2 liver cancer cell line were 7.71, 7.90, and 8.05 μM, respectively. In studies conducted in the DU145 prostate cancer cell line, IC50 values of compounds **1b**, **2b**, and **8b** were found to be 9.90, 10.10, and 15.30 μM, respectively.

GRAPHICAL ABSTRACT



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KEYWORDS
Aminocyanopyridine; ultrasonic irradiation; multi-component reaction; heterocycles; anticancer activity; prostate cancer; breast cancer; liver cancer

Introduction

Cancer is the second of the diseases that cause death worldwide. 16% deaths are related to cancer. Most common seen cancer types are prostate, colorectal, liver, lung, and

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breast cancers. According to American Cancer Society, for 2020, estimated numbers of new cases of breast cancer, liver cancer and prostate cancer are 279,100, 42,860, and 191,930, respectively.[1]

Pyridine moiety is important because it is in the active center of many pharmaceutical drugs, as well as in the structure of natural compounds and important starting materials used in the synthesis of some important heterocyclic compounds.

The biological activity studies of the compounds containing the structure of 2-amino-3-cyanopyridine are limited. However, despite a small number of biological studies, these compounds are included in the literature where they show a wide range of biological activities such as antitumor,[2] antifungal, HIV-1 integrase inhibitory activity,[3] IKK-Serine-Threonine protein kinase inhibitory activity,[4] A_2A adenosine receptor antagonists.[5]

There are many studies in the literature on the synthesis of 2-amino-3-cyanopyridine derivatives. In these studies, besides catalysts such as ytterbium perfluorooctanoate [Yb $(PFO)_3$],[6] Cu_2O,[7] HBF_4,[8] and Fe_3PO_4,[9] cellulose sulfuric acid[10] and liquid–liquid phase transfer catalysts[11] were also used. In addition, there are studies using nano-sized catalysts[7,9,12–17] in recent studies. Studies have also been done on solvent systems using PEG-200,[18] PEG-400[19] and ionic liquids.[20,21] The use of solvent and heavy metal-containing catalysts, long-lasting reactions, low yields, need for separation, and purification processes in these studies indicate the need for more moderate synthesis conditions for the synthesis of 2-amino-3-cyanopyridine derivatives.

Multicomponent reactions have a very important role in the development and advancement of organic synthesis and medicinal chemistry. The main advantage of these reactions is that there is no need for separation and purification methods, thus reducing time and cost and not creating waste products.

In our previous studies, the 2-amino-3-cyano groups on the selenophene ring showed very good anticancer activity on breast cancer and prostate cancer cell lines.[22,23] In this study, 2-amino-3-cyanopyridine derivatives were synthesized in an ultrasonic bath without catalysts and solvents in a short time with high yields, and the anticancer activities of these compounds were tested on three different cancer lines.

Results and discussion

Chemistry

In this study, 2-amino-3-cyanopyridine derivatives were synthesized in a short time and with high yields in an ultrasonic bath without using solvents and catalysts in a single pot multicomponent reaction. Figure 1 shows the synthetic route for the synthesis of aminocyanopyridines.

In this study, 2-amino-3-cyanopyridine compounds were synthesized with high yields in an one pot multicomponent method in an ultrasound bath without using solvents and catalysts. In the studies in the literature, it is seen that aminocyanopyridine compounds are synthesized with the use of solvents, catalysts, and long-lasting reactions at different temperatures. The superiority of this study in the literature is shown in Table 1.

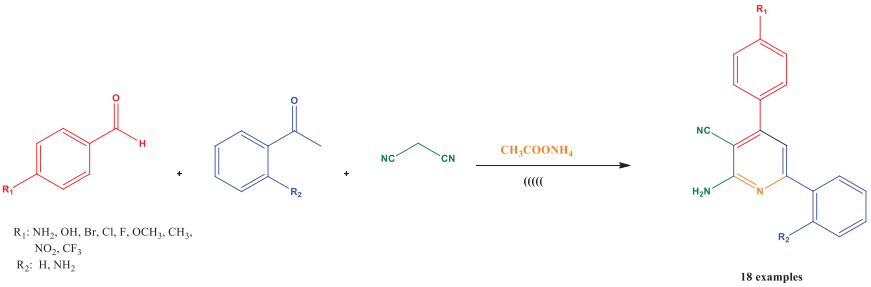


Figure 1. Ultrasound-assisted synthesis of 2-amino-3-cyano-4,6-diphenylpyridine derivatives in solvent-free and catalyst-free environment.

2-Amino-3-cyano-4,6-diphenylpyridine derivatives were synthesized by reacting p-substituted benzaldehyde derivatives with malononitrile, ammonium acetate, and 2′-aminoacetophenone or acetophenone in a solvent-free and catalyst-free environment in an ultrasonic bath with one-pot multicomponent reaction. At the end of the reaction, the products were synthesized for 4–25 min and yields of 85–99% (Table 2).

In this study, products with high yields were obtained without using chemicals and consumables at the end of simple separation and purification processes.

Table 2 shows that, in the presence of electron donating groups on benzaldehyde (1a, 3a, 15a, and 17a), reaction yields are lower and reaction times are longer than the presence of electron withdrawing groups (5a, 7a, 9a, 11a, and 13a). While the reaction time is in the range of 18–25 min in the presence of electron-donating groups (Table 2, entries 1, 3, 15, and 17), it is between 5 and 14 minutes in the presence of electron-withdrawing groups (Table 2, entries 5, 7, 9, 11, and 13).

When we compare the yield and reaction times in the reactions using acetophenone and 2′-aminoacetophenone; in the reactions with 2′-aminoacetophenone the time was shorter but the yields were higher in the presence of other groups except the $-CH_3$, $-OCH_3$, $-CF_3$, and $-NO_2$ groups (Table 2, Entries 2, 4, 6, 8, and 10).

All new compounds were individually characterized and their structures identified by FT-IR, ^{1}H NMR, and ^{13}C NMR.

A cooperative vinylogous anomeric-based oxidation mechanism is proposed as a rational mechanism for the synthesis of 2-amino-3-cyanopyridine derivatives without solvent and catalyst in a single pot multicomponent reaction using p-substituted benzaldehyde, acetophenone, and/or 2′-aminoacetophenone, malononitrile, and ammonium acetate.[25,26] At first, the carbonyl group of aldehyde is activated by the acidic group of ammonium acetate. Malononitrile reacts with the carbonyl group of aldehyde by removing one molecule of H_2O. Then, this intermediate product, respectively, acts as a Michael acceptor, followed by intramolecular cyclocondensation reactions and finally giving the final desired product through a cooperative vinylogous anomeric-based oxidation reaction (Scheme 1).[27,28]

Antiproliferative activity

The anticancer activity of compounds **1a**–**9a** and **1b**–**9b** was determined against to MCF-7 (Breast cancer) cell line via using xCELLigence system. Then, the promising

Table 1. Comparison of our method in the synthesis of 2-amino-3-cyanopyridine compounds with the studies in the literature.

Entry	Reaction conditions	Reference
1	Catalyst free, solvent free, at room temperature for 4–25 min, in an ultrasonic bath	This work
2	$Yb(PFO_3)$ (2,5 mol %), ethanol (2 ml), at refluxing temperature for 4 h	[6]
3	Nano-sized Cu_2O on melamine-formaldehyde resin (0,072 mol%), Ethanol:water (1:1), at refluxing temperature for 1–5 h	[7]
4	HBF_4 (0,1 g), solvent free, at 100°C, under air or nitrogen atmosphere for 150 min.	[8]
5	$Fe_3O_4@TiO_2@O_2PO_2(CH_2)NHSO_3H$ (7 mg), solvent free, at 90 °C for 20 min.	[9]
6	Cellulose–SO_3H (0,05 mmol), water (5 ml), at 60 °C for 2.5 h	[10]
7	i)$NaBH_4$ in Chlorobenzene, Water, Aliquat®336, reflux ii) $NaBH_4$ in CH_3CN, 18-crown-6, at 80 °C	[11]
8	$SrFe_{12}O_{19}$ (0.02 g), solvent free, at 100 °C for 8 min	[12]
9	Cu/C nanocatalyst (2,0 mol%), acetonitrile (2,0 mL) at 80 °C for 6 h	[13]
10	Cu@imineZCMNPs (10 mg), solvent free, at 80 °C for 1 h	[14]
11	$\{Fe_3O_4@SiO_2@(CH_2)_3Im\}C(CN)_3$ (7 mg), solvent free, at 100 °C for 40 min	[15]
12	$Fe_3O_4@SiO_2@Si(CH_2)_3Cl$ (10 mg), solvent free, at 80 °C for 10–25 min	[16]
13	α-zirconium phosphate ($Zr(HPO_4)_2{\cdot}H_2O$) nanocrystals (15 mg), solvent free, at 60 °C for 20–90 min	[17]
14	PEG-200/water, at refluxing temperature for 4 h	[18]
15	PEG-400/water, at 80 °C for 6 h	[19]
16	Trifluoroethanol (TFE), at refluxing temperature for 6 h	[24]
17	Nicotinium methane sulfonate (NMS) (5 mol %), solvent free, at 80 °C for 100 min	[21]

activity shown by tested **6a** and **7a** encouraged us to measure the anticancer activity of the other analogues in selected human cancer cell lines such as liver (HepG2) and prostate (DU-145) by using same method. Results was shown in Table 3.

The mean IC_{50} values for tested **7a** are 1.8 ± 0.11, 7.71 ± 0.41 against to MCF-7 and HepG2, respectively (Table 3 entry 7 and Figure 2). For HepG2, tested **6a**, **7a**, and **3a** showed better anticancer activity than positive control (Table 3, entries 3, 6, and 7).

Moreover, the anticancer properties of tested **1a**−**9a** was determined to substantiate the potentiality of these conjugates (**1b**−**9b**) as anticancer agents. While conjugates **1b**−**9b** exhibited a lower cytotoxicity than **1a**−**9a**, respectively, on MCF-7 and HepG2 cells, this situation was the opposite in DU-145 cells (Figure 3). Compounds **1b** and **2b** showed the closest activity to the positive control in the DU-145 cell line.

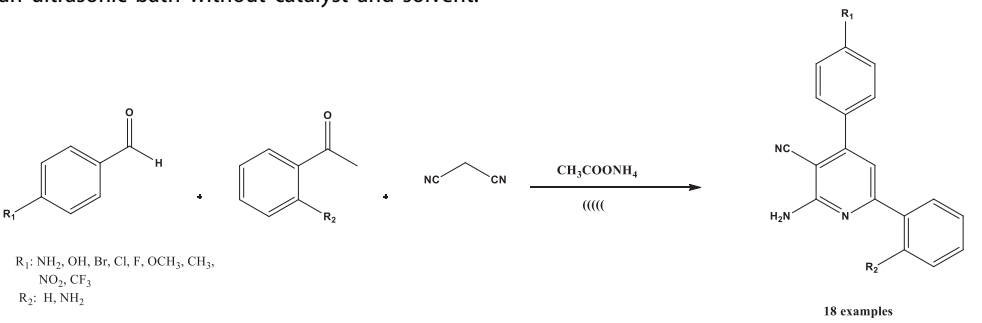
All of the compounds **1a**−**9a** showed better antiproliferative effect on the MCF7 breast cancer cell line than the control compound used. On the other hand, **1b**−**9b** compounds showed cytotoxic effects on the same cell line at IC_{50} values ranging from 8.13 to 12.26 μM (Table 3, entries 10−18). This indicates that synthesized aminocyanopyridine compounds have a very good antiproliferative effect on the MCF7 cell line. Similarly, compounds **1a**−**9a** showed better antiproliferative activity on the HepG2 liver cancer cell line than compounds **1b**−**9b** ($IC_{50} = 7.71 - 13.20$ μM) (Table 3, entries 1−9).

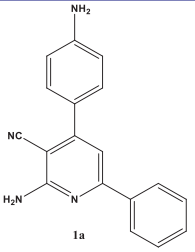
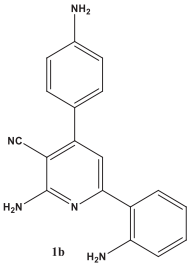
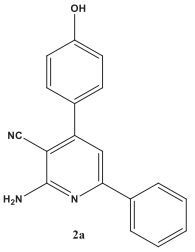
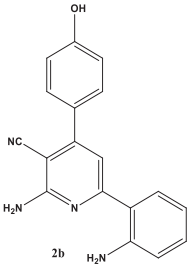
Experimental

General

All the reagents were obtained from different commercial sources. Unless noted otherwise, all of compounds were used as provided without further purification.

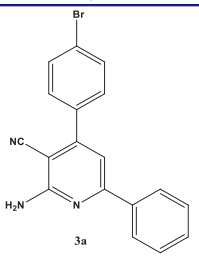
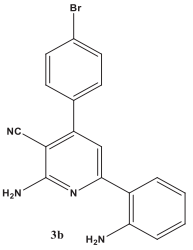
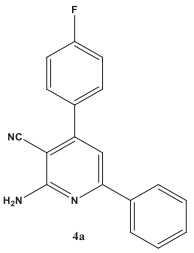
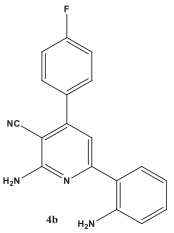
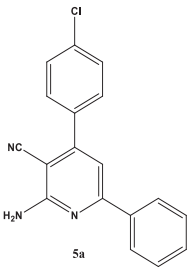
Table 2. Synthesis of 2-amino-3-cyano-4,6-diphenylpyridines with one-pot multicomponent reaction in an ultrasonic bath without catalyst and solvent.



Entry	Compound	Reaction time (min)	Yield (%)
1	 1a	20	88
2	 1b	18	89
3	 2a	25	86
4	 2b	10	92

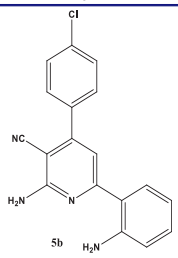
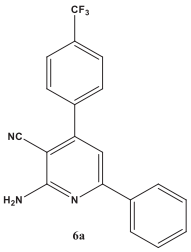
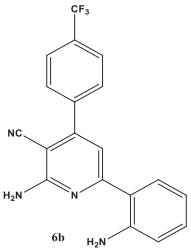
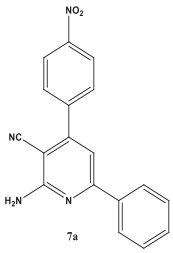
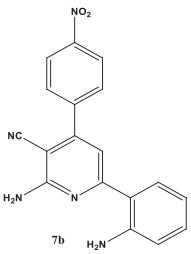
(*continued*)

Table 2. Continued.

Entry	Compound	Reaction time (min)	Yield (%)
5	 3a	5	95
6	 3b	4	99
7	 4a	14	89
8	 4b	8	91
9	 5a	10	90

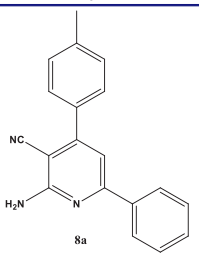
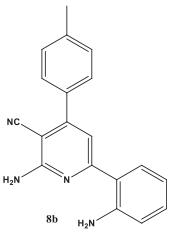
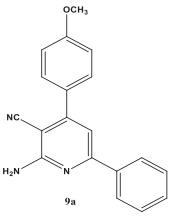
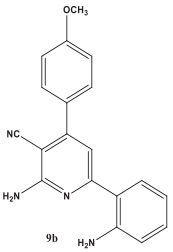
(*continued*)

Table 2. Continued.

Entry	Compound	Reaction time (min)	Yield (%)
10	 5b	4	96
11	 6a	6	99
12	 6b	5	98
13	 7a	5	99
14	 7b	7	97

(*continued*)

Table 2. Continued.

Entry	Compound	Reaction time (min)	Yield (%)
15	 8a	20	85
16	 8b	25	86
17	 9a	18	88
18	 9b	25	87

General preparation of 2-amino-3-cyano-4,6-diphenylpyridine derivatives (1a−9a and 1b−9b)

The p-substituted benzaldehyde derivative (5 mmol), 2′-amino aminoacetophenone or acetophenone (5 mmol), malononitrile (5 mmol), and ammonium acetate (6 mmol) are taken and mixed in a flask. The reaction is carried out in an ultrasonic bath at room temperature. The reaction is controlled by TLC. After the reaction is complete, cold water is added to the mixture, stirred and this mixture is poured into 30 ml of ice water, the solid is filtered off, washed with cold water and recrystallized with ethanol. The product was identified using FT-IR and NMR spectroscopy. Compounds **2a**, **3a**, **4a**, **5a**,

Table 3. In vitro cytotoxic activity results of 2-amino-3-cyano-4,6-diphenylpyridines (**1a**–**9a** and **1b**–**9b**) against MCF7, DU145 and HepG2 cell lines.

Entry	Compound	MCF-7 (μM)	DU-145 (μM)	HepG2 (μM)
1	1a	5.10 ± 0.31	28.10 ± 1.53	13.20 ± 0.33
2	2a	4.90 ± 0.23	27.30 ± 2.12	11.30±.78
3	3a	2.50 ± 0.12	29.20 ± 2.3	8.05 ± 0.32
4	4a	3.40 ± 0.19	32.10 ± 1.67	9.12 ± 0.41
5	5a	3.10 ± 0.14	31.30 ± 1.3	8.75 ± 0.38
6	6a	1.95 ± 0.08	33.50 ± 2.9	7.90 ± 0.33
7	7a	1.80 ± 0.11	36.00 ± 2.4	7.71 ± 0.41
8	8a	4.30 ± 0.12	25.30 ± 1.9	10.79 ± 0.81
9	9a	5.02 ± 0.14	26.30 ± 2.2	12.60 ± 0.73
10	1b	11.20 ± 0.56	9.90 ± 0.43	24.00 ± 1.1
11	2b	11.41 ± 0.71	10.10 ± 0.83	26.30 ± 1.21
12	3b	9.03 ± 0.13	18.10 ± 1.1	21.20 ± 1.04
13	4b	10.49 ± 0.29	19.30 ± 0.59	22.10 ± 0.93
14	5b	10.26 ± 0.23	18.50 ± 0.43	22.30 ± 1.13
15	6b	8.53 ± 0.11	20.10 ± 0.67	19.10 ± 1.03
16	7b	8.13 ± 0.16	21.30 ± 1.2	18.30 ± 0.99
17	8b	10.53 ± 0.32	15.30 ± 1.3	22.80 ± 0.14
18	9b	12.26 ± 0.42	16.20 ± 1.1	31.00 ± 0.23
Doxorubicin		5.93 ± 0.14	6.86 ± 0.13	8.53 ± 0.43

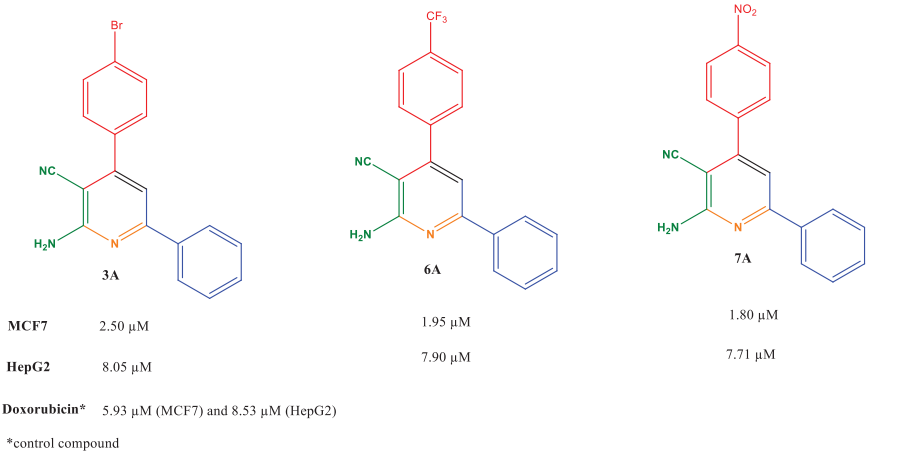


Figure 2. Most active molecules in studies on MCF7 and HepG2 cell lines.

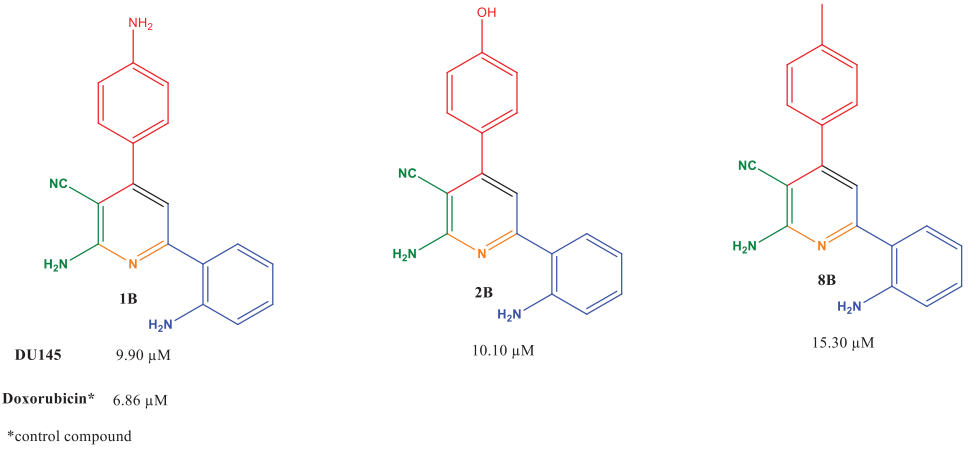
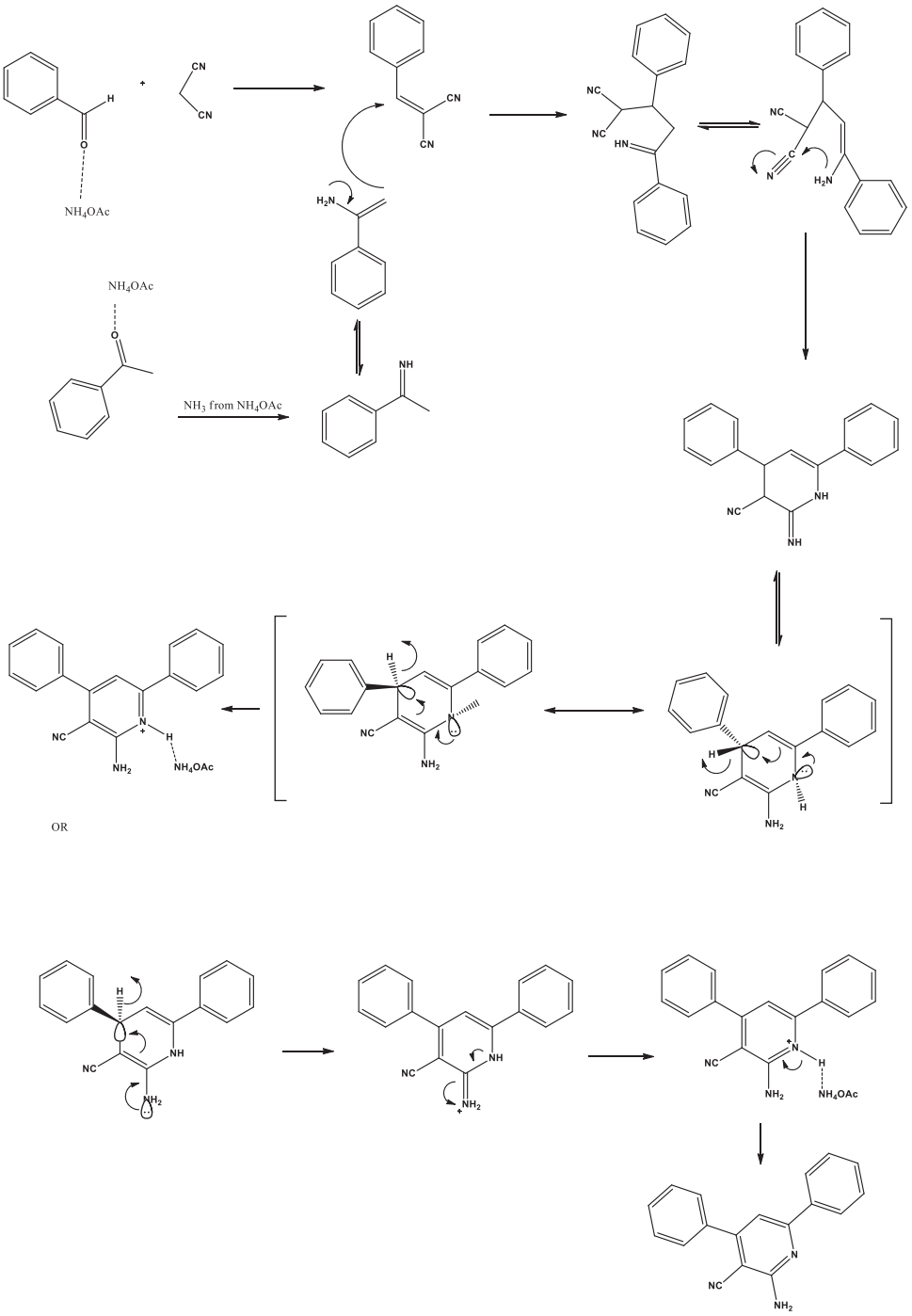


Figure 3. Most active molecules in studies on DU145 cell line.



Scheme 1. A plausible mechanistic pathway for the synthesis of 2-amino-4,6 diphenylnicotinonitrile via a cooperative vinylogous anomeric-based oxidation reaction.

7a, **8a**, and **9a** are included in the literature[6,19,21,29] and spectroscopic data of these compounds are included in the Supplementary File.

2-Amino-6-(2-aminophenyl)-4-(p-tolyl)nicotinonitrile (8b)

orange solid; yield 1.291 g (%86); mp (°C): 148−150; R_f value: 0.47 (hexane/ethylacetate 90−10 (4.5:0.5, v/v)); νmax (KBr): = 3201 (NH_2 stretching), 3036 (CH stretching, aromatic), 2988, 2965, 2917 (C−H stretching, aliphatic) 2225 (CN stretching, aliphatic), 1586, 1551 (C = C stretching, aromatic), 1219 (C−N stretching), 811, 788, 705 (C−H bending, aromatic) cm^{-1}; δH (600 MHz, $CDCl_3$) 8.32 (d, J = 9.0 Hz, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.72 (s, 2H, $-NH_2$), 7.34 (d, J = 9.0 Hz, 2H, Ar-H), 7.26 (d, J = 9.0 Hz, 2H, Ar-H), 7.14 (t, J = 9.0 Hz, 1H, Ar-H), 6.95 (t, J = 9.0 Hz, 1H, Ar-H), 6.65 (d, J = 9.0 Hz, 1H, Ar-H), 6.27 (s, 2H, $-NH_2$), 2.46 (s, 3H, $-CH_3$); δC (150 MHz, $CDCl_3$) 162.67, 159.83, 150.29, 146.43, 134.42, 132.06, 130.95, 130.92, 130.41, 128.49, 123.37, 118.25, 117.23, 115.77, 114.06, 112.91, 81.18, 22.05; Anal. Calcd. for $C_{19}H_{16}N_4$: C, 75.98; H, 5.37; N, 18.65; Found: C, 76.07; H, 5.36; N, 18.62; Exact Mass: 300.14.

Biological assay

Cell culture

MCF-7 (human breast adenocarcinoma), DU-145 (human prostate cancinoma), and HepG2 (human hepatocellular carcinoma) cell lines were obtained from ATCC and cultured in Dulbecco's Modífíed Eagle Medíum (DMEM) suplemented with Fetal Bovíne Serum (FBS) 10 and 1% penicillin–streptomycin. Cells were incubated at 37 °C in 5% CO_2 incubator. When the cells reached, 70–80% confluency were harvested and used for cell viability test.

Cell viability assay

All tested compounds were studied for their anticancer activity against to Hep G2, DU-145, MCF-7 cells by using xCELLigence system. This method based on the assessment of cell-impedance variations. Briefly, all cancer cells were seeded in a 16-well E-plate. Each well containing 1×10^4 cells. Then, the cells were applied different doses of all tested. The doses were chosen according to previous studies.[22,23] The cell lines were incubated with all tested and control for 48 h. Doxorubicin used as control compounds. IC_{50} (50% maximun inhibitory concentration) values were calculated from dose–response curve by using the GNUPLOT package program (http://www.gnuplot. info). Each experiment was carried out triplicate. The results were showed in Table 2. IC_{50} values were expressed as μM.

Conclusion

A total of eighteen 2-amino-3-cyano-4,6-diphenylpyridine derivatives, 11 of which are new, were synthesized with a green method by multicomponent reaction, effective in ultrasonic bath, in a short time and with high yields. The antiproliferative effects of these compounds have been tested in three different cell lines.

The compounds tested in the MCF7 breast cancer cell line, compounds **1a**–**9a** (IC_{50} values 1.80–5.10 μM) showed more active activity than the reference Doxorubicin (IC_{50} = 5.93 μM). While the most effective compound in the DU145 prostate cancer cell line was **1 b** (IC_{50} = 9.90 μM), in the liver cancer cell line, compounds **7a**, **6a**, and **3a** showed a better cytotoxic effect than the reference substance. (IC_{50}=7.71, 7.90, and 8.05 μM, respectively).

As a conclusion, we successfully designed and synthesized a number of 2-amino-3-cyano-4,6-diphenylpyridine compounds as new antitumor candidates on MCF7 breast cancer, DU145 prostate cancer, and HepG2 liver cancer cell lines. However, such an optimization of the structures of these molecules may be necessary.

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Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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