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A Facile Synthesis of Some New Thiazolo[3, 2]pyridines Containing Pyrazolyl Moiety and Their Antimicrobial Activity

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A Facile Synthesis of Some New Thiazolo[3,2-a]-pyridines Containing Pyrazolyl Moiety and Their Antimicrobial Activity

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*Condensation of 2-cyanomethyl-4-thiazolinone **1** with 1,3-diphenyl-pyrazole-4-carboxaldehyde **2** in ethanol containing a few drops of piperidine yielded the novel methylene derivative **3**. Compound **3** was refluxed with malononitrile to give the corresponding thiazolo[3,2-a]pyridine derivative **5**. Also, treatment of compound **3** with benzylidenemalononitriles gave the thiazolo[3,2-a]pyridine derivatives **6a–e**. Refluxing of compound **6d** with triethyl orthoformate furnished the ethoxymethylideneamino derivative **7**. Formic acid and malononitrile were reacted with compound **6d** to produce thiazolo[3,2-a][1,8]naphthyridine derivative **8** and **11**, respectively. Condensation of **2** with cyanoacetohydrazide in ethanol containing piperidine as catalyst gave the hydrazone derivative **12** which, on treatment with salicylaldehyde and 2-cyano-3-(4-fluorophenyl)acrylic acid ethyl ester, yielded the novel chromene **13** and pyridinone **14**, respectively. Structures of the synthesized compounds have been established by elemental analysis and spectral data. Compounds **3**, **5**, **6a–d**, **8**, **11**, **13**, and **14** have been screened for antimicrobial activities.*

Keywords 1,3-Diphenyl-pyrazole; thiazolo[3,2-a]pyridines; thiazolo-naphthyridines and antimicrobial activity

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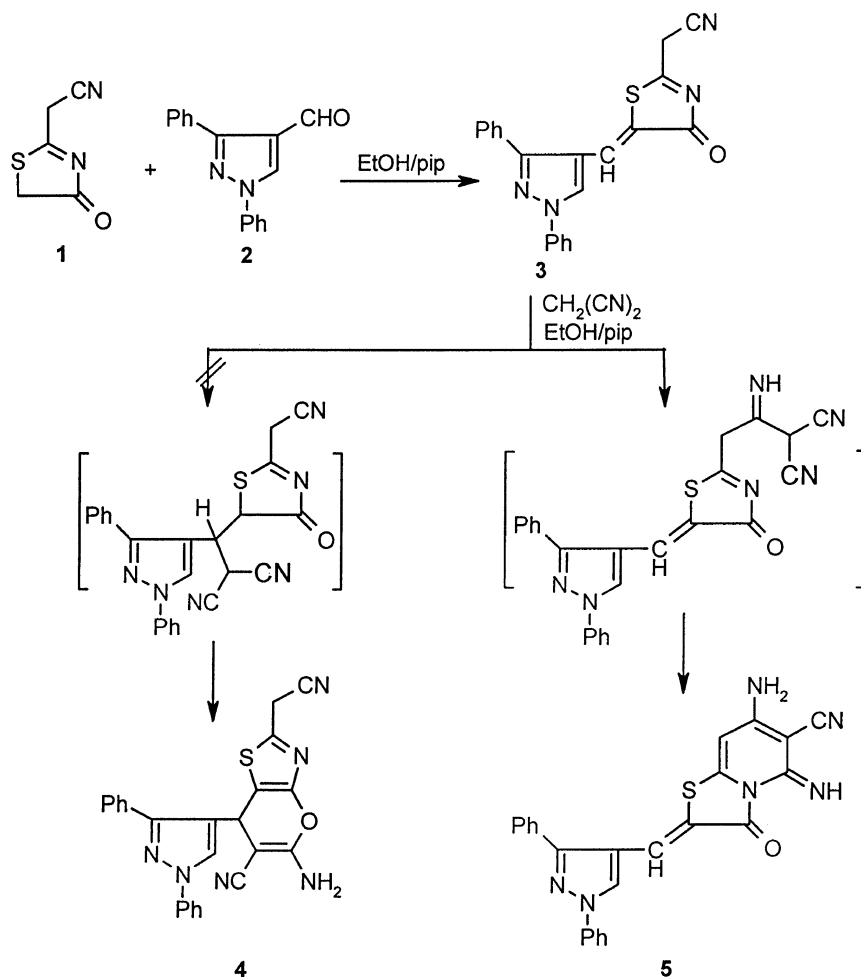
INTRODUCTION

The interesting pharmacological properties of thiazole derivatives¹⁻⁷ in relation to the various changes in the structures of these compounds is worth studying in order to synthesize less toxic and more potent drugs. Therefore the fusion of other heterocyclic moieties to the thiazole ring may lead to the fulfillment of the objective. Pyrazolyl moiety revealed antibacterial, antifungal, analgesic, antiinflammatory,^{8,9} and platelet antiaggregating properties.¹⁰⁻¹³ In continuation of our work on the synthesis of thiazolo[3,2-a]pyridines from readily available starting material¹⁴⁻¹⁷ we report here a facile synthesis of hitherto unknown 2-cyanomethyl-4,5-dihydro-4-oxo-5-(1,3-diphenylpyrazol-4-yl) methylidene thiazole **3** and the result of its utility as building block for the synthesis of novel thiazolo[3,2-a]pyridine derivatives having pyrazolyl moiety in their structures.

RESULTS AND DISCUSSION

2-Cyanomethyl-4-thiazolinone **1** reacts with 1,3-diphenyl-pyrazole-4-carboxaldehyde **2** in ethanol containing a few drops of piperidine to afford the corresponding methylidene derivative **3**. The structure of the compound **3** is in agreement with its spectral data. The IR spectrum of compound **3** exhibited absorption bands for NH₂, C≡N, and C=O (thiazoline) groups. Its ¹H NMR spectrum recorded in DMSO-*d*₆ revealed singlet in the region at δ 5.25 ppm attributed to CH₂CN in addition to ethylene, pyrazole, and aromatic protons. The reaction of compound **3** with malononitrile in refluxing ethanol and piperidine led to the formation of 5-amino-7-imino-2-[1,3-diphenyl-pyrazol-4-yl]methylidene-3-oxo-2,3-dihydro-thiazolo[3,2-a]pyridine-6-carbonitrile **5** and thiazolopyran **4** was eliminated on the basis of analytical and spectral data. ¹H NMR spectrum of compound **5** displayed a singlet in the region δ 4.47 ppm due to pyridine-H. The formation of thiazolopyridine **5** is assumed to proceed via the addition of the active methylene in malononitrile to the cyano group in compound **3**, followed by intramolecular cyclization at the cyano group and tautomerization to furnish **5**, (Scheme 1).

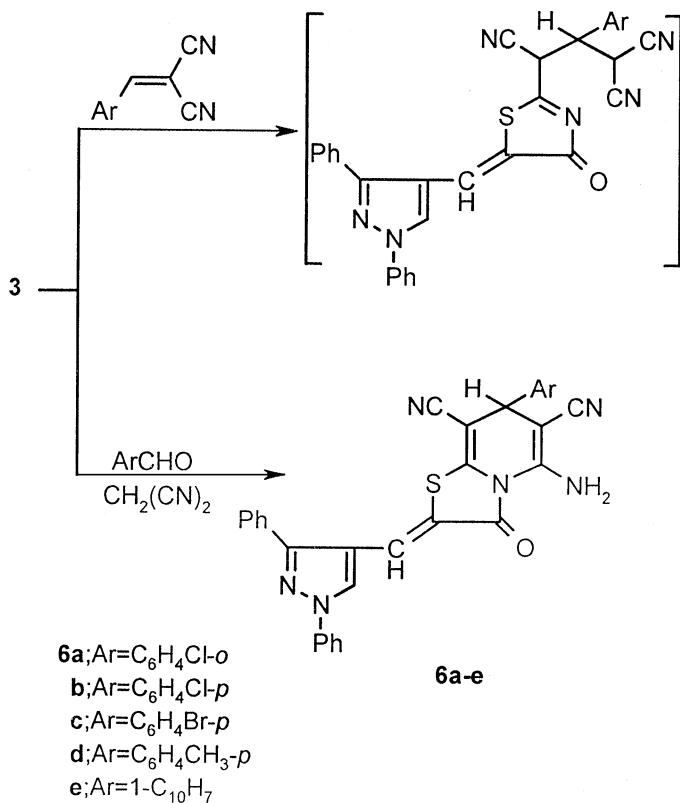
The formation of starting material **3** encouraged us to extend this work to synthesize a novel thiazolo[3,2-a]pyridine derivatives **6a-e** having in their structure pyrazolyl moiety by cyclocondensation of compound **3** with benzylidenemalononitriles (1:1 molar ratio) in ethanol containing few drops of piperidine. The structures of these derivatives were confirmed by elemental analysis and spectral data. The ¹H NMR spectrum of compound **6a** in (DMSO-*d*₆) revealed singlet in the region δ 4.76 ppm was attributed to pyridine-H. The formation



SCHEME 1

of thiazolopyridine **6** is assumed to proceed via initial addition of active methylene in compound **3** to benzylidene moiety to form Michael adduct, followed by intramolecular cyclization,¹⁶ (Scheme 2). Also, the structures of thiazolo[3,2-a]pyridines **6a–e** were established by another synthetic route via ternary condensation of compound **3**, aromatic aldehyde and malononitrile (1:1:1 molar ratio) in refluxing ethanol containing piperidine.

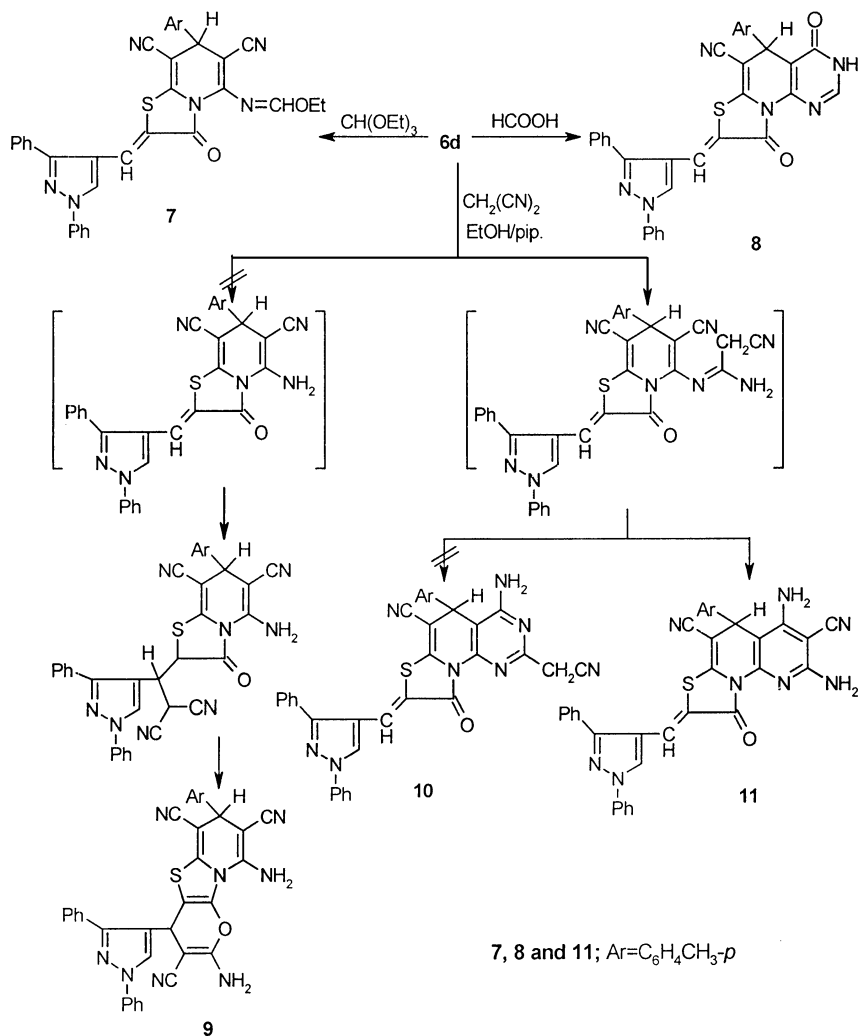
The reactivity of thiazolopyridine **6**, which contains chalcone and enamionitrile moieties, toward some electrophiles and nucleophiles



SCHEME 2

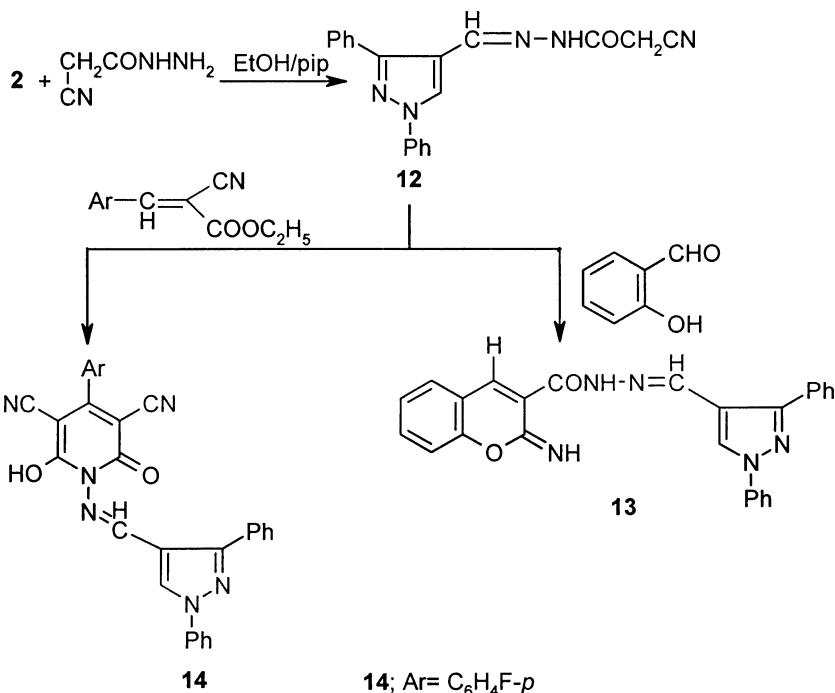
was investigated. Thus compound **6d** was reacted with triethyl orthoformate as electrophile yielded the corresponding ethoxymethylene derivative **7**. Spectral data and elemental analysis are in consistent with its structure. Furthermore cyclization of compound **6d** with formic acid furnished thiazolo[3,2-*a*]-3-aza-[1,8]naphthyridine derivative **8**. Three possible structures **9**, **10**, and **11** can be formulated when compound **6d** was allowed to react with malononitrile in ethanol in the presence of piperidine. Elemental analysis and spectral data are in agreement with structure **11** and excluded the structures **9** and **10**, (Scheme 3). IR spectrum of compound **11** revealed presence of absorption band for C=O (thiazolinone) group and its ¹H NMR not showed any specific signal for CH₂C≡N group.

Compound **2** was condensed with cyanoacetohydrazide in boiling ethanol containing piperidine as a base and gave hydrazone derivative **12**, which was established by correct elemental analysis and spectral



SCHEME 3

data. Its ¹H NMR spectrum in (DMSO-*d*₆) revealed singlet at δ 4.13 ppm which due to CH₂CN, singlet at δ 9.05 ppm assigned to CH=N and singlet at δ 11.63 ppm due to NH. Interaction of compound **12** with salicylaldehyde and in ethanol afforded the hitherto unknown chromene derivative **13**. Finally, compound **12** was cyclized with 2-cyano-3-(4-fluorophenyl)-acrylic acid ethyl ester in EtOH/ piperidine to furnish pyridinone derivative **14**. The formation of pyridine **14** was assumed to proceed via the addition of active methylene in compound **12** to the



SCHEME 4

benzylidene moiety followed by intramolecular cyclization by elimination of ethanol molecule (Scheme 4).

EXPERIMENTAL

All melting points are uncorrected (Stuart Scientific Co., UK). The IR spectra were measured as KBr pellets on Shimadzu IR 200 spectrophotometer (Shimadzu, Japan). ^1H NMR spectra were recorded in $\text{DMSO}-d_6$ at 200 MHz on a Varian Gemini NMR spectrometer (Varian, UK), using tetramethylsilane as internal reference. Elemental analyses were carried out at the Microanalytical Center of Cairo University (Egypt). The characteristic data for the synthesized compounds are given in Table I. The spectral data are collected in Table II. Compound 1 was prepared according to reported method.¹⁸

2-Cyanomethyl-4,5-dihydro-4-oxo-5-(1,3-diphenylpyrazol-4-yl)methylidene Thiazoline (3)

A mixture of thiazolinone 1 (0.01 mol) and 1,3-diphenyl pyrazole-4-carboxaldehyde 2 (0.01 mol) in ethanol (20 ml) containing a few

TABLE I Analytical Data of the Synthesized Compounds

Compound no.	Yield (%)	Solvent crystal	M.P. [°C]	Molecular formula (mol. wt.)	Elemental analyses calcd./found [%]		
					C%	H%	N%
3	75	EtOH/Benzene	200-2	C ₂₁ H ₁₄ N ₄ OS (370.44)	68.10 68.05	3.81 3.75	15.12 15.16
5	66	Benzene	>300	C ₂₄ H ₁₆ N ₆ OS (436.50)	66.05 66.09	3.69 3.62	19.26 19.27
6a	62	Dioxane	280-2	C ₃₁ H ₁₉ ClN ₆ OS (559.05)	66.60 66.58	3.43 3.38	15.04 15.07
6b	74	Dioxane	270-2	C ₃₁ H ₁₉ ClN ₆ OS (559.05)	66.60 66.58	3.43 3.41	15.04 15.03
6c	82	Dioxane	263-5	C ₃₁ H ₁₉ BrN ₆ OS (603.50)	61.70 61.69	3.17 3.13	13.93 13.92
6d	85	Dioxane	270-1	C ₃₂ H ₂₂ N ₆ OS (538.64)	71.36 71.36	4.12 4.11	15.60 15.59
6e	63	EtOH	260-2	C ₃₅ H ₂₂ N ₆ OS (574.67)	73.15 73.16	3.86 3.82	14.62 14.62
7	67	EtOH/Benzene	230-1	C ₃₅ H ₂₆ N ₆ O ₂ S (594.70)	70.69 70.69	4.41 4.36	14.13 14.15
8	79	EtOH/Benzene	140-2	C ₃₃ H ₂₂ N ₆ O ₂ S (566.65)	69.96 69.95	3.91 4.00	14.84 14.86
11	81	Benzene	293-5	C ₃₅ H ₂₄ N ₈ OS (604.70)	69.53 69.57	3.98 3.96	18.53 18.57
12	84	EtOH/Benzene	204-6	C ₁₉ H ₁₅ N ₅ O (329.36)	69.30 69.31	4.59 4.56	21.26 21.27
13	57	EtOH	155-7	C ₂₆ H ₁₉ N ₅ O ₂ (433.47)	72.05 72.05	4.42 4.39	16.16 16.15
14	69	EtOH/Benzene	295-7	C ₂₉ H ₁₇ FN ₆ O ₂ (500.50)	69.60 69.63	3.42 3.43	16.79 16.76

drops of piperidine was refluxed for 6 hours. The solid product obtained was filtered off and recrystallized from suitable solvent to give **3**.

7-Amino-5-imino-2(1,3-diphenylpyrazol-4-yl)methylidene-3-oxo-2,3-dihydro-thiazolo [3,2-a]pyridine-6-carbonitrile (5)

A mixture of thiazolinone **3** (0.01 mol) and malononitrile (0.01 mol) in ethanol (20 ml) containing few drops of piperidine was refluxed for 8 hours. The solid product which produced on heating was collected and recrystallized to give **5**.

TABLE II Spectral Data of the Synthesized Compounds

Compound no.	IR (KBr, cm ⁻¹)	¹ H NMR (δ, ppm) (DMSO- <i>d</i> ₆)
3	2200 (C≡N), 1700 (C=O thiazolinone)	5.25(s, 2H, CH ₂ CN), 6.18–8.07 (m, 11H, 10H Ar-H+pyrazole-H), 8.62 (s, 1H, methine-H)
5	3440, 3347, 3100 (NH ₂ , NH), 2200 (C≡N), 1710 (C=O thiazolinone)	4.47 (s, 1H, pyridine-H), 7.35–7.62 (m, 11H, 10H Ar-H+pyrazole-H), 7.89 (s, 1H, methine-H), 8.06 (s, 1H, NH), 8.40 (s, 2H, NH ₂)
6a	3394, 3317 (NH ₂), 2200 (C≡N), 1710 (C=O thiazolinone)	4.76 (s, 1H, pyridine-H), 7.42–7.68 (m, 15H, 14H Ar-H+pyrazole-H), 8.02 (s, 1H, methine-H) 8.80 (s, 2H, NH ₂)
6b	3400, 3280 (NH ₂), 2200 (C≡N), 1700 (C=O thiazolinone)	
6c	3400, 3280 (NH ₂), 2200 (C≡N), 1700 (C=O thiazolinone)	4.74 (s, 1H, pyridine-H), 7.35–8.05(m, 15H, 14H Ar-H + pyrazole-H), 8.10 (s, 1H, methine-H), 8.38 (s, 2H, NH ₂)
6d	3400, 3371 (NH ₂), 2198 (C≡N), 1705 (C=O thiazolinone)	
6e	3394, 3370 (NH ₂), 2191 (C≡N), 1705 (C=O thiazolinone)	4.73 (s, 1H, pyridine-H), 6.02–8.51 (m, 18H, 17H Ar-H+pyrazole-H), 8.67 (s, 1H, methine-H), 8.84 (s, 2H, NH ₂)
7	2198 (C≡N), 1718 (C=O thiazolinone)	1.23(t, 3H, CH ₃), 2.49 (s, 3H, CH ₃), 3.20 (q, 2H, CH ₂), 4.21 (s, 1H, pyridine-H), 7.42–7.69 (m, 15H, 14H Ar-H+ pyrazole-H) 7.95(s, 1H, methine-H, 9.10(s, 1H, N=CH)
8	3344 (NH), 2216 (C≡N), 1700, 1654 (C=O thiazolinone, amide)	
11	3392, 3373 (NH ₂), 2194 (C≡N), 1718 (C=O thiazolinone)	1.63 (s, 2H, NH ₂), 2.31 (s, 3H, CH ₃), 4.50 (s, 1H, pyridine-H), 7.31–7.67 (m, 15H, Ar-H+pyrazole-H), 7.89 (s, 1H, methine-H), 8.90 (s, 2H, NH ₂)
12	3446 (NH), 2225 (C≡N), 1679 (C=O thiazolinone)	4.13 (s, 1H, pyridine-H), 7.36–8.27 (m, 11H, 10H Ar-H+pyrazole-H), 9.03 (s, 1H, CH=N), 11.63 (s, 1H, NH)
13	3200 (NH), 1650 (C=O)	4.13 (br, 1H, NH), 6.75 (s, 1H, pyrazole-H), 7.06–8.33 (m, 15H, 14H Ar-H+coumarin-H), 8.69 (s, 1H, CH=N), 10.05 (s, 1H, NH)
14	3400 (OH) 2200 (C≡N), 1650 (C=O)	6.60 (s, 1H, pyrazole-H) 7.10–7.50 (m, 14H, Ar-H), 8.55 (s, 1H, CH=N), 9.9 (s, 1H, OH)

5-Amino-2-(1,3-diphenylpyrazol-4-yl)methylidene-3-oxo-6,8-dicyano-2,3,7-trihydro-7-aryl-thiazolo[3,2-a]pyridines (6a–e)**Method A**

A mixture of thiazolinone **3** (0.01 mol) and arylidenemalononitrile (0.01 mol) in ethanol (20 ml) containing few drops of piperidine was refluxed for 3 hours. The solid product which produced on heating was filtered and recrystallized to give **6a–e**.

Method B

A mixture of compound **3** (0.01 mol), aromatic aldehyde (0.01 mol) and malononitrile (0.01 mol) in ethanol (30 ml) in the presence of piperidine (0.5 ml) was refluxed for 3 hours. The solid product produced on heating was collected to give **6**.

5-Ethoxymethyleneamino-2-(1,3-diphenylpyrazol-4-yl)-methylidene-3-oxo-6,8-dicyano-2,3,7-trihydro-7-tolyl-thiazolo[3,2-a]pyridine (7)

A solution of **6d** (0.01 mol) and triethyl orthoformate/acetic anhydride mixture (10 ml; 1:1) was refluxed for 5 hours. The solid obtained was filtered and recrystallized from suitable solvent to give **7**.

2-(1,3-Diphenylpyrazol-4-yl)methylidene-3,8-dioxo-2,3,9-trihydro-7-imino-9-tolyl-10-cyano-thiazolo[3,2-a]-3-aza-[1,8]naphthyridine (8)

A solution of **6d** (0.01 mol) in enough quantity of formic acid (10 ml) was refluxed for 5 hours. The product obtained was filtered and recrystallized from suitable solvent to give **8**.

2-(1,3-Diphenylpyrazol-4-yl)methylidene-3-oxo-2,3,9-trihydro-6,8-diamino-9-tolyl-7,10-dicyano-thiazolo[3,2-a][1,8]naphthyridine (11)

A mixture of thiazolinone **6d** (0.01 mol) and malononitrile (0.01 mol) in ethanol (20 ml) containing few drops of piperidine was refluxed for 8 hours. The solid product obtained was filtered off and recrystallized from suitable solvent to give **11**.

Cyano-Acetic Acid (1,3-Diphenyl-1H-pyrazol-4-ylmethylene)-hydrazide (12)

A solution of **2** (0.01 mol) and cyanoacetohydrazide (0.01 mol) in ethanol (20 ml) containing few drops of piperidine was refluxed for 5 hours.

The product obtained was filtered off and recrystallized from suitable solvent to give **12**.

2-Imino-2*H*-chromene-3-carboxylic Acid (1,3-Diphenyl-1*H*-pyrazol-4-ylmethylene)-hydrazide (13)

A solution of **11** (0.01 mol), salicylaldehyde (0.01 mol) in ethanol (20 ml) and catalytic amount of piperidine was refluxed for 6 hours. The solid obtained was filtered off and recrystallized from suitable solvent to give **13**.

1-[(1,3-Diphenyl-1*H*-pyrazol-4-ylmethylene)-amino]-4-(4-fluorophenyl)-6-hydroxy-1,2-dihydro-2-pyridinone-3,5-dicarbonitrile (14)

A solution of **11** (0.01 mol), 2-cyano-3-(4-fluorophenyl)-acrylic acid ethyl ester and (0.01 mol) in ethanol (20 ml) and catalytic amount of piperidine was refluxed for 6 hours. The solid obtained was filtered off and recrystallized from suitable solvent to give **14**.

BIOLOGICAL SCREENING

Most of the newly synthesized compounds were screened in vitro for their antimicrobial activities against four strains of bacteria: *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Bacillus subtilis* using the paper disc diffusion method.¹⁹ The tested compounds were dissolved in, *N N*-dimethylformamide (DMF) to get a solution of 1 mg mL⁻¹. The inhibition zones were measured in millimeters at the end of incubation period of 48 h at 28°C. Dimethylformamide showed no inhibition zones. Chloramphenicol standard was used as reference to evaluate the potency of the tested compounds. The inhibition zones of microbial growth produced by different compounds are reported in Table III. A novel compound **13** showed activity nearest from chloramphenicol with respect to *Escherichia coli*, *Staphylococcus*, and *Bacillus Subtilis*; This may be attributed to this compound having coumarinyl moiety beside pyrazolyl moiety in its structure. Where compound **5** and compounds **6a**, **6c**, and **8** exhibited the same activities with respect to *Bacillus Subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* respectively. Also, this may be due to presence of pyridine and naphthyridine moieties in their structures. Contrary to this, most of the synthesized compounds showed moderate and lower activity with respect to all tested microorganisms.

TABLE III Antibacterial Activity of the Synthesized Compounds

Compound no.	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>
3	++	+	++	++
5	+	+++	++	+
6a	+	++	+++	++
6b	+	++	++	++
6c	++	++	+++	++
6d	+	+	++	+
8	++	++	+++	+++
11	++	++	++	++
13	+++	+++	+++	++
14	++	+	+	+
Standard	++++	++++	++++	++++

+: (0.2–0.5 cm) less active, ++: (0.6–1.4 cm) moderately active. +++: (1.5–3.0 cm) highly active, ++++: (over 3.0 cm) very highly active.
 Standard: Chloramphenicol (25 $\mu\text{g mL}^{-1}$)

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