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RESEARCH ARTICLE

Facial Synthesis of Some New Pyrazolopyridine, Barbituric and Thiobarbituric Acid Derivatives with Antimicrobial Activities

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Abstract

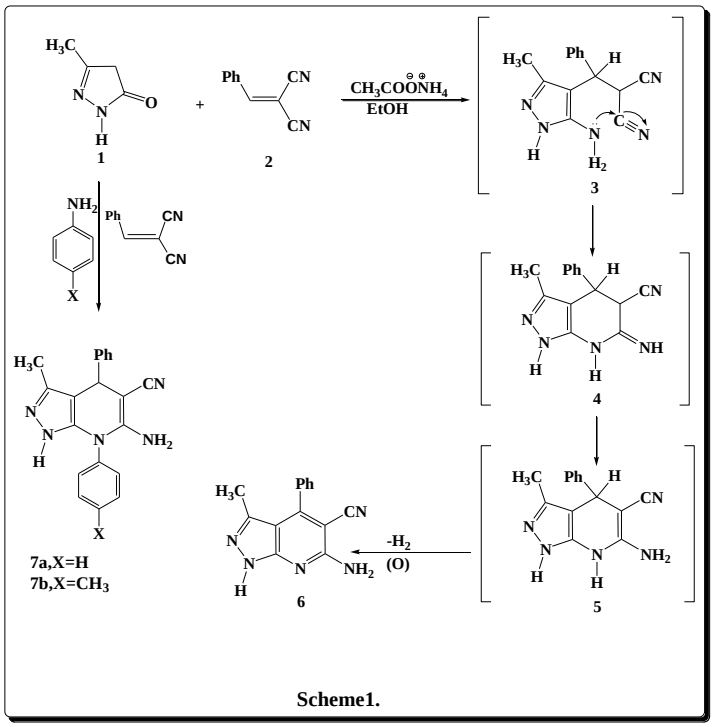
2-amino-3-cyanopyridine derivatives were synthesized by treating cyclic compounds containing active methylene group with arylidenemalononitrile in the presence of ammonium acetate. The behavior of 2-amino-3-cyanopyridine derivatives toward some electrophiles as triethylorthoformate followed by nitrogenious nucleophiles as hydrazine was reported; also, its reactivity toward phenyl isocyanates, thiourea, formic acid and formamide was investigated, with the aim of obtaining some interesting non-mixed heterocyclic compounds. In addition the antimicrobial activity of some selected derivatives was reported

INTRODUCTION

The considerable biological and pharmaceutical activities of pyraazolopyridines, barbituric and thiobarbituric acid derivatives stimulated the recent interest in synthesis of these ring systems. Pyrazolopyridine analogues had proven to be an interesting class of heterocyclic derivatives due to diverse biological activities including antitubercular, antibacterial and antioxidant activities [1-10]. Recently, the pyrazolopyridine compounds found a great importance in the synthesis of some fluorescence dyes [11] and as anti-corrosion protection of stainless steel in aggressive media [12]. On the other hand, the barbiturates (BA) and thiobarbiturates (TBA) exert a broad range of pharmaceutical activities, including sedation, general anesthesia, and anticonvulsant and anxiolytic effects, also, some of the barbituric and thiobarbituric acid analogues have been reported to show antimicrobial [13,14], antifungal [15], antiviral [16] and antitumor [17] activities.

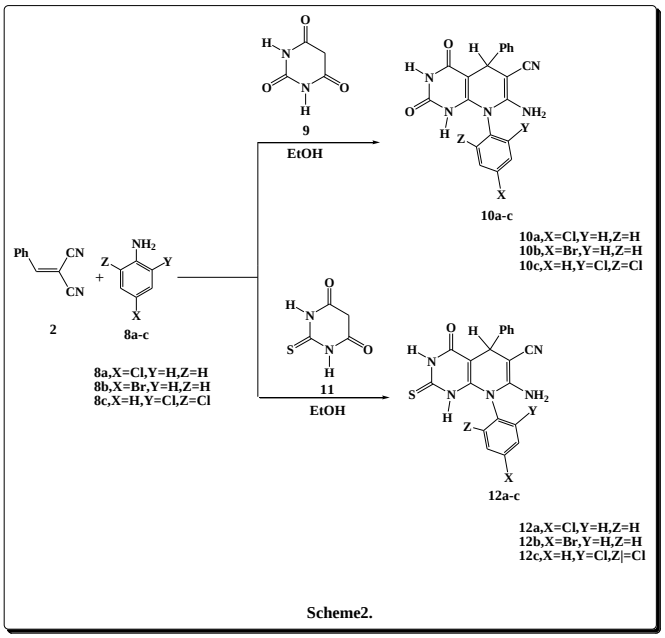
1. Result and discussion

Treatment of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**) with the α,β-unsaturated nitrile derivative (**2**) in the presence of ammonium acetate afforded the 6-amino-3-methyl-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**6**). On the other hand, compounds **7a,b** could be obtained upon the reaction of **1** with **2** in the presence of aniline or *p*-toluidine (Scheme 1).



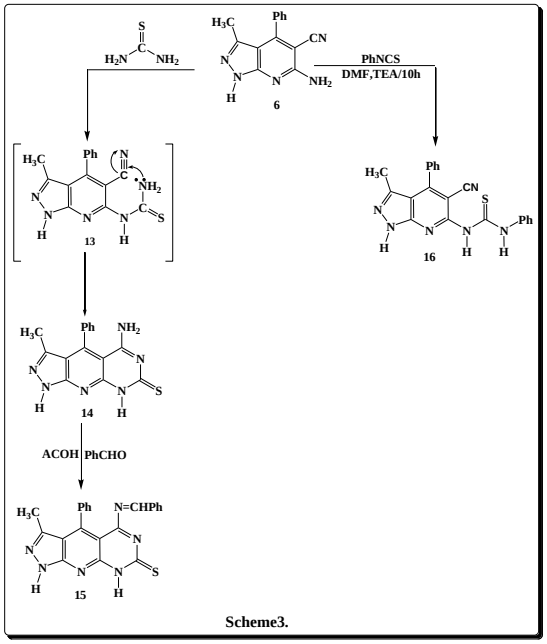
Scheme1.

Similarly, the reaction of barbituric acid or thiobarbituric acid with compound **2** and the appropriate of *p*-chloroaniline, *p*-bromoaniline or 2,6-dichloroaniline in absolute ethanol gave **10a-c** and **12a-c**, respectively (Scheme 2).



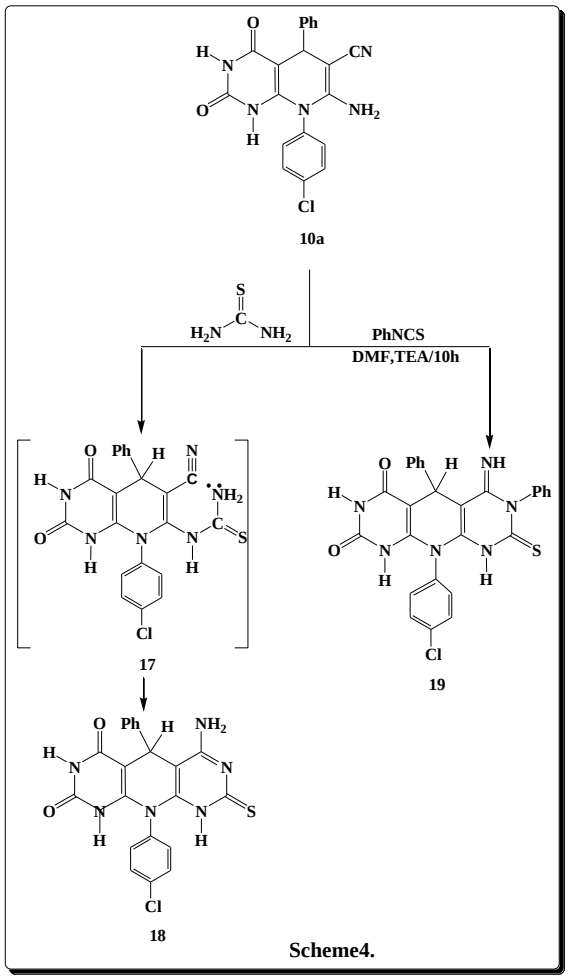
Scheme2.

The ring system **14** was synthesized by the reaction of **6** with thiourea through the intermediate **13**. The compound **14** reacted with benzaldehyde in acetic acid to give **15** through Schiff-base reaction. Moreover, compound **6** reacted with phenyl isothiocyanate to afford the corresponding thiouredo derivative **16** (Scheme 3).



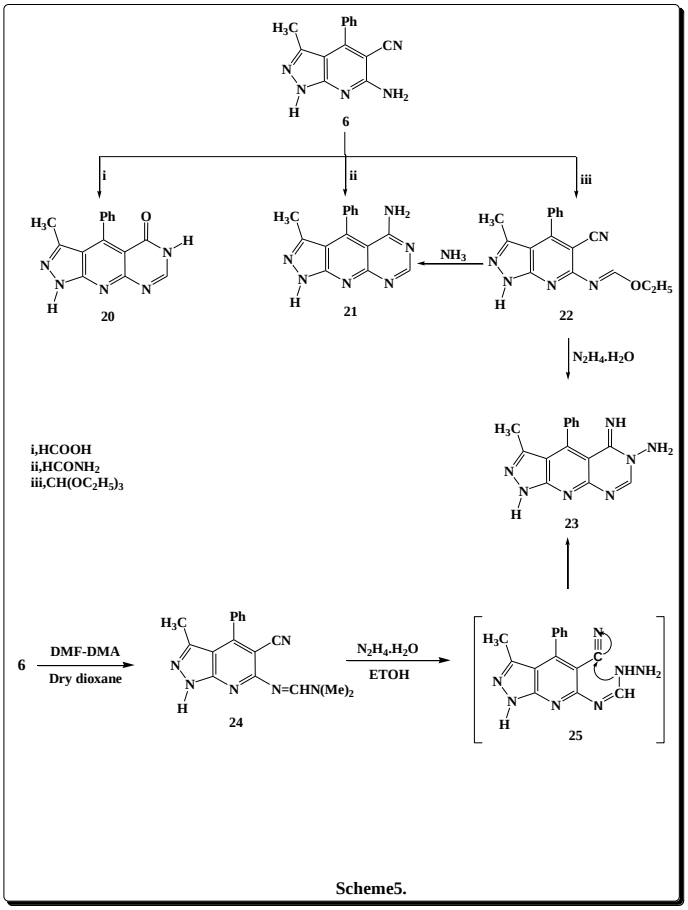
Scheme3.

Compound **10a** was refluxed with thiourea in an ethanol/sodium ethoxide mixture for 6 hrs. to afford **18** through the intermediate **17**. On the other hand, **10a** reacted with phenyl isothiocyanate in DMF in the presence of catalytic amount of TEA to give the corresponding fused heterocyclic system **19** (Scheme 4).



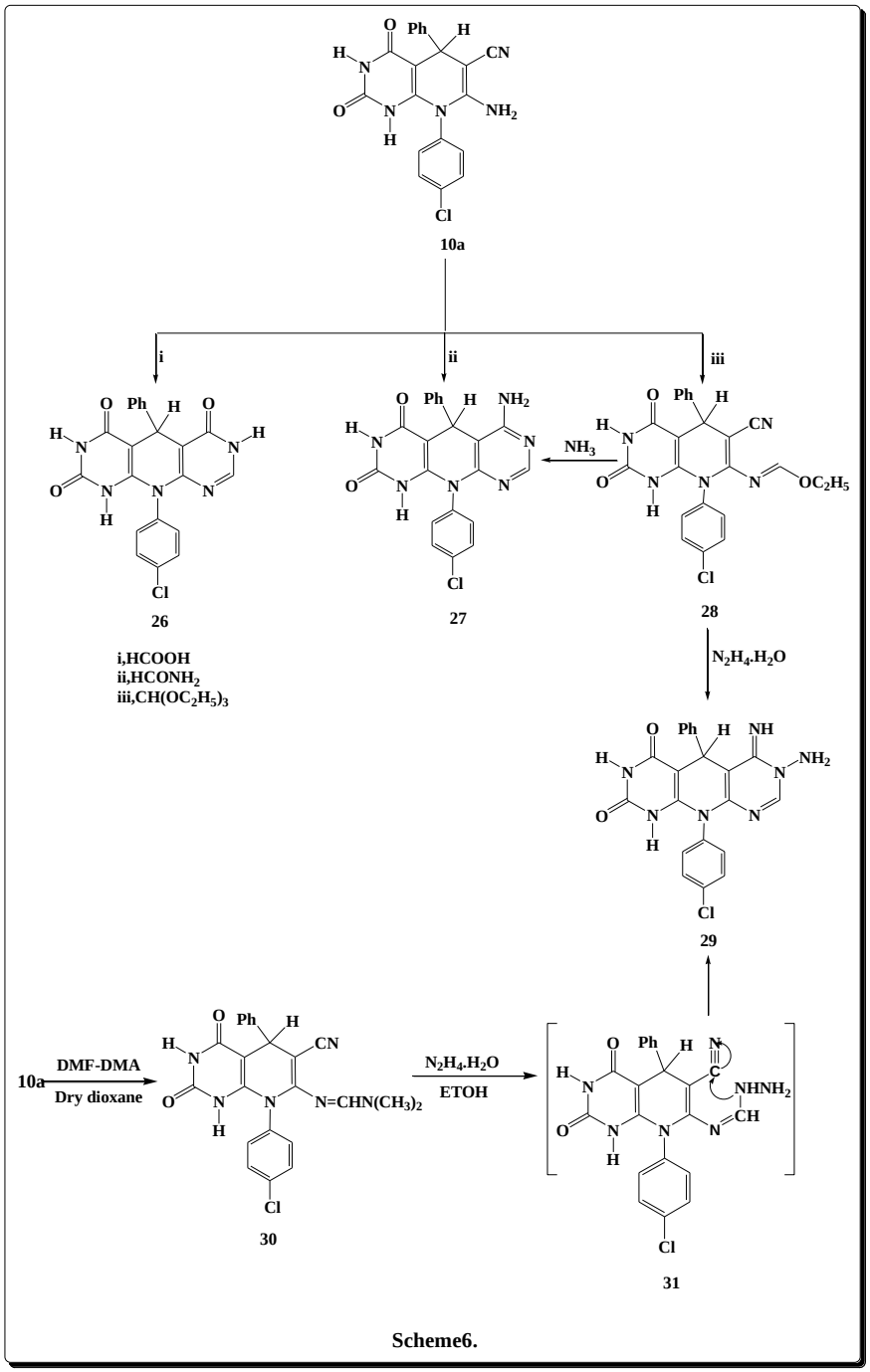
Scheme4.

Compound **6** was converted to **20**, **21** upon its reaction with formic acid and formamide, respectively. Also, compound **6** reacted with triethylorthoformate in acetic anhydride to give **22** which further reacted with hydrazine hydrate to give the corresponding **23**.Structure of compound **23** was confirmed by alternative synthetic route. Thus, compound **6** reacted with dimethyl fomamide-dimethyl acetal (DMF-DMA) in dry dioxane to give **24**. The latter reacted with hydrazine hydrate to give **23** through the intermediate **25.** Compound **22** reacted with ammonia to give compound identical in all aspects (MP, IR, Mass, H^1NMR, elemental analysis) with that of compound **21** (Scheme 5).



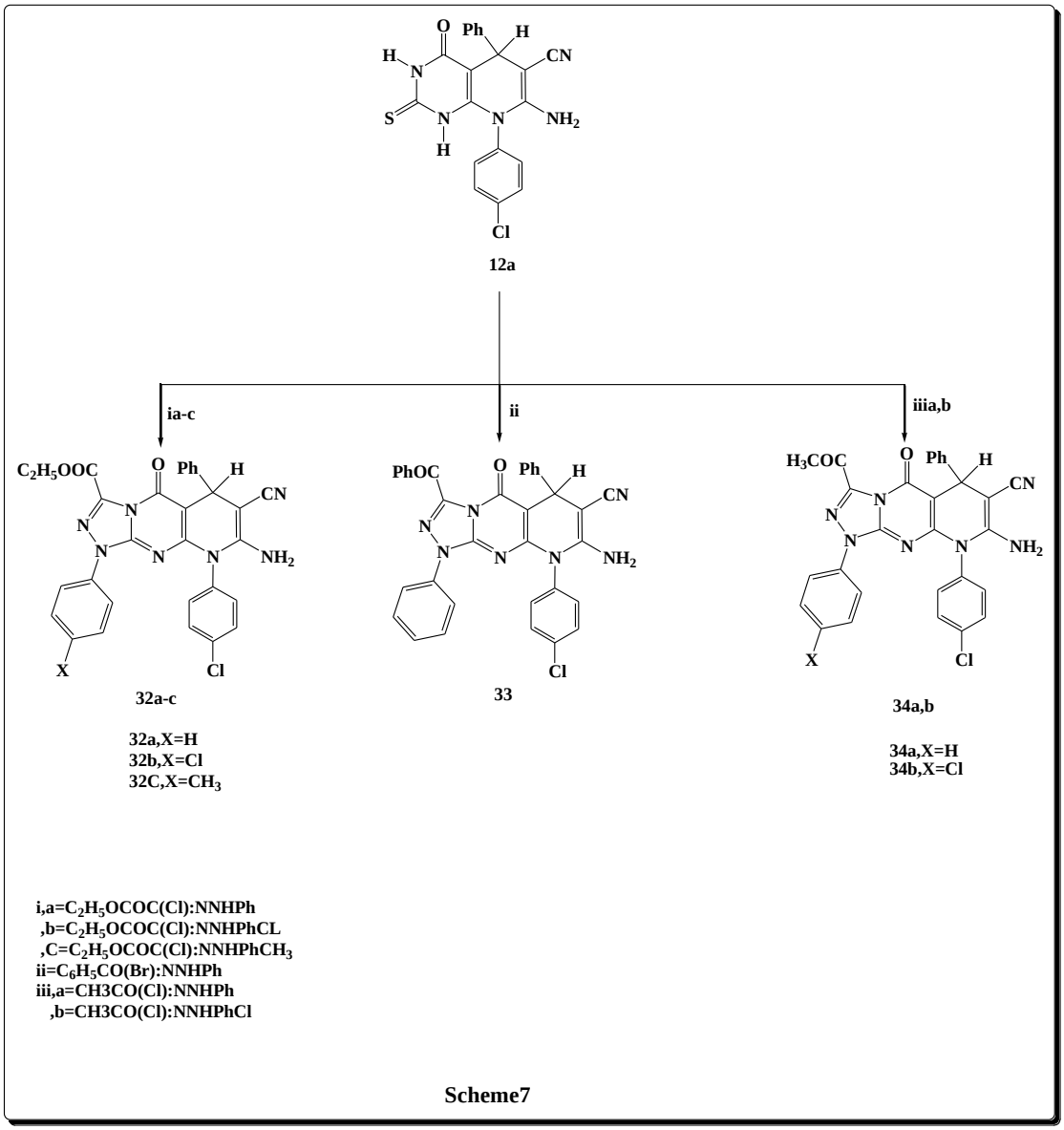
Scheme5.

Analogously, compound **10a** reacted with formic acid and formamide to give **26** and **27**, respectively. Next, compound **10a** reacted with triethylorthoformate in the presence of acetic anhydride to yield the corresponding **28** which further reacted with hydrazine hydrate to give the corresponding **29**. The structure of the latter could be confirmed by the same previous method. Where, compound **10a** reacted with DMF-DMA yielded **30** which treated with hydrazine hydrate to give **29** through the intermediate **31**. Compound **28** converted to **27***via* its reaction with ammonia (Scheme 6).



Scheme6.

Finally, compound **12a** could be reacted with the appropriate of hydrazonoyl halides in chloroform in the presence of catalytic amount of TEA under reflux to give the corresponding compounds **32a-c**, **33** and **34a**,**b (**Scheme7).



Scheme7

2. Biological Activity

Screening of antimicrobial activity was performed at a Microbiology Lab in Faculty of Agriculture, El-Azhar University, Cairo, Egypt. All the tested microorganisms were chosen on bases of their pathogenicity.Where, ***Aspergillus*** caused a broad spectrum of disease in the human host, ranging from hypersensitivity reactions to direct angioinvasion. ***Aspergillus*** primarily affects the lungs, causing 4 main syndromes, including allergic bronchopulmonary aspergillosis (ABPA), chronic necrotizing ***Aspergillus*** pneumonia (or chronic necrotizing pulmonary aspergillosis [CNPA]), aspergilloma, and invasive aspergillosis. However, in patients who are severely immunocompromised, ***Aspergillus*** may hematogenously disseminate beyond the lung, potentially causing endophthalmitis, endocarditis, and abscesses in the myocardium, kidney, liver, spleen, soft tissue, and bone. On the other hand, ***Candida albicans*** is a diploidfungus that grows both as yeast and filamentous cells and a causal agent of opportunisticoral and genital infections in humans.[18][19]. ***C. albicans*** have emerged as important causes of morbidity and mortality in immunocompromised patients (e.g., AIDS, cancer chemotherapy, organ or bone marrow transplantation). Also, ***Staphlococcusaureus*** can cause a range of illnesses, from minor skin infections, such as pimples, impetigo, boils (furuncles), cellulitis folliculitis, carbuncles, scalded skin syndrome, and abscesses, to life-threatening diseases such as pneumonia, meningitis, osteomyelitis, endocarditis, toxic shock syndrome (TSS),

bacteremia, and sepsis. Its incidence ranges from skin, soft tissue, respiratory, bone, joint, endovascular to wound infections. It is still one of the five most common causes of nosocomial infections and is often the cause of postsurgical wound infections. Each year, some 500,000 patients in American hospitals contract a staphylococcal infection [20]. In addition, some ***Bacillus*** species can cause food poisoning; ***Bacillus*** can result in two different kinds of intoxications. It can either cause nausea, vomiting, and abdominal cramps for 1-6 hours, or diarrhea and abdominal cramps for 8-16 hours. The food poisoning usually occurs from eating rice that is contaminated with ***Bacillus subtilis*** (EMBL EBI), Some ***Bacillus*** organisms can cause more severe illnesses, for example causes Anthrax. Also, ***Salmonella typhimurium*** is a pathogenic Gram-negative bacteria predominately found in the intestinal lumen. Its toxicity is due to an outer membrane consisting largely of lipopolysaccharides (LPS) which protect the bacteria from the environment. ***Salmonella typhimurium*** causes gastroenteritis in humans and other mammals. And finally, pathogenic strains of ***E.coli*** are responsible for three types of infections in humans: urinary tract infections (UTI), neonatal meningitis, and intestinal diseases (gastroenteritis). Representative derivatives **6**, **7a**, **10a**, **10c**, **12a**, **12b**, **14**, **15**, **19**, **20**, **23**, **27**, **29**, **30**, **32c**, **33** and **34b** were selected and tested for their antimicrobial activity against two gram(+) bacteria(*Staphlococcus aureus, Bacillus subtilis*),two gram(-) bacteria (*Escherichia coli, salmonella typhimurium*) and a filamentous fungus (*Asperigillus fumigatus*) and a diploid fungus (*Candida albicans*).using the modified Kirby-Bauer disc diffusion method [21][22][23]. For the disc diffusion, the zone diameters were measured with slipping calipers of the national committee for clinical laboratory standards [24].
The results are given in Table 1.

Table 1: Response of various microorganisms to some synthesized compounds in in vitro culture

Inhibition zone diameter (mm/mg sample) Antimicrobial activity%						
Sample	*A.fumigatus*	*C.albicans*	*S.aureus*	*B.subtilis*	*E.coli*	*S.typhimurium*
DMSO (positive control)	0.00	0.00	0.00	0.00	0.00	0.00
Tetracycline (Antibacterial agent)	--	--	30	29	31	30
Clotrimazole (Antifungal Agent)	24	22	--	--	--	--
6	20 83%	10 45%	0.00 0.00	0.00 0.00	5 16%	7 23%
7a	0.00 0.00	0.00 0.00	12 40%	9 31%	11 35%	15 50%
10a	9 38%	15 68%	17 57%	0.00 0.00	8 26%	0.00 0.00
10c	19 79%	0.00 0.00	10 33%	15 52%	0.00 0.00	2 7%
12a	6 25%	19 86%	0.00 0.00	16 55%	8 26%	0.00 0.00
12b	0.00 0.00	7 32%	9 30%	20 69%	9 29%	0.00 0.00
14	9 38%	12 55%	21 70%	0.00 0.00	15 48%	9 30%
15	12 50%	6 27%	15 50%	7 24%	19 61%	8 27%
19	14 58%	0.00 0.00	0.00 0.00	16 55%	0.00 0.00	20 66%
20	19 79%	12 55%	5 17%	15 52%	4 13%	0.00 0.00
23	0.00 0.00	0.00 0.00	0.00 0.00	20 69%	9 29%	0.00 0.00
27	0.00 0.00	0.00 0.00	16 53%	12 41%	24 77%	12 40%

29	3 13%	8 36%	21 70%	0.00 0.00	0.00 0.00	7 23%
30	9 38%	5 23%	24 80%	10 34%	18 58%	0.00 0.00
32c	12 50%	15 68%	15 50%	9 31%	14 45%	19 63%
33	0.00 0.00	9 41%	0.00 0.00	12 41%	0.00 0.00	15 50%
34b	0.00 0.00	14 64%	0.00 0.00	0.00 0.00	10 32%	12 40%

Antimicrobial activity % =Inhibition zone diameter of the tested sample×100
Inhibition zone diameter of the standard

Strong effect means: antimicrobial activity% ≥ 60%
Moderate effect means: 60%>antimicrobial activity%≥40%
Weak effect means: 40%>antimicrobial activity%≥ 1%
No effect means: antimicrobial activity%=0.00%

3. Conclusion

The varied biological activities of the newly synthesized compounds promoted us to synthesize some new derivatives of these ring systems and study their antimicrobial activities. The antifungal activity studies revealed that compounds **6**, **10c** and **20** show strong effects against *Asperigillus fumigatus* also, compounds **10a**, **12a**, **32c** and **34b** show strong effects against *Candida albicans*. On the other hand compounds **14**, **29** and **30** display strong effects against *Staphlococcus aureus*. Compounds **12b** and **23** give strong effects against *Bacillus subtilis*.
Compounds **15** and **27** show strong effects against *Escherichia coli*. And finally compounds **19** and **23c** afford strong effects against *Salmonella typhimurium*. All the other compounds show effects against different types of tested microorganisms ranged from negative effects to moderate effects. So we can say that synthesis of new derivatives of these compounds is still an active area of research. Where, synthesis and study of the antimicrobial activities of new analogous of these compounds will be helpful for medicinal chemist to focus design of novel chemical entities containing pyrazolopyridine, barbituric and thiobarbituric acid derivatives as a part of antimicrobial drugs.

4. Experimental

4.1. Experimental Instrumentation

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on shimadzu FT-IR 8201 PC spectrophotometer. H^1NMR and C^{13}NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz FT-NMR system spectrometer and chemical shifts are expected in δ ppm units using TMS as an initial reference. Mass spectra were recorded on GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of Cairo University.Hydrazonoylhalides [25,26] were prepared as previously reported.

4.2. Synthesis

4.2.1. 6-Amino-3-methyl-4-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (6).

A mixture of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**) (0.98 gm, 10 mmol) and 2-benzylidenemalononitrile (**2**) (1.54 gm, 10 mmol) was heated under reflux in absolute ethanol (30 ml) in the presence of excess amount of ammonium acetate for 3-5 hrs. The solid material which separated while heating was collected by filtration and recrystallized from DMF to give **6** as pale yellow crystals. **Yield:** 82%, **MP:** 246-248°C; **FT-IR (KBr, cm^{-1}):** 3375,3309 (NH_2), 3170 (NH), 2929,2878 (CH-aliphatic), 2191 (CN), 1604 (C=N), 1578 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 2.79 (s, 3H, CH_3), 6.8 (s, 2H, NH_2), 7.1-7.3 (m, 5H, Ar-H), 12.07 (s, 1H, NH); **MS (El, m/z (%)):** 251(M+2, 1%), 250(M+1, 17%), 249(M^+, 100%);**Anal. Calcd. for $C_{14}H_{11}N_5$(249):** C,67.46; H,4.45; N,28.10 **Found:** C,67.44; H,4.43; N,28.11%.

4.2.2. 6-Amino-4,7-dihydro-3-methyl-4,7-diphenyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (7a).

A mixture of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**) (0.98 gm, 10 mmol), 2-benzylidenemalononitrile (**2**) (1.54 gm, 10 mmol) and aniline (0.92 ml, 10 mmol) was heated under reflux in absolute ethanol (30 ml) for 10-12 hrs. then left to cool to room temperature overnight. The solid obtained and recrystallized from DMF to give **7a** as yellow crystals. **Yield:** 87%, **MP:** 258-260°C; **FT-IR (KBr, cm^{-1}):** 3371,3310 (NH_2), 3267 (NH), 2909,2854

(CH-aliphatic), 2197 (CN), 1605 (C=N), 1571 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 2.73 (s, 3H, CH_3); 6.8 (s, 2H, NH_2); 4.5 (s, 1H ,CH); 7-7.5 (m, 10H, Ar-H); 12.05 (s, 1H, NH); **MS (El, m/z (%)):** 329 (M+2, 2%), 328 (M+1, 24%), 327(M^+, 100%), **Anal. Calcd. for $C_{20}H_{17}N_5$ (327):** C,73.37; H,5.23; N,21.39 **Found:** C,73.37; H,5.22; N,21.37%.

4.2.3. 6-Amino-4,7-dihydro-3-methyl-4-phenyl-7-p-tolyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (7b).

A mixture of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**) (0.98 gm, 10 mmol), 2-benzylidenemalononitrile (**2**) (1.54 gm, 10 mmol) and *p*-toluidine (0.92 ml, 10 mmol) was heated under reflux in absolute ethanol (30 ml) for 10-12 hrs. then left to cool to room temperature overnight. The solid obtained and recrystallized from DMF to give **7b** as white crystals. **Yield:** 83%, **MP:** 264-266°C; **FT-IR (KBr, cm^{-1}):** 3370,3312 (NH_2), 3024 (NH), 2970,2874 (CH-aliphatic), 2190 (CN), 1616 (C=N), 1592 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 2.6 (s, 3H, CH_3), 2.8 (s, 3H, CH_3), 4.6 (s, 1H, CH), 6.8 (s, 2H, NH_2), 7-7.3 (m, 9H, Ar-H), 12.0 (s, 1H, NH); **MS (El, m/z (%)):** 343 (M+2, 3%), 342 (M+1, 23%), 341 (M^+, 84%); **Anal. Calcd. for $C_{21}H_{19}N_5$ (341):** C,73.88; H,5.61; N,20.51 **Found:** C,73.88; H,5.62; N,20.51%.

4.2.4. 7-Amino-8-(4-chlorophenyl)-1,2,3,4,5,8-hexahydro-2,4-dioxo-5-phenylpyrido[2,3-d]pyrimidine-6-carbonitrile (10a).

A mixture of barbituric acid (**9**) (1.28 gm, 10 mmol), 2-benzylidenemalononitrile (**2**) (1.54 gm, 10 mmol) and *p*-chloroaniline (**8a**) (1.23 gm, 10 mmol) was heated under reflux in absolute ethanol (30 ml) for 10-12 hrs. then left to cool to room temperature overnight. The solid obtained and recrystallized from DMF to give **10a** as white crystals. **Yield:** 79%, **MP:** 270-272°C; **FT-IR (KBr, cm^{-1}):** 3305,3186 (NH), 3050,3009 (NH_2), 1681 (C=O), 2195 (CN), 1600 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 4.22 (s, 1H, CH), 6.73 (s, 2H, NH_2),7-7.5 (m, 9H,Ar-H), 11.02 (s, 1H, NH), 11.09 (s,1H, NH); **MS (El, m/z (%)):** 393(M+2, 79%), 392(M+1, 7%), 391(M^+, 81%), **Anal. Calcd. for $C_{20}H_{14}N_5O_2Cl$ (391):** C,61.31; H,3.60; N,17.87 **Found:** C,61.32; H,3.63; N,17.87%.

4.2.5. 7-Amino-8-(4-bromophenyl)-1,2,3,4,5,8-hexahydro-2,4-dioxo-5-phenylpyrido[2,3-d]pyrimidine-6-carbonitrile (10b).

A mixture of barbituric acid (**9**) (1.28 gm, 10 mmol), 2-benzylidenemalononitrile (**2**) (1.54 gm, 10 mmol) and *p*-bromoaniline (**8b**) (1.72gm, 10mmol) was heated under reflux in absolute ethanol (30 ml) for 10-12 hrs. then left to cool to room temperature overnight. The solid obtained and recrystallized from DMF to give **10b** as white crystals. **Yield:** 73%, **MP:** 290-292°C; **FT-IR (KBr, cm^{-1}):** 3320, 3109 (NH), 3230,3120 (NH_2), 1680 (C=O), 2210 (CN), 1600(C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 4.52(s, 1H, CH), 6.5(s, 2H, NH_2),7-7.8(m, 9H,Ar-H), 11.02(s, 1H, NH), 11.09 (s, 1H, NH); **MS (El, m/z (%)):** 437(M+2, 17%), 436(M+1, 19%), 435(M^+, 20%), **Anal. Calcd. for $C_{20}H_{14}BrN_5O_2$ (435):** C,55.06; H,3.23; N,16.05 **Found:** C,55.06; H,5.23; N,16.05%.

4.2.6. 7-Amino-8-(2,6-dichlorophenyl)-1,2,3,4,5,8-hexahydro-2,4-dioxo-5-phenylpyrido[2,3-d]pyrimidine-6-carbonitrile (10c).

A mixture of barbituric acid (**9**) (1.28 gm, 10 mmol), 2-benzylidenemalononitrile (**2**) (1.54 gm, 10 mmol) and 2,6-dichloroaniline (**8c**) (1.62 gm, 10 mmol) was heated under reflux in absolute ethanol (30 ml) for 10-12 hrs. then left to cool to room temperature overnight. The solid obtained and recrystallized from DMF to give **10c** as yellow crystals. **Yield:** 86%; **MP:** >300°C; **FT-IR (KBr, cm^{-1}):** 3400,3370 (NH), 3210,3170 (NH_2), 1687 (C=O), 2198 (CN), 1597 (C=C); **H^1NMR(300 MHz, DMSO-*d6*):** 4.5 (s, 1H, CH), 6.2 (s, 2H, NH_2), 7-7.5 (m, 8H,Ar-H), 11.0 (s, 1H, NH), 11.06 (s, 1H, NH); **MS (El, m/z (%)):** 427 (M+2, 64%), 426 (M+1, 22%), 425 (M^+, 70%), **Anal. Calcd. for $C_{20}H_{13}Cl_2N_5O_2$ (425):** C,56.35; H,3.07; N,16.43**Found:** C,56.33; H,3.07; N,16.42%.

4.2.7. 7-Amino-8-(4-chlorophenyl)-1,2,3,4,5,8-hexahydro-4-oxo-5-phenyl-2-thioxopyrido[2,3-d]pyrimidine-6-carbonitrile (12a).

A mixture of thiobarbituric acid (**11**) (1.39 gm, 10 mmol), 2-benzylidenemalononitrile (**2**) (1.54 gm, 10 mmol) and *p*-chloroaniline (**8a**) (1.23 ml, 10 mmol) was heated under reflux in absolute ethanol (30 ml) for 10-12 hrs. then left to cool to room temperature overnight. The solid obtained and recrystallized from DMF to give **12a** as white crystals. **Yield:** 73%, **MP:**280-282°C; **FT-IR (KBr, cm^{-1}):** 3386,3280 (NH), 3080,3012 (NH_2), 1660 (C=O), 2190 (CN),1620 (C=C), 1337 (C=S); **H^1NMR(300 MHz, DMSO-*d6*):** 4.47 (s, 1H, CH), 6.82 (s, 2H, NH_2),7-7.9 (m, 9H, Ar-H), 10.0 (s, 1H, NH), 10.03 (s, 1H, NH); **MS (El, m/z (%)):** 409 (M+2, 87%), 408 (M+1, 17%), 407(M^+, 84%), **Anal. Calcd. for $C_{20}H_{14}ClN_5OS$ (407):** C,58.89; H,3.46; N,17.17**Found:** C,58.87; H,3.45; N,17.17%.

4.2.8. 7-Amino-8-(4-bromophenyl)-1,2,3,4,5,8-hexahydro-4-oxo-5-phenyl-2-thioxopyrido[2,3-d]pyrimidine-6-carbonitrile (12b).

A mixture of thiobarbituric acid (**11**) (1.39 gm, 10 mmol), 2-benzylidenemalononitrile (**2**) (1.54 gm, 10 mmol) and *p*-bromoaniline (**8b**) (1.72 gm, 10 mmol) was heated under reflux in absolute ethanol (30 ml) for 10-12 hrs. then left to cool to room temperature overnight. The solid obtained and recrystallized from DMF to give **12b** as white crystals. **Yield:** 78%, **MP:** >300°C; **FT-IR (KBr, cm^{-1}):** 3310,3240 (NH), 3200,3160 (NH_2), 1676 (C=O), 2220 (CN), 1570 (C=C), 1346 (C=S); **H^{1}NMR(300 MHz, DMSO-*d6*):** 4.8 (s, 1H, CH), 6.0 (s, 2H, NH_2), 7-7.9 (m, 9H, Ar-H), 10.0 (s, 1H, NH),10.2 (s, 1H, NH); **MS (El, m/z (%)):** 453 (M+2, 19%), 452(M+1, 67%), 351(M$^+$, 18%), **Anal. Calcd. for $C_{20}H_{14}BrN_5OS$ (451):** C,53.11; H,3.12; N,15.48 **Found:** C,53.10; H,3.12; N,15.46%.

4.2.9. 7-Amino-8-(2,6-dichlorophenyl)-1,2,3,4,5,8-hexahydro-4-oxo-5-phenyl-2-thioxopyrido[2,3-d]pyrimidine-6-carbonitrile(12c).

A mixture of thiobarbituric acid (**11**) (1.39 gm, 10 mmol), 2-benzylidenemalononitrile (**2**) (1.54 gm, 10 mmol) and 2,6-dichloroaniline (**8c**) (1.62 gm, 10 mmol) was heated under reflux in absolute ethanol (30 ml) for 10-12 hrs. then left to cool to room temperature overnight. The solid obtained and recrystallized from DMF to give **12c** as white crystals. **Yield:** 82%, **MP:** >300°C; **FT-IR (KBr, cm^{-1}):** 3380,3310 (NH), 3210,3100 (NH_2), 1674 (C=O), 2190 (CN),1595 (C=C), 1345 (C=S); **H^{1}NMR(300 MHz, DMSO-*d6*):** 4.5 (s, 1H, CH), 6.8 (s, 2H, NH_2), 7-7.9 (m, 8H,Ar-H), 10.0 (s, 1H, NH), 10.4 (s, 1H, NH); **MS (El, m/z (%)):** 443 (M+2, 74%), 442 (M+1, 28%), 441(M$^+$, 82%), **Anal. Calcd. for$C_{20}H_{13}Cl_2N_5OS$ (441):** C,54.31; H,2.96; N,15.83**Found:**C,54.33; H,2.96; N,15.82%.

4.2.10. 5-Amino-3-methyl-4-phenyl-1H-pyrazolo[4,5:5′,6′]pyrido[3,2-d]pyrimidine-7H-thione(14).

A mixture of **6** (2.49 gm, 10 mmol) and thiourea (0.76gm, 10 mmol) in absolute ethanol (20 ml) containing sodium ethoxide (0.68 gm, 10 mmol) was refluxed for 6 hrs.the reaction mixture was left to cool to room temperature, then poured onto ice cold water (50 ml) and neutralized with dilute hydrochloric acid; the separated material was filtrated off and recrystallized from ethanol to give **14** as brown crystals. **Yield:** 89%, **MP:** 166-168°C; **FT-IR:(KBr, cm^{-1}):** 3363 (NH), 3213,3120 (NH_2), 3090 (NH), 1620 (C=N), 1589 (C=C), 1326(C=S); **H^{1}NMR(300MHz, DMSO-*d6*):** 2.7 (s, 3H, CH_3), 6.5 (s, 2H, NH_2), 7-7.4 (m, 5H, Ar-H), 10.09 (s, 1H, NH), 11.0 (s, 1H, NH); **MS(El, m/z(%)):** 310 (M+2, 7%), 309 (M+1, 26%), 308 (M$^+$, 91%); **Anal. Calcd. for $C_{15}H_{12}N_6S$ (308):** C,58.43;H,3.92; N,27.25**Found:**C,58.42; H,3.91; N,27.23%.

4.2.11. 3-Methyl-4-phenyl-5-(benzylideneamino)-1H-pyrazolo[4,3:5′,6′]pyrido[2,3-d]pyrimidine-7H-thione (15).

Drop wise addition of benzaldhyde to a stirred solution of **14** (3 gm, 10 mmol) in acetic acid (20 ml).The stirring was continued for 2 hrs. Then the solid collected and recrystallized from Dioxane to give white crystals. **Yield:** 75%; **MP:** 210-212°C; **FT-IR:** 3217,3024 (NH), 1589 (C=N), 1342 (C=S); **H^{1}NMR (300MHz, DMSO-*d6*):** 2.7 (s, 3H, CH_3), 4.5 (s,1H, CH), 7-7.5 (m, 10H, Ar-H), 11.03 (s, 1H, NH), 12.07(s, 1H, NH); **Anal. Calcd.for $C_{22}H_{16}N_6S$ (396):** C,66.65; H,4.07; N,21.20**Found:**C,66.65; H,4.07; N,21.20%.

4.2.12. 1-(5-Cyano-3-methyl-4-phenyl-1H-pyrazolo[3,4-b]pyridin-6-yl)-3-phenylthiourea(16).

A mixture of **6** (2.49 gm, 10 mmol) and phenylisothiocyanate (1.35 gm, 10 mmol) in dimethylformamide (30ml) containing a catalytic amount of triethylamine (4-6) drops was refluxed for 10 hrs. and then left to cool to room temperature. The reaction mixture was poured onto cold water for complete precipitation, and then filtered off washed with water dried well and recrystallized from aqueous ethanol to give brown crystals. **Yield:** 65%; **MP:** 231-233°C; **FT-IR:** 3386 (broad, NH), 2210(CN), 1624 (C=N), 1597(C=C), 1315 (C=S); **H^{1}NMR(300MHz, DMSO-*d6*):** 2.7(s, 3H, CH_3), 7-7.5(m, 10H, Ar-H), 8,6 (s, 1H, NH), 10.4(s, 1H, NH), 11.0 (s, 1H, 1NH); **Anal. Calcd. for $C_{21}H_{16}Cl_2N_6S$ (454):** C,65.61; H,4.19; N,21.86 **Found:**C,65.60; H,4.19; N,21.86%.

4.2.13. 6-Amino-10-[4-chlorophenyl-5-phenyl-2-thioxo-1,2,8,9-tetrahydropyrimidino[5,4:6′,5′]pyrido[2,3-d]pyrimidine-8H-one (18).

A mixture of **10a** (3.9 gm, 10 mmol) and thiourea(0.76 gm. 10 mmol) in absolute ethanol (20 ml) containing sodium ethoxide (0.68 gm, 10 mmol) was refluxed for 6 hrs.the reaction mixture was left to cool to room temperature, then poured onto ice cold water (50 ml) and neutralized with dilute hydrochloric acid; the separated material was filtrated off and recrystallized from ethanol to give **18** as brown crystals. **Yield:** 68%, **MP:** 289-291°C; **FT-IR:(KBr, cm^{-1}):** 3359,3290 (NH_2), 3197,3139 (NH), 1655 (C=O), 1616 (C=N), 1516 (C=C), 1365 (C=S); **H^{1}NMR(300MHz, DMSO-*d6*):** 4.5(s,1H,CH), 6.5 (s,2H,NH_2),7-7.3(m,10H, Ar-H, NH), 11.0 (s, 2H, 2NH); **MS(El, m/z(%)):** 452

(M+2, 28%), 451(M+1, 53%), 450(M^+, 29%); **Anal. Calcd. for $C_{21}H_{15}ClN_6O_2S$ (450):** C,55.94; H,3.35; N,18.64**Found:**C,55.94; H,3.36; N,18.65%.

4.2.14. 5,7-Diphenyl-6-imino-8-thino-10-(4-chlorophenyl)pyrimido[5,4:5′,6′]pyrido[3,2-d]pyrimidine-2,4-dione(19).

A mixture of **10a** (3.9 gm, 10 mmol) and phenylisothiocyanate (1.35 gm, 10 mmol) in dimethylformamide (30 ml) containing a catalytic amount of triethylamine (4-6) drops was refluxed for 10 hrs. and then left to cool to room temperature. The reaction mixture was poured onto cold water for complete precipitation, and then filtered off washed with water dried well and recrystallized from aqueous ethanol to give brown crystals. **Yield:** 68%; **MP:** 170-172°C; **FT-IR:** 3452,3228,3059 (NH), 1674 (C=O), 1593 (C=N), 1531 (C=C), 1334 (C=S); **H^1NMR(300MHz, DMSO-*d6*):** 4.5 (s,1H,CH), 7-7.8 (m, 15H, Ar-H, NH), 9.6 (s, 1H, NH), 11.0 (s, 2H, 2NH); **Anal. Calcd. for $C_{27}H_{19}ClN_6O_2S$ (526):** C,61.54; H,3.63; N,15.95**Found:**C,61.54; H,3.62; N,15.93%.

4.2.15. General method for synthesis of (20) and (21).

A mixture of **6** (2.49 gm, 10 mmol) and the appropriate of formic acid (99%, 10 ml) or formamide (10 ml) was boiled under reflux for 7 hrs. The reaction mixture was poured onto ice (50 gm). The resulting solid was collected and recrystallized from the proper solvent to give **20** and **21** respectively.

4.2.15.1. 3-Methyl-4-phenyl-1H-pyrazolo[4,3:5′,6′]pyrido[3,2-d]pyrimidin-5-0ne (20).

White crystals from EtOH. **Yield:** 90%; **MP:** 220-222°C; **FT-IR:** 3406,3286 (NH), 1693 (C=O), 1597 (C=N), 1539 (C=C); **H^1NMR(300MHz, DMSO-*d6*):** 2.87 (s, 3H, CH_3), 7.1-7.3 (m, 5H, Ar-H), 9.3 (s, 1H, CH-pyrimidine), 10.85 (s, br, 2H, 2NH); **MS(El, m/z(%)):** 279 (M+2, 45%), 278 (M+1, 30%), 277 (M^+, 12%); **Anal. Calcd.for $C_{15}H_{11}N_5O$ (277):** C,64.97; H,4.00; N,25.26 **Found:** C,64.96; H,4.00; N,25.26%.

4.2.15.2. 5-Amino-3-methyl-4-phenyl-1H-pyrazolo[4,3:5′,6′]pyrido[3,2-d]pyrimidine (21).

Brown crystals from Dioxane.**Yield:** 89%; **MP:** >300°C; **FT-IR:** 3336,3209 (NH_2), 3035 (NH), 1627 (C=C), 1550 (C=C); **H^1NMR(300MHz, DMSO-*d6*):** 2.6 (s, 3H, CH_3), 6.5 (s, 2H, NH_2), 7.1-7.5 (m, 5H, Ar-H), 9.5 (s, 1H, CH-pyrimidine), 11.08(s, 1H, NH); **MS(El, m/z(%)):** 277 (M+1, 71%), 276 (M^+, 77%); **Anal. Calcd. for $C_{15}H_{12}N_6$ (276):** C,65.21; H,4.38; N,30.42**Found:** C,65.21; H,4.39; N,30.41%.

4.2.16. (E)-ethyl N-5-cyano-3-methyl-4-phenyl-1H-pyrazolo[3,4-b]pyridin-6-ylformimidate (22).

A mixture of **6** (2.49 gm, 10 mmol) and triethylorthoformate (1.48 gm, 10 mmol) in dry acetic anhydride (20 ml) was heated under reflux for 10 hrs. The reaction mixture was poured onto ice (50gm). The resulting solid was collected and recrystallized from EtOH. Yield: 94%; **MP**: 184-186°C; **FT-IR:** 3209 (NH), 2935,2854 (aliphatic hydrogen), 2214 (CN), 1624 (C=N), 1512 (C=C); **H^1NMR(300MHz, DMSO-*d6*):** 1.28-1.33 (t, 3H, $CH_2\underline{CH_3}$), 2.53 (s,3H,CH_3), 4,3-4.37 (q, 2H, $\underline{CH_2}CH_3$), 4.97 (s , 1H, CH-aliphatic), 7.26-7.39 (m, 5H-Ar-H), 8.63 (s, 1H, NH); **MS(El, m/z(%)):** 307 (M+2, 35%), 306 (M+1, 30%), 305 (M^+, 17%); **Anal. Calcd. for $C_{17}H_{15}N_5O$ (305):** C,66.87; H,4.95; N,22.94 **Found:** C,66.86; H,4.93; N,22.93%.

4.2.17. 6-Amino-5-imino-3-methyl-4-phenyl-1H-pyrazolo[4,3:5′,6′]pyrido[3,2-d]pyrimidine (23).

A mixture of **22** or **24** (10mmol) and hydrazine hydrate (99.9%, 10ml, 20mmol) was heated under reflux in absolute ethanol (20 ml) for 3-5 hrs. The reaction mixture was left to cool overnight, the solid collected and recrystallized to give white crystals from EtOH. **Yield:** 90%; **MP:** 220-222°C; **FT-IR:** 3398,3298 (NH_2), 3205,3058 (NH), 1624 (C=N), 1566 (C=N); **H^1NMR(300MHz, DMSO-*d6*):** 2.7 (s, 3H, CH_3), 7.1-7.3 (m, 5H, Ar-H), 6.5 (s, 2H, NH_2), 9.58 (s, 1H, CH-pyrimidine), 11.0 (s, 1H, 1NH), 12.0 (s, 1H, NH); **MS(El, m/z(%)):** 293(M+2, 15%), 292(M+1, 30%), 291(M^+, 12%); **Anal. Calcd. for $C_{15}H_{13}N_7$ (291):** C,61.84; H,4.50; N,33.66 **Found:** C,61.84;H,4.52;N,33.68%.

4.2.18. N'-(5-cyano-3-methyl-4-phenyl-1H-pyrazolo[3,4-b]pyridin-6-yl)-N,N-dimethylformamidine (24).

A mixture of **6** (2.49 gm, 10 mmol) and DMF-DMA (11.9 gm, 14 ml, 10 mmol) in dry dioxane (20 ml) was refluxed for 4 hrs. The reaction mixture was cooled to room temperature, the solid collected and recrystallized to give orange crystals from EtOH. **Yield:** 93%; **MP:**184-186°C; **FT-IR:** 3306 (NH), 2191 (CN), 1620 (C=N), 1569(C=C); **H^1NMR(300MHz, DMSO-*d6*):** 2.7(s,3H,CH_3), 2.8(s, 6H , $2CH_3$), 7.1-7.3 (m, 5H, Ar-H), 4.5

(s,1H,CH), 11.0 (s, 1H, NH); **MS(El, m/z(%)):** 306 (M+2, 85%), 305 (M+1, 36%), 304 (M^+, 16%); **Anal. Calcd. for $C_{17}H_{16}N_6$ (304):** C,67.09; H,5.30; N,27.61 **Found:** C,67.07; H,5.30; N,27.61%.

4.2.19. General method for synthesis of (26), (27).

A mixture of **10a** (3.91 gm, 10mmol) and the appropriate of formic acid (99%, 10 ml) or formamide (10 ml) was boiled under reflux for 7 hrs. The reaction mixture was poured onto ice (50 gm.). The resulting solid was collected and recrystallized from the proper solvent to give **26** and **27** respectively.

4.2.19.1. 5-Phenyl-10-(4-chlorophenyl)pyrimido[5,4:5′,6′]pyrido[3,2-d]pyrimidine-2,4,6-trione(26).

White crystals from EtOH. **Yield:** 91%; **MP:** 240-242°C; **FT-IR:** 3128,3040 (NH), 2935,2800 (CH-aliphatic), 1686 (C=O), 1635 (C=N), 1596 (C=C); **H^1NMR(300MHz, DMSO-*d6*)** 4.45 (s, 1H, CH), 7.2-7.3 (m, 10H, Ar-H, NH), 9.5 (s, 1H, pyrimidine), 12.0 (s,br, 2H, 2NH) ; **MS(El, m/z(%)):** 421(M+2, 13%), 419(M^+, 12%); **Anal. Calcd. for$C_{21}H_{14}ClN_5O_3$ (419):** C,60.08; H,3.36; N,16.68 **Found:** C,60.08; H,3.36; N,16.68%.

4.2.19.2. 6-Amino-5-phenyl-10-(4-chlorophenyl)pyrimido[5,4:5′,6′]pyrido[3,2-d]pyrimidin-2,4-dione (27).

Brown crystals from EtOH. **Yield:** 71%; **MP:** 205-207°C ; **FT-IR:** 3360 (NH), 3275,3213 (NH_2), 3074 (NH), 1678 (C=O), 1604 (C=N); **H^1NMR(300MHz, DMSO-*d6*):** 4.05 (s, 1H, CH), 6.8 (s, 2H, NH_2), 7.1-7.5 (m, 9H, Ar-H), 9.5 (s, 1H, CH-pyrimidine), 11.09 (s,br, 2H,2NH); **MS(El, m/z(%)):** 418 (M^+, 15%); **Anal. Calcd. for $C_{21}H_{15}ClN_6O_2$ (418):** C,60.22; H,3.61; N,20.07 **Found:** C,60.21; H,3.61; N,20.07%.

4.2.20. (E)-ethyl N-8-(4-chlorophenyl)-6-cyano-2,4-dioxo-5-phenyl-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidin-7-ylformimidate (28).

A mixture of **10a** (3.91 gm, 10 mmol) and triethylorthoformate (1.48 gm, 10 mmol) in dry acetic anhydride (20 ml) was heated under reflux for 10 hrs. The reaction mixture was poured onto ice (30 gm). The resulting solid was collected and recrystallized from EtOH. **Yield**: 81%; **MP:** 195-197°C ; **FT-IR:** 3309,3100 (NH), 2962,2839 (aliphatic hydrogen), 2206 (CN), 1693 (C=O), 1600 (C=N), 1512 (C=C); **H^1NMR(300MHz, DMSO-*d6*):** 1.12-1.14(t, 3H, $CH_2\underline{CH_3}$) , 4,31-4.36(q, 2H, $\underline{CH_2}CH_3$), 4.03(s, 1H, CH), 4.5 (s , 1H, CH), 7.1-7.3(m, 9H, Ar-H), 11.09(s,br, 2H,2NH); **MS(El, m/z(%)):**449(M+2, 24%), 447(M^+, 26%); **Anal. Calcd. for $C_{23}H_{18}ClN_5O_3$ (447):** C,61.68; H,4.05; N,15.64 **Found:** C,61.68; H,4.05; N,15.64%.

4.2.21. 7-Amino-6-imino-5-phenyl-10-(4-chlorophenyl)pyrimido[5,4:5′,6′]pyrido[3,2-d]pyrimidin-2,4,6-trione (29).

A mixture of **28** or **30** (10 mmol) and hydrazine hydrate (99.9%, 10 ml, 20 mmol) was heated under reflux in absolute ethanol (20 ml) for 3-5 hrs. The reaction mixture was left to cool overnight, the solid collected and recrystallized to give white crystals from acetic acid. **Yield:** 77%; **MP:** 230-232°C ; **FT-IR:** 3367,3325 (NH), 3213,3163(NH_2), 1680 (C=O), 1543(C=C);**H^1NMR(300MHz,DMSO-*d6*):** 4.57(s,1H,CH), 6.5 (s,2H,NH_2), 7.1-7.3 (m, 9H, Ar-H), 9.3 (s, 1H, CH-pyrimidine), 10.8 (s, 2H,2NH), 11.09 (s, 1H, NH); **MS(El, m/z(%)):** 433 (M^+, 45%); **Anal. Calcd. for $C_{21}H_{16}ClN_7O_2$ (433):** C,58.14; H,3.72; N,22.60 **Found:** C,58.14; H,3.72; N,22.59%.

4.2.22. N′-(8-(4-chlorophenyl)-6-cyano-1,2,3,4,5,8-hexahydro-2,4-dioxo-5-phenylpyrido[2,3-d]pyrimidin-7-yl)-N,N-dimethylformamidine (30).

A mixture of **10a** (3.91gm, 10 mmol) and DMF-DMA (11.9 gm, 14 ml, 10 mmol) in dry dioxane (20 ml) was refluxed for 4 hrs. The reaction mixture was cooled to room temperature, the solid collected and recrystallized to give orange crystals from acetic acid. **Yield:**94%; **MP:** 210-212 °C; **FT-IR:** 3330,3210 (NH), 2990,2845 (CH-aliphatic), 2220 (CN), 1680 (C=O), 1620 (C=N); **H^1NMR(300MHz, DMSO-*d6*):** 4.37(s,1H,CH), 4.95(s,1H,CH),2.8(s,6H,$2CH_3$), 7.1-7.3(m, 9H, Ar-H), 11.06 (s,2H,2NH); **MS(El, m/z(%)):** 448 (M+2, 32%), 447 (M+1, 25%), 446 (M^+, 100%); **Anal. Calcd. for $C_{23}H_{19}ClN_6O_2$ (446):** C,61.82; H,4.29; N,18.81 **Found:** C,61.82; H,4.28; N,18.80%.

4.2.23. General method for synthesis of 32a-c, 33, 34aand34b

A mixture of **12a** (4 gm, 10 mmol), and the appropriate of hydrazonoyl halides(10 mmol) was boiled under reflux in chloroform(30ml) containing catalytic amount of TEA (10 drops) for12-15hrs.the reaction mixture was left overnight for cooling, the solid collected and recrystallized from the proper solvent to give the corresponding **32a-c, 33, 34a** and **34b**.

4.2.23.1. Ethyl (1,6-diphenyl-5-oxo-7-cyano-8-amino-9-(4-chlorophenyl) 1,2,4-triazolo(4,3-6\`,7\`)-3,4,5,8-tetrahydropyrido[2,3-d] pyrimidine)acetate (32a).

Yellow crystals from EtOH.**Yield:** 75%, **MP:** 165-167°C, **FT-IR:** 3280,3200 (NH_2), 2920,2800 (CH-aliphatic), 2200 (CN), 1735,1680 (C=O); **H^1NMR(300MHz, DMSO-*d6*):** 1.21-1.23 (t, 3H, $CH_2\underline{CH_3}$), 4.3-4.35 (q, 2H, $\underline{CH_2}CH_3$), 4.83(s, 1H, CH), 5.5 (s, 2H, NH_2), 7-7.3 (m, 14H, Ar-H), **MS(El, m/z(%)):** 565 (M+2, 10%), 564 (M+1, 56%) , 563(M^+, 12%), **Anal. Calcd. for $C_{30}H_{22}ClN_7O_3$ (563):** C,63.89; H,3.93; N,17.38 **Found:** C,63.88; H,3.93; N,17.38%.

4.2.23.2. Ethyl (1-diphenyl-5-oxo-6,9-bis-(4-chlorophenyl) 7-cyano-8-amino-1,2,4-triazolo(4,3-6\`,7\`)-3,4,5,8-tetrahydropyrido[2,3-d] pyrimidine)acetate (32b).

Yellow crystals from EtOH. **Yield:** 73%, **MP:** 134-136°C, **FT-IR:** 3320,3300 (NH_2), 2900,2820 (CH-aliphatic), 2197 (CN), 1715,1689 (C=O); **H^1NMR(300MHz, DMSO-*d6*):** 1.22-1.25 (t, 3H, $CH_2\underline{CH_3}$), 4.3-4.35 (q, 2H, $\underline{CH_2}CH_3$), 4.9 (s, 1H, CH), 5.7(s, 2H, NH_2), 7-7.5 (m, 13H, Ar-H); **MS(El, m/z(%)):** 599 (M+2, 71%), 598 (M+1, 18%) , 597 (M^+, 67%), **Anal. Calcd. for $C_{30}H_{21}Cl_2N_7O_3$ (597):** C,60.21; H,3.54; N,16.38 **Found:** C,60.21; H,3.54; N,16.37%.

4.2.23.3. Ethyl (1-diphenyl-5-oxo-6-(p-tolyl)-7-cyano-8-amino-9-(4-chlorophenyl)-1,2,4-triazolo(4,3-6\`,7\`)-3,4,5,8-tetrahydropyrido [2,3-d] pyrimidine)acetate (32c).

Yellow crystals from EtOH. **Yield:** 77%, **MP:** 151-153°C, **FT-IR:** 3380,3320 (NH_2), 2920,2800 (CH-aliphatic), 2220 (CN), 1720,1686 (C=O); **H^1NMR(300MHz, DMSO-*d6*):** 1.1-1.13 (t,3H, $CH_2\underline{CH_3}$),2.7(s, 3H, CH_3), 4.32-4.33 (q, 2H, $\underline{CH_2}CH_3$), 4.89(s, 1H, CH), 5.5(s, 2H, NH_2), 7.1-7.3(m, 13H, Ar-H), **MS(El, m/z(%)):** 579 (M+2, 87%), 578(M+1, 16%) , 577(M^+, 89%), **Anal. Calcd. for $C_{31}H_{24}ClN_7O_3$ (577):** C,64.41; H,4.19; N,16.96**Found:** C,64.41; H,4.18; N,16.97%.

4.2.23.4. 1,6-Diphenyl-3-benzoyl-5-oxo-8-amino-9-(4-chlorophenyl)-1,2,4-triazolo(4,3-6\`,7\`)-3,4,5,8-tetrahydropyrido[2,3-d] pyrimidine-7-carbonitrile (33).

Orange crystals from acetic acid. **Yield:** 71%, **MP:** 179-181°C, **FT-IR:** 3280,3120 (NH_2), 2910,2890 (CH-aliphatic), 2200 (CN), 1680,1665(CO); **H^1NMR(300MHz, DMSO-*d6*):** 4.5(s, 1H, CH), 5.7 (s, 2H, NH_2), 7-7.3 (m, 19H, Ar-H); **MS(El, m/z(%)):** 596 (M+1, 16%) , 595(M^+, 14%), **Anal. Calcd. for $C_{34}H_{22}ClN_7O_2$ (595):** C,68.51; H,3.72; N,16.45**Found:** C,68.51; H,3.72; N,16.46%.

4.2.23.5. 1,9-Bis-(4-chlorophenyl)-3-acetyl-5-oxo-8-amino-1,2,4-triazolo(4,3-6\`,7\`)-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-7-carbonitrile (34a).

Yellow crystals from EtOH. **Yield:** 81%, **MP:** 172-174°C, **FT-IR:** 3290,3200 (NH_2), 2920,2890 (CH-aliphatic), 2197(CN), 1690 (CO); **H^1NMR(300MHz, DMSO-*d6*);** 3.2 (s, 3H, CH_3), 4.56 (s, 1H, CH), 5.5 (s, 2H, NH_2), 7-7.5(m, 14H, Ar-H), **MS(El, m/z(%)):** 534(M+1, 15%) , 533(M^+, 100%), **Anal. Calcd. for $C_{29}H_{20}ClN_7O_2$ (533):** C,62.23; H,3.78; N,18.36 **Found:** C,62.22; H,3.78; N,18.36%.

4.2.23.6. 1-Phenyl-3-acetyl-5-oxo-8-amino-9-(4-chlorophenyl)-1,2,4-triazolo(4,3-6\`,7\`)-3,4,5,8-tetrahydropyrido[2,3-d] pyrimidine-7-carbonitrile (34b).

Yellow crystals from EtOH. **Yield:** 79%, **MP:** 191-193°C, **FT-IR:** 3380,3300 (NH_2), 2920,2800 (CH-aliphatic), 2210 (CN), 1689 (CO); **H^1NMR(300MHz, DMSO-*d6*):** 3.2 (s, 3H, CH_3), 4.5 (s, 1H, CH), 5.56 (s,2H,NH_2), 7.3-7.6(m, 13H, Ar-H), **MS(El, m/z(%)):** 569 (M+2, 10%), 578 (M+1, 14%) , 567 (M^+, 87%), **Anal. Calcd. for $C_{29}H_{19}Cl_2N_7O_2$ (567):** C,61.28; H,3.37; N,17.25 **Found:** C,61.28; H,3.38; N,17.25%.

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