Heteroannulation of Pyrido[2,3-d]Pyrimidines. Synthesis and Spectral Characterization of Pyridotriazolopyrimidines, Pyridopyrimidotriazine and Pyridopyrimidotriazepine Derivatives

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Abstract Number of pyridotriazo-, pyridothiazol-, pyridotetrazolopyrimidines and pyrido-pyrimidotriazepine derivatives were prepared using the readily obtainable starting material pyrido[2,3-d]pyrimidinethione and its hydrazino derivative. The antimicrobial screening of selected synthesized compounds was done using the agar diffusion assay. The IR, 1H NMR and mass spectra of the synthesized compounds were investigated.

Keywords Fused Pyrimidines, One Carbon Donor, Fused [1,2,4]Triazepine

1. Introduction

Pyridopyrimidines were reported to constitute series of compounds which showed broad biological activity such as anticonvulsive, antitumor, antiasthmatic, antiallergic, anti-hypertensive and useful as diuretic compounds, together with many other applications. As a continuation for our interest for the studies on synthesis of different heterocycles of expected biological activity, the present investigation deals with the synthesis and chemistry of new heteroannulated pyrido[2,3-d]pyrimidine derivatives with the aim of finding new chemotherapeutic agents.

2. Results and Discussions

The reaction of equimolar portions of m-chloro-α-cyano-cinnamonic acid 1 with 6-aminouracil 2 in refluxing ethanol in the presence of a catalytic amount of piperidine afforded 7- amino- 5-(3-chlorophenyl)- 4- oxo- 2-thioxo-1H, 3H-pyrido[2,3-d]pyrimidin-6-carbonitrile 3. The structure 3 was established as pyridopyrimidine rather than thiazinopyrimidine 4 on the basis of IR and 1H-NMR spectra which revealed a pattern completely in accord with the structure 3. (Scheme 1)

Thus, the i.r spectrum of 3 exhibited the well defined absorption bands at 3447, 3299, 3216 (\(\nu_{\text{NH, NH}}\)), 2216 (\(\nu_{\text{C≡N}}\)), 1696 (\(\nu_{\text{C=O}}\)), 1623 (\(\nu_{\text{C=N}}\)) and 1170 (\(\nu_{\text{C=S}}\)). 1H-NMR spectrum (DMSO-\(d_6\)) revealed the following signals at \(\delta\) 12.7 (s, 1H, NH, exchangeable with D\(_2\)O), 12.2 (s, 1H, NH, exchangeable with D\(_2\)O), 7.7 (br.s, 2H, NH\(_2\), exchangeable with D\(_2\)O), 7.04-6.8 (m, 4Harom.). The structure 3 was further supported by its mass spectrum which displayed the correct molecular ion peak at m/z = 330 (M, 100%) which is the base peak together with M+1 and M+2 peaks at m/z = 331 (17.6%), 332 (31.2%), respectively.

The formation of 3 was assumed to proceed via nucleophilic addition of thiouracil C -5 to the β-carbon of the activated double bond in cinnamonic acid followed by cycloaddition of the acyclic Michael adduct and aromatization as shown in scheme 2.

Compelling chemical evidence for the structure 3 is forthcoming from the reaction with methyl iodide, 1,2-dichloroethane and ethylchloroacetate under different conditions and in all cases S-alkylated products were isolated (Scheme 3).

Refluxing compound 3 with methyl iodide in ethanolic...
sodium hydroxide (4N) yielded 7-amino-5-(3-chloro-phenyl)-4-oxo-2-methythio-3H-pyrido[2,3-d]pyrimidin-6-carbonitrile 5. 1H-NMR spectrum of 5 shows the characteristic signal for S-CH₃ group as singlet at δ 3.3 (ppm). Furthermore, the mass spectrum of 5 shows the correct molecular ion peak at m/z = 343 (28.4%) which in a good accord with the proposed structure. When compound 3 was allowed to react with 1,2-dichloroethane in boiling DMF in the presence of anhydrous potassium carbonate yielded Bis-S-[7-amino-5-(3-chlorophenyl)-6-cyano-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl]ethane-1,2-dithiol 6. 1H-NMR spectrum (DMSO-d₆) of compound 6 showed the following signals at δ (ppm) 12.4 (br.s, 1H, exchangeable with D₂O), 11.8 (s, 1H, exchangeable with D₂O), 7.77-7.3 (m, 8H arom.), 4.2 (br.s, 4H, exchangeable with D₂O) and 2.6 (br.s, 4H). On the other hand, the mass spectrum of 6 devoid the molecular ion peak but retained peak at m/z = 462 (97.1%) attributable for the radical cation [M-2Ar].

Ethyl-S-[7-amino-5-(3-chlorophenyl)-6-cyano-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl]thioacetate 7 was obtained in a fairly good yield as the sole product upon alkylation of 3 with ethylchloroacetate in boiling pyridine. IR spectrum of 7 displayed ν_NH₂ at 3470, 3300, 3170 cm⁻¹, ν_C≡N at 2208 cm⁻¹ and ν_C=O at 1667 cm⁻¹ (lower than the expected value for the ester group due to chelated H-bonding). 1H-NMR spectrum of compound 7 revealed signals at δ (ppm) 12.5 (s, 1H, NH, exchangeable with D₂O), 11.8 (s, 1H, exchangeable with D₂O), 7.77-7.3 (m, 8H arom.), 4.2 (br.s, 4H, exchangeable with D₂O) and 2.6 (br.s, 4H). On the other hand, the mass spectrum of 6 devoid the molecular ion peak but retained peak at m/z = 462 (97.1%) attributable for the radical cation [M-2Ar].
The formation of the hydrazino derivative 8 from 3 or 5 could be visualized on the basis of tetrahedral and $S_N^2$ aromatic mechanisms. (Scheme 4)

As a part of this work, the utility of readily obtainable hydrazino derivatives in heterocyclic synthesis was investigated. The work resulted in development of several new approaches for the synthesis of otherwise difficulty accessible multifunctional heterocyclic derivatives of utility for further chemical transformations and for biological activity evaluation. We report here the results of our investigation on the behaviour of 8 towards varieties of electrophilic reagents.

Upon treatment of compound 8 with ethoxymethylene malononitrile in boiling pyridine, a yellow solid product with molecular formula $C_{18}H_{10}ClN_9O$ [403] was obtained as the sole product. Three structures for this product seemed possible 9-11. (Scheme 5) The i.r spectrum of this product displayed the absorption bands for NH$_2$, NH at 3406, 3323, 3222, 3172 cm$^{-1}$ and one sharp stretching absorption band for C≡N at 2225 cm$^{-1}$, $\nu$C=O at 1685 cm$^{-1}$ and $\nu$C=N at 1641 cm$^{-1}$. The alcoholic solution of this product does not show the characteristic colour of the pyrazole ring upon treatment with ferric chloride solution, this eliminate structure 10. The mass spectrum of this product show the correct molecular ion peak at m/z = 403 (62.7%) together with M+1 and M+2 at m/z = 404 (39.2%), 405 (20.7%), respectively. The base peak represented at m/z = 402 (M-1, 100%). All these data agree well with structure 11. (Scheme 5)
The formation of 11 could be explained on the basis of nucleophilic attack by the hydrazino nitrogen at the β-carbon atom of the activated nitrile with simultaneous elimination of ethanol molecule followed by 1,7-exo-dig. cyclization. (Scheme 6)

![Scheme 6](image)

Treatment of compound 8 with phthalic anhydride in boiling acetic acid yielded the phthalazinedione derivative 12 as the sole product (one spot in TLC). (Scheme 5) The analytical and spectral data were completely in accord with the assigned structure. Thus, the i.r spectrum of 12 displayed the ν(NH2) at 3388, 3334, 3217 cm-1, ν(C=O) at 1715 cm-1 and ν(C≡N) at 2215 cm-1. The mass spectrum of 12 shows the correct molecular ion peak at m/z = 458 (35.15%) together with the base peak at m/z = 456 (100%) attributable for [M-H2]. (C.f Exp.) (Scheme 5)

The reaction of 8 with benzil in refluxing ethanol in the presence of triethylamine afforded the pyrido[2,3-d]pyrimidin-6-carbonitrile 14a,b. Furthermore, the reaction of compound 8 with ethylacetoacetate in refluxing pyridine yielded 7-amino – 5 -(3-chlorophenyl)-2-(3,5-disubstituted pyrazol-1-yl)-3,4-dihydro-pyrido [2,3-d]pyrimidin-6-carbonitile 14. Structures 14a,b and 15 were deduced from the full analysis of IR, 1H-NMR and mass spectra (C.f Exp.). (Scheme 5)

The formation of the pyrazole derivatives 14a,b and 15 from the hydrazine derivative 8 could be visualized via the nucleophilic addition of the amino group of the hydrazino on the carbonyl group of the acetyl group rather than that of the benzoyl and/or carboethoxy group which less positively charged and more crowded through tetrahedral mechanism with elimination of water to give the condensation product (not isolated) followed by 1,5-exo-trig cyclization (Scheme 8).

![Scheme 8](image)

When compound 8 was reacted with penta-2,4-dione and/or 1-phenyl-buta-1,3-dione in molar ratio (1:1) in refluxing pyridine afforded 7-amino-5-(3-chlorophenyl)-2-(3,5-disubstituted pyrazol-1-yl)-3,4-dihydro-pyrido [2,3-d]pyrimidin-6-carbonitrile 14a,b. Furthermore, the reaction of compound 8 with ethylacetoacetate in refluxing pyridine yielded 7-amino – 5 - (3-chlorophenyl)-2-(3-methyl pyrazol-5-on-1-yl)-4–oxo-3,4-dihydro-pyrido [2,3-d]pyrimidin-6-carbonitile 14. Structures 14a,b and 15 were deduced from the full analysis of IR, 1H-NMR and mass spectra (C.f Exp.). (Scheme 5)

[1,2,4]Triazoles represent a class of heterocyclic compounds of significant importance in medicine. They used in metalorganic chemistry as polyfunctional ligands and exhibit a broad spectrum of biological activity. Pronounced pharmacological and biological activities are also intrinsic for pyridopyrimidines. This stimulated us to combine the above pharmacophoric fragments in a single molecule with the aim of finding new chemotherapeutic agents.

The hydrazine derivative 8 was used as the key intermediate for exclusive synthesis of pyridotriazolopyrimidines through the reaction with one carbon donors such as phenyl isothiocyanate, carbon disulfide, formic acid, ethyl chloroformate and acetyl chloride. (Scheme 9)
Thus, the reaction of 8 with phenyl isothiocyanate in refluxing pyridine yielded the pyridotriazolopyrimidine derivative 16. The same product 16 was obtained upon treatment of a solution of 8 in pyridine with carbon disulphide for 18hrs on water-bath. Identity was confirmed by m.p, mixed m.p, IR and MS spectra. The formation of 16 is assumed to proceed via nucleophilic addition of nitrogen nucleophile of amino group of the hydrazino group to the activated double bond –N=C=S in the phenyl isothiocyanate followed by 1,5-exo-trig. cyclization through loss of aniline molecule while, in case of addition to carbon disulphide, the nucleophilic attack occurred at the C=S group of carbon disulphide followed by cyclization and elimination of H₂S molecule. (Scheme 10)

The structure 16 was confirmed from the correct analytical and spectroscopic data (C.f Exp.). The EI-MS shows the molecular ion peak which is the base peak at m/z = 369 (100%).

Upon refluxing the hydrazino derivative 8 with formic acid, a yellow solid product was obtained which identified as pyridotriazolopyrimidine derivative 17. The infrared spectrum of 17 displayed the well defined absorption bands at 3312 (br.), 3165 (br.) cm⁻¹ (ν₅NH₂), 2227 cm⁻¹ (νc≡N), 1706 cm⁻¹ (νC=O) higher than that of 8 which indicates the absence of enolic form and 1634 cm⁻¹ (νC=N). Full analysis of the mass spectrum of 17 shows the correct molecular ion peak at m/z = 338 (57.3%) and the base peak at m/z = 337 (100%) attributable to M-1 peak.

The reaction of 8 with ethyl chloroformate in refluxing pyridine yielded the pyridotriazolopyrimidine derivative 18 whose structure was confirmed by analytical and spectroscopic data. Thus, the mass spectrum of 18 shows the correct molecular ion peak at m/z = 353 (74.1%) together with M+1 and M+2 peaks at m/z = 354 (44.4%), 355 (24.7%), respectively. The peak at m/z = 352 (100%) is attributable for M-1 peak.

Surprisingly, the reaction of 8 with phenyl isocyanate in refluxing pyridine afforded the same compound 18 (identity m.p, mixed m.p, TLC, IR comparison). Other product was formed when the mother liquor was diluted with water which detected to be the diphenyl urea by identity with authentic sample and the mass spectrum of this compound show the molecular ion peak at m/z = 212 (10.9%).

Reflexing of 8 with acetyl chloride in boiling pyridine for 30 min. afforded a product with molecular formula C₁₈H₁₄ClN₇O₂ [M⁺ = 393 (18.31%)]. The microanalysis and mass spectrum indicates the incorporation of two moles of acetyl groups in the reaction product followed by elimination.
of water molecule. This product was identified as 8-acetamido-6-(3-chlorophenyl)-3-methyl-5-oxo-1H-1,2,4-triazolo[4,3-a]pyrido[2,3-d] pyrimidin-7-carbonitrile 19. (Scheme 9)

The i.r. spectrum of 19 devoid the absorption bands for ν\textsubscript{NH2} which suggest the N-acetylation for this product, furthermore, the higher value for \textsubscript{νC=O} (pyrimidone) at 1720 cm\textsuperscript{-1} than the starting material (1692 cm\textsuperscript{-1}) together with bands at 1704 cm\textsuperscript{-1} for acetyl group were in accordance with the proposed structure. \textsuperscript{1}H-NMR spectrum of 19 (DMSO-d\textsubscript{6}) revealed signals at δ 11.06 (s, 1H, exchangeable with D\textsubscript{2}O), 7.6-7.3 (m, 4Harom.), 3.3 (br.s, 1H, exchangeable with D\textsubscript{2}O), 2.4 (s, 3H) and 2.1 (s, 3H). Full analysis for the mass spectrum of 19 shows the correct molecular ion peak at m/z = 393 (100%) together with the base peak at m/z = 351 (100%) characteristic for the radical cation resulted from loss of a ketone molecule.

When compound 8 was subjected to react with 2-cyano-4-chloro-cinnamonitrile in refluxing pyridine for 6hrs until no more substrates (TLC), pyridotriazolopyrimidine derivative 20 was obtained in fairly good yield.

The mass spectrum of 20 showed a fragmentation pattern which in harmony with the proposed structure. The molecular ion peak displayed at m/z = 450 (28.3%) together with a peaks characteristic for M+1 and M+2 at m/z = 451 (7.6%), 452 (6.3%), respectively. The base peak at m/z = 338 (28.3%) together with the base peak at m/z = 451 (17.6) together with the base peak at m/z = 351 (100%) characteristic for the radical cation resulted from loss of a ketene molecule.

The conversion of 8 to 20 could be visualized on the basis of the nucleophilic attack by nitrogen of the hydrazino group at the electron deficiency β-carbon of the arylidene followed by elimination of malononitrile molecule under the reaction conditions and 1,5-endo-trig. cyclization. (C.f. Scheme 11)

![Scheme 11](image)

4. Experimental

Melting points are uncorrected and were measured by an electric melting point apparatus (G-K). The IR spectra were recorded on a Pye-Unicam SP1200 spectrophotometer using KBr Wafer technique. The \textsuperscript{1}H-NMR spectra were determined on a Varian GEMINI 200 MHz NMR spectrophotometer using CDCl\textsubscript{3} or DMSO-d\textsubscript{6} as solvent and TMS as an internal standard. All chemical shifts are in ppm downfield from TMS. The elemental analysis were carried out in microanalytical lab of Faculty of Science, Ain Shams University. MS were recorded on Shimadzu GC-MS QP1000EX instrument in microanalytical lab, Cairo University. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds were carried out by TLC.

**Reaction of 6-aminothiouracil with arylidine malononitrile:** Formation of 7-amino-5-(3-chlorophenyl)-4-oxo-2-thioxo-1H,3H-pyrido[2,3-d]pyrimidin-6-carbonitrile 3

A mixture of 6-aminothiouracil (1.43 g, 0.01 mole) and 2-cyano-m-chloro cinnamonic acid (0.01 mole) in ethanol (50 ml) containing piperidine (1 ml) was heated under reflux for 6 hrs (TLC). The deposited solid during reflux was collected by filtration with suction, washed by ethanol, dried and crystallized from dioxane to give 3 as yellow crystals, m.p. 302-4°C, yield 64%. IR (KBr): 3447, 3299, 3216 (ν\textsubscript{NH2, NH}), 1623 cm\textsuperscript{-1} and 1170 (ν\textsubscript{C=S}). \textsuperscript{1}H-NMR (DMSO-d\textsubscript{6}): δ (ppm) 12.77 (s, 1H, NH, exchangeable with D\textsubscript{2}O), 12.2 (s, 1H, NH, exchangeable with D\textsubscript{2}O), 7.7 (br.s, 2H, NH\textsubscript{2}, exchangeable with D\textsubscript{2}O), 7.04-6.8 (m, 4Harom.) MS (m/z): 330 (M, 100), 331 (M+1=1, 17.6), 332 (M+2, 31.2), 305 (28.6), 271 (14.8), 190 (10.5), 84 (83.7), 56 (85.7). Anal. Calcd. for C\textsubscript{15}H\textsubscript{10}ClN\textsubscript{5}O\textsubscript{5}: C, 52.4; H, 2.6; N, 21.2; S, 10.0; Cl, 10.82. Found: C, 51.21; H, 2.6; N, 21.06; S, 10.0; Cl, 10.82.

**Alkylation of 3 using methyl iodide:** Formation of 7-amino-5-(3-chlorophenyl)-4-oxo-2-methylthio-3H-pyrido[2,3-d]pyrimidin-6-carbonitrile 5

A mixture of 3 (3.3 g, 0.01 mole), methyl iodide (1.4 ml, 0.01 mole) and 4N sodium hydroxide (10 ml) in ethanol (50 ml) was refluxed for 3 hrs. The excess solvent was distilled and the reaction mixture was poured into ice-water and acidified with conc. HCl. The separated solid was filtered off, washed several times with water, dried and recrystallized from ethanol as colourless crystals, m.p. > 300°C, yield 86%. IR (KBr): 3465, 3300, 3230 cm\textsuperscript{-1} (ν\textsubscript{NH2, NH}), 2214 cm\textsuperscript{-1} (ν\textsubscript{C=O}), 1664 cm\textsuperscript{-1} (ν\textsubscript{C=N}) and 1623 cm\textsuperscript{-1} (ν\textsubscript{C=S}). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}): δ (ppm) 12.12 (s, 1H, NH, exchangeable with D\textsubscript{2}O), 7.7 (br.s, 2H, NH\textsubscript{2}, exchangeable with D\textsubscript{2}O), 7.0-6.8 (m, 4Harom.) MS (m/z): 344 (M+1, 1.7), 345 (M+2, 7.2), 343 (M, 28.4), 302 (17.9), 185 (20.3), 129 (52.4), 97 (96.6), 69 (100). Anal. Calcd. for C\textsubscript{16}H\textsubscript{12}ClN\textsubscript{5}O\textsubscript{5}: C, 52.4; H, 2.9; N, 20.37; S, 9.3; Cl, 10.33. Found: C, 52.46; H, 2.31; N, 20.16; S, 9.09; Cl, 10.11.

**Reaction of 3 with 1,2-dichloroethane:** Formation of Bis-S-S-(7-amino-5-(3-chlorophenyl)-4-oxo-2-methylthio-3H-pyridine-2,3-dipyrimidin-2-yl)ethan-1,2-dithiol 6

To a solution of 3 (0.01 mole) in DMF (50ml), 1,2-dichloroethane (0.01 mole) was added with stirring in the presence of anhydrous K\textsubscript{2}CO\textsubscript{3} (2.5 g). The reaction mixture was heated under reflux for 12 hrs (TLC), then poured into water and stirred for 30 min. The deposited was filtered off, dried then crystallized from DMF to give 6 as yellow crystals, m.p. > 300°C, yield 34%. IR (KBr): 3452, 3343, 3208 (br.)
A mixture of compound 3 (0.01 mole), ethyl chloroacetate (0.01 mole) in pyridine (30 ml) was refluxed for 6 hrs (TLC). The reaction mixture was poured into water and then acidified with ice cold HCl. The separated colourless product was collected by filtration, dried and then recrystallized from DMF to give 14a and 14b, respectively.

Recrystallized from ethanol as pale yellow crystals, m.p. >330 °C, yield 22.6% and 58.2%, respectively. IR (KBr): 3460, 3334, 3217 cm⁻¹ (νN-H), 2208 cm⁻¹ (νC≡N), 1670 cm⁻¹ (νC=O), 1652 cm⁻¹ (νC=N). 1H-NMR (DMSO-d₆): δ (ppm) 11.45 (s, 1H, NH), 2215 cm⁻¹ (νC≡N), 1670 cm⁻¹ (νC=O). MS (m/z): 391 (M, 100), 392 (M+1, 51.6), 393 (M+2, 31.8), 296 (76.3), 295 (75.4), 254 (19.4). Anal. Calcd. for C₁₉H₁₀ClN₇O (391.5): C, 57.99; H, 2.48; N, 21.35. Found: C, 57.7; H, 2.62; N, 21.42. Found: C, 57.99; H, 2.48; N, 21.35. At 100 °C.

A mixture of 8 (0.01 mole) and ethoxymethylene malononitrile: Formation of 7-amino-(5-(3-chlorophenyl)-2-ethoxycarbonylmethylthio-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-6-carbonitrile 7

A mixture of compound 3 or 5 (0.01 mole) and hydrazine (0.01 mole) in dioxane (30 ml) was refluxed for 8 hrs (TLC). After cooling, the content was diluted with water and acidified with ice cold acetic acid. The precipitated solid was collected by suction, dried and recrystallized from methanol to give the phthalizindione derivative 13 as brown crystals, m.p. 350-2 °C, yield 28.6%. IR (KBr): 3460, 3343, 3217 cm⁻¹ (νN-H), 2209 cm⁻¹ (νC≡N), 1668 cm⁻¹ (νC=O), 1656 cm⁻¹ (νC=N). MS (m/z): 347 (M-2Ph, 12.4), 327 (M-Ph-C≡C-Ph, 100). Anal. Calcd. for C₂₂H₁₄ClN₁₀O₂S₂ (501.5): C, 66.99; H, 3.19; N, 19.54. Found: C, 67.04; H, 3.21; N, 19.38.

To a solution of compound 8 (3.3 g, 0.01 mole) in pyridine (30 ml), pentan-2,4-dione and/or 1-phenyl-butan-1,3-dione (0.01 mole) was added and the reaction mixture was refluxed for 6 hrs (TLC). After cooling, the content was diluted with water and acidified with ice cold acetic acid. The precipitated solid was collected by suction, dried and recrystallized from the proper solvent to give 14a and 14b, respectively.

7-amino-(5-(3-chlorophenyl)-2-(3,5-dimethylpyrazol-1-yl)-3,4-dihydroxydipyridero[2,3-d]pyrimidin-6-carbonitrile 14a

Recrystallized from ethanol as pale yellow crystals, m.p. >330 °C, yield 58%. IR (KBr): 3475, 3446, 3365, 3325 cm⁻¹ (νN-H), 2214 cm⁻¹ (νC≡N), 1670 cm⁻¹ (νC=O) and 1630 cm⁻¹ (νC=N). IR (KBr): 3475, 3446, 3365, 3325 cm⁻¹ (νN-H), 2214 cm⁻¹ (νC≡N), 1670 cm⁻¹ (νC=O) and 1630 cm⁻¹ (νC=N). IR (KBr): 3460, 3335, 3218 cm⁻¹ (νN-H), 2208 cm⁻¹ (νC≡N), 1692 cm⁻¹ (νC=O) and 1652 cm⁻¹ (νC=N). IR (KBr): 3460, 3335, 3218 cm⁻¹ (νN-H), 2208 cm⁻¹ (νC≡N), 1692 cm⁻¹ (νC=O) and 1652 cm⁻¹ (νC=N). 1H-NMR (DMSO-d₆): δ (ppm) 9.66 (s, 1H, NH, exchangeable with D₂O), 8.9 (s, 1H, NH, exchangeable with D₂O), 8.7 (s, 1H, NH, exchangeable with D₂O), 8.5 (s, 1H, NH, exchangeable with D₂O). MS (m/z): 327 (M, 100), 328 (M+1, 12.6), 329 (328, 54.5), 298 (67.7), 296 (83.2), 254 (19.4). Anal. Calcd. for C₁₉H₁₂ClN₉O₂S (515.5): C, 51.29; H, 3.05; N, 29.92. Found: C, 51.54; H, 2.91; N, 29.76.

A mixture of compound 8 (0.01 mole) and ethoxymethylene malononitrile (0.01 mole) in pyridine (30 ml) was heated under reflux for 6 hrs. The solid separated on hot was filtered off, dried and recrystallized from DMF to give the pyridopyrimidotriazine derivative 13 as brown crystals, m.p. 350-2 °C, yield 28.6%. IR (KBr): 3460, 3334, 3217 cm⁻¹ (νN-H), 2209 cm⁻¹ (νC≡N), 1668 cm⁻¹ (νC=O), 1656 cm⁻¹ (νC=N). MS (m/z): 347 (M-2Ph, 12.4), 327 (M-Ph-C≡C-Ph, 100). Anal. Calcd. for C₂₂H₁₄ClN₁₀O₂S₂ (501.5): C, 66.99; H, 3.19; N, 19.54. Found: C, 67.04; H, 3.21; N, 19.38.

Reaction of 8 with 1,3-diketones: Formation of 7-amino-(5-(3-chlorophenyl)-2-(3,5-dimethylpyrazol-1-yl)-3,4-dihydroxydipyridero[2,3-d]pyrimidin-6-carbonitrile 14b

Reactions of 9-amino-(7-(3-chlorophenyl)-3,4-diphenyl-6-oxo-pyrido-[2,3-d]pyrimidin-2-yl]phthalalzindione 12

A mixture of compound 8 (0.006 mole) and phthalic anhydride (0.006 mole) in acetic acid (30 ml) was heated under reflux for 3 hrs (TLC). The excess acetic was collected by distillation and left a semi solid product which triturated with ethanol and the precipitate was filtered off, dried and recrystallized from methanol to give the phthalalzindione derivative 12 as pale yellow crystals, m.p. 280-2 °C, yield 69.3%. IR (KBr): 3388 (br.), 3144 cm⁻¹ (νC≡N), 2987, 2922, 2225 cm⁻¹ (νC≡N), 1715 cm⁻¹ (νC=O), 1630 cm⁻¹ (νC=N). MS (m/z): 458 (M, 35.1, 456 (M-H₂, 100). Anal. Calcd. for C₂₂H₁₂ClN₁₀O₂S₂ (457.5): C, 57.7; H, 2.62; N, 21.42. Found: C, 57.99; H, 2.48; N, 21.35.
Recrystallized from dilute methanol as yellowish-white crystals, m.p. 287-9°C, yield 69%. IR (KBr): br. centered at 3153 cm⁻¹ (νNHN₂, NH), 2218 cm⁻¹ (νC=O), 1678 cm⁻¹ (νC=O) and 1632 cm⁻¹ (νC=O). ¹H-NMR (DMSO-d₆): δ (ppm) 12.03 (s, 1H, NH, exchangeable with D₂O), 8.09-8.06 (d, 1H, J = 8.7 Hz), 7.74 (br.s, 2H, NH₂, exchangeable with D₂O), 7.4-6.9 (m, 9H arom.), 2.79 (s, 3H, C₃-Me). MS (m/z): 343 [M+Ar, +1, 100]. Anal. Calcd. for C₁₅H₁₂ClN₇O₂ (393.5): C, 53.33; H, 2.37; N, 29.03. Found: C, 53.42; H, 2.44; N, 28.83.

Reactions of 8 with β-ketoesters: Formation of 7-amino-5-(3-chlorophenyl)-2-(3-methyl-pyrazol-5-on-1-yl)-4-oxo-3,4-dihydropyrido[2,3-d] pyrimidin-6-carbonitrile 15

A mixture of hydrazinopyridopyrimidine 8 (0.01 mole) and ethyl acetocetate (0.01 mole) in pyridine (30 ml) was refluxed for 8 hrs (TLC). The excess solvent was collected by distillation and the whole mixture was acidified with ice cold acetic acid. The solid deposited was filtered off, washed several times with water, dried and recrystallized from dioxane to give 15 as pale yellow crystals, m.p 273-6 (85%), IR (KBr): 3324, 3207, 3158 cm⁻¹ (νC≡N), 1726, 1654 cm⁻¹ (νC=O), 1234 cm⁻¹ (νC=O). MS (m/z): 296 (M, 100), 255 (12.6), 224 (28.2), 199 (14.1). Anal. Calcd. for C₂₃H₂₁ClN₇O₂ (453.5): C, 63.5; H, 3.52; N, 21.6. Found: C, 63.76; H, 3.61; N, 21.8.

Reactions of 8 with ethyl chloroformate and/or phenyl isocyanate: Formation of pyrido[1,2-a] triazolopyrimidine 18

Method 1:
A mixture of hydrazinopyridopyrimidine 8 (0.01 mole) and ethyl chloroformate (0.01 mole) in pyridine (20 ml) was refluxed for 8 hrs. The solid separated on hot was filtered off, washed several times with water, dried and recrystallized from ethanol to give 18 as light brown crystals, m.p. 246-50°C, yield 79%. IR (KBr): 3334, 3221 cm⁻¹ (br. (νNHN₂, NH)), 2216 cm⁻¹ (νC=O), 1706 (w), 1685 cm⁻¹ (νC=O) and 1618 cm⁻¹ (νC=O). MS (m/z): 353 (M, 74.1), 354 (M+1, 44.4), 355 (24.7), 352 (M-1, 100), 296 (51.9), 226 (28.4), 190 (22.2), 137 (27.2), 110 (35.8). Anal. Calcd. for C₁₅H₁₄ClN₇O₂ (353.5): C, 50.92; H, 2.26; N, 27.72. Found: C, 50.76; H, 2.11; N, 27.56.

Method 2:
To a solution of compound 8 (0.01 mole) in pyridine (20 ml), phenyl isocyanate (0.01 mole) was added and the reaction mixture was heated under reflux for 6 hrs. The separated solid on hot collected by filtration, washed with water, dried and recrystallized from ethanol to give 18 as identity m.p, mixed m.p, TLC and IR comparison. The mother liquor when diluted with H₂O gave a colourless solid which collected by filtration and identified as sym. diphenyl urea [M = 212 (10.9)].

Reactions of 8 with acetyl chloride: Formation of 8-acylamino-6-(3-chlorophenyl)-7-cyano-5-oxo-1H-triazolo[4,3-a] pyrido[2,3-d]pyrimidin-3(H)thione 16

Method 1:
A mixture of compound 8 (0.01 mole) and phenyl isothiocyanate (0.01 mole) in pyridine (20 ml) was stirred with reflux for 2 hrs (TLC). The reaction mixture poured onto water and acidified with dilute acetic acid. The dark precipitated was collected by filtration, dried and then recrystallized from ethanol to give 16 as pale yellow crystals, m.p. 287-9 (85%), IR (KBr): 3391, 3327, 3230 cm⁻¹ (νNHN₂, NH), 2222 cm⁻¹ (νC=O), 1726, 1654 cm⁻¹ (νC=O), 1234 cm⁻¹ (νC=O). MS (m/z): 369 (M, 100), 373 (82.4), 296 (25.4), 226 (28.2), 199 (17.9), 163 (10.7). Anal. Calcd. for C₁₃H₁₀ClN₇O₂ (346.5): C, 55.07; H, 2.99; N, 24.67.

Method 2:
To a solution of compound 8 (0.01 mole) in pyridine (20 ml), phenyl isothiocyanate (0.01 mole) was added and the reaction mixture was heated under reflux for 6 hrs. The separated solid on hot collected by filtration, washed with water, dried and recrystallized from ethanol to give 16, yield 69%. IR (KBr): 3324, 3207, 3158 cm⁻¹ (νNHN₂, NH), 2210 cm⁻¹ (νC=O), 1686 cm⁻¹ (νC=O). MS (m/z): 380 (M, 380), 344 (M-Me, Cl, 100). Anal. Calcd. for C₁₃H₁₀ClN₇O₂ (393.5): C, 54.89; H, 3.04; N, 24.9. Found: C, 54.92; H, 2.95; N, 24.46.

Reactions of compound 8 with phenyl isothiocyanate and/or carbon disulphide: Formation of 8-amino-6-(3-chlorophenyl)-7-cyano-5-oxo-1H-1,2,4-triazolo[4,3-a] pyrido[2,3-d]pyrimidin-3(3H)thione 16

Method 1:
A mixture of compound 8 (0.01 mole) and phenyl isothiocyanate (0.01 mole) in pyridine (20 ml) was stirred with reflux for 2 hrs (TLC). The reaction mixture poured onto water and acidified with dilute acetic acid. The dark crude product was collected and washed several times with dilute ethanol, dried and recrystallized from dioxane to give 16 as light brown crystals, m.p 316-8°C, yield 62%. IR (KBr): br. 3312, br. 3165 cm⁻¹ (νNHN₂), 2227 cm⁻¹ (νC=O), 1706 cm⁻¹ (νC=O) and 1634 cm⁻¹ (νC=O). MS (m/z): 338 (M, 57.3), 337 (M-1, 100), 339 (M+1, 45.8), 340 (M+2, 19.1), 310 (26.7), 225 (16.8), 199 (17.9), 163 (10.7). Anal. Calcd. for C₁₅H₁₁ClN₇O₂ (373.5): C, 53.33; H, 2.37; N, 29.03. Found: C, 53.42; H, 2.44; N, 28.83.
236-8°C, yield 82%. IR (KBr): 3354, 3187 cm⁻¹ (ν(NH₂, NH)), 2216 cm⁻¹ (ν(C≡N)), 1716 cm⁻¹ (w) (ν(C=O)) and 1647 cm⁻¹ (ν(C=N)).

MS (m/z): 450 (M, 28.3), 451 (M+1, 7.6), 452 (M+2, 6.3), 338 (M-Ar', 100), 180 (10.9), 124 (17.6), 89 (27.9). Anal. Calcd. for C₂₁H₁₃Cl₂N₇O (450): C, 56.0; H, 2.88; N, 21.77; Cl, 15.77. Found: C, 56.13; H, 3.1; N, 21.52; Cl, 15.44.

Authentic sample of 20

A mixture of compound 8 (0.9 g, 0.002 mole) and 4-chlorobenzaldehyde (0.002 mole) was dissolved in n-butanol (20 ml) and refluxed for 2 hrs. The excess n-butanol was removed by distillation and left a yellowish-white solid which recrystallized from benzene to give 20 (identity m.p., mixed m.p., TLC and IR comparison).

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