A new series of hydrazide-hydrazones based 2-oxonicotinonitriles as antimicrobial agents: Design, synthesis and antimicrobial evaluation

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SUMMARY

Regiospecific alkylation of 2-oxonicotinonitriles **1a,b** with ethyl bromoacetate followed by hydrozinolysis afforded acetic acid hydrazides **3a,b**. The latter compounds were condensed with a variety of carbonyl containing compounds to give the target compounds of hydrazones **4a,b, 5a,b, 6a-h** and **7a,b**. The antimicrobial activity of the new synthesized compounds do not showed activity against tested micro-organisms except compounds **4b, 5c, 5d** and **6b** showed moderate activity towards *B. subtilus*

Keywords: 2-Oxonicotinonitrile; alkylation; acid hydrazide; hydrazide-hydrazone; antimicrobial.

RESUMEN

Alquilación regioespecífica de 2-oxonicotinonitrilos **1a,b** con bromoacetato de etilo seguida de la hidrazinolisis permitida por las hidrazidas de ácido acético **3a,b**. Estos últimos compuestos se condensaban con una variedad de compuestos que contienen carbonilo para dar lugar a los compuestos destinatarios a base de hidrazonas **4a,b, 5a,b, 6a-h** y **7a,b**. La actividad antimicrobiana de los nuevos compuestos sintetizados no era evidente contra los microorganismos analizados a excepción de los compuestos **4b, 5c, 5d** y **6b** que mostraban una actividad moderada hacia el *B. subtilus*.

Palabras clave: 2-Oxonicotinonitrilo; alquilación; hidrazida ácida; hidrazida-hidrazona; antimicrobiana.

RESUM

Alquilació regioespecífica de 2-oxonicotinonitrilos **1a,b** amb bromoacetato de etilo seguida de la hidrazinolisis permès per les hidrazides d'àcid acètic **3a,b**. Aquests últims compostos es condensaven amb una varietat de compostos que tenen carbonil, per donar lloc a compostos "target" a base de hidrazones **4a,b, 5a,b, 6a-h** y **7a,b**. La activitat antimicrobiana dels nous compostos sintetitzats no va aparèixer contra els microorganismes avaluats a excepció dels compostos **4b, 5c, 5d** i **6b** que mostraven una activitat moderada versus el *B. subtilus*

Paraules clau: 2-Oxonicotinonitrilo; alquilació; hidrazida àcida; hidrazida-hidrazona; antimicrobiana.

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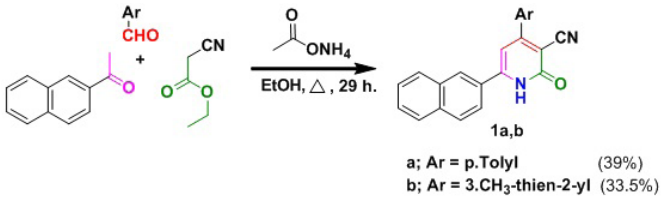
1. INTRODUCTION

2-Oxonicotinonitrile (2-ONN) and its derived compounds are an important class of nitrogen containing heterocyclic systems, which have been undergo to extensive study in the recent years due to their chemical and pharmaceutical interest. Nicotinonitriles have been reported to have antimicrobial[1,2], analgesic, anti-inflammatory, antipyretic[3,4] anticancer[2], cardiotonic[5], antihypertensive[6,7] properities. Another interested biological scaffold is given by hydrazide-hydrazone (CO-NHN=C) system, which are used to improve the biological activity of a main compound. For example, many compounds containing hydrazide-hydrazone moiety posses a wide range of remarkable biological properties such as antimalarial[8], antituberculosis[9], anti-HIV[10], antimicrobial[11,12], anti-inflammatory[13] and anticonvulsant[14,15]. In recent years, our research efforts focused on the synthesis of functionalized pyridines for biological evaluation[1,2,16,17]. Herein, we linked hydrazide-hydrazone moiety to nicotinonitrile ring and investigate the antimicrobial activity of such products.

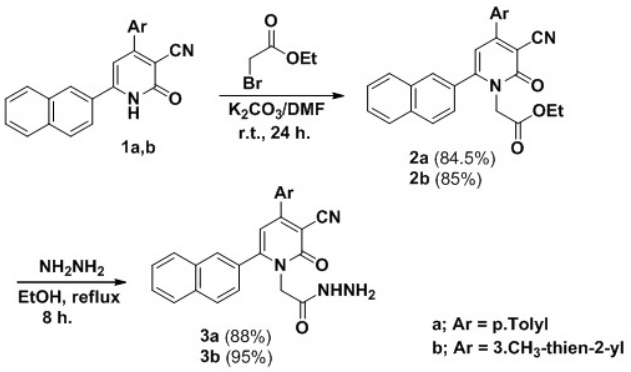
2. RESULTS AND DISCUSSION

2.1. Chemistry

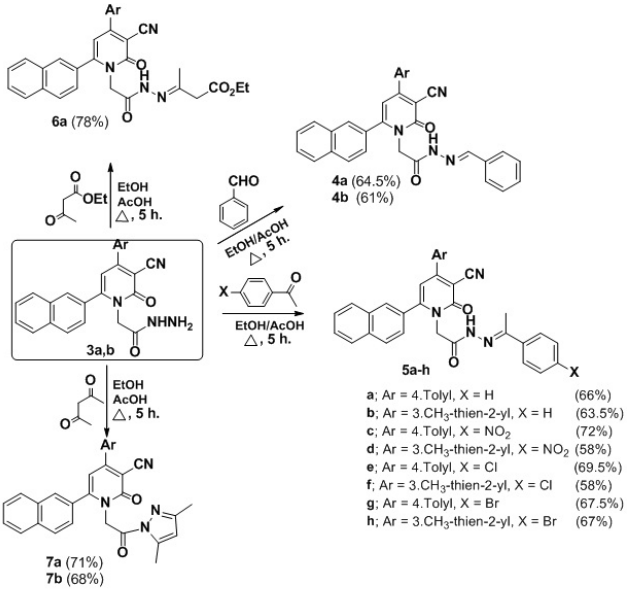
4-Aryl-6-naphth-2-yl-2-oxo-1,2-dihydronicotinonitriles **1a,b** were selected as starting synthon for this research work. Compounds **1a,b** have been synthesized as in literature[2,16] via one pot multicomponent condensation of 2-acetyl naphthalene, aromatic aldehyde (namely, 4-methyl benzaldehyde and 3-methyl thiophene-2-carboxaldehyde), ethyl cyanoacetate and ammonium acetate in refluxing ethanol (Scheme 1). The spectroscopic data and microanalysis were agreed with the assigned structure. Base mediate alkylation of compounds **1a,b** produced compounds **2a,b** (Scheme 2), which identified from IR bands as *N*-alkylated nicotinonitriles. Treatment of **2a,b** with ethanolic solution of hydrazine hydrate under refluxing temperature afforded pyridin-1-yl acetohydrazides **3a,b** (Scheme 2). ^{1}H NMR signals showed presence of acetohydrazide moiety as three singlts at 4.45, 5.06 and 9.53 ppm corresponding to NH_2, CH_2 and NH protons, respectively.



Scheme 1. One-pot four component synthesis of 2-ONN derivatives 1a,b.



Scheme 2. Synthetic route of hydrazides 3a,b.



Scheme 3. Synthetic route of target compounds 4-7.

Scheme 3 illustrates the synthetic routes of target compounds **4-7**. Where, condensation of hydrazides **3a,b** with benzaldehyde, acetophenone, 4-nitroacetophene, 4-chloroacetophenone, 4-bromoacetophenone and ethyl acetoacetate afforded hydrazones **4a,b, 5a-h** and **6a,b**, respectively, in good yield (58-67%). The spectroscopic data and microanalysis were agreed with the assigned structure of these compounds. The ^{1}H NMR of compound **5h** illustrated two singlets at 2.31 and 2.35 ppm for $2CH_3$, in addition to aromatic and NH protons signals in their regions. IR Bands of compound **6a** indicated the ester-carbonyl and amide groups at 1747 and 1664 cm^{-1}, respectively. Its ^{1}H NMR data confirmed that the reaction tookplace at ketonic carbonyl forming the target hydrazone, where ethoxy signals are present at 1.21 and 4.20 ppm as triplet and quartet. Another evidence for this explanation is ^{13}C NMR data, where the ethoxy and ester-carbonyl carbons appeared at 14.20 and 64.45 and 168.4 ppm, respectively, in additon, no signal for ketonic-carbonyl carbon is present.

Finally, condensation of **3a,b** with acetyl acetone gave the unexpected pyrazole derivatives **7a,b** via interamoleculare cyclization reaction. ^{1}H NMR and IR data confirmed the formation of pyrazol ring. (*c.f.* the experimental part) (Scheme 3).

2.2. Antimicrobial activity

The antimicrobial activity of new compounds were investigated using the agar well diffusion method as modified from[18], compared with Cefotaxime as control. For antifungal, Nystatin was used as standaed drug. It is clearly observed that, from the obtained data in Table **1**, all the tested compounds donot showed significant antibacterial and antifungal activities against the mention microorganisms, except compounds **4b, 5c,5d** and **6b** showed moderate antimicrobial activity towrds *B. subtilus*

Table 1: *Antimicrobial activities of some new synthesized compounds (Inhibition zones mm). Diameter (mm) of inhibition zones against the corresponding standard microbial strains*

Copd. No.	Gm (+ve) bacteria		Gm (–ve) bacteria		Fungi
	B. subtilus	B. cereus	P. aeruginosa	E. coli	Aspergillus niger
2a	17	19	24	18	-
2b	15	22	23	18	-
4a	19	30	14	22	-
4b	33	15	16	21	16
5a	23	21	23	18	-
5b	22	14	12	24	-
5c	46	18	22	19	19
5d	35	17	20	17	-
5e	25	20	21	21	20
5f	27	21	20	25	-
5g	30	24	21	18	-
5h	18	21	16	23	-
6a	28	28	19	24	-
6b	34	28	30	31	15
Cefotaxime	32	28	32	34	-
Nystatin	-	-	-	-	20
DMSO	-	-	-	-	-

4. EXPERIMENTAL

General

The elemental analyses were obtained on a Perkin Elmer 240. The mass spectra (Ms) were measured with Shimadzu GCMS-QP 1000 EX mass spectrometer. The IR spectra were acquired in KBr (discs) on a Pye Unicam Sp-3–300 infrared spectrophotometer. The ^{1}H NMR spectra were measured on a Bruker Avance 400 spectrometer at 400.0 MHz and ^{13}C NMR at 100 MHz in Nucleic Acid Center at Zagazig University, Zagazig, Egypt. The chemical shifts were measured relative to DMSO-d_6 proton signal. The melting points were determined on an Electro thermal IA 9100 apparatus and are uncorrected and elemental analyses were carrying at Micro-analysis Center, Cairo University, Cario, Egypt.

General procedure for preparation of pyridin-2-(*1H*)-one-3-carbonitriles (1a,b)

A mixture of 2-acetylnaphthalene (10 mmol), 4-bromoacetophenone (10 mmol), aromatic aldehydes namely (*p*-tolualdehyde and 3-methyl-2-thiophenecarboxaldehyde) (10 mmol), ethyl cyanoacetate (10 mmol), and excess from ammonium acetate (80 mmol), in absolute ethanol (30 mL) was refluxed for 29 h., the reaction mentioned by TLC using (methylene chloride / MeOH 10:1), leave to cooling at room temperature, the formed precipitate was filtered off, washed with ethanol, dried and crystallized from methanol / acetic acid (1:2) ratio.

6-(Naphthalen-2-yl)-2-oxo-4-(*p*-tolyl)-1,2-dihydro-pyridine-3-carbonitrile (1a)

Yellow powder; yield 39%; m. p. 303-305 °C. IR (KBr): 3455 cm^{-1} (NH), 2219 cm^{-1} (C=N) and 1682 cm^{-1} (C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 2.41 (s, 3H, CH_3), 6.96 (s, 1H, pyridone H-5), 7.39 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.63 (m, 4H, A-H), 8.01 (m, 4H, A-H), 8.55 (s, 1H, Ar-H), 12.64 (br, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 20.94 (CH_3), 97.99, 106.5, 116.6, 124.3, 127.0, 127.6, 127.9, 128.1, 128.2, 128.5, 128.8, 129.3, 132.4,133.2, 133.8, 140.4, 151.2, 159.6, 162.1 and 172.0, (C=N, Ar-C and C=O). Anal. Calcd for $C_{23}H_{16}N_2O$ (336.39): C, 82.12; H, 4.79; N, 8.33. Found: C, 82.07; H, 4.82; N, 8.29.

4-(3-Methylthien-2-yl)-6-(naphthalen-2-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (1b)

Yellow powder; yield 33.5%; m. p. 283-285 °C. IR (KBr): 3442 cm^{-1} (NH), 2217 cm^{-1} (C=N) and 1640 cm^{-1} (C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 2.32 (s, 3H, CH_3), 6.95 (s, 1H, pyridone H-5), 7.13 (d, 1H, *J* = 4.80 Hz, thiophene), 7.63 (m, 2H, Ar-H), 7.79 (d, 1H, *J* = 4.80 Hz, thiophene), 8.03 (m, 4H, Ar-H), 8.53 (s, 1H, Ar-H), 12.92 (s, 1H, NH), ^{13}C NMR (DMSO-d_6): δ = 15.20 (CH_3), 116.2, 124.2, 127.0.127.6, 127.9, 128.1, 128.2, 128.5, 128.9, 131.0, 131.1, 132.3, 133.8, 138.1, 160.2 (C=N, Ar-C and C=O). Anal. Calcd for $C_{21}H_{14}N_2OS$ (342.41): C, 73.66; H, 4.12; N, 8.18. Found: C, 73.72; H, 4.16; N, 8.21.

General procedure for synthesis of compounds 2a,b

A mixture of pyridin-2-(1*H*)-one-3-carbonitriles **1a,b** (10 mmol) and (11 mmol) potassium carbonate or potassium hydroxide was stirred in dry DMF (20 mL) for 1h, followed by the addition of ethyl bromoacetate (10 mmol), the reaction mixture was stirred at room temperature for 24 h., then poured into ice-water to give the crude product as precipitate, which in turn was filtered off and dried. The product was crystallized from methanol.

Ethyl 2-(3-cyano-6-(naphthalen-2-yl)-2-oxo-4-(*p*-tolyl)pyridin-1(*2H*)-yl)acetate (2a)

White powder; yield 84.5%; m. p. 180 °C. IR (KBr): 2214 cm^{-1} (CN), 1747 cm^{-1} (C=O, acetoxy), 1636 cm^{-1} (C=O, amide) and 1137 cm^{-1} (-O-, ether). ^{1}H NMR (DMSO-d_6): δ = 1.22 (t, 3H, *J* = 6.90 Hz, CH_3CH_2O), 2.43 (s, 3H, CH_3), 4.33 (q, 2H, *J* = 7.20 Hz, NCH_2CH_3), 5.22 (s, 2H, OCH_2CO), 7.42 (d, 2H, *J* = 7.10 Hz, Ar-H), 7.59 (m, 2H, Ar-H), 7.69 (d, 2H, *J* = 8.10 Hz, Ar-H), 7.96-8.02 (m, 4H, Ar-H), 8.28 (d, 1H, *J* = 6.80 HZ, Ar-H), 8.80 (s, 1H, Ar-H). Anal. Calcd for $C_{27}H_{22}N_2O_3$ (422.48): C, 76.76; H, 5.25; N, 6.63. Found: C, 76.69; H, 5.29; N, 6.58.

Ethyl 2-(3-cyano-4-(3-methylthien-2-yl)-6-(naphthalen-2-yl)-2-oxo-pyridin-1*(2H)*-yl)acetate (2b)

Pale brown powder; yield 85%; m. p. 160-162 °C. IR (KBr): 2220 cm^{-1} (C=N), 1740 cm^{-1} (C=O, ester) and 1635 cm^{-1} (C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 1.22 (t, 3H, *J* = 6.90 Hz, CH_3CH_2), 2.31 (s, 3H, CH_3),

4.22 (q, 2H, *J* = 6.90 Hz, $C\underline{H}_2CH_3$), 5.21 (s, 2H, NCH_2C=O), 7.16 (d, 1H, *J* = 5.10 Hz, thiophene-H), 7.60 (m, 2H,Ar-H), 7.80 (d,1H, *J* = 5.15 Hz, thiophene-H), 7.98-8.06 (m, 4H, Ar-H and pyridine-H) and 8.24 (d,1H, *J* = 8.70 Hz, Ar-H) 8.80 (s, 1H, Ar-H). Anal. Calcd for $C_{25}H_{20}N_2O_3S$ (428.50): C, 70.07; H, 4.70; N, 6.54. Found C, 70.00; H, 4.67; N, 6.49.

General procedure for synthesis of acid hydrazide 3a,b

The ester **2a,b** (10 mmol) was added to hydrazine hydrate (99%) (20 mmol) in absolute ethanol (20 mL) and refluxed for 8 h, and followed by TLC. The reaction mixture was concentrated and cooling, the precipitate obtained was filtered off, dry, crystallized from ethanolto give **3a,b**.

2-(3-Cyano-6-(naphthalen-2-yl)-2-oxo-4-(*p*-tolyl)pyridin-1(*2H)*-yl)acetohydrazide (3a): Yellow powder; yield 88%; m. p. 210-215 °C. IR (KBr): 3283 cm^{-1} (br, NH and NH_2), 2216 cm^{-1} (CN) and 1664 cm^{-1} (2C=O, amide). ^1H NMR (DMSO-d_6): δ = 1.84 (s, 2H, NH_2, exchange with D_2O), 2.42 (s, 3H, CH_3), 5.04 (s, 2H, NCH_2CO), 7.42 (d, 2H, *J* = 8.10 Hz, Ar-H), 7.59 (m, 2H, Ar-H), 7.70 (d, 2H, *J* = 8.10 Hz, Ar-H), 7.99-8.04 (m, 4H, Ar-H), 8.30 (d, 1H, *J* = 6.80 Hz, Ar-H), 8.88 (s, 1H, Ar-H), 9.68 (s, 1H, NH). Anal. Calcd for $C_{25}H_{20}N_4O_2$ (408.45): C, 73.51; H, 4.94; N, 13.72. Found: C, 73.57; H, 4.88; N, 13.68.

2-(3-Cyano-4-(3-methylthien-2-yl)-6-(naphthalen-2-yl)-2-oxo-pyridin-1(*2H*)-yl)acetohydrazide (3b): Yellow powder; yield 95%; m. p. 200-202 °C. IR (KBr): 3436, 3281 cm^{-1} (NH, NH_2) 2213 cm^{-1} (C=N), 1658 cm^{-1} (2C=O, amide). ^1H NMR (DMSO-d_6): δ = 2.31 (s, 3H, CH_3, thiophene), 4.45 (s, 2H, NH_2), 5.06 (s, 2H, NCH_2CO), 7.15 (d,1H, *J* = 4.80 Hz, thiophene-H) 7.57 (m, 2H, Ar-H), 7.80 (d, 1H, *J* = 4.80 Hz, thiophene-H), 7.92-8.09 (m, 4H, Ar-H and pyridine-H), 8.28 (d, 1H, *J* = 8.8 Hz, Ar-H), 8.83 (s, 1H, Ar-H) and 9.53 (s, 1H, NH). Anal. Calcd for $C_{23}H_{18}N_4O_2S$ (414.48): C, 66.65; H, 4.38; N, 13.52. Found C, 66.72; H, 4.43; N, 13.47.

General procedure for synthesis of acid hydrazide 4a,b, 5a-h, 6a,b and 7a,b

A mixture of compounds **3a,b** (10 mmol) and appropriate amount of ethyl actoacetate, acetophenone, *p*-nitroacetophenone, 4-chloroacetophenone, 4-bromoacetophenone, benzaldehyde and acetyl acetone (20 mmol) in absolute ethanol (20 mL) and acetic acid (4 mL) was refluxed for 5h., after cooling, the separated solid was filtered off; dry and crystallized from methanol.

(N'-Benzylidene-2-(3-cyano-6-(naphthalen-2-yl)-2-oxo-4-(*p*-tolyl)pyridin-1(*2H*)-yl)acetohydrazide (4a)

Brown powder; yield 64.5%; m. p. 293-240 °C. IR (KBr): 3382 cm^{-1} (NH), 2214 cm^{-1} (C=N), 1678 cm^{-1} (br, 2C=O, amide) and 1580 cm^{-1} (CH=N). ^1H NMR (DMSO-d_6): δ = 2.42 (s, 3H, CH_3), 5.68 (s, 2H NCH_2CO), 7.38-7.47(m, 6H, Ar-H), 7.65 (m, 2H, Ar-H), 7.72 (d, 2H, $_J$ = 8.10 Hz, Ar-H), 7.79 (m, 2H, Ar-H), 7.95 (m, 2H, Ar-H), 8.01 (s, 1H, Ar-H), 8.16 (s, 1H, NH), 8.24 (d, 1H, *J* = 6.80 Hz, Ar-H), 8.26 (s, 1H, Ar-H), 8.38 (s,1H, CH=N). ^{13}C NMR (DMSO-d_6): δ = 20.48 (CH_3), 63.68 (NCH_2), 91.92, 92.00, 114.2, 114.4, 115.4, 124.0, 126.9, 127.6, 128.7, 128.8, 129.5, 132.6, 132.7, 132.9, 133.0, 140.1, 142.5, 144.0, 145.1, 156.6, 163.4, 165.2, 168.0, 169.1, 172.0 and 174.1 (Ar-C, C=N and 2C=O). Anal. Calcd for $C_{32}H_{24}N_4O_2$ (496.54): C, 77.40; H, 4.87; N, 11.82. Found: C, 77.33; H, 4.90; N, 11.76.

N'-Benzylidene-2-(3-cyano-4-(3-methylthien-2-yl)-6-(naphthalen-2-yl)-2-oxopyridin-1(*2H*)-yl)acetohydrazide (4b)

Brown powder; yield 61%; m. p. 230 °C. IR (KBr): 3198 cm^{-1} (NH), 2218 Cm^{-1} (C=N), 1674 cm^{-1} (2C=O, amide). ^1H NMR (DMSO-d_6): δ = 2.32 (s, 3H, CH_3), 5.18 (s, 2H, NCH_2CO), 5.70 (s, 1H, CH=N), 7.16 (d, 1H, *J* = 5.20 Hz, thiophene-H), 7.43-8.40 (m, 13H, Ar-H and pyridine-H), 8.80 (s, 1H, Ar-H) and 11.82 (s, 1H, NH). Anal. Calcd for $C_{30}H_{22}N_4O_2S$ (502.59): C, 71.69; H, 4.41; N, 11.51. Found C, 71.75; H, 4.38; N, 11.56.

2-(3-Cyano-6-(naphthalen-2-yl)-2-oxo-4-(*p*-tolyl)pyridin-1(*2H*)-yl)-N'-(1-phenylethylidene) acetohydrazide (5a)

Yellow powder; yield 66%; m. p. 220-221 °C. IR (KBr): 3340 cm^{-1} (NH), 2220 cm^{-1} (C=N) and 1663 cm^{-1} (br, 2C=O, amide). ^1H NMR (DMSO-d_6): δ = 2.37 (CH_3), 2.42 (CH_3), 5.64 (s,2H, NCH_2CO), 7.37-7.45 (m, 6H, Ar-H), 7.71 (d, 2H, *J* = 8.10 Hz, Ar-H), 7.74 (m, 1H, Ar-H), 7.80 (d, 1H, *J* = 7.90 Hz, Ar-H), 7.88-7.93 (m, 4H, Ar-H), 8.01 (s, 1H, NH), 8.24 (d, 2H, *J* = 6.80 Hz, Ar-H), 8.76 (s, 1H, Ar-H). Anal. Calcd for $C_{33}H_{26}N_4O_2$ (510.21): C, 77.63; H, 5.13; N, 10.97. Found: C, 77.57; H, 5.10; N, 11.01.

2-(3-Cyano-4-(3-methylthien-2-yl)-6-(naphthalen-2-yl)-2-oxo-pyridin-1(*2H)*-yl)-N'-(1-phenylethylidene)acetohydrazide (5b)

Yellow powder; yield 63.5%; m. p. 110-113 °C. IR (KBr): 3431 cm^{-1} (NH), 2221 cm^{-1} (C=N), 1692 cm^{-1} (2C=O, amide). ^1H NMR (DMSO-d_6): δ = 2.31, 2.37 (2s, 6H, $2CH_3$), 5.70 (s, 2H, NCH_2CO) 7.16 (d, 1H, *J* = 5.50 Hz, thiophene-H), 7.39-7.95 (m, 12H, Ar-H, and pyridine-H), 8.23 (d, 1H, *J* = 8.50 Hz, Ar-H), 8.75 (s, 1H, Ar-H), 11.07 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 13,7, 15.3 ($2CH_3$), 64.3 (NCH_2CO), 93.6 ($NCCH_3$), 115.0, 115.4, 115.7, 124.0, 124.1, 126.1, 126.3, 127.0, 127.4, 127.6, 128.0, 128.5, 128.9, 129.3, 131.0, 132.4, 133.0, 133.5, 138.0, 148.6, 149.9, 152.1, 156.6, 163.3, 169.5, (C=N, Ar-C and 2C=O). Anal. Calcd for $C_{31}H_{23}N_4O_2S$ (516. 61): C, 72.07; H, 4.68; N, 10.85. Found C, 72.01; H, 4.71; N, 10.82.

2-(3-Cyano-6-(naphthalen-2-yl)-2-oxo-4-(*2-oxonicotinonitriles* tolyl)pyridin-1(*2H*)-yl)-N'-(1-(4-nitrophenyl)ethylidene) acetohydrazide (5c)

Yellow powder; yield 72%; m. p. 232-234 °C. IR (KBr): 3349 cm^{-1} (NH), 2218 cm^{-1} (C=N) and 1687 cm^{-1} (br, 2C=O, amide). ^1H NMR (DMSO-d_6): δ = 2.42 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 5.74 (s, 2H, NCH_2CO), 7.42 (d, 2H, *J* = 8.10 Hz, Ar-H), 7.71 (d, 2H, *J* = 7.50 Hz, Ar-H), 7.93 (d, 2H, *J* = 8.50 HZ, Ar-H), 8.01 (s, 1H, NH), 8.16 (m, 4H, Ar-H), 8.25 (m, 4H, Ar-H), 8.34 (d, 2H, *J* = 7.00 Hz, Ar-H). Anal. Calcd for $C_{33}H_{25}N_5O_4$ (555.58): C, 71.34; H, 4.54; N, 12.61. Found: C, 71.28; H, 4.58; N, 12.56.

2-(3-Cyano-4-(3-methylthien-2-yl)-6-(naphthalen-2-yl)-2-oxopyridin-1(*2H*)-yl)-*N'*-(1-(4-nitrophenyl)ethylidene)acetohydrazide (5d)

Yellow powder; yield 58%; m. p. 130 °C. IR (KBr): 3432 cm^{-1} (NH), 2213 cm^{-1} (C=N), 1699 Cm^{-1} (2C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 2.31, 2.42 (2s, 6H, $2CH_3$), 5.75 (s, 1H, NCH_2CO), 7.16 (d, 1H, *J* = 5.0 Hz, thiophene-H), 7.51-8.27 (m, 11H, Ar-H, pyridine and thiophene-H), 8.39 (d, 1H, *J* = 8.50 Hz, Ar-H), 8.75 (s, 1H, Ar-H) and 11.33 (s,1H, NH). Anal. Calcd for $C_{31}H_{23}N_5O_4S$ (561.61): C, 66.30; H, 4.13; N, 12.47. Found C, 66.24; H, 4.16; N, 12.51.

***N'*-(1-(4-Chlorophenyl)ethylidene)-2-(3-cyano-6-(naphthalen-2-yl)-2-oxo-4-(*p*-tolyl)pyridin-1(*2H*)-yl)acetohydrazide (5e)**

White powder; yield 69.5%; m. p. 260-261 °C. IR (KBr): 3431 cm^{-1} (NH), 2221 cm^{-1} (C=N) and 1698 cm^{-1} (2C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 2.35 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 5.70 (s, 2H, NCH_2CO), 7.43 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.48-7.57 (m, 4H, Ar-H), 7.71 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.81 (m, 1H, Ar-H), 7.92 (m, 2H, Ar-H), 8.00 (s, 1H, NH), 8.10 (m,1H, Ar-H), 8.23 (d, 1H, *J* = 6.60 Hz, Ar-H), 8.25 (d, 1H, *J* = 6.80 Hz, Ar-H), 8.75 (s, 1H, Ar-H), 8.81 (s, 1H, Ar-H). Anal. Calcd for $C_{33}H_{25}BrN_4O_2$ (545.03): C, 72.72; H, 4.62; N, 10.28. Found: C, 72.66; H, 4.59; N, 10.33.

***N'*-(1-(4-Chlorophenyl)ethylidene)-2-(3-cyano-4-(3-methylthien-2-yl)-6-(naphthalen-2-yl)-2-oxopyridin-1(*2H*)-yl)acetohydrazide (5f)**

Yellow powder; yield 58%; m. p. 200-203 °C. IR (KBr): 3434 cm^{-1} (NH), 2219 cm^{-1} (C=N), 1691 cm^{-1} (2C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 2.31, 2.36 (2s, 6H, $2CH_3$), 5.71 (s, 2H, NCH_2CO), 7.16 (d, 1H, *J* = 5.50 Hz, thiophene-H), 7.48-7.94 (m, 11H, Ar-H, pyridine-H and thiophene-H), 8.20 (d, 1H, *J* = 8.50 Hz, Ar-H), 8.75 (s, 1H, Ar-H), 11.14 (s, 1H, NH). Anal. Calcd for $C_{31}H_{23}ClN_4O_2S$ (551.06): C, 67.57; H, 4.21; N, 10.17. Found C, 67.50; H, 4.18; N, 10.21.

***N'*-(1-(4-Bromophenyl)ethylidene)-2-(3-cyano-6-(naphthalen-2-yl)-2-oxo-4-(*p*-tolyl)pyridin-1(*2H*)-yl)acetohydrazide (5g)**

White powder; yield 67.5%; m. p. 270-272 °C. IR (KBr): 3431 cm^{-1} (NH), 2219 cm^{-1} (C=N) and 1697 cm^{-1} (2C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 2..95 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 5.70 (s, 2H, NCH_2CO), 7.42 (d, 2H, *J* = 8.00 Hz, Ar- H), 7.56 (m, 2H, Ar-H), 7.63 (d, 2H, *J* = 8.50 Hz, Ar-H), 7.72 (d, 2H, *J* = 9.50 Hz, Ar-H), 7,85 (d, 2H, *J* = 10.0 Hz, Ar-H), 7.92 (m, 1H, Ar-H), 8.01 (s, 1H, NH), 8.53 (m, 1H, Ar-H), 8.23 (d, 1H, *J* = 6.80 Hz, Ar-H), 8.25 (d, 1H, *J* = 6.70 Hz, Ar-H), 8.75 (s, 1H, Ar-H), 8.81 (s, 1H, Ar-H). Anal. Calcd for $C_{33}H_{25}BrN_4O_2$ (589.48): C, 67.24; H, 4.27; N, 9.50. Found: C, 67.18; H, 4.30; N, 9.54.

***N'*-(1-(4-Bromophenyl)ethylidene)-2-(3-cyano-4-(3-methylthien-2-yl)-6-(naphthalen-2-yl)-2-oxopyridin-1(*2H*)-yl)acetohydrazide (5h)**

Brown powder; yield 67%; m. p. 210-212 °C. IR (KBr): 3426 cm^{-1} (NH), 2215 cm^{-1} (C=N), 1693 cm^{-1} (2C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 2.31, 2.35 (2s, 6H, $2CH_3$), 5.69 (s, 2H, $N\underline{C}H_2CO$), 8.21 (d, 1H, *J* = 8.50 Hz, Ar-H), 8.74 (s, 1H, Ar-H) and 11.04 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 13,68, 14.94 ($2CH_3$), 64.27 (NCH_2CO), 93.75 ($NCCH_3$), 114.1, 115.0, 115.2, 117.3, 126.0, 126.8, 127.0, 127.6, 128.2, 128.6, 129.3, 131.4, 133.0, 135.0, 137.1, 138.9, 146.8, 147.5, 149.9, 152.2, 155.6, 157.7, 162.5, 163.3, 169.6 (C=N, Ar-C and 2C=O). Anal. Calcd for $C_{31}H_{23}BrN_4O_2S$ (595.51): C, 62.52; H, 3.89; N, 9.41. Found C, 62.56; H, 3.92; N, 9.37.

Ethyl3-(2-(2-(3-cyano-6-(naphthalen-2yl)-2-oxo-4-(*p*-tolyl)pyridin-1*(2H)*-yl)acetylhydrazono) butanoate (6a)

White powder; yield 78%; m. p. 225-226 °C. IR (KBr): 3425 cm^{-1} (NH), 2215 cm^{-1} (C=N), 1747 cm^{-1} (C=O, ester), 1664 cm^{-1} (2C=O, amide) and 1146 cm^{-1} (-O-, ether). ^{1}H NMR (DMSO-d_6): δ = 1.21 (t, 3H, *J* = 7.0 Hz, CH_3CH_2O), 2.39 (s, 3H, CH_3) 2.42 (s, 3H, CH_3), 4.20 (q, 2H, *J* = 6.50 Hz, $NC\underline{H}_2CH_3$), 5.22 (s, 2H, CH_2CO), 5..70 (s, 2H, OCHCO), 7.34 (d,2H, *J* = 7.50 Hz, Ar-H), 7.59 (m, 2H, Ar-H), 7.70 (d, 2H, *J* = 8.0 Hz, Ar-H), 8.0 (s, 1H, NH), 8.30 (m, 2H, Ar-H), 8.32 (d, 1H, *J* = 10.0 Hz, Ar-H), 8.83 (s, 1H, Ar-H), 9.52 (s, 1H, Ar-H). ^{13}C NMR (DMSO-d_6): δ = 14.20, 20.94 ($3CH_3$), 60.79 (CH_2CO), 63.79 (NCH_2), 64.45 (OCH_2CO), 91.92, 92.30, 114.3, 114.6, 115.1, 115.4, 125.2, 127.2, 127.6, 128.4, 128.5, 129.4, 134.1, 134.6, 140.0, 140.2, 156.4, 156.7, 163.0, 163.3, 166.8 and 168.4 (C=N, Ar-C and 3C=O). Anal. Calcd for $C_{31}H_{28}N_4O_4$ (520.58): C, 71.52; H, 5.42; N, 10.76. Found: C, 71.45; H, 5.46; N, 10.80.

1-(2-(3,5-Dimethyl-*1H*-pyrazol-1-yl)-2-oxoethyl)-6-(naphthalen-2-yl)-2-oxo-4-(*p*-tolyl)-1,2-dihydropyridine-3-carbonitrile (7a)

Brown powder; yield 71%; m. p. 120-130 °C. IR (KBr): 2221 cm^{-1} (CN), 1699 cm^{-1},1656 cm^{-1} (2C=O, amide) and 1145 cm^{-1} (-O-, ether). ^{1}H NMR (DMSO-d_6): δ = 2.10 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.44 (s, 3H,CH_3), 5.42 (s, 2H, NCH_2CO), 7.42 (d, 2H, *J* = 8.10 Hz, Ar-H), 7.60 (m, 2H, Ar-H), 7.72 (d,2H, *J* = 8.10 Hz, Ar-H), 7.99-8.04 (m, 4H, Ar-H), 8.72 (d, 1H, *J* = 6.80 Hz, Ar-H), 8.80 (s, 1H, Ar-H). Anal. Calcd for $C_{30}H_{24}N_4O_2$ (472.54): C, 76.25; H, 5.12; N, 11.86. Found: C, 76.32; H, 5.08; N, 11.91.

1-(2-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-oxo) ethyl)-4-(3-methylthien-2-yl)-6-(naphthalen-2-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (7b)

Brown powder; yield 68%; m. p. 100-103 °C. IR (KBr): 2222 cm^{-1} (C=N), 1653 cm^{-1} (2C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 2.11 (s, 3H, CH_3), 2.31 (s, 6H, $2CH_3$), 5.16 (s, 2H, NCH_2CO), 7.16 (d, 1H, *J* = 3.80 Hz, thiophene-H), 7.60 (m, 2H, Ar-H), 7.80 (d, 1H, *J* = 4.80 Hz, thiophene-H), 7.97-8.29 (m, 4H, Ar-H and pyridine-H), 8.24 (d, 1H, *J* = 9.2 Hz, Ar-H) and 8.80 (s, 1H, Ar-H), Anal. Calcd for $C_{28}H_{22}N_4O_2S$ (478.56): C, 70.34; H, 4.59; N, 11.59. Found C, 70.27; H, 4.52; N, 11.65.

CONCLUSIONS

A new series of some hydrazide-hydrazones based nicotinonitrile were synthesized from available reagents. The new compounds donot have antimicrobial acitivity against the tested micro-organisms except compounds **4b, 5c, 5d** and **6b** showed moderate activity against *B. subtilus.*

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