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Conventional and Microwave Synthesis of Some New Pyridine Derivatives and Evaluation Their Antimicrobial and Cytotoxic Activities

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THE NEWLY synthesized compounds based on 2-amino-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)nicotinonitrile **1**. The reactivity of pyridine derivative **1** was studied towards different reagents by its reaction with malononitrile, 2-(4-chlorobenzylidene) malononitrile, ethyl cyanoacetate, cyano acetic acid, m-nitro benzaldehyde, sodium azide, formamide, acetic anhydride and/or acetic anhydride/H_2SO_4 to give compounds **2-5**,**7**, **10-13**, respectively. The reaction of **5** with acetyl acetone gave the bipyridine derivative **6**, while reaction of compound **7** with chloroacetyl chloride and phenacyl bromide gave the azetidinone derivatives **8** and **9**. The formimidate **14** were obtained via reaction of compound **1** with triethylorthoformate, while reaction of **14** with phenylene diamine and/or acetamide gave the formimidamide and pyridopyrimidine derivatives **15** and **16** respectively. Compound **1** was also allowed to react with urea, thiourea, phthalic anhydride, succinic anhydride, benzoyl chloride, chloroacetonitrile, chloroacetyl chloride, p-toluenesulfonylchloride and ethyl bromoacetate to give compounds **17a**,**b - 24**. Reaction of compound **1** with dichloro reagents in 1:1 ratio gave the bicyclic derivatives **25a–c**, while its reaction with oxalyl chloride, dichloro and tetrachlorobenzoquinone derivatives, and/or dichloronaphthoquinone gave the imidazopyridine derivatives **26-29**. Reaction of compound **29** with o-phenylenediamine in 1:2 ratio afforded the di-condenesed product **30** while, reaction of compound **1** with dichlororeagents in 1:2 ratio gave the polyalkyl derivatives **31a-b**. The newly synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra. On the other hand the antimicrobial and anticancer activities of some of the newly synthesized compounds were studied and evaluated.

Keywords: Pyridine, One pot condensation, Naphthyridine, Pyrimidine, Imidazole, Antimicrobial, Anticancer, Microwave irradiation.

Introduction

In the last several decades, pyridine derivatives have been claimed to possess interesting biological activity [1]. Pyridine derivatives are reported to exhibit anti-microbial [2], cardiotonic [3], anti-inflammatory [4,5], anti-parkinsonism [6] and anti-tumor activities [7]. Also they have been identified as novel IKK-β inhibitors [4], A2A adenosine receptor antagonists [6] and potent inhibitor of HIV-1 [8]. Among pyridine derivatives sorfenib and nilotnib are used as anticancer drug against a panel of cell lines, namely; the liver cancer line [9-10] (Fig 1).

Encouraged by these observations, we synthesized new pyridine derivatives by conventional and microwave methods. Some of the synthesized compounds were evaluated against gram-positive Staphylococcus aureus, Bacillus subtilis and gram-negative Escherichia coli, Pseudomonas aeuroginosa. The anti-fungal activities of the compounds were tested against two fungi Candida albicans, Aspergillus flavus. Also, some of the compounds were tested against two human tumor cell lines namely; mammary gland breast cancer (MCF-7) and colon cancer (HCT-118). The obtained results revealed that some of the tested compounds showed high antimicrobial and cytotoxic activities.

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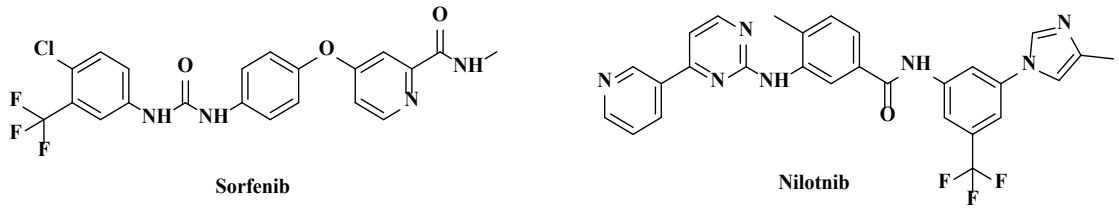
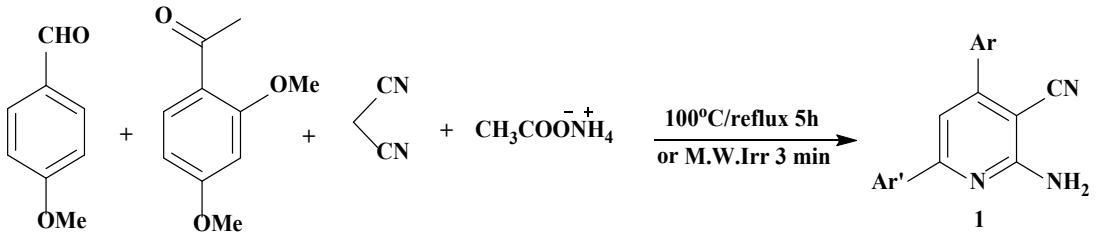


Figure 1

Results and Discussion

Our strategy for the synthesis of pyridine derivative 2-amino-6- (2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)nicotinonitrile **1** was simply through a multicomponent reaction of 2,4-dimethoxyacetophenone with p-anisaldehyde and the active methylene compound malononitrile in the presence of ammonium acetate at 100° C for five hours. The appearance of the cyano and the amino functions in the IR of compound **1** supported its structure.

According to new green chemistry trend used to minimize harmful organic solvents, to reduce time of reactions and to improve the yield of the reactions, the previous reaction was carried out using microwave irradiation, where compound



Scheme 1. Synthetic methods for the preparation of the starting compound 1.

TABLE 1. Antimicrobial and Antimitotic Activities in terms of % Activity index.

Compound	E. coli (mg/ml)		Pseudomonas aeuroginosa (mg/ml)		S. aureus (mg/ml)		Bacillus subtilis (mg/ml)		C. Albicans (mg/ml)		A. flavus (mg/ml)	
	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	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index
1	16	64.0	21	91.3	19	79.2	18	78.3	23	85.2	20	80.0
11	2	8.0	6	26.1	4	16.7	7	30.4	10	37.0	12	48.0
18	5	20.0	10	43.5	6	25.0	11	47.8	7	25.9	8	32.0
4	5	20.0	11	47.8	8	33.3	12	52.2	7	25.9	12	48.0
6	9	36.0	13	56.5	10	41.7	15	65.2	12	44.4	16	64.0
9	NA	----	NA	----	NA	----	2	8.7	2	7.4	3	12.0
8	NA	----	NA	----	NA	----	2	8.7	2	7.4	3	12.0
16	13	52.0	18	78.3	16	66.7	17	73.9	25	92.6	21	84.0
10	NA	----	NA	----	NA	----	2	8.7	NA	----	2	8.0
27	11	44.0	18	78.3	10	41.7	15	65.2	14	51.8	17	68.0
Ampicillin	25	100	23	100	24	100	23	100	NA	----	NA	----
Colitrimazole	NA	----	NA	----	NA	----	NA	----	27	100	25	100

1 was obtained within 3 minutes. Similarly all the synthesized new compounds were prepared by conventional method and under microwave irradiation (Table 1).

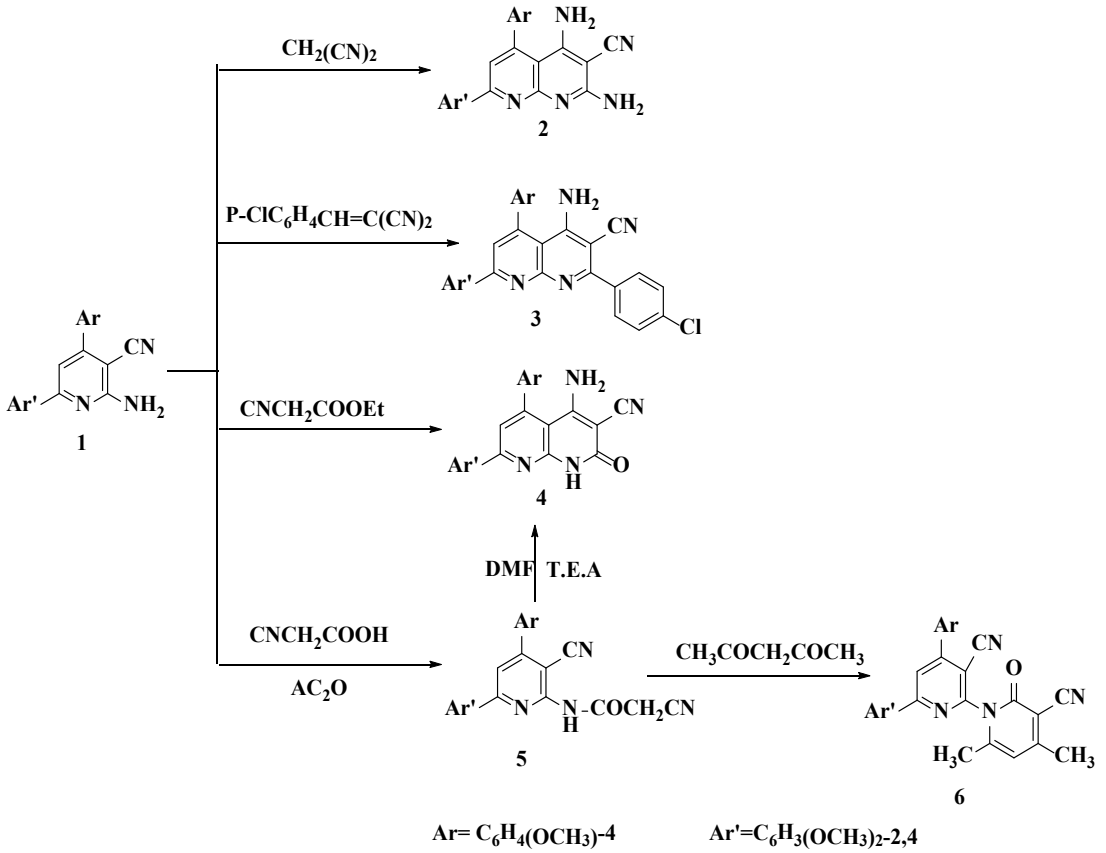
The interesting pharmacological properties of naphthyridine derivatives as antimicrobial [11], anti-inflammatory [12] and antioxidant [13] led us to synthesize new naphthyridine derivatives via the reaction of the bifunctional compound **1** with malononitrile, 2-(4-chlorobenzylidene) malononitrile and/or ethyl cyanoacetate to give compounds **2-4**, respectively. The structure of the obtained compounds was supported by correct elemental analysis, IR, ^{1}H-NMR and mass spectra.

Alternatively, compound **4** can be prepared by reaction of compound **1** with cyanoacetic acid to give compound **5** through elimination of one molecule of water. Cyclization of compound **5** to the corresponding naphthyridine derivatives **4** can be achieved by refluxing in DMF in presence of few drops of trimethylamine. The obtained product was identical in all aspects (m.p, mixed m.p and IR spectra) with compound **4** [14].

The structure of compound **5** was further supported by its reaction with acetyl acetone to give the bipyridine derivative **6** (Scheme 2).

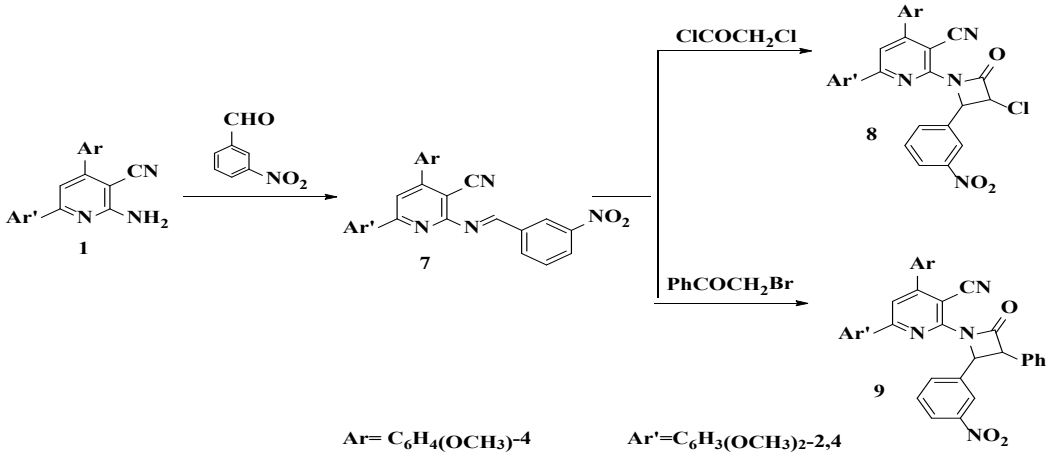
The reactivity of compound 1 towards electrophilic reagent was investigated. Thus, condensation of compound 1 with m-nitrobenzaldehyde in refluxing ethanol and in the presence of a catalytic amount of piperidine as a basic catalyst gave imino derivative 7. Its IR revealed the absence of absorption bands of the amino group frequencies.

Due to the biological significance of pyridines, azetidinones as antibacterial, antifungal [15], anticancer [16], anti-inflammatory [17], antituberculous, antitumor, analgesic, anticonvulsant [18], and antimicrobial [19] agents. We have synthesized new hybrid compounds containing both entities through the reaction of the obtained imino derivative **7** with chloroacetyl chloride and phenacyl bromide to give compounds **8** and **9**, respectively. This is in accordance with



Scheme 2

Scheme 2. Synthetic methods for compounds 2-6.



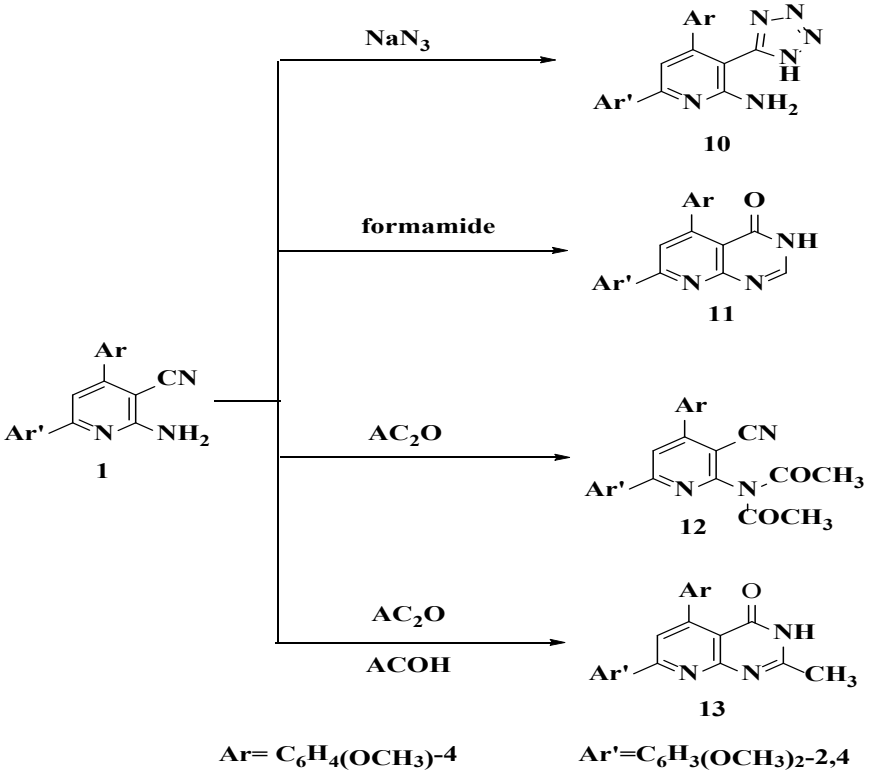
Scheme 3. Synthetic methods for compounds 7-9.

previous publication [20] (Scheme 3).

Reaction of compound **1** with sodium azide afforded the pyridotetrazole derivative **10**. This structure was supported by the disappearance of the absorption band of the cyano group and the presence of a strong absorption band specific for the tetrazole ring at 1455 cm^{-1} in its IR spectrum.

Treatment of compound **1** with formamide afforded the pyridopyrimidinone derivative **11** [21]. Refluxing compound **1** with acetic anhydride for 7h afforded the N,N-diacetyl derivative **12**.

Surprisingly, carrying the same reaction in presence of drops of concentrated sulphuric acid and under microwave irradiation the pyridopyrimidinone derivative **13** was obtained. The reaction probably proceeds through hydrolysis of the cyano group to amide group, then acetylation of the amino group to give the

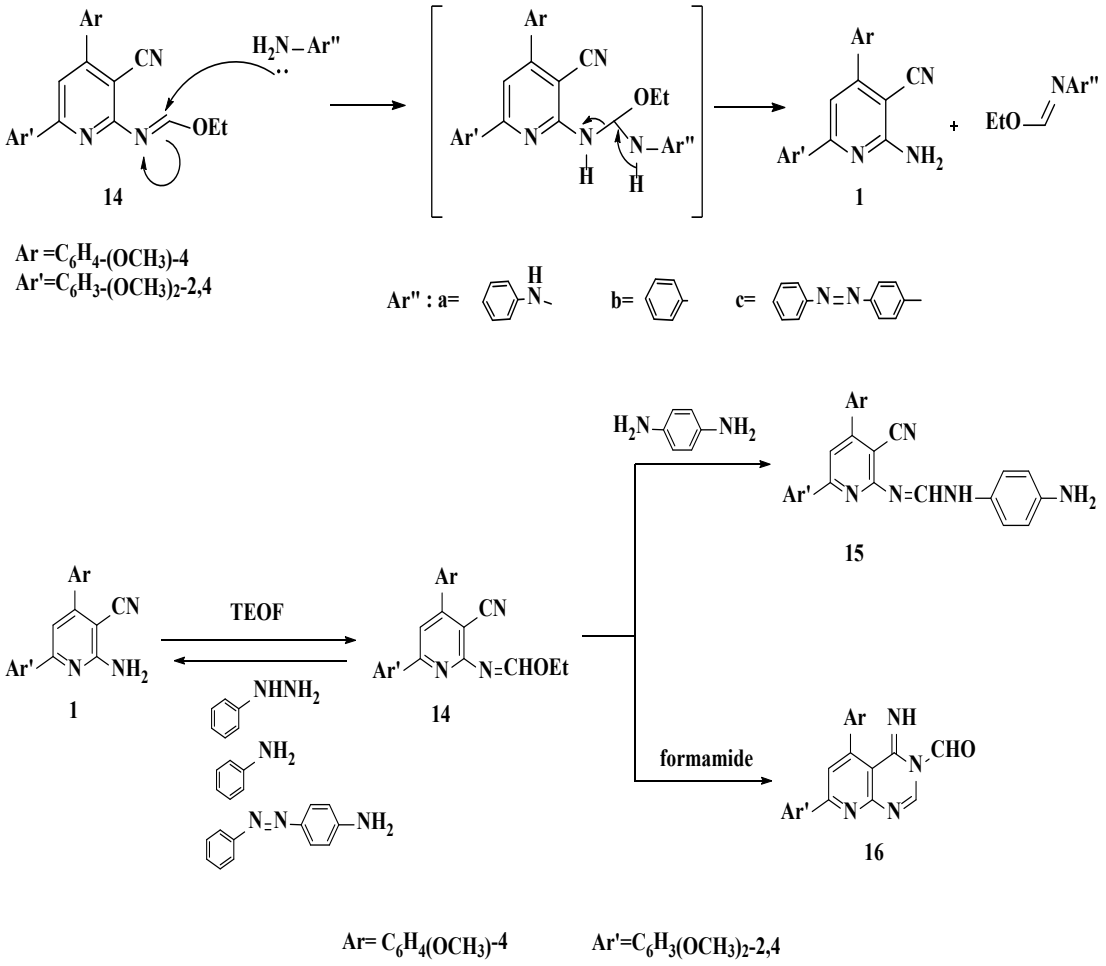


Scheme 4. Synthetic methods for compounds 10-13.

monoacetyl derivative, followed by ring closure through the nucleophilic addition of the amino group of the amide on the carbonyl of the acetyl group, then elimination of one molecule of water (Scheme 4).

Reaction of **1** with triethylorthoformate afforded the corresponding formimidate **14**. The structure of compound **14** was supported by the precise elemental analysis and spectral data and its reactions with p-phenylenediamine to give the pyridine formimidamide derivative **15** and with acetamide to give the pyridopyrimidine derivative **16**(Scheme 5).

Interestingly, reaction of compound **14** with phenyl hydrazine, aniline and/ or p-aminoazobenzene gave one and the same compound **1**. The reaction probably takes place according to the following mechanism:



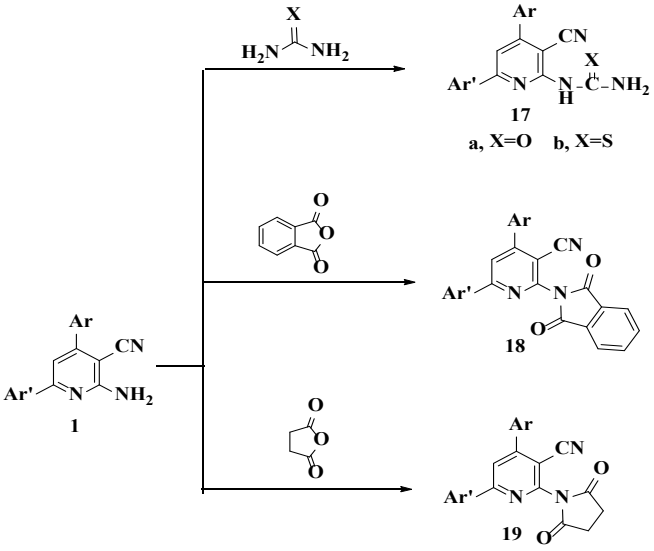
Scheme 5. Synthetic methods for compounds 14-16.

The reaction proceeds via attack of the amino group on the C=N moiety to give a non- isolable intermediate which undergo rearrangement to give product identical in all aspects (m.p, mixed m.p and IR spectra) with compound **1** [22].

Compound **1** reacted with urea and/or thiourea to give **17a**,**b**, respectively via losing of ammonia molecule.

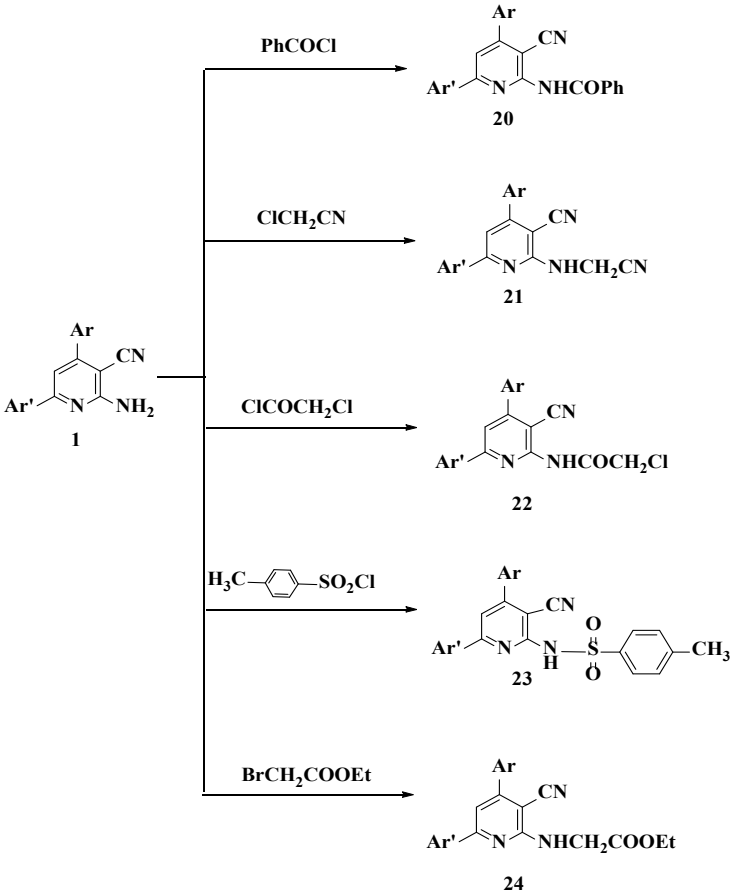
In order to synthesize nicotinonitrile derivatives attached to 1,3-dioxoisoindoline and/ or 2,5-dioxopyrrolidine rings, compound **1** was allowed to react with phthalic anhydride and succinic anhydride to give compounds **18** and **19**, respectively (Scheme 6).

Benzoylation of compound **1** with benzoyl chloride afforded the benzoylated product **20**.



Ar= $C_6H_{4(OCH_3)}$-4 Ar'=$C_6H_{3(OCH_3)_2}$-2,4

Scheme 6. Synthetic methods for compounds 17-19.



Ar= $C_6H_{4(OCH_3)}$-4 Ar'=$C_6H_{3(OCH_3)_2}$-2,4

Scheme 7. Synthetic methods for compounds 20-24.

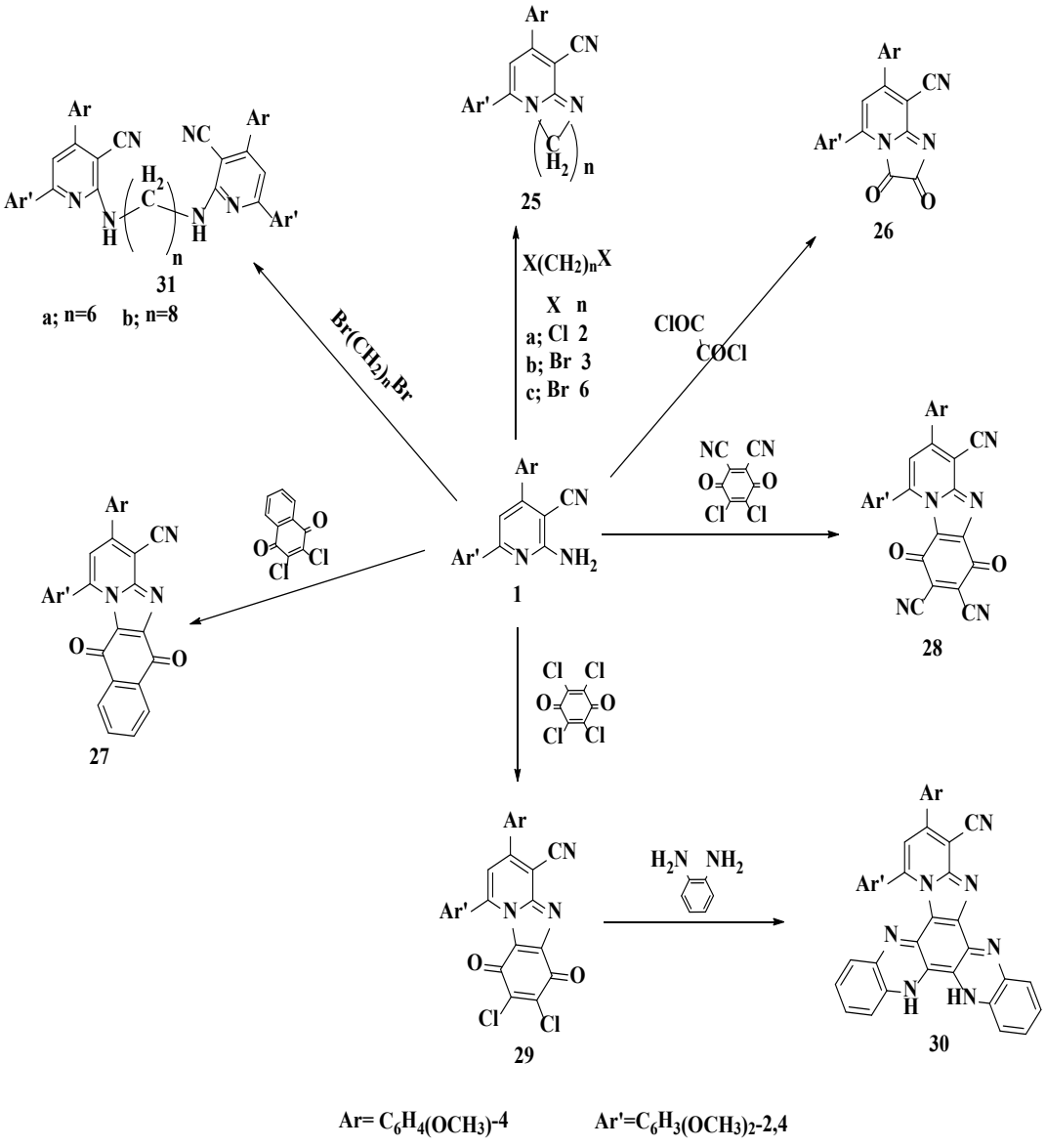
Similarly, compound **1**was reacted with chloroacetonitrile, chloroacetyl chloride, p-toluene sulfonyl chloride and/or ethyl bromoacetate to give the corresponding nicotinonitrile, acetamide, 4-methyl sulfonamide and/or glycinate derivatives **21-24**, respectively via losing of hydrogen halide (Scheme 7).

Compound **1** was allowed to undergo cycloalkylation by reacting with some dihalo-reagents in 1:1 ratio namely 1,2-dichloroethane, 1,3-dibromopropane, 1,6-dibromohexane, oxalyl chloride, 2,3-dichloro-1,4-naphthoquinone, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and/or 2,3,5,6-tetrachloro-1,4-benzoquinone to give compounds **25a-c**, **26-29**, respectively.

The IR spectra of these compounds revealed the absence of absorption bands of the amino group frequencies, while exhibit absorption bands at 1643-1759cm^{-1} corresponding to C=O in the case of compounds **26-29**.

Structure of compound **29** was further supported by its reaction with o-phenylenediamine in 1:2 ratio to give the dicondenesed product **30**.

Interestingly, polyalkyl derivatives **31a,b** were obtained when compound **1** was allowed to react with 1,6-dibromohexane or 1,8-dibromooctane in 1:2 ratio (Scheme 8).



Scheme 8. Synthetic methods for compounds 25-31.

TABLE 1. Antimicrobial and Antimitotic Activities in terms of % Activity index.

Compound	E. coli (mg/ml)		Pseudomonas aeuroginosa (mg/ml)		S. aureus (mg/ml)		Bacillus subtilis (mg/ml)		C. Albicans (mg/ml)		A. flavus (mg/ml)	
	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	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index
1	16	64.0	21	91.3	19	79.2	18	78.3	23	85.2	20	80.0
11	2	8.0	6	26.1	4	16.7	7	30.4	10	37.0	12	48.0
18	5	20.0	10	43.5	6	25.0	11	47.8	7	25.9	8	32.0
4	5	20.0	11	47.8	8	33.3	12	52.2	7	25.9	12	48.0
6	9	36.0	13	56.5	10	41.7	15	65.2	12	44.4	16	64.0
9	NA	----	NA	----	NA	----	2	8.7	2	7.4	3	12.0
8	NA	----	NA	----	NA	----	2	8.7	2	7.4	3	12.0
16	13	52.0	18	78.3	16	66.7	17	73.9	25	92.6	21	84.0
10	NA	----	NA	----	NA	----	2	8.7	NA	----	2	8.0
27	11	44.0	18	78.3	10	41.7	15	65.2	14	51.8	17	68.0
Ampicillin	25	100	23	100	24	100	23	100	NA	----	NA	----
Colitrimazole	NA	----	NA	----	NA	----	NA	----	27	100	25	100

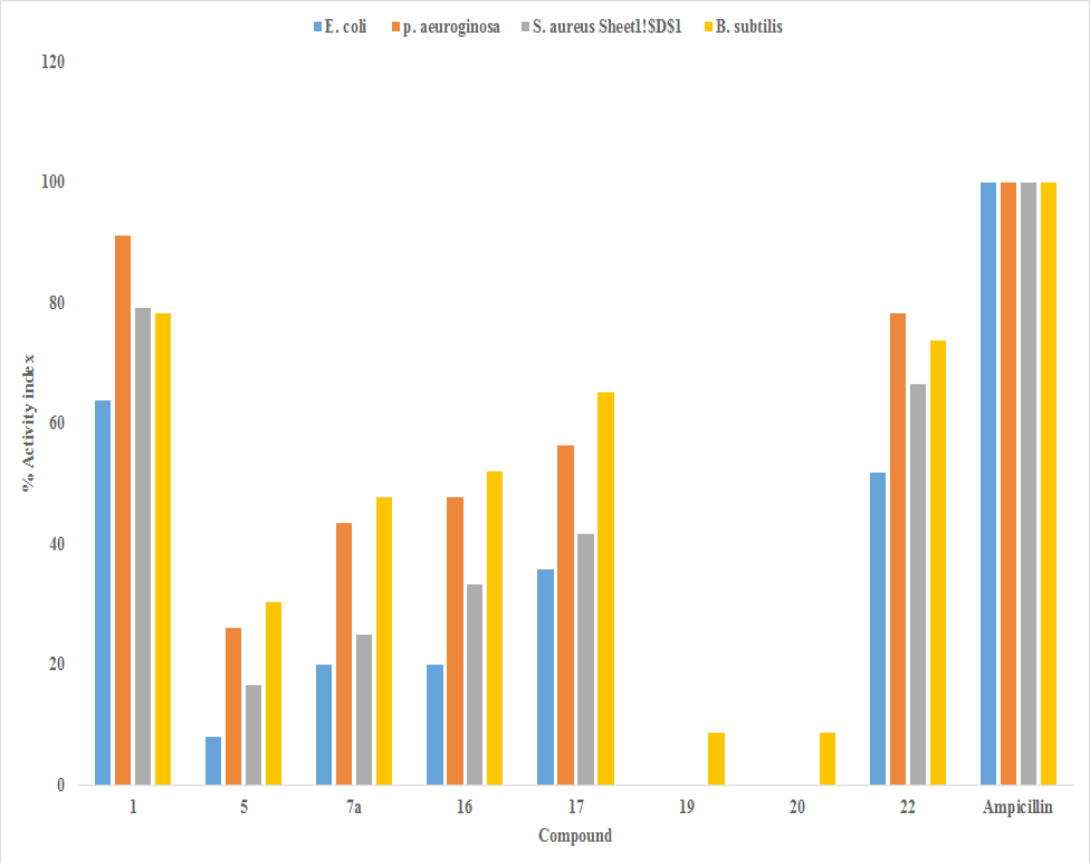


Fig. 1. % Activity index of most potent compounds against bacteria.

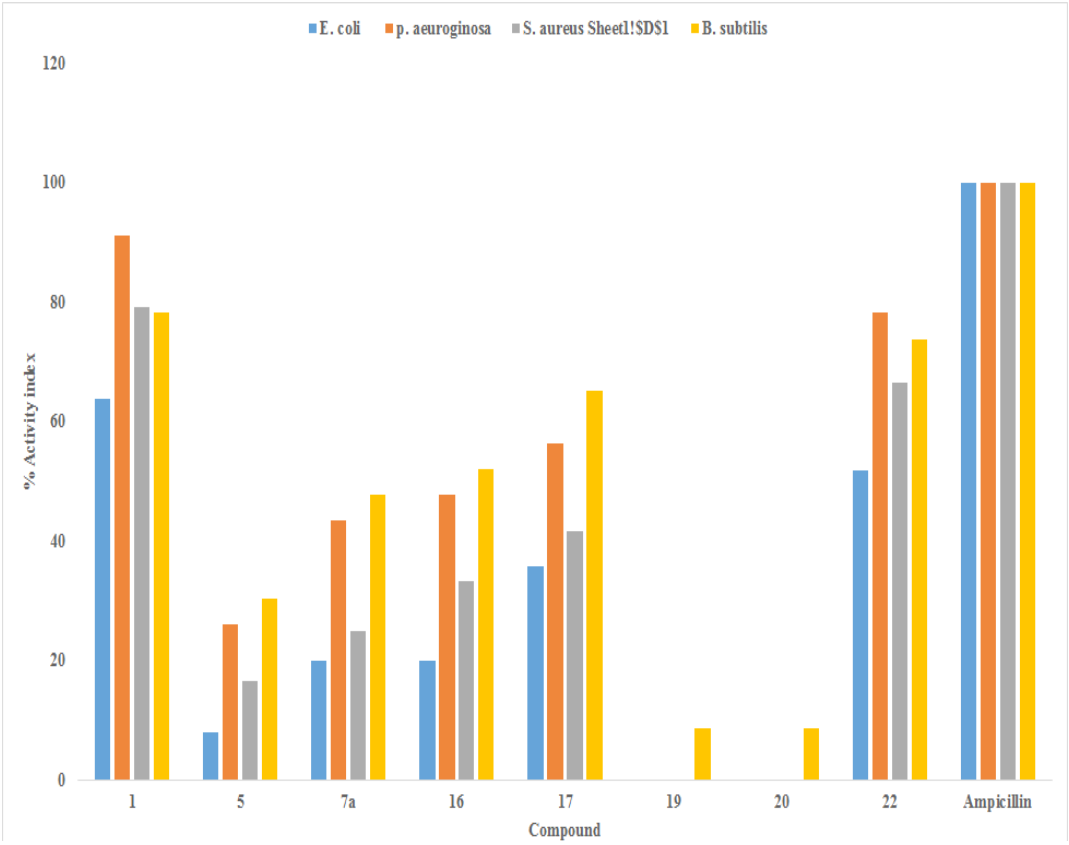


Fig. 2. % Activity index of most potent compounds against fungi.

The results in Table **1**demonstrate that tested fungi were more sensitive to all compounds compared with bacteria. The most active compounds against fungi, Gram negative and positive were **1**, **6** and **16**. In addition, Gram negative bacteria were more sensitive to the compounds compared with Gram positive ones.

The results in Table **2** revealed that compounds **1 and 6** showed very strong cytotoxic activity and compound **6** showed strong cytotoxic activity against (MCF7) and (HCT-116).

Experimental

Instrumentation

All melting points were measured on a digital Stuart SMP3 electric melting point apparatus and are uncorrected. All microwave reactions were carried out in a domestic microwave oven (Galanza 950). The infrared spectra were recorded using KBr disks on a Perkin-Elmer 293 spectrophotometer were carried out at Unit for CentralLaboratory, Faculty of Science, Ain Shams University, Egypt. ^{1}H-NMR and ^{13}C-NMR spectra were run on Varian Mercury 400 MHz spectrometer in DMSO-d_6 as a solvent using TMS as internal standard Chemical shifts are quoted (δ) inppm were carried out at The Main Chemical Warfare Laboratories, Chemical Warfare Department, Ministry of Defense, Egypt. The mass spectra were recorded on a GC-2010 Shimadzu Gas chromatography instrument mass spectrometer (70 eV) using the electron ionization technique at the micro analytical Center of Cairo University. Elemental analyses were in agreement with the proposed structures within ± 0.4% of the theoretical values and were carried out on a Perkin-Elmer CHN-2400 analyzer at the micro analytical Center of Cairo University. Egypt. The biological evaluations were carried out at Department of Pharmacology, Faculty of Pharmacy, Mansoura University, Egypt.

Note

Ar= $C_6H_4(OCH_3)$-4, Ar'=$C_6H_3(OCH_3)_2$-2,4.
Ar''= $C_6H_4(Cl)$-4. Compound (3)
Ar''= $C_6H_4(NO_2)$-3. Compounds (7,8 and 9)
Ar''= $C_6H_4(NH_2)$-4. Compound (15)
Ar''= $C_6H_4(SO_2)$-4. Compound (23)

Synthesis

2-amino-6-(2,4-dimethoxyphenyl)-4-(4-

TABLE 2. Cytotoxic activity of some compounds against human tumor cells.

Compounds	In vitro Cytotoxicity IC50 (µM)•	
	HCT-116	MCF-7
DOX	5.23±0.3	4.17±0.2
1	6.38±0.5	8.53±0.6
11	55.12±2.9	31.29±1.9
18	40.26±2.3	57.09±3.3
4	50.12±1.9	24.29±1.7
6	9.71±0.8	7.24±0.4
9	36.07±2.1	44.72±2.5
8	29.14±1.7	23.75±1.6
16	55.12±2.9	31.29±1.9
10	83.34±4.2	71.64±4.1
G 23	14.58±1.2	10.82±0.9

IC50 (µM): 1 – 10 (very strong). 11 – 20 (strong). 21 – 50 (moderate). 51 – 100 (weak) and above 100 (non-cytotoxic), **DOX:** Doxorubicin.

methoxyphenyl)pyridine-3-carbonitrile (1)

Equimolar amounts of anisaldehyde (0.01 mol), 2,4-dimethoxyacetophenone (0.01 mol), malononitrile (0.01 mol) and ammonium acetate (0.015 mol) was fused in an oil bath at 100°C for 5h. After cooling, the solid product was washed with water and recrystallized.

Color: pale yellow,solvent: methanol, yield: 69%, m.p.: 200-202°C, IR (KBr) ν : 3300, 3163 (NH_2), 2200 (CN), 1643 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6)δ : 3.83 (s, 3H, OCH_3), 3.86 (s, 6H, $2OCH_3$), 6.63(s, 2H, NH_2, D_2O exchangeable), 6.70 (d, 1H, J=7.82 Hz, Ar'), 6.72 (s, 1H, Ar'), 7.13 (d, 2H, J=8.81 Hz, Ar), 7.60 (d, 2H, J=7.22 Hz, Ar),7.86 (d, 1H, J=7.04 Hz, Ar'),7.87 (s, 1H, C4-H). MS m/z (%): 361 ($M^{+\cdot}$, 2.43). Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.81; H, 5.26; N, 11.63. Found: C, 69.78; H, 5.30; N, 11.61 %. [23]

General procedure; reaction of 1 with malononitrile, 2-(4-chlorobenzylidene malononitrile) and/or ethyl cyanoacetate

A mixture of compound **1** (0.01mol), malononitrile, 2-(4-chloro -benzylidene malononitrile) and/or ethyl cyanoacetate (0.01mol) in DMF (15ml) in the presence of few drops of triethyl amine was refluxed for 6-8h, the solid that separated out after cooling was filtered and recrystallized.

2,4-Diamino-7-(2,4-dimethoxyphenyl)-5-(4-methoxyphenyl)-1,8-naphthyridine-3-carbonitrile (2)

Color: yellow, solvent:DMF,yield: 62%. m.p.: 250-252 °C. IR (KBr) ν : 3463, 3429 (NH_2), 2202 (CN), 1643, 1613 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ : 3.81 (s, 3H, OCH_3), 3.83 (s, 6H, $2OCH_3$),6.59 (d, 1H, J=7.82 Hz, Ar'), 6.62 (s, 1H, Ar'), 7.13 (d, 2H, J= 8.83 Hz, Ar),7.50 (d, 2H, J=7.20 Hz, Ar),7.70 (d, 1H, J=7.05 Hz, Ar'),7.73 (s, 1H, C4-H), 8.49 (s, 4H, NH_2, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 52.9, 53.7, 56.7, 94.3, 98.3, 100.9, 104.1, 110.6, 113.2, 114.3, 125.5, 126.4, 130.8, 139.0, 143.8, 151.3, 153.9, 157.1, 157.9 and 159.8. MS m/z (%): 427 ($M^{+\cdot}$, 5.59). Anal. Calcd for $C_{24}H_{21}N_5O_3$: C, 67.45; H, 4.92; N, 16.39. Found: C, 67.44; H, 4.95; N, 16.36 %.

2-(4-chlorophenyl)-7-(2,4-dimethoxyphenyl)-4-imino-5-(4-methoxyphenyl)-1,4-dihydro-1,8-naphthyridine-3-carbonitrile (3)

Color: beige, solvent: methanol, yield: 66%. m.p.: 244-246 °C. IR (KBr) ν : 3218, 3169 (2NH), 2206 (CN), 1636, 1611 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ : 3.81 (s, 3H, OCH_3), 3.84 (s, 6H, $2OCH_3$),6.63 (d, 1H, J= 7.83 Hz, Ar'), 6.65 (s, 1H, Ar'),7.07 (d, 2H, J=8.80 Hz, Ar), 7.09 (d, 2H, J=7.00 Hz, Ar''), 7.18(s, 2H, NH_2, D_2O exchangeable), 7.54 (d, 2H, J=7.28 Hz, Ar), 7.56 (d, 2H, J= 6.67 Hz, Ar''), 7.79 (d, 1H, J= 7.06 Hz, Ar'), 7.81 (s, 1H, C4-H). ^{13}C-NMR (DMSO-d_6) δ: 53.9, 55.1, 56.7, 96.3, 97.9, 103.4, 109.2, 110.1, 119.2, 120.6, 125.5, 126.4, 130.8, 135.4, 137.2, 140.8, 151.3, 155.1, 158.4 and 159.2. MS m/z (%): 522 ($M^{+\cdot}$, 1.35). Anal. Calcd for $C_{30}H_{23}N_4O_3Cl$: C, 68.97; H, 4.41; N, 10.73; Cl, 6.80. Found: C, 68.90; H, 4.43; N, 10.70; Cl, 6.77 %.

4-amino-7-(2,4-dimethoxyphenyl)-5-(4-methoxyphenyl)-2-oxo-1,2-dihydro-1,8-

naphthyridine-3-carbonitrile (4)

Color: deep brown, solvent: acetone, yield: 64%. m.p. =258-260 °C. IR (KBr) ν : 3431, 3308 (NH_2), 3177 (NH), 2207 (CN), 1745 (C=O), 1608 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.81 (s, 3H, OCH_3), 3.98 (s, 6H, 2 OCH_3), 4.17 (s, 2H, NH_2, D_2O exchangeable), 6.69 (d, 1H, J= 7.79 Hz, Ar'), 6.72 (s, 1H, Ar'), 7.27 (d, 2H, J=8.79 Hz, Ar), 7.55 (d, 2H, J=7.26 Hz, Ar),7.69 (d, 1H, J=7.01 Hz, Ar'), 8.03 (s, 1H, C4-H),11.41 (s, H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 53.9, 54.1, 57.8, 93.9, 99.7, 106.1, 111.7, 112.2, 112.3, 125.5, 133.9, 137.7, 146.8, 151.5, 155.1, 156.8, 158.4, 158.9 and 169.5.MS m/z (%): 428 ($M^{+\cdot}$, 7.56). Anal. Calcd for $C_{24}H_{20}N_4O_4$: C, 67.29; H, 4.67; N, 13.08. Found: C, 67.28; H, 4.71; N, 13.10 %.

2-Cyano-N-(3-cyano-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridin-2-yl)acetamide (5)

A mixture of compound **1** (0.01mol) and cyanoacetic acid (0.01mol) in acetic anhydride (10ml) was refluxed for 11h. The reaction mixture after cooling was poured onto crushed ice and recrystallized to give the solid product **5**.

Color: brown, solvent: acetone, yield: 71%. m.p.: 128-130 °C. IR (KBr) ν : 3429 (NH, broad), 2222 (CN), 1726 (C=O), 1607 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.70 (s, 2H, CO$\underline{CH_2}$CN), 3.83 (s, 3H, OCH_3), 3.87 (s, 6H, 2 OCH_3), 6.66 (d, 1H, J=7.84 Hz, Ar'), 6.70 (s, 1H, Ar'), 7.15 (d, 2H, J=8.81 Hz, Ar),7.60 (d, 2H, J=7.27 Hz, Ar), 7.84 (d, 1H, J=7.07 Hz, Ar'), 8.15 (s, 1H, C4-H), 10.76 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 26.9, 52.8, 53.7, 55.6, 93.4, 100.4, 102.2, 111.9, 115.4, 123.0, 126.1, 128.1, 132.6, 138.0, 144.8, 152.6, 154.7, 159.3 and 166.3. MS m/z (%): 428 ($M^{+\cdot}$, 5.05). Anal. Calcd for $C_{24}H_{20}N_4O_4$: C, 67.29; H, 4.67; N, 13.08. Found: C, 67.30; H, 4.68; N, 13.09 %.

Method B: compound 4

A mixture of compound **5** (0.01mol) in DMF (15ml) in the presence of few drops of triethyl amine was refluxed for 8h. The reaction mixture after cooling was poured onto crushed ice and recrystallized to give the solid product **4**.

6'-(2,4-Dimethoxyphenyl)-4'-(4-methoxyphenyl)-4,6-dimethyl-2-oxo-2H-[1,2'-bipyridine]-3,3'-dicarbonitrile (6)

A mixture of compound **5** (0.01mol) and acetyl acetone (0.01mol) in DMF (15ml) was refluxed for 11h. The reaction mixture after cooling was poured onto crushed iceand recrystallized to give compound **6**.

Color: black, solvent: methanol,yield: 58%. m.p. >300 °C. IR (KBr) ν : 2217 (CN), 1672 (C=O), 1607 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.13 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.87 (s, 6H, 2 OCH_3), 6.71(s,1H, olefinic-H), 6.74 (d, 1H, J=7.79 Hz, Ar'), 6.77 (s, 1H, Ar'), 7.14 (d, 2H, J=8.81Hz, Ar), 7.62 (d, 2H, J=7.25 Hz, Ar), 7.85 (d, 1H, J= 7.01 Hz, Ar'), 7.87 (s, 1H, C4-H). ^{13}C-NMR (DMSO-d_6) δ: 23.8, 25.9, 52.6, 54.1, 56.2, 90.3, 103.4, 112.3, 116.7, 124.0, 126.1, 129.9, 131.7, 136.4, 143.8, 151.7, 155.6, 158.3, 159.0 and 169.5.MS m/z (%): 492 ($M^{+\cdot}$, 5.14). Anal. Calcd for $C_{29}H_{24}N_4O_4$: C, 70.73; H, 4.88; N, 11.38. Found: C, 70.71; H, 4.86; N, 11.36 %.

6-(2,4-Dimethoxyphenyl)-4-(4-methoxyphenyl)-2-((3-nitrobenzylidene)amino) pyridine-3-carbonitrile (7)

A mixture of compound 1 (0.01mol) and m-nitrobenzaldehyde (0.01mol) in DMF (15ml) in the presence of few drops of acetic acid was refluxed for 6h.The reaction mixture after cooling was poured onto crushed ice and recrystallized to give compound 7.

Color: grey, solvent: acetone,yield: 72%. m.p.: 130-132 °C. IR (KBr) ν : 2205 (CN), 1608 (C=N), 1350 (NO_2) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.83 (s, 3H, OCH_3), 3.87 (s, 6H, 2OCH_3),6.63 (d, 1H, J=7.84 Hz, Ar'), 6.76 (s, 1H, Ar'), 7.09 (d, 2H, J=8.78 Hz, Ar), 7.50 (d, 2H, J=7.33 Hz, Ar),7.53 (d, 1H, J=7.95 Hz, CH-Ph-NO_2), 7.56 (t, 1H, J= 7.88 Hz, CH-Ph-NO_2), 7.58 (d, 1H, J=7.97 Hz, CH-Ph- NO_2), 7.71 (s, 1H, CH-Ph-NO_2), 7.79 (d, 1H, J=7.04 Hz, Ar'), 7.81 (s, 1H, C4-H), 8.68 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6) δ: 53.7, 54.6, 57.2, 96.5, 98.3, 100.4, 106.1, 109.2, 110.1, 113.6, 116.0, 123.4, 127.6, 131.4, 137.0, 141.9, 144.2, 150.3, 152.6, 156.1, and 158.3.MS m/z (%): 494 ($M^{+\cdot}$, 15.94 %). Anal. Calcd for $C_{28}H_{22}N_4O_5$: C, 68.02; H, 4.45; N, 11.34. Found: C, 68.01; H, 4.48; N, 11.31 %.

General procedure; reaction of 7 with chloroacetyl chloride and phenacyl bromide

A mixture of compound **7** (0.01mol) and chloroacetyl chloride and/or phenacyl bromide (0.01mol) in DMF (15ml) was refluxed for 7-10h. The solid obtained after cooling in case of chloroacetyl chloride was filtered, while in case of phenacyl bromide, the reaction mixture was poured onto crushed ice, the solid obtained was filtered and recrystallized.

2-(3-Chloro-2-(3-nitrophenyl)-4-oxoazetidin-1-yl)-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridine-3-carbonitrile (8)

Color: brown, solvent: methanol,yield: 57%. m.p.: 84-86 °C. IR (KBr) ν : 2223 (CN), 1703 (C=O), 1605 (C=N), 1384 (NO_2) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.88 (s, 3H, OCH_3), 3.91 (s, 6H, 2 OCH_3), 4.32 (d, 1H, J= 4.75 Hz,CH-Ar),4.62 (d, 1H, J= 4.75 Hz, CHCl), 7.14 (d, 1H, J=7.80 Hz, Ar'), 7.17 (s, 1H, Ar'), 7.22 (d, 2H, J=8.79 Hz, Ar), 7.66 (s, 1H, Ar''), 7.74 (d, 2H, J=7.31 Hz, Ar), 7.81 (d, 1H, J=7.99 Hz, Ar''), 7.83 (t, 1H, J=7.84 Hz, Ar''), 7.86 (d, 1H, J=7.96 Hz, Ar''), 7.91 (d, 1H, J=7.08 Hz, Ar'), 8.11 (s, 1H, C4-H). ^{13}C-NMR (DMSO-d_6) δ: 53.8, 55.1, 56.1, 64.8, 69.6, 91.2, 99.3, 103.1, 109.9, 112.2, 116.3, 120.1, 126.8, 128.2, 134.6, 138.0, 144.8, 152.3, 153.4, 157.9, 158.6 and 165.7.MS m/z (%): 570 ($M^{+\cdot}$, 6.64). Anal. Calcd for $C_{30}H_{23}N_4O_6Cl$: C, 63.16; H, 4.04; N, 9.82; Cl, 6.23. Found: C, 63.11; H, 4.10; N, 9.85; Cl, 6.21 %.

6-(2,4-Dimethoxyphenyl)-4-(4-methoxyphenyl)-2-(2-(3-nitrophenyl)-4-oxo-3-phenylazetidin-1-yl)pyridine-3-carbonitrile (9)

Color: brown, solvent: acetone, yield: 59%. m.p.: 284-286 °C. IR (KBr) ν : 2206 (CN), 1701 (C=O), 1608 (C=N), 1371(NO_2) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.86 (s, 3H, OCH_3), 3.90 (s, 6H, 2 OCH_3), 4.37 (d, 1H, J= 4.92 Hz, CH-Ph), 4.98 (d, 1H, J= 4.92 Hz, CH-Ar), 7.12 (d, 1H, J=7.87 Hz, Ar'), 7.18 (s, 1H, Ar'), 7.22 (d, 2H, J=8.81 Hz, Ar),7.23-7.29 (m, 5H, ph), 7.56 (d, 2H, J=7.29 Hz, Ar), 7.68 (s, 1H, Ar''), 7.80 (d, 1H, J=7.95 Hz, Ar''), 7.84 (t, 1H, J=7.88 Hz, Ar''), 7.86 (d, 1H, J=7.97 Hz, Ar''), 7.89 (d, 1H, J=7.01 Hz, Ar'), 8.23 (s, 1H, C4-H). ^{13}C-NMR (DMSO-d_6) δ: 54.0, 54.7, 55.9, 64.9, 69.2, 94.5, 102.2, 109.3, 112.6, 118.2, 123.2, 124.6, 125.0, 127.8, 130.9, 133.6, 136.8, 139.8, 146.2, 153.8, 157.9, 158.2 and 169.1. MS m/z (%): 612 ($M^{+\cdot}$, 9.44 %). Anal. Calcd for $C_{36}H_{28}N_4O_6$: C, 70.59; H, 4.58; N, 9.15. Found: C, 70.61; H, 4.60; N, 9.26 %.

6-(2,4-Dimethoxyphenyl)-4-(4-methoxyphenyl)-3-(1H-tetrazol-5-yl)pyridin-2-amine (10)

A mixture of compound **1** (0.01mol), sodium azide (0.01 mol) and ammonium chloride (0.01mol) in DMF (15ml) was refluxed for 12h. The solid product obtained after cooling was collected by filtration and recrystallized to give 10.

Color: grey, solvent: DMF,yield: 53%. m.p. >300 °C. IR (KBr) ν : 3449 (NH_2, NH, broad), 1635 (C=N), 1455 (tetrazole ring) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.81 (s, 3H, OCH_3), 3.83 (s, 6H, 2 OCH_3), 6.64 (d, 1H, J=7.89 Hz, Ar'), 6.68 (s, 1H, Ar'), 7.00 (d, 2H, J=8.79 Hz, Ar), 7.44 (d, 2H, J=7.22 Hz, Ar), 7.46 (d, 1H, J=7.03 Hz, Ar'), 7.76 (s, 1H, C4-H), 9.15 (s, 1H, NH, D_2O exchangeable), 9.94 (s, 2H, NH_2, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 53.7, 54.2, 56.6, 57.6, 91.9, 100.3, 104.9, 113.7, 115.2, 112.3, 125.5, 132.8, 135.1, 137.0, 142.5, 148.0, 152.3, 157.4, 157.1 and 158.9.MS m/z (%): 404 ($M^{+\cdot}$, 3.44). Anal. Calcd for $C_{21}H_{20}N_6O_3$: C, 62.38; H, 4.95; N, 20.79. Found: C, 62.41; H, 4.98; N, 20.81 %.

7-(2,4-Dimethoxyphenyl)-5-(4-methoxyphenyl) pyrido[2,3-d]pyrimidin-4(3H)-one (11)

Compound **1** (0.01mol) in formamide (30 ml) was refluxed for 10h.The reaction mixture after cooling was poured onto crushed ice and recrystallized to give compound **11**.

Color: black, solvent: methanol,yield: 57%. m.p. >300 °C. IR (KBr) ν : 3420 (NH, broad), 1678 (C=O), 1637 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.82 (s, 3H, OCH_3), 3.86 (s, 6H, 2 OCH_3), 6.70(d, 1H, J=7.85 Hz, Ar'), 7.12(s, 1H, Ar'), 7.18(d, 2H, J=8.88 Hz, Ar), 7.62 (d, 2H, J=7.32 Hz, Ar), 7.86 (d, 1H, J=7.13 Hz, Ar'), 7.96 (s, 1H, C4-H),8.20 (s, 1H, N=CH), 12.42 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6): 52.9, 54.4, 56.6, 91.4, 99.8, 104.2, 110.8, 118.4, 122.9, 127.2, 129.4, 132.3, 134.0, 138.7, 146.5, 151.6, 155.7, 158.3, 158.7 and 167.6.MS m/z (%): 389 ($M^{+\cdot}$, 12.24). Anal. Calcd for $C_{22}H_{19}N_3O_4$: C, 67.87; H, 4.88; N, 10.80. Found: C, 67.90; H, 4.92; N, 10.79 %.

N-Acetyl-N-(3-cyano-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridin-2-yl)acetamide (12)

A mixture of compound **1** (0.01mol) in acetic anhydride (20 ml) was refluxed for 7h. The reaction mixture after cooling was poured onto crushed ice. The obtained solid was collected by filtrationand recrystallized to give **12.**

Color: beige, solvent: acetone,yield: 66%. m.p. =258-260 °C. IR (KBr) ν : 2221 (CN), 1730, 1710 (C=O), 1608 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.17 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 3.85 (s, 6H, 2 OCH_3), 7.13 (d, 1H, J=7.86 Hz, Ar'), 7.16 (s, 1H, Ar'), 7.18(d, 2H, J=8.77 Hz, Ar), 7.55 (d, 2H, J=7.23 Hz, Ar), 7.83 (d, 1H, J=7.09 Hz, Ar), 7.96 (s, 1H, C4-H). ^{13}C-NMR (DMSO-d_6) δ: 26.3, 52.4, 53.5, 55.1, 93.1, 102.0, 111.6, 115.4, 123.9, 126.8,

128.2, 132.7, 138.5, 144.7, 152.9, 154.4, 159.2 and 165.2. MS m/z (%): 445 ($M^{+\cdot}$, 16.41). Anal. Calcd for $C_{25}H_{23}N_3O_5$: C, 67.42; H, 5.17; N, 9.44. Found: C, 67.45; H, 5.20; N, 9.43 %.

7-(2,4-Dimethoxyphenyl)-5-(4-methoxyphenyl)-2-methylpyrido[2,3-d]pyrimidin-4(3H)-one (13)

A mixture of compound **1** (0.01mol), acetic anhydride (2ml) and concentrated H_2SO_4(3 drops) was heated under microwave irradiation for 1/2min at power 340 watt. After cooling, the solid product was washed with ethanol, filtered, dried and recrystallized to give compound**13.**

Color: black,solvent: DMF, yield: 95%. m.p. >300 °C. IR (KBr) ν : 3403 (NH, broad), 1653 (C=O), 1628 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.51 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 3.86 (s, 6H, 2 OCH_3), 6.71 (d, 1H, J=7.87 Hz, Ar'), 6.76 (s, 1H, Ar'), 7.13 (d, 2H, J=8.76 Hz, Ar'), 7.45 (d, 1H, J=7.02 Hz, Ar'), 7.60 (d, 2H, J=7.21 Hz, Ar), 7.87 (s, 1H, C4-H), 11.69 (s, 1H, NH, D_2O exchangeable). MS m/z (%): 403 ($M^{+\cdot}$, 1.38). Anal. Calcd for $C_{23}H_{21}N_3O_4$: C, 68.49; H, 5.21; N, 10.42. Found: C, 68.47; H, 5.19; N, 10.46 %.

Ethyl-N-(3-cyano-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridin-2-yl)formimidate (14)

A mixture of compound **1** (0.01mol), TEOF (15ml) and acetic anhydride (15ml) was refluxed for 9h and left to cool. The separated solid formed was filtered and recrystallized to give compound **14.**

Color: beige, solvent: acetone, yield: 74%. m.p.: 242-244 °C. IR (KBr) ν : 2208 (CN), 1643, 1613 (C=N), 1580 (C=C) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.38 (t, 3H, J=8.02 Hz, $OCH_2\underline{CH_3}$), 3.83 (s, 3H, OCH_3), 3.86 (s, 6H, 2 OCH_3),4.50 (q, 2H, J=8.02 Hz, $O\underline{CH_2}CH_3$), 6.63 (d, 1H, J=7.85 Hz, Ar'), 6.65 (s, 1H, Ar'), 7.17 (d, 2H, J=8.81 Hz, Ar),7.56 (d, 2H, J=7.28 Hz, Ar), 7.79 (d, 1H, J=7.09 Hz, Ar'), 7.83 (s, 1H, C4-H), 8.03 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6) δ: 17.8, 36.9, 52.7, 54.6, 56.4, 90.1, 101.2, 107.8, 113.2, 118.4, 122.2, 125.3, 128.9, 133.4, 136.6, 142.9, 151.2, 156.0, 158.2 and 158.7. MS m/z (%): 417 ($M^{+\cdot}$, 1.47). Anal. Calcd for $C_{24}H_{23}N_3O_4$: C, 69.06; H, 5.52; N, 10.07. Found: C, 69.05; H, 5.55; N, 10.05 %.

N-(4-Aminophenyl)-N'-(3-cyano-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridin-2-yl)formimidamide (15)

A mixture of compound **14** (0.01mol), p-phenylenediamine (0.01mol) in dimethyl formamide (20ml) was refluxed for 9h. The reaction mixture after cooling poured onto crushed ice. The obtained solid was filtered and recrystallized to give compound **15.**

Color: dark yellow, solvent: acetone,yield: 63%. m.p. >300 °C. IR (KBr) ν : 3305, 3428 (NH_2), 3173 (NH), 2203 (CN), 1640, 1612 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.75 (s, 3H, OCH_3), 3.81 (s, 6H, 2 OCH_3), 4.06 (s, 2H, NH_2-D_2O exchangeable), 6.63 (d, 1H, J=7.84 Hz, Ar'), 6.65 (s, 1H, Ar'), 7.09 (d, 2H, J=7.77 Hz, Ar''), 7.17 (d, 2H, J=8.85 Hz, Ar),7.50 (d, 2H, J=7.56 Hz, Ar''),7.55 (d, 2H, J=7.34 Hz, Ar),7.81 (d, 1H, J=7.06 Hz, Ar'), 7.93 (s, 1H, C4-H),7.93 (s, 1H, N=CH), 10.42 (s, 1H, NH-D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 53.5, 55.0, 56.9, 92.7, 99.6, 100.3, 105.2, 112.8, 115.3, 120.2, 124.5, 128.9, 132.9, 135.2, 140.7, 148.2, 152.3, 156.0 and 158.4. MS m/z (%): 479 ($M^{+\cdot}$, 2.57). Anal. Calcd for $C_{28}H_{25}N_5O_3$: C, 70.15; H, 5.22; N, 14.61. Found: C, 70.13; H, 5.26; N, 14.58 %.

7-(2,4-Dimethoxyphenyl)-4-imino-5-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine-3(4H)-carbaldehyde (16)

Compound **14** (0.01mol) in formamide (20 ml) was refluxed for 9h and left to cool. The separated solid was filtered and recrystallized to give compound **16**.

Color: dark brown, solvent: acetone,yield: 61%. m.p. >300 °C. IR (KBr) ν : 3201 (NH), 1663 (C=O), 1608 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.81 (s, 3H, OCH_3), 3.84 (s, 6H, 2 OCH_3),6.66 (d, 1H, J= 7.82 Hz, Ar'), 6.69 (s, 1H, Ar'), 7.11 (d, 2H, J=8.89Hz, Ar),7.41 (s, H, NH, D_2O exchangeable),7.68 (d, 2H, J=7.35 Hz, Ar),7.88 (d, 1H, J= 7.10 Hz, Ar'), 7.91 (s, 1H, C4-H), 8.19 (s, 1H, N=CH), 8.44 (s, 1H, CH=O). ^{13}C-NMR (DMSO-d_6) δ: 53.4, 54.7, 57.2, 99.8, 106.4, 109.7, 113.9, 119.4, 120.6, 124.6, 127.9, 129.8, 132.7, 136.5, 142.4, 146.3, 150.7, 155.4, 158.7, 159,2 and 174.6. MS m/z (%): 416 ($M^{+\cdot}$, 4.46). Anal. Calcd for $C_{23}H_{20}N_4O_4$: C, 66.35; H, 4.81; N, 13.46. Found: C, 66.34; H, 4.84; N, 13.45 %.

General procedure; reaction of compound 14 with phenyl hydrazine, aniline and/ or p-aminoazobenzene.

a) A mixture of compound **14** (0.01 mol), aniline or p-aminoazobenzene (0.01 mol), butanol (20 ml) was refluxed for 7h, the solids that separated after cooling were filtered and recrystallized from methanol.

b) A mixture of compound **14** (0.01 mol), phenyl hydrazine (0.01 mol), DMF (20 ml) was refluxed for 9h. The reaction mixture after cooling was poured onto crushed ice containing few drops of concentrated HCl. The obtained solid was collected by filtration and recrystallized from methanol.

The three previous products were identical in all aspects (m.p, mixed m.p and IR spectra) with **1**.

1-(3-Cyano-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridin-2-yl)urea (17a)

A mixture of compound **1** (0.01mol), urea (0.01mol), DMF (20ml) in the presence of few drops of acetic acid was refluxed for 7h, the solid that separated after cooling was filtered and recrystallized to give compound **17a**.

Color: white, solvent: methanol,yield: 57%. m.p.: 256-258 ^{o}C. IR (KBr) ν : 3400, 3299 (NH_2), 3168 (NH), 2207 (CN), 1700 (C=O), 1638 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.82 (s, 3H, OCH_3), 3.86(s, 6H, 2 OCH_3),6.63 (d, 1H, J= 7.88 Hz, Ar'), 6.67 (s, 1H, Ar'), 7.17 (d, 2H, J= 8.81Hz, Ar), 7.46 (d, 2H, J=7.28 Hz, Ar), 7.51 (d, 1H, J= 7.07 Hz, Ar'), 7.54 (s, 1H, C4-H),, 8.96 (s, 2H, NH_2-D_2O exchangeable), 9.74 (s, 1H, NH-D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 52.9, 54.2, 56.9, 96.7, 100.1, 104.3, 110.6, 113.7, 123.3, 125.7, 128.3, 130.4, 136.0, 142.4, 148.2, 151.7, 156.5, 158.1, 158.6 and 163.9.MS m/z (%): 404 ($M^{+\cdot}$, 3.07). Anal. Calcd for $C_{22}H_{20}N_4O_4$: C, 65.35; H, 4.95; N, 13.86. Found: C, 65.34; H, 4.98; N, 13.85 %.

1-(3-Cyano-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridin-2-yl)thiourea (17b)

A mixture of compound **1** (0.01mol), thiourea (0.01mol), acetic acid (15ml) and few drops of HCl was refluxed for 6h. The reaction mixture after cooling was poured onto crushed ice. The obtained solid was collected by filtrationand recrystallized to give compound **17b**.

Color: orang,solvent: acetic acid, yield: 59%. m.p.: 272-274 ^{o}C. IR (KBr) ν : 3382, 3453 (NH_2), 3216 (NH), 2221 (CN), 1614 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.82 (s, 3H, OCH_3), 3.84(s, 6H, 2 OCH_3),6.61 (d, 1H, J= 7.82 Hz, Ar'), 6.68 (s, 1H, Ar'), 7.09 (d, 2H, J= 8.84Hz, Ar), 7.42 (d, 2H, J=7.33 Hz, Ar), 7.48 (d, 1H, J= 7.10 Hz, Ar'), 7.50 (s, 1H, C4-H),9.72 (s, 2H, NH_2-D_2O exchangeable), 11.94 (s, 1H, NH-D_2O exchangeable). MS m/z (%): 420 ($M^{+\cdot}$, 4.47). Anal. Calcd for $C_{22}H_{20}N_4O_3S$: C, 62.86; H, 4.76; N, 13.33; S, 7.62. Found: C, 62.84; H, 4.79; N, 13.32; S, 7.62 %.

6-(2,4-Dimethoxyphenyl)-2-(1,3-dioxoisoindolin-2-yl)-4-(4-methoxyphenyl)pyridine-3-carbonitrile (18)

A mixture of compound **1** (0.01mol), phthalic anhydride (0.01mol) in acetic acid (15ml) was refluxed for 12h and left to cool. The separated solid was filtered and recrystallized to give compound **18**.

Color: orang, solvent: acetic acid,yield: 54%. m.p.: 180-182 ^{o}C. IR (KBr) ν : 2225 (CN), 1788, 1732 (C=O), 1608 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.81 (s, 3H, OCH_3), 3.86 (s, 6H, 2 OCH_3),6.64 (d, 1H, J= 7.83 Hz, Ar'), 6.69 (s, 1H, Ar'), 7.19 (d, 2H, J= 8.88Hz, Ar), 7.55 (d, 2H, J=7.24 Hz, Ar), 7.73 (d, 2H, J=7.19 Hz, Phthalic), 7.86 (d, 2H, J= 6.89Hz, Phthalic), 7.89 (d, 1H, J= 7.07 Hz, Ar'), 8.24 (s, 1H, C4-H). MS m/z (%): 491 ($M^{+\cdot}$, 41.14). Anal. Calcd for $C_{29}H_{21}N_3O_5$: C, 70.88; H, 4.28; N, 8.55. Found: C, 70.85; H, 4.31; N, 8.55 %.

6-(2,4-Dimethoxyphenyl)-2-(2,5-dioxopyrrolidin-1-yl)-4-(4-methoxyphenyl)pyridine-3-carbonitrile (19)

A mixture of compound **1** (0.01mol), succinic anhydride (0.01mol) in acetic acid (15ml) was refluxed for 6h. The reaction mixture after cooling was poured onto crushed ice. The obtained solid was filtered and recrystallized to give compound **19**.

Color: yellow, solvent: acetic acid**,** yield: 58%. m.p.: 284-286 ^{o}C. IR (KBr) ν : 2206 (CN), 1707, 1693 (C=O), 1611 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.97 (d, 4H, J= 6.64 Hz, $2CH_2$), 3.80 (s, 3H, OCH_3), 3.87 (s, 6H, 2 OCH_3), 6.44 (d, 1H, J= 7.83 Hz, Ar'), 6.60 (s, 1H, Ar'), 7.15 (d, 2H, J= 8.77Hz, Ar), 7.52 (d, 2H, J=7.29 Hz, Ar), 7.80 (d, 1H, J= 7.14 Hz, Ar'), 7.93 (s, 1H, C4-H). ^{13}C-NMR (DMSO-d_6) δ: 26.7, 27.2, 53.1, 54.2, 56.9, 91.2, 99.8, 104.8, 110.2, 114.4, 120.2, 125.5, 129.0, 134.2, 136.7, 142.9, 146.5, 151.2, 157.0, 158.2 and 179.2. MS m/z (%): 443 ($M^{+\cdot}$, 8.21). Anal. Calcd for $C_{25}H_{21}N_3O_5$: C, 67.72; H, 4.74; N, 9.48. Found: C, 67.71; H, 4.77; N, 9.45 %.

General procedure:

An equimolar mixture of compound **1** (0.01mol) and the appropriate halocompound (0.01mol), namely benzoyl chloride, chloroacetonitrile, chloroacetyl chloride, p-toluene sulfonyl chloride

and/or ethyl bromoacetate in DMF (15ml) was refluxed for 6-9h and left to cool.

N-(3-Cyano-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridin-2-yl)benzamide (20)

Color: yellow,solvent: acetone, yield: 68%. m.p. >300 °C. IR (KBr) ν : 3351 (NH) broad, 2204 (CN), 1667 (C=O), 1613 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.80 (s, 3H, OCH_3), 3.86 (s, 6H, 2 OCH_3), 6.62 (d, 1H, J=7.81 Hz, Ar'), 6.70 (s, 1H, Ar'), 7.19 (d, 2H, J=8.79 Hz, Ar), 7.52(d, 2H, J=7.31 Hz, Ar), 7.56-7.60 (m, 5H, Ph), 7.80 (d, 1H, J=7.08 Hz, Ar'), 7.83 (s, 1H, C4-H), 10.98 (s, 1H, NH-D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 53.4, 54.5, 57.1, 92.5, 99.9, 105.3, 111.5, 114.6, 120.8, 126.8, 129.1, 132.8, 137.2, 140.5, 143.4, 145.8, 151.2, 157.0, 158.2 and 166.5.MS m/z (%): 465 ($M^{+\cdot}$, 1.47). Anal. Calcd for $C_{28}H_{23}N_3O_4$: C, 72.26; H, 4.95; N, 9.03. Found: C, 72.25; H, 4.98; N, 9.08 %.

2-((Cyanomethyl)amino)-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridine-3-carbonitrile (21)

Color: black, solvent: methanol, yield: 67%. m.p. >300 °C. IR (KBr) ν : 3212 (NH), 2221, 2204 (CN), 1608 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.80 (s, 3H, OCH_3), 3.84 (s, 6H, 2 OCH_3),4.29 (s, 2H, $\underline{CH_2}CN$), 6.44 (d, 1H, J=7.77 Hz, Ar'), 6.65 (s, 1H, Ar'), 7.07 (d, 2H, J=8.76Hz, Ar), 7.54 (d, 2H, J=7.32 Hz, Ar), 7.81 (d, 1H, J=7.09 Hz, Ar'), 7.93 (s, 1H, C4-H), 9.38 (s, 1H, NH-D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 37.8, 53.7, 54.1, 57.8, 93.3, 100.9, 105.1, 110.4, 117.9, 122.8, 126.5, 128.8, 130.2, 136.7, 144.0, 151.2, 155.4, 155.2, 158.1 and 158.6. MS m/z (%): 400 ($M^{+\cdot}$, 2.77). Anal. Calcd for $C_{23}H_{20}N_4O_3$: C, 69.00; H, 5.00; N, 14.00. Found: C, 68.98; H, 5.03; N, 13.97 %.

2-Chloro-N-(3-cyano-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridin-2-yl)acetamide (22)

Color: yellow, solvent:methanol, yield: 69%. m.p.: 248-250 °C. IR (KBr) ν : 3171 (NH), 2221 (CN), 1746 (C=O), 1643 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.77 (s, 3H, OCH_3), 3.82 (s, 6H, 2 OCH_3), 4.07 (s, 2H, CO$\underline{CH_2}$Cl),6.44 (d, 1H, J= 7.83 Hz, Ar'), 6.66 (s, 1H, Ar'), 7.12 (d, 2H, J= 8.80Hz, Ar), 7.55 (d, 2H, J=7.26 Hz, Ar), 7.83 (d, 1H, J= 7.05 Hz, Ar'), 7.98 (s, 1H, C4-H),13.79 (s, 1H, NH-D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 46.7, 52.9, 54.3, 56.9, 94.5, 101.5, 106.2, 110.5, 114.5, 122.6, 125.5, 126.9, 131.1, 137.7, 143.9, 151.6, 154.1, 155.5, 156.2, 158.6 and 167.3. MS m/z (%): 437 ($M^{+\cdot}$, 6.98). Anal. Calcd for $C_{23}H_{20}N_3O_4Cl$: C, 63.16; H, 4.58; N, 9.61; Cl, 8.12. Found: C, 63.09; H, 4.60; N, 9.60; Cl, 8.10 %.

N-(3-Cyano-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridin-2-yl)-4-methylbenzenesulfonamide (23)

Color: white,solvent: acetone, yield: 70%. m.p. >300 °C. IR (KBr) ν : 3352 (NH), 2204 (CN), 1612 (C=N) scm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.50 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 3.87 (s, 6H, 2 OCH_3),6.71 (d, 1H, J=7.81 Hz, Ar'), 6.77 (s, 1H, Ar'), 7.13 (d, 2H, J=8.84 Hz, Ar), 7.60 (d, 2H, J=7.28 Hz, Ar), 7.33 (d, 2H, J=8.04 Hz, Ar''), 7.72 (d, 2H, J=6.66 Hz, Ar''), 7.79 (d, 1H, J=7.07 Hz, Ar'), 7.87 (s, 1H, C4-H),10.76 (s, 1H, NH-D_2O exchangeable). MS m/z (%): 515 ($M^{+\cdot}$, 2.49). Anal. Calcd for $C_{28}H_{25}N_3O_5S$: C, 65.24; H, 4.85; N, 8.16; S, 6.21. Found: C, 65.23; H, 4.89; N, 8.15; S, 6.22 %.

Ethyl (3-cyano-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridin-2-yl)glycinate (24)

Color: brown,solvent: acetone, yield: 66%. m.p. >300 °C. IR (KBr) ν : 3297 (NH), 2205 (CN), 1666 (C=O), 1607 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.46 (t, 3H, J=6.61 Hz, $OCH_2\underline{CH_3}$), 3.70 (s, 3H, OCH_3), 3.76 (s, 6H, 2 OCH_3), 4.01 (s, 2H, NH$\underline{CH_2}$CO), 4.12 (q, 2H, J=8.63 Hz, O$\underline{CH_2}CH_3$),6.63 (d, 1H, J=7.79 Hz, Ar'), 6.77 (s, 1H, Ar'), 7.09 (d, 2H, J=8.80 Hz, Ar), 7.56 (d, 2H, J=7.25 Hz, Ar), 7.81 (d, 1H, J=7.16 Hz, Ar'), 8.18 (s, 1H, C4-H),10.07 (s, 1H, NH-D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 16.9, 37.3, 44.6, 53.1, 54.2, 56.7, 98.4, 100.6, 107.0, 112.8, 117.4, 122.3, 124.8, 128.9, 132.9, 135.6, 144.3, 150.9, 154.5, 157.4 and 173.2. MS m/z (%): 447 ($M^{+\cdot}$, 9.71). Anal. Calcd for $C_{25}H_{25}N_3O_5$: C, 67.11; H, 5.59; N, 9.40. Found: C, 67.09; H, 5.63; N, 9.43 %.

General procedure: Reaction of 1 with dihalogen reagents: Synthesis of compounds 25-29.

A mixture of compound **1** (0.01 mol), and dihalogen reagents namely 1,2-dichloroethane; 1,3-dibromopropane; 1,6-dibromohexane; oxalylchloride; 2,3-dichloro-1,4-naphthoquinone; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; 2,3,5,6-tetrachloro-1,4-benzoquinone (0.01mol) in butanol (**25a,b** and **26**) or DMF (**25c, 27- 29**) (15 ml) was refluxed for 4-10h, the solid that separated after cooling was filtered (**25a,b, 26, 28, 29**), in case of compounds**25c** and **27**, the reaction mixture was poured onto crushed ice and the solid obtained was filtered and recrystallized.

5-(2,4-Dimethoxyphenyl)-7-(4-methoxyphenyl)-

2,3-dihydroimidazo[1,2-a]pyridine-8-carbonitrile (25a)

Color: orange,solvent: butanol, yield: 60%. m.p. >300 °C. IR (KBr) ν : 2206 (CN), 1591 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ:3.02-3.17 (m, 4H, $2CH_2$), 3.64 (s, 3H, OCH_3), 3.87 (s, 6H, 2 OCH_3), 6.74 (d, 1H, J= 7.87 Hz, Ar'), 6.79 (s, 1H, Ar'), 7.11 (d, 2H, J=8.79 Hz, Ar), 7.40 (d, 2H, J=7.21 Hz, Ar), 7.51 (d, 1H, J=7.02 Hz, Ar'), 7.58 (s, 1H, C4-H). MS m/z (%): 387 ($M^{+\cdot}$, 43.77). Anal. Calcd for $C_{23}H_{21}N_3O_3$: C, 71.32; H, 5.42; N, 10.85. Found: C, 71.30; H, 5.46; N, 10.86 %.

6-(2,4-Dimethoxyphenyl)-8-(4-methoxyphenyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrimidine-9-carbonitrile (25b)

Color: white,solvent: butanol, yield: 59%. m.p. >300 °C. IR (KBr) ν : 2216 (CN), 1608 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ:3.78 (s, 3H, OCH_3), 3.82 (s, 6H, 2 OCH_3), 3.70-3.86 (m, 6H, $3CH_2$),6.48 (d, 1H, J=7.80 Hz, Ar'), 6.59 (s, 1H, Ar'), 7.13 (d, 2H, J=8.85Hz, Ar), 7.65 (d, 2H, J=7.30 Hz, Ar), 7.70 (d, 1H, J=7.12 Hz, Ar'), 7.72 (s, 1H, C4-H). MS m/z (%): 401 ($M^{+\cdot}$, 19.61). Anal. Calcd for $C_{24}H_{23}N_3O_3$: C, 71.82; H, 5.73; N, 10.47. Found: C, 71.80; H, 5.77; N, 10.45 %.

9-(2,4-Dimethoxyphenyl)-11-(4-methoxyphenyl)-2,3,4,5,6,7-hexahydropyrido[1,2-a][1,3]diazonine-12-carbonitrile (25c)

Color: orange,solvent:acetone, yield: 56%. m.p. = 148-150 °C. IR (KBr) ν : 2218 (CN), 1607 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ:1.56-1.16 (m, 10H, CH_2), 2.08 (t, 2H,CH_2), 3.81 (s, 3H, OCH_3), 3.87 (s, 6H, 2 OCH_3),6.57 (d, 1H, J=7.78 Hz, Ar'), 6.77 (s, 1H, Ar'), 7.17 (d, 2H, J=8.76 Hz, Ar), 7.71 (d, 2H, J=7.31 Hz, Ar), 7.80 (d, 1H, J=7.04 Hz, Ar'), 8.21 (s, 1H, C4-H). ^{13}C-NMR (DMSO-d_6) δ: 27.4, 33.2, 36.4, 41.2, 53.1, 54.0, 56.7, 94.6, 99.8, 100.7, 107.6, 116.0, 118.2, 121.5, 124.7, 128.6, 132.8, 136.3, 140.6, 146.6, 154.1, 157.4 and 158.2. MS m/z (%): 443 ($M^{+\cdot}$, 29.40). Anal. Calcd for $C_{27}H_{29}N_3O_3$: C, 73.14; H, 6.55; N, 9.48. Found: C, 73.11; H, 6.59; N, 9.47 %.

5-(2,4-Dimethoxyphenyl)-7-(4-methoxyphenyl)-2,3-dioxo-2,3-dihydroimidazo[1,2-a]pyridine-8-carbonitrile (26)

Color: brown, solvent:acetone, yield: 56%. m.p.>300 °C. IR (KBr) ν : 2206 (CN), 1734-1759 (C=O), 1601 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ:3.65 (s, 3H, OCH_3), 3.86 (s, 6H, 2 OCH_3),6.47 (d, 1H, J=7.88 Hz, Ar'), 6.60 (s, 1H, Ar'), 7.19 (d, 2H, J=8.76 Hz, Ar), 7.59 (d, 2H, J=7.23 Hz, Ar), 7.88 (d, 1H, J=7.09 Hz, Ar'), 8.16 (s, 1H, C4-H).^{13}C-NMR (DMSO-d_6) δ: 52.7, 54.3, 56.6, 93.3, 98.6, 101.4, 107.1, 112.9, 118.2, 120.6, 123.9, 127.8, 133.7, 136.3, 140.9, 146.1, 152.1, 156.1, 158.9, 172.5 and 173.1. MS m/z (%): 415 ($M^{+\cdot}$, 36.35). Anal. Calcd for $C_{23}H_{17}N_3O_5$: C, 66.51; H, 4.10; N, 10.12. Found: C, 66.50; H, 4.14; N, 10.11 %.

1-(2,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-6,11-dioxo-6,11-dihydronaphtho[2',3':4,5]imidazo[1,2-a]pyridine-4-carbonitrile (27)

Color: black, solvent: methanol, yield: 64%. m.p. > 300 °C. IR (KBr) ν : 2206 (CN), 1672-1714 (C=O), 1608 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ:3.79 (s, 3H, OCH_3), 3.82 (s, 6H, 2 OCH_3),6.71 (d, 1H, J= 7.75 Hz, Ar'), 6.97 (s, 1H, Ar'),7.17 (d, 2H, J= 8.81Hz, Ar),7.49 (d, 2H, J=7.33 Hz, Ar), 7.78 (d, 1H, J= 7.12 Hz, Ar'), 7.93 (d, 2H, J=7.47 Hz, naphthalene-dione),7.98 (d, 2H, J= 7.79Hz, naphthalene-dione), 8.02 (s, 1H, C4-H). ^{13}C-NMR (DMSO-d_6) : 54.0, 54.8, 56.1, 94.5, 99.2, 102.5, 109.4, 112.6, 114.6, 119.7, 123.4, 123.6, 124.5, 125.7, 127.8, 130.8, 132.6, 136.7, 138.9, 142.6, 145.2, 151.7, 156.7, 159.2 and 177.9. MS m/z (%): 515 ($M^{+\cdot}$, 8.47). Anal. Calcd for $C_{31}H_{21}N_3O_5$: C, 72.23; H, 4.08; N, 8.16. Found: C, 72.25; H, 4.11; N, 8.15 %.

1-(2,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-6,9-dioxo-6,9-dihydrobenzo[4,5]imidazo[1,2-a]pyridine-4,7,8-tricarbonitrile (28)

Color: brown,recrystallized from acetone, yield: 86%. m.p. > 300 °C. IR (KBr) ν : 2203, 2180 (CN), 1681-1643 (C=O), 1607 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ:3.79 (s, 3H, OCH_3), 3.84 (s, 6H, 2 OCH_3),6.67 (s, 1H, Ar'), 6.75 (d, 1H, J=7.80 Hz, Ar'), 7.14 (d, 2H, J=8.77 Hz, Ar), 7.56 (d, 2H, J=7.31 Hz, Ar), 8.01 (d, 1H, J=7.03 Hz, Ar'), 8.32 (s, 1H, C4-H). MS m/z (%): 515 ($M^{+\cdot}$, 8.05). Anal. Calcd for $C_{29}H_{17}N_5O_5$: C, 67.57; H, 3.30; N, 13.59. Found: C, 67.55; H, 3.31; N, 13.61 %.

7,8-Dichloro-1-(2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-6,9-dioxo-6,9-dihydrobenzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile (29)

Color: black, solvent: methanol, yield: 61%. m.p. =284-286°C. IR (KBr) ν : 2206 (CN), 1681-1691 (C=O), 1591 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ:3.77 (s, 3H, OCH_3), 3.82 (s, 6H, 2 OCH_3),6.74 (d, 1H, J= 7.81 Hz, Ar'), 6.77 (s, 1H, Ar'), 7.14 (d, 2H, J=8.88 Hz, Ar), 7.69 (d, 2H, J=7.29 Hz, Ar),7.89 (d, 1H, J=7.07 Hz, Ar'), 8.19 (s, 1H, C4-H). ^{13}C-NMR (DMSO-d_6)

δ: 53.2, 54.5, 56.1, 93.1, 99.4, 102.3, 107.6, 111.5, 118.4, 120.6, 124.5, 127.6, 133.2, 136.6, 140.9, 143.0 146.2, 152.6, 157.3, 158.2, 159.9 and 179.3.MS m/z (%): 533 ($M^{+\cdot}$, 9.12). Anal. Calcd for $C_{27}H_{17}N_3O_5Cl_2$: C, 60.78; H, 3.19; N, 7.88; Cl, 13.32. Found: C, 60.69; H, 3.21; N, 7.86; Cl, 13.27 %.

1-(2,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-11,12-dihydropyrido[1',2':1,2]imidazo[4,5-a]quinoxalino[2,3-c]phenazine-4-carbonitrile (30)

A mixture of compound **29** (0.01 mol), o-phenylene diamine (0.02), DMF (10 ml) in presence of potassium hydroxide (0.01mol) was fused for 5h. The reaction mixture after cooling was poured onto crushed ice. The obtained solid was filtered and recrystallized to give compound **29**.

Color: beige,solvent: acetone, yield: 66%. m.p. =276-278°C. IR (KBr) ν : 3173 (NH), 2207 (CN), 1609 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ:3.79 (s, 3H, OCH_3), 3.86 (s, 6H, 2 OCH_3),6.46 (d, 1H, J=7.77 Hz, Ar'), 6.66(s, 1H, Ar'), 6.93-7.07 (m, 8H, CH-phenazine), 7.09 (d, 2H, J= 8.89Hz, Ar), 7.67 (d, 2H, J=7.35 Hz, Ar), 7.82 (d, 1H, J=7.13 Hz, Ar'), 7.96 (s, 1H, C4-H),12.69 (s, 2H, NH-D_2O exchangeable).

TABLE 3. Microwave synthesis of compounds 1-31.

Compound no.		Time		Yield %		Compound no.		Time		Yield %	
	Method	Conventional hours	M.W Min	conventional	M.W		method	conventional hours	M.W Mins	Conventional	M.W
1	A	5	3	69	92	**18**	C	11	3	54	89
2	A	7	2	62	89	**19**	C	6	1	58	86
3	A	8	2	66	91	**20**	A	9	0.5	68	93
4	A	6	0.5	64	86	**21**	A	9	1	67	88
5	D	11	3	71	92	**22**	F	8	1.5	69	91
6	A	11	2	58	90	**23**	C	7	2	70	92
7	B	6	2	72	96	**24**	A	9	1	66	88
8	A	10	0.5	57	84	**25a**	A	8	4	60	89
9	A	7	0.5	59	85	**25b**	A	4	4	59	83
10	A	12	1	53	84	**25c**	A	10	1	59	81
11	E	10	4	57	84	**26**	A	9	1	56	81
12	D	7	2	66	90	**27**	A	7	1	64	85
13	G		0.5		95	**28**	A		0.33		86
14	D	9	3	74	96	**29**	A	10	0.33	61	90
15	A	9	3	63	89	**30**	H	5	1	66	93
16	E	9	3	61	89	**31a**	A	12	1.5	68	91
17a	B	7	57	83	83	**31b**	A	12	1.5	63	91
17b	C	6	2	59	82						

^{13}C-NMR (DMSO-d_6) δ: 53.6, 54.2, 56.3, 92.9, 100.6, 102.5, 106.4, 108.2, 111.1, 114.6, 116.2, 120.7, 122.3, 125.3, 127.6, 130.5, 133.7, 134.9, 136.5, 141.9, 142.6, 143.0, 146.2, 151.7, 155.2, 157.4, 157.9, 158.1 and 159.3. MS m/z (%): 641 ($M^{+\cdot}$, 0.76). Anal. Calcd for $C_{39}H_{27}N_7O_3$: C, 73.01; H, 4.21; N, 15.29. Found: C, 73.00; H, 4.24; N, 15.27 %.

General procedure: Synthesis of compounds 31a and 31b

A mixture of compound 1 (0.02 mol), 1,6-dibromohexane or 1,8-dibromooctane (0.01 mol), NaOH (0.01 mol) in DMF (15 ml) was refluxed for 12h. The reaction mixture after cooling was poured onto crushed ice. The obtained solids were filtered and recrystallized.

2,2'-(Hexane-1,6-diylbis(azanediyl))bis(6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridine-3-carbonitrile) (31a)

Color: dark yellow,solvent: dioxane, yield: 68%. m.p.> 300°C. IR (KBr) ν : 3012, 3151 (NH), 2204 (CN), 1601 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ:1.25 (m, 4H, $2CH_2$), 1.66 (q, 4H, $2CH_2$),3.16 (t, 4H, $2CH_2$), 3.86 (s, 6H, $2OCH_3$),

3.88 (s, 12H, 4 OCH_3),6.72 (d, 2H, J=7.77 Hz, Ar'), 6.77 (s, 2H, Ar'), 7.15 (d, 4H, J=8.89Hz, Ar), 7.62 (d, 4H, J=7.35 Hz, Ar), 7.98 (d, 2H, J=7.13 Hz, Ar'), 8.04 (s, 2H, C4-H),9.01 (s, 2H, NH-D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 27.9, 28.3, 30.2, 34.6, 36.9, 52.5, 53.6, 56.8, 94.5, 98.3, 101.2, 105.7, 110.2, 116.2, 119.2, 122.5, 123.3, 126.9, 131.9, 133.2, 136.3, 140.6, 154.1 and 157.4.MS m/z (%): 804 ($M^{+\cdot}$, 3.46). Anal. Calcd for $C_{48}H_{48}N_6O_6$: C, 71.64; H, 5.97; N, 10.45. Found: C, 71.62; H, 6.01; N, 10.44 %.

2,2'-(Octane-1,8-diylbis(azanediyl))bis(6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyridine-3-carbonitrile) (31b)

Color: orange, solvent:acetone,yield: 63%. m.p. = 266-268°C. IR (KBr) ν : 3103, 3149 (NH), 2206 (CN), 1590 (C=N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.23-1.39 (m, 8H, 4CH_2), 1.60 (q, 4H, 2CH_2), 3.17 (t, 4H, 2CH_2), 3.85(s, 6H, 2 OCH_3), 3.88 (s, 12H, 4 OCH_3),6.72 (d, 2H, J=7.79 Hz, Ar'), 6.77 (s, 2H, Ar'), 7.10 (d, 4H, J=8.87 Hz, Ar), 7.64 (d, 4H, J=7.34 Hz, Ar), 7.93 (d, 2H, J=7.16 Hz, Ar'), 8.04 (s, 2H, C4-H), 8.51 (s, 2H, NH-D_2O exchangeable). MS m/z (%): 832 ($M^{+\cdot}$, 0.32). Anal. Calcd for $C_{50}H_{52}N_6O_6$: C, 72.12; H, 6.25; N, 10.10. Found: C, 72.09; H, 6.29; N, 10.09 %.

Experimental work under Microwave irradiation

The preparation of the target compounds was achieved by irradiating an equimolar amounts of the reactants (0.01 mol) at 340 Watt in presence of:

A- DMF (1-1.5 ml)

B- DMF (1.5 ml) + drops of HCl

C- AcOH (2 ml)

D- Ac_2O (2 ml)

E- Formamide (2 ml)

F- Butanol (2 ml)

G- Ac_2O (2 ml)+ 3 drops of Conc H_2SO_4

H- Compound 29 (0.01 mol) + o-phenylene diamine (0.02 mol) + KOH (0.01 mol) in DMF (1.5ml)

I- After cooling and washing with ethanol. The solid products were recrystallized from the proper solvents.

According to Table **3**, synthesis of the target compounds under these conditions showed improvement in the yield and the time of the reactions.

Antibacterial activity

a) Antimicrobial Activity

The anti-bacterial activity of the synthesized compounds was tested against a panel of two Gram positive bacteria (Staphylococcus aureus, Bacillus subtilis), and two Gram-negative bacteria (Escherichia coli, Pseudomonas aeuroginosa). The anti-fungal activity of the compounds were tested against two fungi (Candida albicans, Aspergillus flavus). Each compound was dissolved in DMSO and a solution of concentration 1 mg /ml was prepared separately paper discs of Whatman filter paper [24] were prepared with standard size (5cm) were cut and sterilized in an autoclave. The paper discs were soaked in the desired concentration of the complex solution and placed aseptically in the petri dishes containing nutrient agar media (agar 20g + beef extract 3g + peptone 5g) seeded with Staphylococcus aureus, Bacillus subtilis, E. coli, Pseudomonas aeuroginosa, Candida albicans and Aspergillus flavus. The petri dishes were incubated at 36° C and the inhibition zones were recorded after 24 h of incubation. Each treatment was replicated three times. The antibacterial activity of a common standard antibiotic Ampicillin and antifungal Colitrimazole was also recorded using the same procedure as above at the same concentration and solvents. The % activity index for the complex was calculated by the following formula:

$$\%\ ActivityIndex = \frac{Zoneofinhibitionbytestcompound\ (diametre)}{Zoneofinhibitionbystandard(diametre)} \times 100$$

b) Cytotoxicity assay

Materials and Methods

Cell line

Some of the synthesized compounds were tested against two human tumor cell lines namely; Colorectal carcinoma (HCT-116) and mammary gland (MCF-7). The cell line was obtained from ATCC via Holding company for biological products and vaccines (VACSERA), Cairo, Egypt.

Chemical reagents

The reagents RPMI-1640 medium, MTT and DMSO (sigma co., St. Louis, USA), Fetal Bovine serum (GIBCO, UK). Doxorubicin was used as a

standard anticancer drug for comparison.

MTT assay

The different cell line mentioned above were used to determine the inhibitory effects of compounds on cell growth using the MTT assay [25]. This colorimetric assay is based on the conversion of the yellow tetrazolium bromide (MTT) to a purple formazan derivative by mitochondrial succinate dehydrogenase in viable cells. The cells were cultured in RPMI-1640 medium with 10% fetal bovine serum. Antibiotics added were 100 units/ml penicillin and 100µg/ml streptomycin at 37° C in a 5% CO_2 incubator. The cells were seeded in a 96-well plate at a density of 1.0x104 cells/well. At 37°C for 48 h under 5% CO_2. After incubation the cells were treated with different concentration of compounds and incubated for 24 h. After 24 h of drug treatment, 20 µl of MTT solution at 5mg/ml was added and incubated for 4 h. Dimethyl sulfoxide (DMSO) in volume of 100 µl is added into each well to dissolve the purple formazan formed. The colorimetric assay is measured and recorded at absorbance of 570 nm using a plate reader (EXL 800, USA). The relative cell viability in percentage was calculated as (A570 of treated samples/A570 of untreated sample) X 100.

Conclusion

1. Our strategy for the synthesis of pyridine derivative 2-amino-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl) nicotinonitrile **1** was simply through a multicomponent reaction of 2,4-dimethoxy-acetophenone with p-anisaldehyde and the active methylene compound malononitrile in the presence of ammonium acetate.
2. Studied The reactivity of amino and cyano groups of pyridine derivative **1** towards different reagents was studied by its reaction with malononitrile, 2-(4-chlorobenzylidene) malononitrile, ethyl cyanoacetate, cyano acetic acid, m-nitro benzaldehyde, sodium azide, formamide, acetic anhydride and/or acetic anhydride/H_2SO_4.
3. Prepared bipyridine derivative **6** by reaction of compound **5** with acetyl acetone.
4. Prepared azetidinone derivatives **8** and **9** were obtained via reaction of compound **7** with chloroacetyl chloride and phenacyl bromide.
5. Prepared formimidate **14** via reaction of starting compound **1** with triethylorthoformate.
6. Studied The reactivity of compound **1** was also allowed to react with urea, thiourea, phthalic anhydride, succinic anhydride, benzoyl chloride, chloroacetonitrile, chloroacetyl chloride, p-toluenesulfonylchloride and ethyl bromoacetate.
7. Prepared bicyclic derivatives **25a–c** by reaction of compound 1 with dichloro reagents in 1:1ratio, while compound **1** reacted with oxalyl chloride, dichloro and tetrachlorobenzoquinone derivatives, and/or dichloronaphthoquinone gave the imidazopyridine derivatives **26-29**.
8. Reaction of compound **29** with o-phenylenediamine in 1:2 ratio afforded the dicondenesed product **30**.
9. Polyalkyl derivatives **31a-b** was prepared by reaction of compound **1** with dichloro reagents in 1:2 ratio.
10. All the newly synthesized compounds were prepared by conventional method and under microwave irradiation.
11. The anticancer and biological activities of the produced compounds have been evaluated.

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تحضير بعض مشتقات البيريدين الجديده بالطرق التقليديه و الميكروويف و تقييم نشاطها كمضادات للبكتريا و الخلايا السرطانيه

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المركبات الجديده المحضره تعتمد علي ٢-امينو-٦-(٢,٤-داي ميثوكسي فينيل)-٤-(٤-ميثوكسي فينيل) نيكوتينونيتريل ١. تم دراسة فاعليه مشتق البيريدين ١ تجاه بعض الكواشف من خلال تفاعلها مع مالونوانيتيرايل، ٢-(٤-كلوروابنزيليدين)مالونوانيتيرايل، ايثيل سيانوا اسيتيت، سيانوا حمض الخليك، ٣-نيتروابنيزالديدهيد، ازيد الصوديوم، الفورماميد، انهيدريد حمض الخليك، انهيدريد حمض الخليك/حمض الكبريتيك المركز لتعطي المركبات **٢-٥ ،٧ ، ١٠-١٣** علي التوالي. أعطى تفاعل **٥** مع اسيتونيل اسيتون مشتق البيريدين **٦**، بينما أعطى تفاعل المركب **٧** مع كلورا اسيتيل كلوريد وفيناثيل بروميد اعطي مشتقات الأزيتود **٨**، **٩**. الفورميد **١٤** تكون من تفاعل المركب **١** مع تراي اورثوا فورميت ، بينما تفاعل **١٤** مع ثنائي امين الفينيلين و الفورماميد اعطي المشتقات **١٥،١٦**. سمح للمركب **١** بالتفاعل مع اليوريا، ثيويريا، أنهيدريد حمض الفثاليك، حمض السكسينك، كلوريد البنزويل، كلوا اسيتونيتريل، كلوريد استيل كلوريد، تلوين سلفونيل كلوريد، إيثيل بروموا اسيتيت لإعطاء مركبات **١٧-٢٤**. أعطت تفاعل المركب **١** مع كواشف ثنائي كلورو في نسبة ١: ١ اعطي المشتقات **25a-c** ، بينما تفاعل المركب 1 مع الاوجزيليل كلوريد، مشتقات ثنائي و رباعي كلوروالبنزوكينون، و ثاني كلوا النفثوكينون اعطي المشتقات **26-29**. تفاعل المركب **29** مع ثاني امين الفنيلين بنسبه 1:2 اعطي المشتق **30**. تغاعل المركب **1**مع كواشف ثنائي الكلور بنسبه 1:2 اعطي المشتقات **13a-b.**تم اثبات التراكيب البنائيه للمركبات الجديده بأستخدام التحاليل الدقيقه للعناصر و بأستخدام الوسائل الطيفيه المختلفه. كذلك تم دراسه و تقييم بعض من المركبات الجديده كمضادات للبكتريا و الخلايا السرطانيه.