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ORIGINAL PAPER

Utility of 2-furan-2-yl-4-mercapto-6-methylpyrimidine-5-carbonitrile as a precursor for the synthesis of some novel pyrimidines: antibacterial activity

Atef M. Abdel Hamid[1] · **W. Shehta**[1]

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Abstract
The starting material 2-furan-2-yl-4-mercapto-6-methylpyrimidine-5-carbonitrile **3** was reacted with various reagents resulting in the formation of a group of new pyrimidines and condensed pyrimidines including quinazoline **6** tetrazolopyrimidine **12**, pyrazolopyrimidines **14, 18**, and **19**, triazolopyrimidine **16**, and pyrimidopyridazine **20**. The antibacterial activity was evaluated for a group of the synthesized compounds against examples of Gram-positive and Gram-negative bacteria.

Keywords Pyrazolopyrimidine · Triazolopyrimidine · Pyrimidopyridazine · Cyclocondensation · Antibacterial

Introduction

The chemistry of pyrimidines still attracts the attention and interest of researchers around the world because of their wide applications, especially in the therapeutic field. The literature survey showed that a wide range of pharmacological activities are exhibited by the compounds containing pyrimidine nucleus in their structures, for example, pyrimidines are used for antibacterial [1–3] (Fig. 1), antifungal [4, 5], anti-allergic [6], diuretic, antitumor, anti-HIV, and cardiovascular [7], anticonvulsant [8], antileishmanial [9], antihistaminic [10], antidiabetic [11], anti-inflammatory [12], analgesic [13], antihypertensive [14], antipyretic [15], antiviral [16], antioxidant [17], and anticancer activities [18, 19]. In the light of these reports, we have synthesized some new pyrimidines and evaluated the antibacterial activity for a group of the synthesized compounds against examples of Gram-positive and Gram-negative bacteria.

Results and discussion

As a part of our interest in the synthesis and biological evaluation of new heterocyclic compounds [20, 21], we have synthesized some new pyrimidines using the starting material 2-furan-2-yl-4-mercapto-6-methylpyrimidine-5-carbonitrile **3** which was synthesized by heterocyclization of 2-furoyl isothiocyanate **1** with 3-aminocrotononitrile **2** [22]. The behavior of compound **3** towards benzylidene malononitrile was investigated under different basic conditions, thus reaction of **3** with benzylidene malononitrile in refluxing ethoxide solution did not give the expected thiopyranopyrimidine derivative **4** but instead, it gave 5-ethoxypyrimidine derivative **5** as a sole product. The ^{1}H NMR of **5** showed a triplet at $\delta = 1.06$ ppm and a quartet at $\delta = 3.45$ ppm for OCH_2CH_3 substituent. The formation of **5** may proceed via the initial addition of SH function to the olefinic double bond of benzylidene malononitrile affording *S*-alkyl adduct intermediate which was subjected to the nucleophilic attack of ethoxide ion resulting in displacement of S-alkyl substituent to afford 6-ethoxypyrimidine **5** (Scheme 1).

When the previous reaction was carried out under the catalytic effect of piperidine, quinazoline derivative **6** was obtained. The ^{1}H NMR spectrum of **6** confirmed its structure based on the following data:

1. Disappearance of CH_3 signal.
2. Appearance of a broad singlet at $\delta = 3.47$ ppm for NH_2.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13738-018-1464-2) contains supplementary material, which is available to authorized users.

✉ Atef M. Abdel Hamid
atefmohamed40@yahoo.com

[1] Department of Chemistry, Faculty of Science, Zagazig University, Zagazig 44519, Egypt

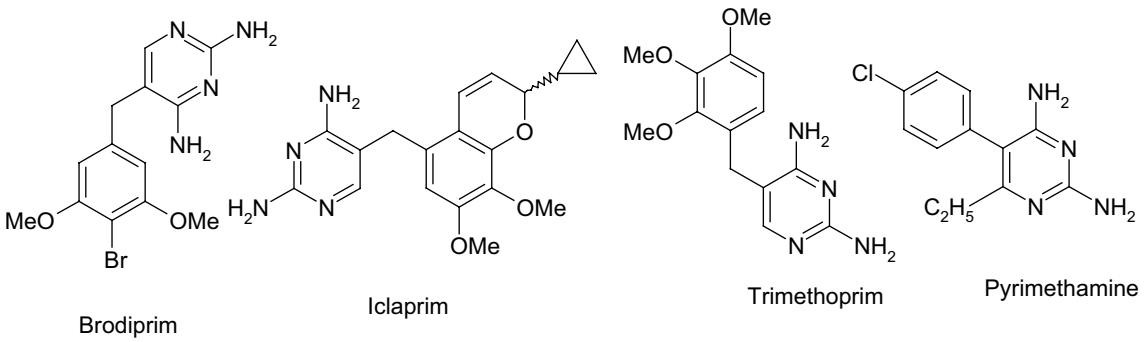
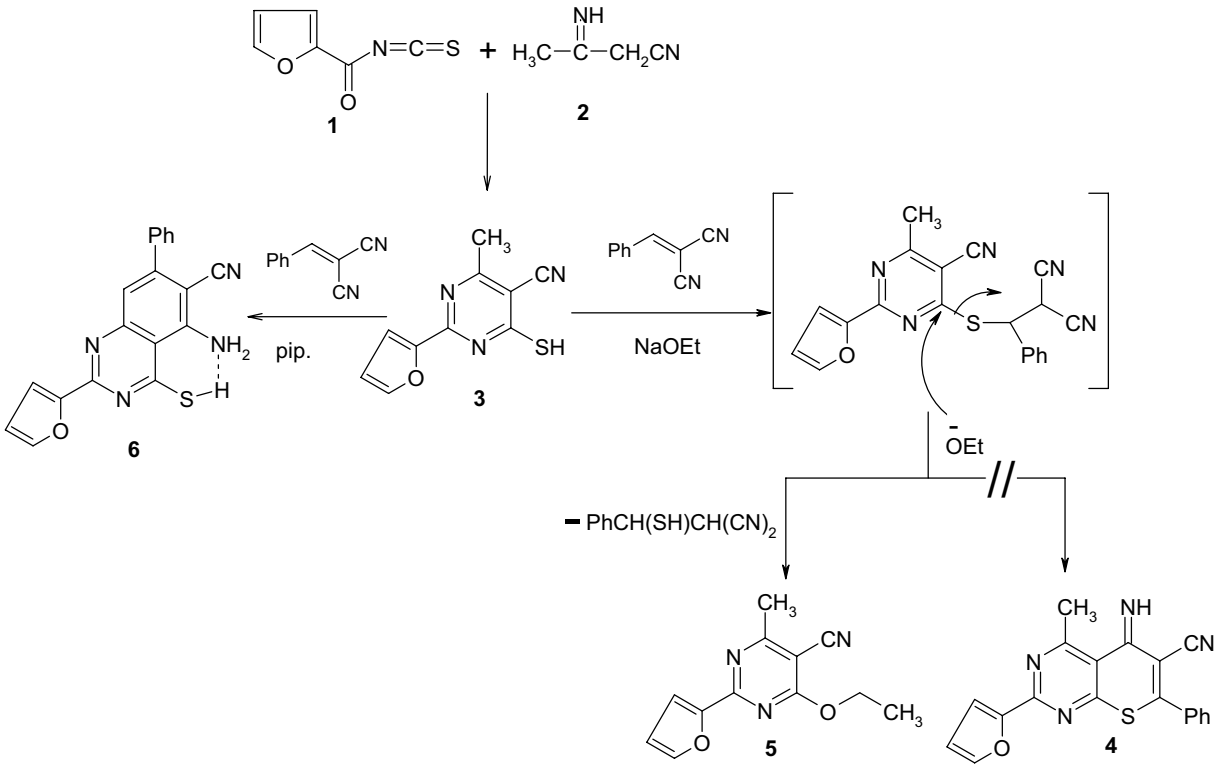


Fig. 1 Antibacterial drugs containing pyrimidines



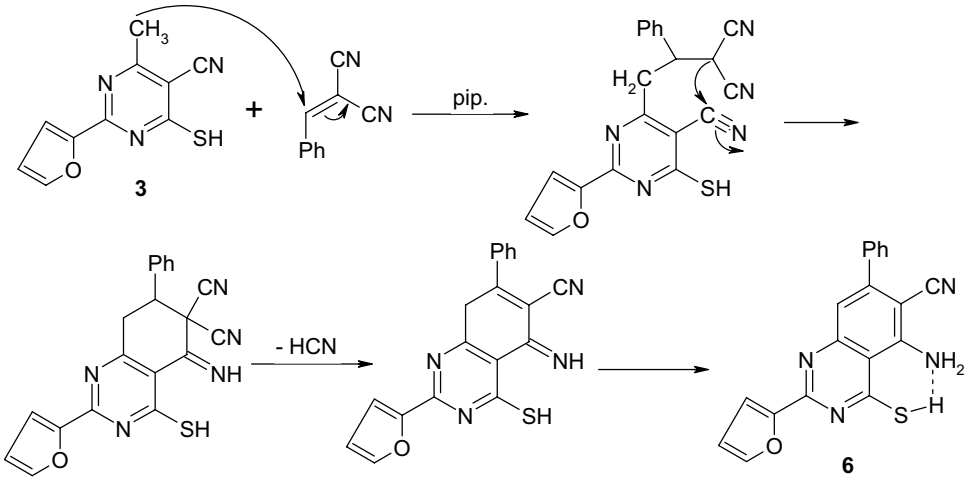
Scheme 1 Reaction of compound **3** with benzylidene malononitrile under different basic conditions

3. The SH signal appeared highly deshielded at $\delta = 14.53$ ppm which indicated that the SH proton is involved in an intramolecular H-bonding with the neighboring NH_2 group.

The formation of compound **6** may proceed via the initial Michael-type addition of the methyl group in position 4 to the double bond of benzylidene malononitrile, followed by an intermolecular cycloaddition to the cyano function and subsequent elimination of HCN to give **6** (Scheme 2).

Hydrolysis of pyrimidine thione **3** afforded pyrimidone **7** whose IR spectrum showed an absorption band at $\upsilon = 1651$ cm^{-1} for C=O and its ^{1}H NMR revealed a singlet at $\delta = 13.52$ ppm for NH. Compound **7** was chlorinated with phosphorous oxychloride to give 5-chloropyrimidine **8**. IR spectrum of **8** showed disappearance of C=O band, and its ^{1}H NMR showed disappearance of NH signal. Methylation of pyrimidine thione **3** with methyl iodide gave methyl thiopyrimidine derivative **9**. The ^{1}H NMR of **9** showed a singlet at $\delta = 2.69$ ppm for SCH_3. Hydrazinolysis of **9** gave a mixture of two products, the major product was identified to be the expected 2-furan-2-yl-4-hydrazinopyrimidine **10**, and the minor product was identified to be 2-pyridazin-3-yl-4-hydrazinopyrimidine

Scheme 2 Proposed mechanism for formation of compound **6**



11. The structure of **10** was confirmed based on the following data:

1. ^{1}H NMR of **10** showed two broad singlets at $\delta = 4.75$ and 9.31 ppm for NH_2 and NH, respectively.
2. Mass spectrum of **10** showed a molecular ion peak at $m/z = 215$.
3. Treatment of **10** with nitrous acid gave tetrazolopyrimidine **12** which is identical with that synthesized by treatment of chloropyrimidine **8** with sodium azide.

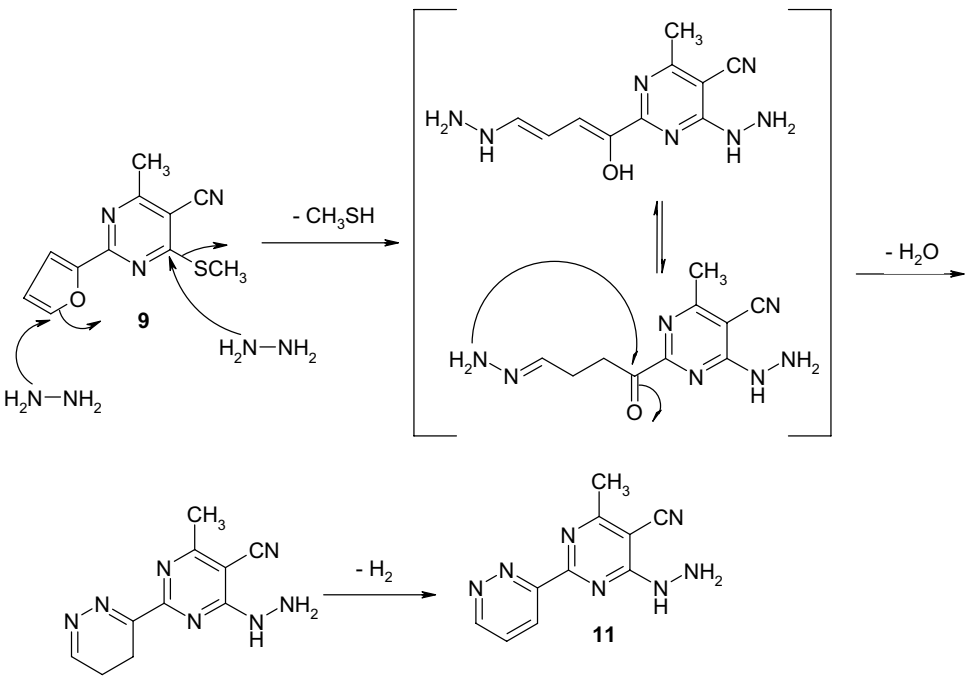
The structure of **11** was confirmed by its spectral data; ^{1}H NMR of **11** showed two broad singlets at $\delta = 4.73$ and 9.27 ppm for NH_2 and NH, respectively. Its mass spectrum showed a molecular ion peak at $m/z = 227$.

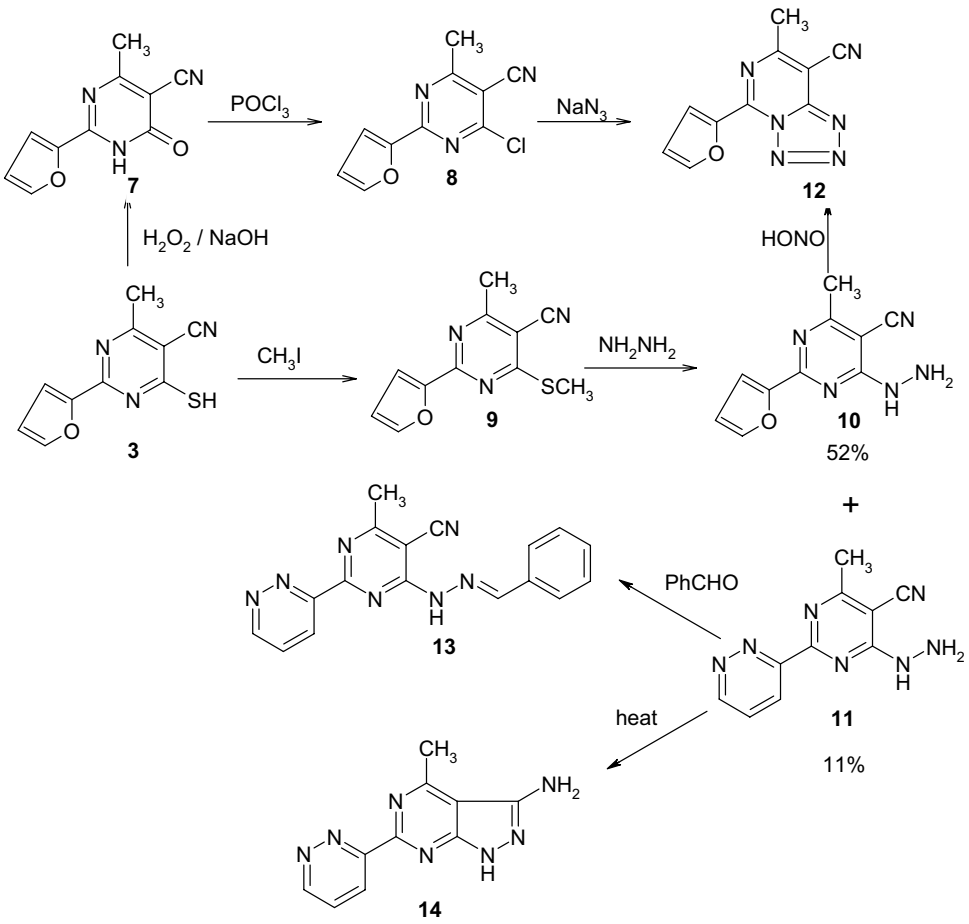
Compound **11** may be formed from **9** by ring transformation via attack of two molecules of NH_2NH_2 leading to displacement of methylthio group and ring opening of furan ring, and this was followed by an intramolecular cyclocondensation and subsequent loss of H_2 to give **11** (Scheme 3).

Treatment of hydrazinopyrimidine **11** with benzaldehyde afforded the hydrazone **13**. ^{1}H NMR of **13** revealed a singlet at $\delta = 12.38$ ppm for NH, and the NH_2 signal disappeared. Heating of compound **11** in sodium ethoxide solution gave the corresponding pyrazolopyrimidine **14**. IR spectrum of **14** showed disappearance of the cyano band, and its ^{1}H NMR spectrum showed two broad singlets at $\delta = 5.60$ and 12.40 ppm for NH_2 and NH, respectively (Scheme 4).

The reactivity of 2-furan-2-yl-5-hydrazinopyrimidine **10** was investigated towards various reagents, thus the

Scheme 3 Proposed mechanism for the formation of compound **11**





Scheme 4 Synthesis of 2-furan-2-yl-4-hydrazinopyrimidine **10** and 2-pyridazin-3-yl-4-hydrazinopyrimidine **11**

cyclocondensation of **10** with acetylacetone yielded 6-pyrazolylpyrimidine **15**. ^{1}H NMR of **15** showed three singlets at $\delta = 2.24$, 2.68, and 2.73 ppm for three methyl groups and a singlet at $\delta = 6.31$ ppm for the pyrazole-H. Also, heating of **10** with triethyl orthoformate afforded triazolopyrimidine **16**. ^{1}H NMR of **15** showed a singlet at $\delta = 8.88$ ppm for the triazole-H.

Reaction of **10** with acetic anhydride did not give the expected triazolopyrimidine **17**, but it gave *N*-acetyl aminopyrazolopyrimidine **18**. This result was proved by IR spectrum of **18** which revealed disappearance of C≡N and appearance of a C=O band at 1669 cm^{-1}, also ^{1}H NMR of **18** showed three singlets at $\delta = 2.13$, 10.34, and 13.68 ppm for $COCH_3$ and two NH, respectively. Similarly, when compound **10** was condensed with phthalic anhydride, it gave pyrazolopyrimidine **19**. IR of **19** indicated disappearance of C≡N and appearance of C=O. ^{1}H NMR of **19** showed a highly deshielded singlet at $\delta = 14.47$ ppm for NH which may be involved in an intramolecular H-bonding. The cyclocondensation of **10** with 2-chlorobenzaldehyde in presence of catalytic amount of piperidine yielded pyrimidopyridazine **20**. IR of **20** showed disappearance of C≡N, whereas its ^{1}H NMR showed two NH signals at $\delta = 9.49$ and 13.89 ppm. Compound **20** may be formed by initial formation of the hydrazone which underwent an intramolecular cycloaddition to the cyano function followed by rearrangement to give **20** which is thermodynamically stable by the extended conjugation present in the compound (Scheme 5). Finally, the condensation of **10** with isatin afforded the hydrazone **21**. ^{1}H NMR of **21** revealed two NH signals at $\delta = 11.33$ and 13.00 ppm (Scheme 6).

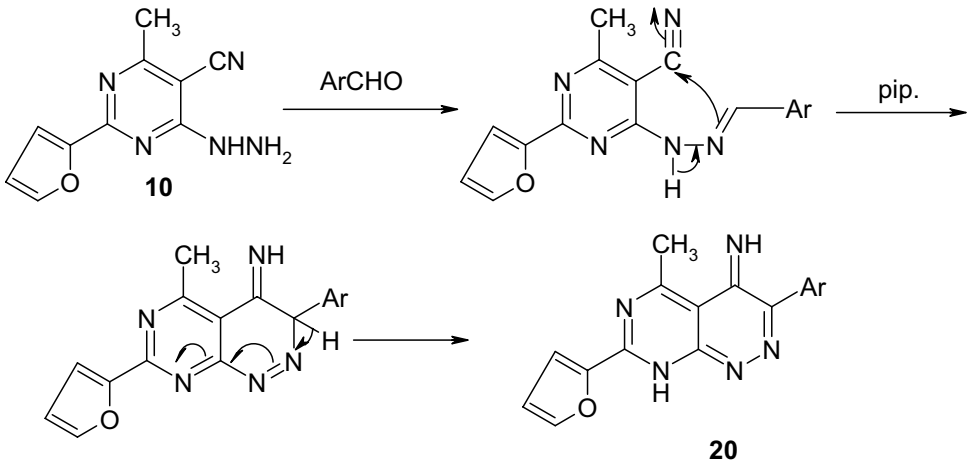
Antibacterial activity

Compounds **5, 7, 8, 9, 10, 11** and **14** were tested in vitro for antibacterial activity against Gram-positive bacteria (*Bacillus subtilis, Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*) using disc diffusion method [23] at 1 mg/ml disc concentration. Ciprofloxacin was used as antibacterial agent standard. DMSO was used as solvent. The zone of inhibition of bacterial growth was observed.

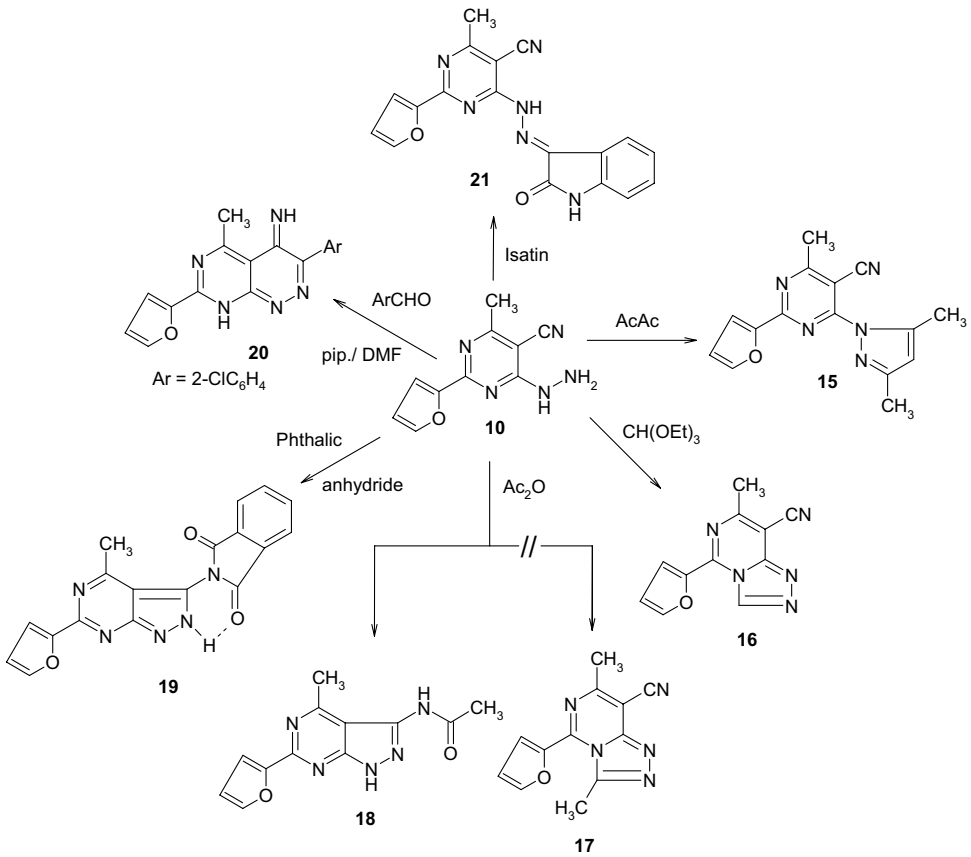
The results given in Table 1 indicated that:

1. Compounds **5, 10** and **11** have high antibacterial activity against the tested microorganisms.

Scheme 5 Proposed mechanism for formation of compound **20**



Scheme 6 Reactivity of 2-furan-2-yl-4-hydrazinopyrimidine **10** towards various reagents



2. Compounds **7** and **8** have moderate antibacterial activity against the tested microorganisms.
3. Compounds **9** and **14** have no antibacterial activity against the tested microorganisms.

Experimental

All melting points are uncorrected. IR spectra (KBr) were run

Table 1 In vitro antibacterial activity for a group of the synthesized compounds

Sample	Inhibition zone diameter (mm/mg sample)			
	Bacterial species			
	G+		G−	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*
Control: DMSO	0.0	0.0	0.0	0.0
Standard ciprofloxacin	19	22	28	24
5	23	26	23	20
7	14	16	14	14
8	12	11	12	11
9	0.0	0.0	0.0	0.0
10	22	23	24	21
11	22	23	25	23
14	0.0	0.0	0.0	0.0

on a Unicam SP 1200G infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra (DMSO-d6) were run on a Bruker spectrometer (400 MHz) with a TMS as internal standard. Elemental analyses and in vitro antimicrobial activities were carried out at Micro Analytical Center, Cairo University. Compound **3** was prepared by the procedure described in the literature [22].

4-Ethoxy-2-(furan-2-yl)-6-methylpyrimidine-5-carbonitrile (5)

A mixture of **3** (0.01 mol) and benzylidene malononitrile (0.01 mol) in sodium ethoxide solution (50 ml) was refluxed for 3 h, cooled then poured into cold water and neutralized with dil. HCl. The solid formed was filtered off, dried and recrystallized from ethanol to give **5** as yellow crystals. m.p. = 250–252 °C, Yield: 71%. IR (KBr) υ_{max}: 2222 (C≡N), 1596 (C=N) cm$^{-1.}$ ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.06 (t, 3H, $OCH_2\underline{CH_3}$), 2.72 (s, 3H, CH_3), 3.46 (q, 2H, $O\underline{CH_2}CH_3$), 6.84–8.16 (m, 3H, furan-H). ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 23.9 (CH_3), 39.3, 40.6 (OCH_2CH_3), 110.7, 149.7, 168.8, 182.9 (pyrimidine carbons), 114.1, 120.2, 144.7, 148.5 (furan carbons), 116.4 (C≡N). MS: *m/z* = 229 (M^+), 228 (M^+–H), 214 (M^+–CH_3), 200 (M^+–CH_2CH_3), 184 (M^+–OCH_2CH_3). Anal. Calc. for $C_{12}H_{11}N_3O_2$ (229.24): C, 62.87; H, 4.84; N, 18.33; Found: C, 62.74; H, 4.69; N, 18.41.

5-Amino-2-(furan-2-yl)-4-mercapto-7-phenylquinazoline-6-carbonitrile (6)

A mixture of **3** (0.01 mol) and benzylidene malononitrile (0.01 mol) in absolute ethanol (50 ml) and 3 drops of piperidine was refluxed for 4 h, cooled then poured into cold water. The solid formed was filtered off, dried and recrystallized from ethanol to give **6** as orange crystals. m.p. = 278–280 °C, Yield: 82%. IR (KBr) υ_{max}: 3107, 3021 (NH_2), 2217 (C≡N), 1592 (C=N) cm$^{-1.}$ ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.48 (s, br., 2H, NH_2), 6.85–8.22 (m, 9H, furan-H + phenyl-H + quinazoline-H), 14.53 (s, 1H, SH). ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 108.2, 136.5, 144.1, 145.1, 148.4, 149.6, 160.6, 183.2 (quinazoline carbons), 114.0, 120.1, 121.9, 129.1 (furan carbons), 129.3, 129.7, 131.4, 134.9, (phenyl carbons) 115.9 (C≡N). Anal. Calc. for $C_{19}H_{12}N_4OS$ (344.40): C, 66.26; H, 3.51; N, 16.27; Found: C, 66.34; H, 3.42; N, 16.19.

2-(Furan-2-yl)-1,6-dihydro-4-methyl-6-oxopyrimidine-5-carbonitrile (7)

Compound **3** (0.01 mol) was dissolved in a solution of NaOH (20 ml, 5%), then H_2O_2 (60 ml) was added and the mixture was stirred for 1 h. The solid obtained after neutralization with HCl was filtered off, dried and recrystallized from ethanol to give **7** as white crystals. m.p. = 228–230 °C, Yield: 43%. IR (KBr) υ_{max}: 3429 (NH), 2223 (C≡N), 1651(C=O), 1591 (C=N) cm$^{-1.}$ ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.70 (s, 3H, CH_3), 6.81–8.12 (m, 3H, furan-H), 13.52 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 23.8 (CH_3), 97.4, 150.3, 160.8 (pyrimidine carbons), 113.9, 118.9, 145.5, 149.1 (furan carbons), 115.7 (C≡N), 172.8 (C=O). Anal. Calc. for $C_{10}H_7N_3O_2$ (201.19): C, 59.70; H, 3.51; N, 20.89; Found: C, 59.57; H, 3.62; N, 20.96.

4-Chloro-2-(furan-2-yl)-6-methylpyrimidine-5-carbonitrile (8)

A mixture of **7** (0.01 mol) and $POCl_3$ (15 ml) was heated gently under reflux for 3 h, cooled and poured into crushed ice. The solid formed was filtered off, dried and recrystallized from ethanol to give **7** as brown crystals.

m.p. = 164–166 °C, Yield: 81%. IR (KBr) υ_{max}: 2220 (C≡N), 780 (C–Cl) cm$^{-1.}$ ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.70 (s, 3H, CH_3), 6.81–8.11 (m, 3H, furan-H).^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 23.7 (CH_3), 97.3, 150.2, 156.8, 162.0 (pyrimidine carbons), 113.9, 118.9, 145.5, 149.3 (furan carbons), 115.6 (C≡N). Anal. Calc. for $C_{10}H_6ClN_3O$ (219.63): C, 54.69; H, 2.75; N, 19.13; Found: C, 54.51; H, 2.83; N, 19.21.

2-(Furan-2-yl)-4-methyl-6-(methylthio)pyrimidine-5-carbonitrile (9)

A mixture of **3** (0.01 mol), K_2CO_3 (0.01 mol), and CH_3I (0.01 mol) in DMF (15 ml) was stirred at room temperature for 3 h, then the reaction mixture was poured into cold water

and the solid formed was filtered off, dried and recrystallized from ethanol to give **9** as pale brown crystals.

m.p. = 170–172 °C, Yield: 76%. IR (KBr) υ_{max}: 2208 (C≡N), 1585 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.58 (s, 3H, CH_3), 2.69 (s, 3H, SCH_3), 6.78–8.06 (m, 3H, furan-H). ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 12.8, 23.5 (2 CH_3), 102.0, 155.8, 170.0, 173.2 (pyrimidine carbons), 113.6, 117.9, 148.3, 150.9 (furan carbons), 115.0 (C≡N). MS: *m/z* = 231 (M^+), 230 (M^+–H), 216 (M^+–CH_3), 184 (M^+-SCH_3). Anal. Calc. for $C_{11}H_9N_3OS$ (231.28): C, 57.13; H, 3.92; N, 18.17; Found: C, 57.04; H, 3.81; N, 18.09.

2-(Furan-2-yl)-4-hydrazinyl-6-methylpyrimidine-5-carbonitrile (10) and 4-hydrazinyl-6-methyl-2-(pyridazin-3-yl)pyrimidine-5-carbonitrile (11)

A mixture of **9** (0.01 mol) and hydrazine hydrate (2 ml) in ethanol (30 ml) was heated under reflux for 5 h. the solid formed on hot was filtered off, dried and recrystallized from *n*-butanol to give **10** as pale yellow crystals. The mother liquor was poured into water and the solid formed was filtered off, dried and recrystallized from ethanol to give **11** as brown crystals.

Compound (10)

m.p. = 194–196 °C, Yield: 52%. IR (KBr) υ_{max}: 3324, 3241 (NH_2, NH), 2205 (C≡N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.51 (s, 3H, CH_3), 4.75 (s, br., 2H, NH_2), 6.69–7.93 (m, 3H, furan-H), 9.31 (s, br., 1H, NH) .^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 23.6 (CH_3), 84.8, 156.8, 162.9, 171.2 (pyrimidine carbons), 113.0, 117.2, 146.8, 151.8 (furan carbons), 115.9 (C≡N). MS: *m/z* = 215 (M^+), 214 (M^+–H), 200 (M^+–CH_3), 199 (M^+–NH_2), 184 (M^+–$NHNH_2$), 67 (furan-2-yl). Anal. Calc. for $C_{10}H_9N_5O$ (215.22): C, 55.81; H, 4.22; N, 32.54; Found: C, 55.69; H, 4.15; N, 32.63.

Compound (11)

m.p. = 186–188 °C, Yield: 11%. IR (KBr) υ_{max}: 3325, 3244 (NH_2, NH), 2206 (C≡N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.46 (s, 3H, CH_3), 4.73 (s, br., 2H, NH_2), 6.68–7.91 (m, 3H, pyridazine-H), 9.27 (s, br., 1H, NH) .^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 23.5 (CH_3), 84.8, 156.8, 162.4, 170.8 (pyrimidine carbons), 112.7, 113.0, 146.8, 151.7 (pyridazine carbons), 115.9 (C≡N). MS: *m/z* = 227 (M^+), 226 (M^+–H), 212 (M^+–CH_3), 211 (M^+–NH_2), 196 (M^+–$NHNH_2$), 79 (pyridazin-3-yl). Anal. Calc. for $C_{10}H_9N_7$ (227.23): C, 52.86; H, 3.99; N, 43.15; Found: C, 52.79; H, 3.87; N, 43.21.

5-(Furan-2-yl)-7-methyltetrazolo[1,5-f]pyrimidine-8-carbonitrile (12)

Method (a)

A solution of $NaNO_2$ (0.01 mol) in H_2O (5 ml) was added drop wise to a cold solution of **10** (0.01 mol) in acetic acid (20 ml). The mixture was stirred for 1 h then poured into cold water and the solid formed was filtered off, dried and recrystallized from ethanol to give **12** as pale brown crystals.

Method (b)

A mixture of **8** (0.01 mol) and NaN_3 (0.01 mol) in acetic acid (20 ml) was heated under reflux for 3 h. the reaction mixture was cooled then poured into cold water and the solid formed was filtered off, dried and recrystallized from ethanol.

m.p. = 174–176 °C, Yield: 67%. IR (KBr) υ_{max}: 2219 (C≡N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.85 (s, 3H, CH_3), 6.79–8.08 (m, 3H, furan-H). ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 23.7 (CH_3), 93.6, 164.1, 173.1, 173.3 (pyrimidine carbons), 113.8, 148.6, 150.2, 156.7 (furan carbons), 118.4 (C≡N). MS: *m/z* = 226 (M^+), 225 (M^+–H), 211 (M^+–CH_3), 199 (M^+–HCN). Anal. Calc. for $C_{10}H_6N_6O$ (226.20): C, 53.10; H, 2.67; N, 37.15; Found: C, 53.19; H, 2.75; N, 37.04.

4-(2-Benzylidenehydrazinyl)-6-methyl-2-(pyridazin-3-yl)pyrimidine-5-carbonitrile (13)

A mixture of **11** (0.01 mol) and benzaldehyde (0.01 mol) in ethanol acid (30 ml) was heated under reflux for 3 h. the reaction mixture was cooled and the solid formed was filtered off, dried and recrystallized from ethanol to give **13** as white crystals.

m.p. = 206–208 °C, Yield: 72%. IR (KBr) υ_{max}: 3313 (NH), 2206 (C≡N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.59 (s, 3H, CH_3), 6.72–8.17 (m, 9H, pyridazine-H + phenyl-H + N=CH), 12.38 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 24.0 (CH_3), 86.0, 156.6, 160.1, 173.3 (pyrimidine carbons), 127.7, 129.2, 130.4, 134.8 (phenyl carbons), 113.2, 116.2, 147.1, 151.3 (pyridazine carbons), 117.3 (C≡N), 145.4 (N=CH). Anal. Calc. for $C_{17}H_{13}N_7$ (315.34): C, 64.75; H, 4.16; N, 31.09; Found: C, 64.84; H, 4.09; N, 31.03.

4-Methyl-6-(pyridazin-3-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-amine (14)

Compound **11** (0.01 mol) in sodium ethoxide solution (20 ml) was heated under reflux for 3 h. the reaction mixture

was cooled, poured into cold water, then neutralized with dil. AcOH. The solid formed was filtered off, dried and recrystallized from ethanol to give **14** as orange crystals.

m.p. = 218–220 °C, Yield: 64%. IR (KBr) υ_{max}: 3119, 3011 (NH_2, NH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.73 (s, 3H, CH_3), 5.60 (s, br., 2H, NH_2), 6.68–7.99 (m, 3H, pyridazine-H), 12.40 (s, br., 1H, NH). Anal. Calc. for $C_{10}H_9N_7$ (227.23): C, 52.86; H, 3.99; N, 43.15; Found: C, 52.93; H, 3.91; N, 43.06.

2-(Furan-2-yl)-4-methyl-6-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyrimidine-5-carbonitrile (15)

A mixture of **10** (0.01 mol) and acetylacetone (0.01 mol) in *n*-butanol (30 ml) was heated under reflux for 6 h. the reaction mixture was cooled and the solid formed was filtered off, dried and recrystallized from *n*-butanol to give **15** as white crystals.

m.p. = 166–168 °C, Yield: 81%. IR (KBr) υ_{max}: 2216 (C≡N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.24 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 6.31 (s, 1H, pyrazole-H), 6.80–8.08 (m, 3H, furan-H) .^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 13.9 (CH_3), 14.9 (CH_3), 24.4 (CH_3), 95.4, 156.1, 157.9, 174.8 (pyrimidine carbons), 111.9, 113.8, 143.7, 148.4 (furan carbons), 115.7, 150.7, 151.9 (pyrazole carbons), 117.9 (C≡N). MS: *m/z* = 279 (M^+), 278 (M^+–H), 264 (M^+–CH_3), 252 (M^+–HCN). Anal. Calc. for $C_{15}H_{13}N_5O$ (279.30): C, 64.51; H, 4.69; N, 25.07; Found: C, 54.60; H, 4.58; N, 25.13.

5-(Furan-2-yl)-7-methyl-[1, 2, 4] triazolo[4,3-f] pyrimidine-8-carbonitrile (16)

Compound **10** (0.01 mol) in triethyl orthoformate (50 ml) was heated under reflux for 6 h. the solid formed on hot was filtered off, dried and recrystallized from ethanol to give **16** as brown crystals.

m.p. = 230–232 °C, Yield: 45%. IR (KBr) υ_{max}: 2223 (C≡N), 1597 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.79 (s, 3H, CH_3), 6.99–8.33 (m, 3H, furan-H), 8.88 (s, 1H, triazole-H).^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 23.5 (CH_3), 93.7, 156.5, 160.1, 161.9 (pyrimidine carbons), 121.1, 124.3, 145.4, 152.3 (furan carbons), 139.8 (triazole carbon), 114.6 (C≡N). MS: *m/z* = 225 (M^+), 224 (M^+–H), 198 (M^+–HCN). Anal. Calc. for $C_{11}H_7N_5O$ (225.21): C, 58.67; H, 3.13; N, 31.10; Found: C, 58.73; H, 3.04; N, 31.17.

N-(6-(Furan-2-yl)-4-methyl-1*H*-pyrazolo[3,4-d] pyrimidin-3-yl)acetamide (18)

Compound **10** (0.01 mol) in acetic anhydride (30 ml) was heated under reflux for 8 h, then the reaction mixture was cooled and poured into crushed ice. The solid formed was filtered off, dried and recrystallized from ethanol to give **18** as white crystals.

m.p. > 300 °C, Yield: 51%. IR (KBr) υ_{max}: 3428, 3253 (NH), 1669 (C=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.13 (s, 3H, $COCH_3$), 2.65 (s, 3H, CH_3), 6.72–7.93 (m, 3H, furan-H), 10.34 (s, 1H, NH), 13.68 (s, 1H, NH).^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 22.3 (CH_3), 23.1 (CH_3), 107.5, 154.2, 154.9, 163.9 (pyrimidine carbons), 112.9, 114.3, 139.8, 146.2 (furan carbons), 152.4 (pyrazole carbon), 171.2 (C=O). Anal. Calc. for $C_{12}H_{11}N_5O_2$ (257.25): C, 56.03; H, 4.31; N, 27.22; Found: C, 56.12; H, 4.25; N, 27.18.

2-(6-(Furan-2-yl)-4-methyl-2*H*-pyrazolo[3,4-d] pyrimidin-3-yl)isoindoline-1,3-dione (19)

A mixture of **10** (0.01 mol) and phthalic anhydride (0.01 mol) in acetic acid (50 ml) was heated under reflux for 6 h. the reaction mixture was cooled and the solid formed was filtered off, dried and recrystallized from DMF to give **19** as pale brown crystals.

m.p. > 300 °C, Yield: 61%. IR (KBr) υ_{max}: 3323 (NH), 1786, 1731 (C=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.73 (s, 3H, CH_3), 6.73–8.11 (m, 7H, furan-H + isoindoline-H), 14.47 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 22.2 (CH_3), 107.9, 154.7, 155.4, 163.3 (pyrimidine carbons), 113.1, 115.1, 135.9, 146.6 (furan carbons), 152.1 (pyrazole carbon), 124.7, 131.6, 133.1 (isoindoline carbons), 167.2 (C=O). Anal. Calc. for $C_{18}H_{11}N_5O_3$ (345.32): C, 62.61; H, 3.21; N, 20.28; Found: C, 62.55; H, 3.13; N, 20.37.

3-(2-Chlorophenyl)-7-(furan-2-yl)-5-methylpyrimido [4,5-c]pyridazin-4(8*H*)-imine (20)

A mixture of **10** (0.01 mol), 2-chlorobenzaldehyde (0.01 mol), and catalytic amount of piperidine in DMF (30 ml) was heated under reflux for 6 h. the reaction mixture was cooled and the solid formed was filtered off, dried and recrystallized from DMF to give **20** as yellow crystals.

m.p. = 296–298 °C, Yield: 76%. IR (KBr) υ_{max}: 3433, 3159 (NH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.91 (s, 3H, CH_3), 6.74–8.58 (m, 7H, furan-H + 2-chlorophenyl-H), 9.49 (s, 1H, NH), 13.89 (s, 1H, NH). MS: *m/z* = 337 (M^+), 236 (M^+–H), 322 (M^+–CH_3). Anal. Calc. for $C_{17}H_{12}ClN_5O$ (337.77): C, 60.45; H, 3.58; N, 20.73; Found: C, 60.52; H, 3.67; N, 20.80.

2-(Furan-2-yl)-4-methyl-6-[2-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazinyl]pyrimidine-5-carbonitrile (21)

A mixture of **10** (0.01 mol) and isatin (0.01 mol) in n-butanol (50 ml) was heated under reflux for 3 h. The solid formed on

hot was filtered off, dried and recrystallized from acetic acid to give **21** as yellow crystals.

m.p. = 290–292 °C, Yield: 82%. IR (KBr) υ_{max}: 3432 (NH), 2211 (C≡N), 1695 (C=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.67 (s, 3H, CH_3), 6.77–8.03 (m, 7H, furan-H + indole-H), 11.33 (s, 1H, NH), 13.00 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 23.9 (CH_3), 111.6, 157.0, 159.0, 163.3 (pyrimidine carbons), 113.5, 131.9, 142.6, 150.8, (furan carbons), 120.2, 121.3, 124.5., 129.4, 123.1, 135.0, 147.8 (isatin carbons), 117.3 (C≡N), 173.0 (C=O). Anal. Calc. for $C_{18}H_{12}N_6O_2$ (344.34): C, 62.79; H, 3.51; N, 24.41; Found: C, 62.71; H, 3.42; N, 24.34.

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