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Design and Synthesis of Hydrazide-Hydrazones Based 2-Oxonicotinonitrile Derivatives as Potential Antimicrobial Agents

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Abstract: Synthesis and antimicrobial screening of new series of hydrazide-hydrazones were described. Where, regiospacific alkylation of 2-oxonicotinonitriles1a,b with ethyl bromoacetate followed by hydrozinolys is afforded acetic acid hydrazides3a,b. The latter compounds were condensed with a variety of carbonyl containing compounds to give the target compounds of hydrazide- hydrazone derivatives 4a,b, 5a,b and6a-h. While, reaction of 3 a,b with acetyl acetone gave pyrazole derivatives7a,b. The antimicrobial activity of the new synthesized compounds 4b, 5c, 5e and 6bshowed a good activity against tested fungi (Aspergillus niger), while, all the tested compounds have a good and moderate activity against G (+ve) and G (-ve) bacteria.
Keywords: 2-Oxonicotinonitrile, Hydrazide-hydrazone, Antimicrobial.

1 Introduction

Nicotinonitrile and its derived compounds are an important class of nitrogen containing heterocyclic system, which have been undergo to extensive study in the recent years due to their chemical and pharmaceutical importance. Nicotinonitriles have been reported to have antimicrobial [1,2], anti-analgesic, anti inflammatory, antipyretic [3,4] anticancer [2], cardiotonic [5], antihypertensive [6,7] prosperities. Another interested biological scaffold is given by hydrazide-hydrazones (CO-NHN=C) system, which are used to improve the biological activity of a main compound. Recently, many compounds containing hydrazide-hydrazone moiety posses a wide range of remarkable biological prosperities 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 synthesis of functionalized pyridines for biological evaluation [1,2,16, 17]. Herein, we introduce hydrazide-hydrazone moiety to pyridine ring system and study the antimicrobial of the products.

2 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-(1*H*)-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.

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.	G (+ve) bacteria		G (–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	-	-	-	-	-

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 H N OS (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(2*H*)-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(2*H*)-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, CH_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(2*H*)-yl)acetohydrazide(3a): Yellow powder; yield 88%; m. p. 210-215 ^oC. 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(2*H*)-yl)acetohydrazide (3b): Yellow powder; yield 95%; m. p. 200-202 ^oC. 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(2*H*)-yl)acetohydrazide (4a): Brown powder; yield 64.5%; m. p. 293-240 ^oC. 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(2*H*)-yl) acetohydrazide (4b)**: Brown powder; yield 61%; m. p. 230 ^oC. 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(2*H*)-yl)-*N*'-(1-phenylethylidene)aceto-hydrazide (5a): Yellow powder; yield 66%; m. p. 220-221 ^oC. 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 (s, 3H, CH_3), 2.42 (s, 3H, 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(2*H*)-yl)-*N*'-(1-phenylethylidene)-acetohydrazide (5b): Yellow powder; yield 63.5%; m. p. 110-113 ^oC. 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 ($N=CCH_3$), 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-(*p*-tolyl)pyridin-1(2*H*)-yl)-*N*'-(1-(4-nitrophenyl)ethylidene)acetohydrazide (5c): Yellow powder; yield 72%; m. p. 232-234 ^oC. 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(2*H*)-yl)-*N*'-(1-(4-nitrophenyl)-ethylidene)acetohydrazide (5d): yellow powder; yield 58%; m. p. 130 ^oC. IR (KBr): 3432 cm^{-1} (NH), 2213 cm^{-1} (C≡N), 1699 cm^{-1} (2C=O, amide). ^1H 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(2*H*)-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(2*H*)-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(2*H*)-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(2*H*)-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<u>C</u>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 (N=CCH_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.

Ethyl 3-(2-(2-(3-cyano-6-(naphthalen-2-yl)-2-oxo-4-(*p*-tolyl)pyridin-1(2*H*)-yl)acetyl)hydrazono)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, O<u>C</u>H_2CH_3), 5.22 (s, 2H, CH_2CO), 5..70 (s, 2H, NCH_2CO), 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_2), 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-1*H*-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.

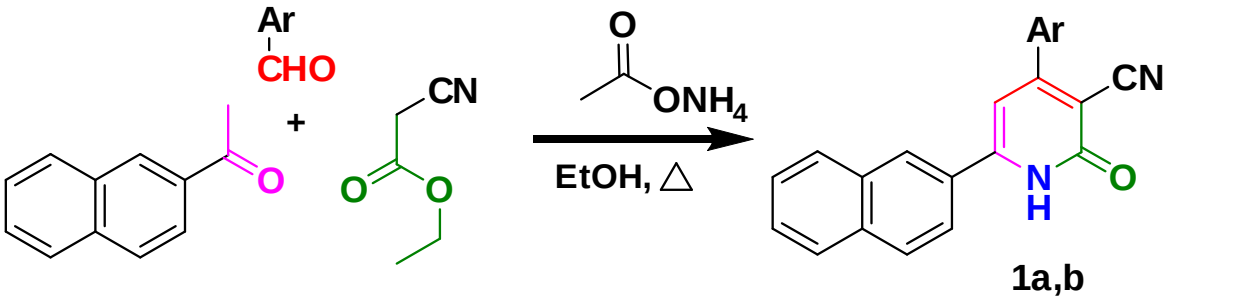
1-(2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-oxo)ethyl)-4-(3-methylthien-2-yl)-6-(naphthalen-2-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (7b): Brown powder; yield 68%; m. p. 100-103 °C. IR (KBr): 2222 cm^{-1} (C≡N), 1653 cm^{-1} (2C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 2.11 (s, 3H, CH_3), 2.31 (s, 6H, $2CH_3$), 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.

3 Results and Discussion

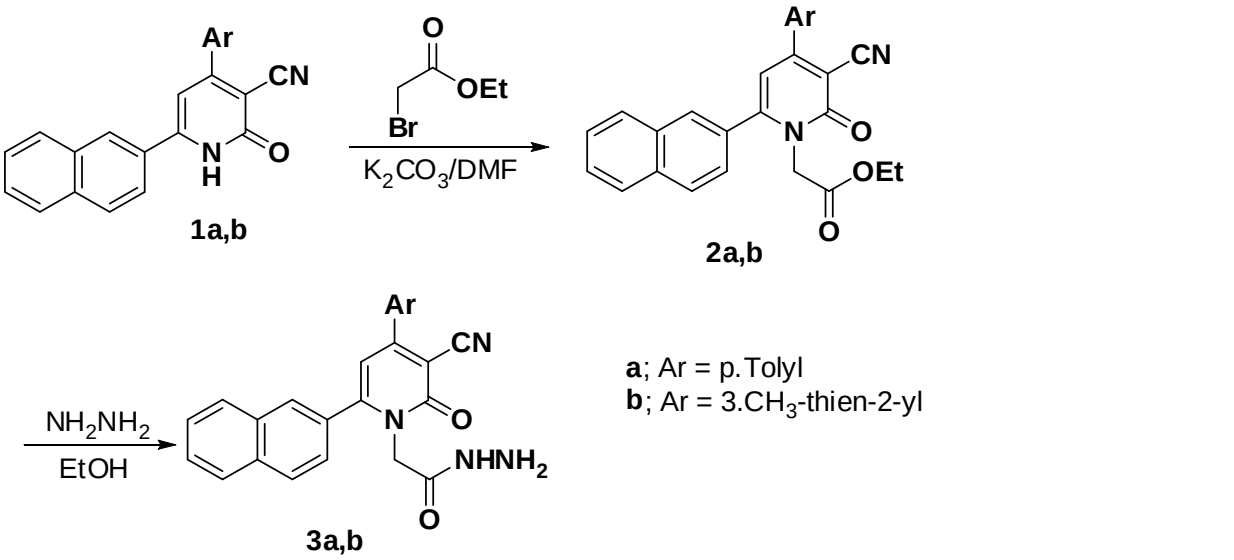
3.1 Chemistry

4-Aryl-6-naphth-2-yl-2-oxo-1,2-dihydronicotinonitrile **1a,b** were selected as starting synthon for this research work. They were synthesized as reported method [2,16] via one

pot multi component condensation of 2-acetyl naphthalene, aromatic aldehydes (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 *N*-alkylated estercompounds **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 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** indicate the ester-carbonyl and amide groups at 1747 and 1664 cm^{-1}, respectively. Its [1]H NMR data confirmed that the reaction took place at ketonic carbonyl and not the ester group forming the target hydrazone, where ethoxy signals are present at 1.21 and 4.20 ppm as triplet and quartet. Another 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.



Scheme 2.

Scheme 3 illustrates the synthetic routes of target compounds **4-7**. Where, the 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. Where [1]H NMR of

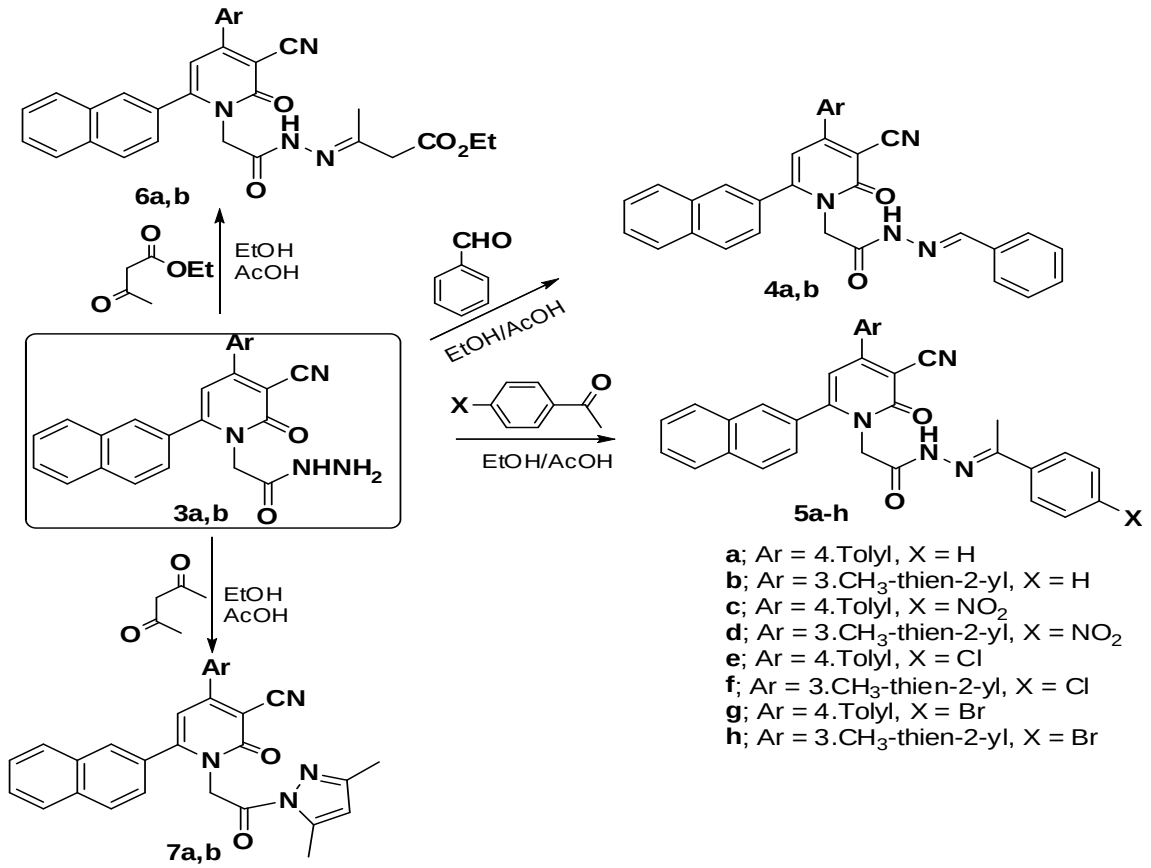
Evidence for this explanation is [13]C NMR data, where the ethoxy and ester-carbonyl carbons appeared at 14.20 and 64.45 and 168.4 ppm, respectively, in addition to, no signal for ketonic-carbonyl carbon present.

Finaly, condensation of **3a,b** with acetyl acetone gave the unexpected pyrazole derivative **7a,b** via intermolecular cyclization reaction. [1]H NMR and IR data confirmed formation of the pyrazole ring. Where, no NH and ketonic

carbonyl bands present in its IR, in addition, no NH signal present in their ^{1}H NMR(Scheme 3).

3.2 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 showeda good and moderate activity against G (+ve) *B. Subtilus, B .*



a; Ar = 4.Tolyl, X = H
b; Ar = 3.CH_3-thien-2-yl, X = H
c; Ar = 4.Tolyl, X = NO_2
d; Ar = 3.CH_3-thien-2-yl, X = NO_2
e; Ar = 4.Tolyl, X = Cl
f; Ar = 3.CH_3-thien-2-yl, X = Cl
g; Ar = 4.Tolyl, X = Br
h; Ar = 3.CH_3-thien-2-yl, X = Br

Scheme 3.

Cereus, and G (+ve)*P. aeruginosa*, *E. coli*, whlie, compounds 4b, 5c, 5d and 6a showed the significant activity against G (+ve) *B. Subtilus* more than the control. Compounds **4b, 5c,5e** and **6b** showed a good effects against Fungi *Aspergillus niger*.

4 Conclusions

A new series of some hydrazide-hydrazones based nicotinonitrile were synthesized from available reagents.

The antimicrobial activity of the new synthesized compounds 4b, 5c, 5e and 6a showed a good activity against tested fungi (Aspergillus niger), while, all the tested compounds have a good and moderate activity against G (+ve) and G (-ve) bacteria.

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