

Annellation of Triazole and Tetrazole Systems onto Pyrrolo[2,3-*d*]pyrimidines: Synthesis of Tetrazolo[1,5-*c*]-pyrrolo[3,2-*e*]-pyrimidines and Triazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines as Potential Antibacterial Agents

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Abstract: Syntheses of several novel 4-chloropyrrolo[2,3-*d*]pyrimidines (**1**), 4-hydrazinopyrrolo[2,3-*d*]pyrimidines (**2**) and 3-amino-4-iminopyrrolo[2,3-*d*]pyrimidines (**7**) and their use in the synthesis of tetrazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines (**3**) and triazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines (**4**) required for biological screening are reported.

Keywords: Tetrazolopyrrolopyrimidines, triazolopyrrolopyrimidines, pyrrolo[2,3-*d*]pyrimidines, antibacterial activity

Introduction

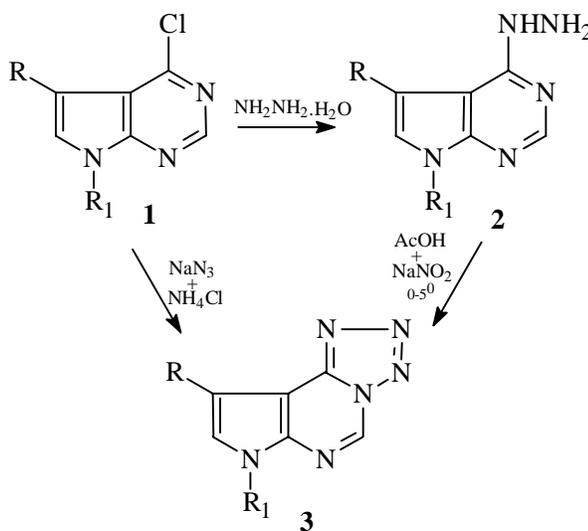
It is well known that organofluorine compounds display a variety of interesting pharmacological and agrochemical properties [1-7]. Moreover, pyrimidines having halogen groups at positions 2 or 4 appear to be more labile, displaying powerful reactivity in nucleophilic substitution reactions with reagents such as piperidine, piperazine, morpholines, hydrazines, azides, etc. These replacements also permit the combination of two active moieties [8-9] forming potent bi- and triheterocycles [8-12]. Further, the resulting compounds were found to undergo reactions with carbon or nitrogen donor

moieties giving triazole or tetrazole ring formation [10-11] onto the pyrimidine rings. In addition, many fused triazolopyrimidines, tetrazolopyrimidines and fluoropyrimidines are well known for their antibacterial and antifungal activities [1,13,14]. Studies of nucleophilic substitution reactions of pyrrolopyrimidines are scarce [15-17]. Herein, we wish to report the synthesis of 7,9-disubstituted 7*H*-tetrazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines (**3**) and 7,9-disubstituted 7*H*-triazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines (**4**) from 5,7-disubstituted 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidines (**1**) [17-19].

Results and Discussion

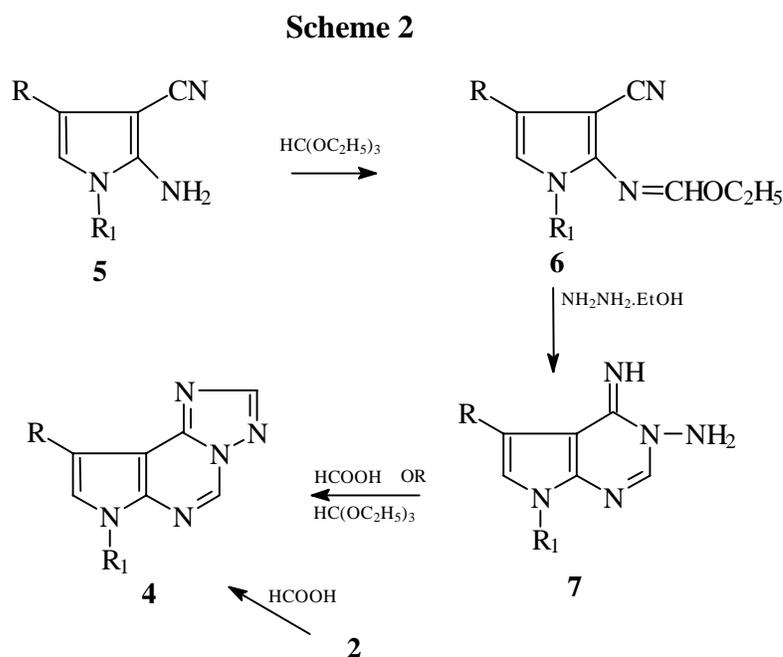
Reaction between **1** and sodium azide in presence of ammonium chloride and DMSO as a solvent afforded the target tetrazolopyrrolopyrimidines **3**. Ammonium chloride was used for *in situ* generation of ammonium azide and the reaction was found to be incomplete in the absence of ammonium chloride. The same 7,9-disubstituted 7*H*-tetrazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines (**3**) can also be synthesized by the diazotization of 5,7-disubstituted 4-hydrazino-7*H*-pyrrolo[2,3-*d*]pyrimidines (**2**) [17-19], obtained from **1** on treatment with hydrazine hydrate in hot alcohol. Thus obtained compounds **2** were reacted with sodium nitrite in acetic acid under cooling (0-5 °C) to give the same tetrazolopyrrolopyrimidines **3**. The complete reaction sequences leading to compounds **3** is depicted in Scheme 1.

Scheme 1



1,2,3	R	R ₁	1,2,3	R	R ₁
a	C ₆ H ₅	C ₆ H ₅	g	4-OCH ₃ C ₆ H ₄	4-FC ₆ H ₄
b	C ₆ H ₅	4-ClC ₆ H ₄	h	4-OCH ₃ C ₆ H ₄	3-Cl-4-FC ₆ H ₃
c	C ₆ H ₅	4-FC ₆ H ₄	i	4-ClC ₆ H ₄	C ₆ H ₅
d	C ₆ H ₅	3-Cl-4-FC ₆ H ₃	j	4-ClC ₆ H ₄	4-ClC ₆ H ₄
e	4-OCH ₃ C ₆ H ₄	C ₆ H ₅	k	4-ClC ₆ H ₄	4-FC ₆ H ₄
f	4-OCH ₃ C ₆ H ₄	4-OCH ₃ C ₆ H ₄	l	4-ClC ₆ H ₄	3-Cl-4-FC ₆ H ₃

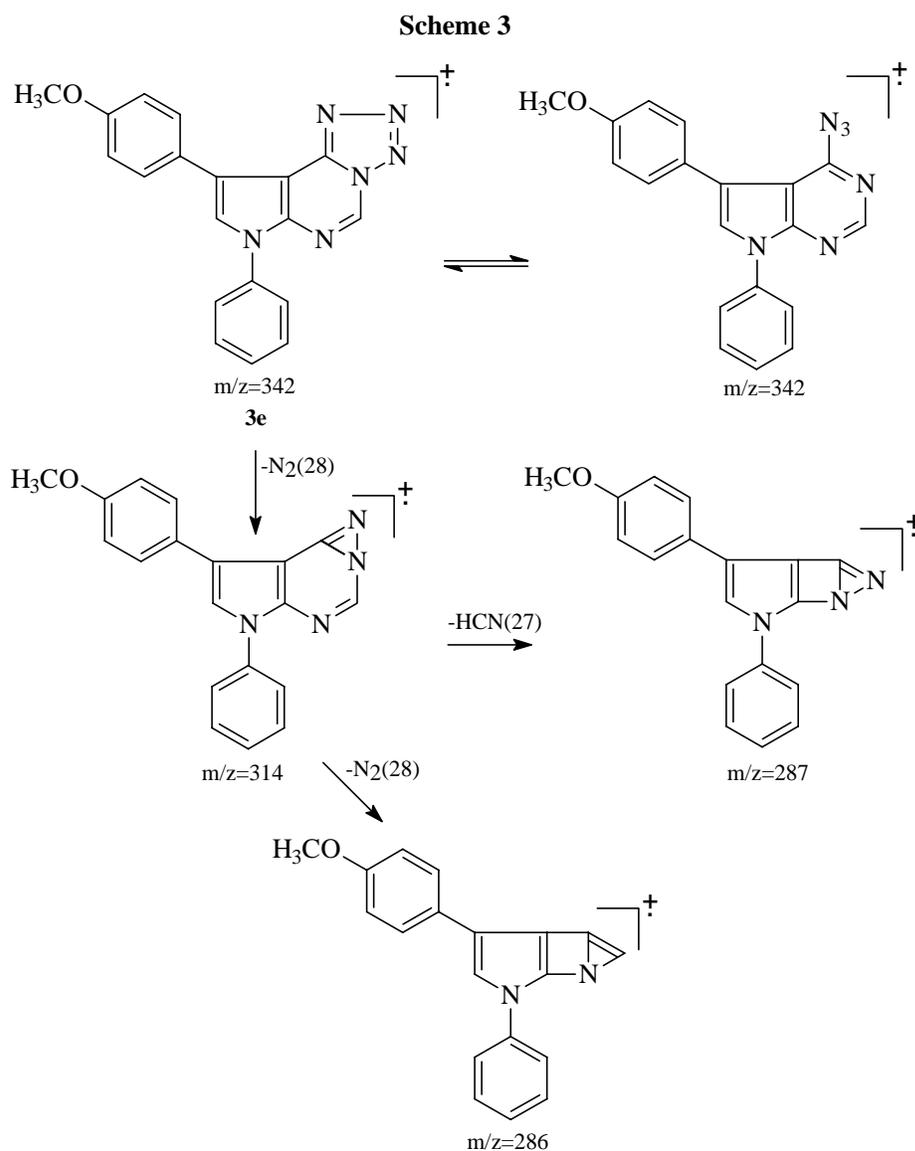
The synthesis of novel 7,9-disubstituted 7*H*-triazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines (**4**) has also been carried out from **2** upon reaction with hot formic acid. The same triazolopyrrolopyrimidines **4** have been prepared by another method, starting from 2-amino-3-cyanopyrroles (**5**) [17-21], whereby compounds **5** were treated with triethyl orthoformate giving 1,4-disubstituted *N*-ethoxymethylene 2-amino-3-cyanopyrroles (**6**), which on condensation with hydrazine hydrate afforded 5,7-disubstituted 3-amino-4-imino-7*H*-pyrrolo[2,3-*d*]pyrimidines (**7**). Cyclocondensation of **7** with hot formic acid or triethyl orthoformate resulted in the formation of the same 7,9-disubstituted 7*H*-triazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines **4** (Scheme 2).



2,4,5,6,7	R	R₁
a	C ₆ H ₅	4-ClC ₆ H ₄
b	4-OCH ₃ C ₆ H ₄	C ₆ H ₅
c	4-OCH ₃ C ₆ H ₄	4-OCH ₃ C ₆ H ₄
d	4-ClC ₆ H ₄	C ₆ H ₅
e	4-ClC ₆ H ₄	4-ClC ₆ H ₄

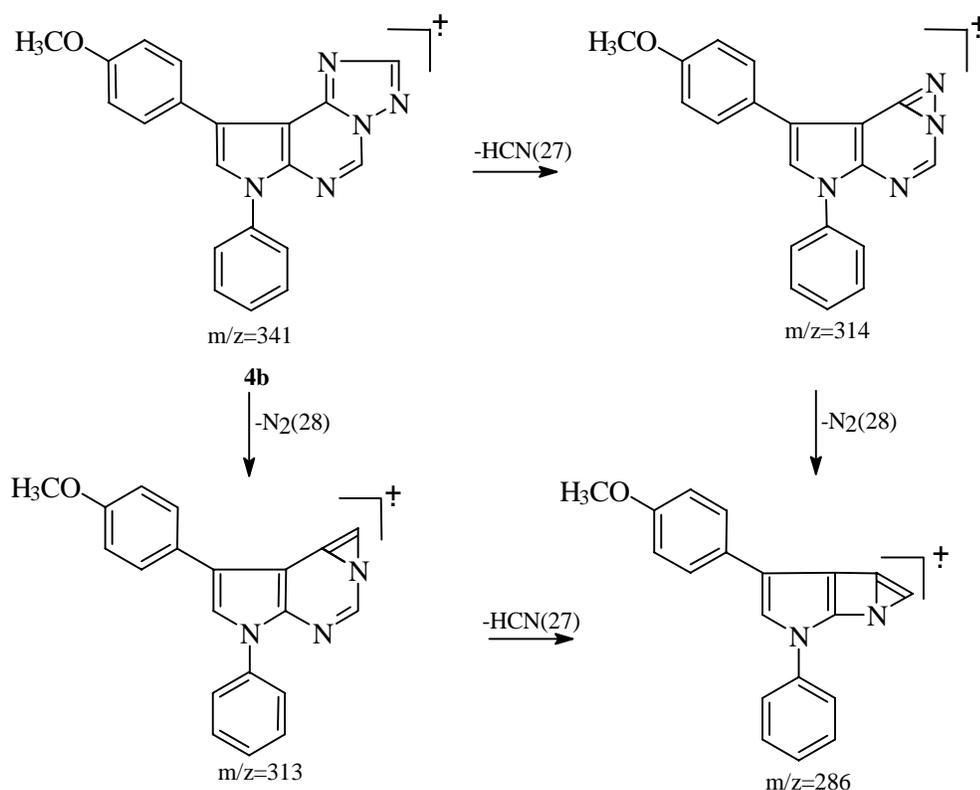
The identity of compounds **3** and **4** obtained by both methods was proven on the basis of melting points (mp), thin layer chromatography (TLC) and spectral data. The IR spectra of compounds **3** and **4** exhibited C=C and C=N stretching vibrations near 1624-1488 cm⁻¹. The absence of absorptions near 2100 cm⁻¹ excluded the possibility of azide formation [22] in case of compounds **3**. The formation of **3** from **2**, and **4** from **2** as well as of **4** from **7** was also supported by absence in their IR spectra of bands at 3400-3150 and at 1648-1640 cm⁻¹ for the respective stretching and bending vibrations of NH in imino, amino as well hydrazino functionalities, which were found to be present in case of compounds **2**

[17, 18] and **7**. In the IR spectra of compounds **6** the cyano and ester carbonyl groups exhibited bands in the 2210-2200 and 1720-1710 cm^{-1} regions, respectively. The $^1\text{H-NMR}$ spectra of the compounds **3** and **4** displayed resonances due to aromatic protons near δ 8.3-6.95, and, in case of **4**, the C_2 proton resonated at δ 9.15–9.1. In the $^1\text{H-NMR}$ spectra of the compounds **6** and **7** the aromatic protons appeared as a multiplet near δ 6.9-7.95. Amino protons appeared as a broad peak in the δ 5.46-5.43 region, integrating for 2H, while the imino proton appeared at δ 8.1-8.0 in the spectra of compounds **6**. Both imino and amino protons were found to be D_2O exchangeable. The CH proton of the $\text{NCH}=\text{OEt}$ group in **6** also appeared downfield at δ 8.5-8.45, whereas a triplet (3H) at δ 1.42-1.2 and quartet (2H) at δ 4.3-4.2 were assigned to the methyl and methylene protons of the ethyl group in the same functionality. The mass spectra of tetrazolopyrrolopyrimidine **3e** was found to show a regular fragmentation pattern [22] giving a molecular ion peak at m/e 342 along with the fragments at 314, 287 and 286, resulting from successive elimination of nitrogen and hydrogen cyanide or subsequent elimination of two nitrogen molecules (Scheme 3).



The mass fragmentation pattern of triazolopyrrolopyrimidine **4b** was also in agreement with that reported for fused triazolopyrimidines [23-24], showing a M^+ peak at 341 together with signals at m/e 313, 314 and 286 resulting from subsequent removal of nitrogen and hydrogen cyanide or hydrogen cyanide and nitrogen molecules (Scheme 4).

Scheme 4



Antibacterial activity

The antibacterial activity of all the newly synthesized compounds **3** and **4** was investigated. Assays against different bacterial cultures comprising *E. coli*, *E. entericus*, *P. aeruginosa*, *S. aureus* and *B. subtilis* were carried out by the agar plate diffusion method [25-26]. The bacterial cultures were streaked across grooves filled with 0.6 mL of a 1 % solution in DMSO of each compound **3** and **4**, which were then allowed to diffuse in the agar nutrient plate. The antibiotic ampicillin and the DMSO solvent were used as positive and negative controls, respectively. The results are recorded in Table 1 as the relative extent of inhibition observed around the grooves compared to the negative control. Against *E. coli* all the compounds tested displayed comparable activities except for **3e** and **3j**. Compounds **4** were found to be moderately active. Compounds **3c** and **3j** exhibited better activity than ampicillin against *E. entericus* while the remaining compounds were found to be either less active or inactive. Activity against *P. aeruginosa* was similar for all active compounds, while **3g**, **3k** and **4d** failed to give

any inhibition. Against *S. typhi* better to good activity was shown by most of the derivatives **3** and **4**, except **3l** and **4a**, which were inactive. **3h** and **3k** gave better inhibition than the positive control against *S. aureus* species while **4c** and **4d** showed remarkable activity against *B. subtilis*.

Table 1: Antibacterial activity data of compounds **3** and **4**. Inhibition in mm after 48 hr

Compd.	<i>E. coli</i>	<i>E. entericus</i>	<i>P. aeruginosa</i>	<i>S. typhi</i>	<i>S. aureus</i>	<i>B. subtilis</i>
3a	15.0	5.0	5.0	10.0	-	-
3b	15.5	5.0	10.0	5.0	-	3.0
3c	15.0	15.0	15.0	15.0	-	5.0
3d	15.0	3.0	10.0	5.0	5.0	-
3e	10.0	-	10.0	15.0	10.0	-
3f	15.5	-	5.0	10.0	-	-
3g	15.0	-	-	15.0	-	-
3h	15.0	10.0	5.0	10.0	15.0	-
3i	15.0	-	15.0	5.0	-	-
3j	5.0	5.0	10.0	10.0	15.0	-
3k	15.0	15.0	-	-	-	3.0
3l	15.0	5.0	10.0	15.0	3.0	-
4a	5.0	5.0	5.0	-	5.0	5.0
4b	-	5.0	15.0	10.0	-	5.0
4c	5.0	3.0	15.5	5.5	-	3.5
4d	5.0	-	-	5.0	5.0	10.0
4e	10.0	-	10.0	10.5	5.0	10.0
Ampicillin	15.0	11.0	12.0	11.0	15.5	0.5
DMSO	-	-	-	-	-	-

Conclusions

A series of novel tetrazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines (**3**) and triazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines (**4**) have been synthesized by two different routes and their antimicrobial activity investigated. Compound **3c** exhibited better activity than ampicillin against all the tested cultures except *S. aureus*.

Acknowledgements

Thanks are due to RSIC, Chandigarh for the NMR data, CDRI, Lucknow for mass spectral analysis and Dishman Pharmaceuticals and Chemicals Ltd, Ahmedabad, for the IR spectral data.

Experimental Section

General

Melting points were determined on an Electrothermal apparatus in an open capillary tube and are uncorrected. The IR spectra were recorded in cm^{-1} for KBr pellets on a Buck Scientific spectrophotometer. $^1\text{H-NMR}$ spectra were recorded on a Varian 300MHz spectrometer using DMSO-d_6 or CDCl_3 as the solvent and TMS as the internal reference standard. Chemical shifts are expressed in δ ppm. Mass spectra were taken on a LKB 9000 mass spectrometer. The purity of the compounds was routinely checked by TLC using Silica G and the spots were exposed in iodine vapour for visualization.

Synthesis of 7,9-disubstituted 7H-tetrazolo[1,5-c]pyrrolo[3,2-e]pyrimidines 3a-l: General Procedure.

Method A: A mixture of sodium azide (0.011 mole, 0.072 g) and ammonium chloride (0.011 mole, 0.059 g) in DMSO (20 mL) was stirred for five min. at 90°C and the 5,7-disubstituted 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**1**, 0.01 mole) was added in portions with stirring. After the addition the reaction mixture was further stirred for 2.0-2.5 hr at the same temperature and for 1 hr at room temperature. Then it was decomposed on ice. The solid obtained was filtered, washed with water, dried and crystallized from toluene or a mixture of ethanol-chloroform (8:2) to give the title compounds **3**.

Method B: An aqueous solution of sodium nitrite (20% w/v, 4.2 mL) was slowly added in portions to a stirred mixture of 5,7-disubstituted 4-hydrazino-7H-pyrrolo[2,3-d]pyrimidine (**2**, 0.01 mole) in acetic acid (40 mL) at $0-5^\circ\text{C}$. The reaction mixture was then further stirred for 2 hr at the same temperature, then it was diluted with cold water and the solid obtained was filtered, washed with water, sodium bicarbonate (20 % w/v), followed by water, dried and crystallized to furnish compounds **3**.

7,9-Diphenyltetrazolo[1,5-c]pyrrolo-7H-[3,2-e]pyrimidine (3a): Yield: 61 % (Method A), 60 % (Method B); mp: $215-17^\circ\text{C}$; IR: 1608, 1504 (C=C, C=N ring); $^1\text{H-NMR}$ (DMSO-d_6): 8.0-7.1 (m, 12H, ArH); MS: 312 m/z (M^+); Anal. Calcd. for $\text{C}_{19}\text{H}_{12}\text{N}_6$: C 73.06, H 3.87, N 26.11 %, found: C 73.26, H 3.71, N 26.60 %.

7-(4-Fluorophenyl)-9-phenyltetrazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (3b): Yield: 70 % (Method A), 56 % (Method B); mp: $217-19^\circ\text{C}$; IR: 1604, 1516 (C=C, C=N ring); $^1\text{H NMR}$ (DMSO-d_6): 8.0-7.2 (m, 11H, ArH); MS: 330 m/z (M^+); Anal. Calcd. for $\text{C}_{18}\text{H}_{11}\text{FN}_6$: C 65.45, H 3.36, N 25.45 %, found: C 65.66, H 3.27, N 25.09 %.

7-(4-Chlorophenyl)-9-phenyl-7H-tetrazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (3c): Yield: 70 % (Method A), 64 % (Method B); mp: $218-20^\circ\text{C}$; IR: 1612, 1492 (C=C, C=N ring); $^1\text{H-NMR}$

(DMSO- d_6): 8.0-7.3 (m, 11H, ArH); MS: 347 m/z (M^+); Anal. Calcd. for $C_{18}H_{11}ClN_6$: C 62.34, H 3.20, N 24.24 %, found: C 62.46, H 3.27, N 24.56 %.

7-(3-Chloro-4-fluorophenyl)-9-phenyl-7H-tetrazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (**3d**): Yield: 64 % (Method A), 63 % (Method B); mp: 212-14°C; IR: 1604, 1492 (C=C, C=N ring); 1H -NMR (DMSO- d_6): 8.1-7.2 (m, 10H, ArH); MS: 365 m/z (M^+); Anal. Calcd. for $C_{18}H_{10}ClFN_6$: C 59.27, H 2.76, N 23.04 %, found: C 59.54, H 2.50, N 22.86 %.

7-Phenyl-9-(4-methoxyphenyl)tetrazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (**3e**): Yield: 70 % (Method A), 56 % (Method B); mp: 216-18°C; IR: 1604, 1516 (C=C, C=N ring); 1H -NMR (DMSO- d_6): 3.9 (s, 3H, OCH₃), 8.0-7.2 (m, 11H, ArH); MS: 342 m/z (M^+); Anal. Calcd. for $C_{19}H_{14}N_6O$: C 66.65, H 4.12, N 24.55 %, found: C 66.46, H 4.27, N 24.78 %.

7,9-Di(4-methoxyphenyl)tetrazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (**3f**): Yield: 77 % (Method A), 75 % (Method B); mp: 237-39°C; IR: 1596, 1500 (C=C, C=N ring); 1H -NMR (DMSO- d_6): 3.95 (s, 6H, OCH₃), 8.1-7.3 (m, 10H, ArH); MS: 372 m/z (M^+); Anal. Calcd. for $C_{20}H_{16}FN_6O_2$: C 64.50, H 4.33, N 22.57 %, found: C 64.39, H 4.28, N 22.33 %.

7-(4-Fluorophenyl)-9-(4-methoxyphenyl)tetrazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (**3g**): Yield: 63 % (Method A), 61 % (Method B); mp: 245-47°C; IR: 1600, 1504 (C=C, C=N ring); 1H -NMR (DMSO- d_6): 4.0 (s, 3H, OCH₃), 8.1-7.3 (m, 10H, ArH); MS: 360 m/z (M^+); Anal. Calcd. for $C_{19}H_{13}FN_6O$: C 63.33, H 3.64, N 23.33 %, found: C 63.09, H 3.45, N 23.44 %.

7-(3-Chloro-4-fluorophenyl)-9-(4-methoxyphenyl)tetrazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (**3h**): Yield: 56 % (Method A), 58 % (Method B); mp: 219-21°C; IR: 1608, 1504 (C=C, C=N ring); 1H -NMR (DMSO- d_6): 3.95 (s, 3H, OCH₃), 8.3-7.3 (m, 9H, ArH); MS: 395 m/z (M^+); Anal. Calcd. for $C_{19}H_{12}ClFN_6O$: C 57.80, H 3.07, N 21.29 %, found: C 57.45, H 3.25, N 21.60 %.

7-(4-Phenyl)-9-(4-chlorophenyl)-7H-tetrazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (**3i**): Yield: 80 % (Method A), 71 % (Method B); mp: 233-35°C; IR: 1608, 1508 (C=C, C=N ring); 1H -NMR (DMSO- d_6): 8.0-7.2 (m, 11H, ArH); MS: 347 m/z (M^+); Anal. Calcd. for $C_{18}H_{10}ClN_6$: C 62.45, H 3.36, N 24.24 %, found: C 62.46, H 3.27, N 24.56 %.

7-(4-Fluorophenyl)-9-(4-chlorophenyl)-7H-tetrazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (**3j**): Yield: 67 % (Method A), 66 % (Method B); mp: 226-28°C; IR: 1612, 1496 (C=C, C=N ring); 1H -NMR (DMSO- d_6): 8.2-7.1 (m, 10H, ArH); MS: 365 m/z (M^+); Anal. Calcd. for $C_{18}H_{12}ClFN_6$: C 59.27, H 2.76, N 23.04 %, found: C 59.06, H 2.49, N 23.46 %.

7,9-Di(4-chlorophenyl)-7H-tetrazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (**3k**): Yield: 77 % (Method A), 70 % (Method B); mp: 224-25°C; IR: 1608, 1500 (C=C, C=N ring); ¹H-NMR (DMSO-d₆): 8.2-7.1 (m, 11H, ArH); MS: 381 m/z (M⁺); Anal. Calcd. for C₁₈H₁₀Cl₂N₆: C 56.70, 2.64, N 22.05 %, found: C 56.49, H 2.39, N 21.88 %.

7-(3-Chloro-4-fluorophenyl)-9-(4-chlorophenyl)tetrazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (**3l**): Yield: 65 % (Method A), 63 % (Method B); mp: 220-22°C; IR: 1604, 1508 (C=C, C=N ring); ¹H-NMR (DMSO-d₆): 8.3-7.2 (m, 9H, ArH); MS: m/z 399 (M⁺); Anal. Calcd. for C₁₈H₉Cl₂FN₆: C 54.15, H 2.27, N 21.05 %, found: C 54.01, H 2.11, N 20.88 %.

Synthesis of 1,4-disubstituted N-ethoxymethylene-2-amino-3-cyanopyrroles 6a-e: General Procedure.

A mixture of 1,4-disubstituted 2-amino-3-cyanopyrrole (**5**, 0.01 mole) in triethylorthoformate (10 mL) was refluxed for 3-4 hr, then the excess reagent was distilled in *vacuo*. The solid thus obtained was treated with ice water, filtered, washed with water, dried and crystallized from ethanol.

1-(4-Chlorophenyl)-N-ethoxymethylene-2-amino-3-cyano-4-phenylpyrrole (**6a**): Yield: 70 %; mp: 130-31°C; IR: 2210 (CN), 1720 (C=O), 1616, 1504 (C=C, C=N ring); ¹H-NMR (CDCl₃): 1.4-1.2 (*J* = 6Hz, t, 3H, OCH₂CH₃), 4.3-4.2 (*J* = 6Hz, q, 2H, OCH₂CH₃), 7.8-7.2 (m, 10H, ArH), 8.5 (s, 1H, N=CHOEt); Anal. Calcd. for C₂₀H₁₆ClN₃O: C 68.67, H 4.61, N 12.01 %, found: C 68.77, H 4.62, N 12.23 %.

1-Phenyl-N-ethoxymethylene-2-amino-3-cyano-4-(4-methoxyphenyl)pyrrole (**6b**): Yield: 72 %; mp: 159-60°C; IR: 2220 (CN), 1716 (C=O), 1632, 1520 (C=C, C=N ring); ¹H-NMR (CDCl₃): 1.4-1.25 (*J* = 5.9Hz, t, 3H, OCH₂CH₃), 3.9 (s, 3H, OCH₃), 4.3-4.2 (*J* = 5.9Hz, q, 2H, OCH₂CH₃), 7.8-7.1 (m, 10H, ArH), 8.45 (s, 1H, N=CHOEt); Anal. Calcd. for C₂₁H₁₉N₃O₂: C 72.88, H 5.55, N 12.17 %, found: C 73.02, H 5.32, N 12.02 %.

1,4-Di(4-methoxyphenyl)-N-ethoxymethylene-2-amino-3-cyanopyrrole (**6c**): Yield: 73 %; mp: 117-18°C; IR: 2210 (CN), 1712 (C=O), 1616, 1504 (C=C, C=N ring); ¹H-NMR (CDCl₃): 1.41-1.2 (*J* = 6Hz, t, 3H, OCH₂CH₃), 3.95 (s, 6H, OCH₃), 4.32-4.2 (*J* = 6Hz, q, 2H, OCH₂CH₃), 7.9-7.2 (m, 9H, ArH), 8.5 (s, 1H, N=CHOEt); Anal. Calcd. for C₂₂H₂₁N₃O₃: C 70.38, H 5.64, N 11.19 %, found: C 70.28, H 5.44, N 11.01 %.

1-Phenyl-N-ethoxymethylene-2-amino-3-cyano-4-(4-chlorophenyl)pyrrole (**6d**): Yield: 70 %; mp: 167-68°C; IR: 2210 (CN), 1710 (C=O), 1616, 1504 (C=C, C=N ring); ¹H-NMR (CDCl₃): 1.42-1.2 (*J* = 6.5Hz, t, 3H, OCH₂CH₃), 4.32-4.2 (*J* = 6.5Hz, q, 2H, OCH₂CH₃), 7.9-7.2 (m, 10H, ArH), 8.5 (s, 1H, N=CHOEt); Anal. Calcd. for C₂₀H₁₆ClN₃O: C 68.67, H 4.61, N 12.01 %, found: C 68.77, H 4.62, N 12.23 %.

1,4-Di(4-chlorophenyl)-N-ethoxymethylene-2-amino-3-cyanopyrrole (6e): Yield: 81 %; mp: 200-01°C; IR: 2200 (CN), 1720 (C=O), 1600, 1508 (C=C, C=N ring); ¹H-NMR (CDCl₃): 1.41-1.22 (*J* = 6Hz, t, 3H, OCH₂CH₃), 4.3-4.21 (*J* = 6Hz, q, 2H, OCH₂CH₃), 7.9-7.1 (m, 9H, ArH), 8.45 (s, 1H, N=CHOEt); Anal. Calcd. for C₂₀H₁₅Cl₂N₃O: C 62.50, H 3.93, N 10.93 %, found: C 62.81, H 3.81, N 11.09 %.

Synthesis of 5,7-Disubstituted 3-amino-4-imino-7H-pyrrolo[2,3-d]pyrimidines 7a-e: General Procedure.

1,4-Disubstituted *N*-ethoxymethylene-2-amino-3-cyanopyrroles (**6**, 0.01 mole) were treated with refluxing hydrazine hydrate (99 %, 10 mL) for 3-4 hr. The reaction mixture was allowed to cool, poured onto crushed ice and neutralized with 50 % acetic acid. The solid obtained was filtered, washed with water, dried and recrystallized from benzene or dioxane.

3-Amino-4-imino-5-phenyl-7-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidine (7a): Yield: 89 %; mp: 201-02°C; IR: 3380, 3270, 3170, 1640 (NH), 1600, 1504 (C=C, C=N ring); ¹H-NMR (DMSO-d₆): 5.45 (s, 2H, NH₂), 7.9-7.2 (m, 11H, ArH), 8.0 (s, 1H, NH); Anal. Calcd. for C₁₈H₁₄ClN₅: C 64.38, H 4.20, N 20.86 %, found: C 64.49, H 4.33, N 20.99 %.

3-Amino-4-imino-5-(4-methoxyphenyl)-7-phenyl-7H-pyrrolo[2,3-d]pyrimidine (7b): Yield: 88 %; mp: 193-95°C; IR: 3400, 3320, 3280, 1648 (NH), 1624, 1508 (C=C, C=N ring); ¹H-NMR (CDCl₃): 3.9 (s, 3H, OCH₃), 5.43 (s, 2H, NH₂), 7.85-7.2 (m, 11H, ArH), 8.05 (s, 1H, NH); Anal. Calcd. for C₁₉H₁₇N₅O: C 68.886, H 5.17, N 21.123 %, found: C 68.53, H 5.27, N 21.01 %.

3-Amino-4-imino-5,7-di(4-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (7c): Yield: 84 %; mp: 154-55°C; IR: 3330, 3380, 3150, 1644 (NH), 1620, 1488 (C=C, C=N ring); ¹H-NMR (CDCl₃): 3.95 (s, 6H, OCH₃), 5.44 (s, 2H, NH₂), 7.8-7.1 (m, 10H, ArH), 8.1 (s, 1H, NH); Anal. Calcd. for C₂₀H₁₉N₅O₂: C 66.47, H 5.29, N 19.39 %, found: C 66.27, H 5.14, N 19.11 %.

3-Amino-4-imino-5-(4-chlorophenyl)-7-phenyl-7H-pyrrolo[2,3-d]pyrimidine (7d): Yield: 86 %; mp: 204-06°C; IR: 3380, 3270, 3170, 1644 (NH), 1620, 1504 (C=C, C=N ring); ¹H-NMR (DMSO-d₆): 5.44 (s, 2H, NH₂), 7.9-7.1 (m, 11H, ArH), 8.05 (s, 1H, NH); Anal. Calcd. for C₁₈H₁₄ClN₅: C 64.38, H 4.20, N 20.86 %, found: C 64.21, H 4.01, N 20.49 %.

3-Amino-4-imino-5,7-di(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidine (7e): Yield: 70 %; mp: 224-25°C; IR: 3340, 3280, 3190, 1648 (NH), 1620, 1516 (C=C, C=N ring); ¹H-NMR (DMSO-d₆): 5.46 (s, 2H, NH₂), 7.95-7.2 (m, 10H, ArH), 8.0 (s, 1H, NH); Anal. Calcd. for C₁₈H₁₃ClN₅: C 58.39, H 3.54, N 18.92 %, found: C 58.09, H 3.44, N 18.62 %.

Synthesis of 7,9-disubstituted 7H-triazolo[1,5-c]pyrrolo[3,2-e]pyrimidines 4a-e: General Procedure.

Method A. A mixture of 5,7-disubstituted 4-hydrazino-7H-pyrrolo[2,3-d]pyrimidine (**2**, 0.01 mole) in formic acid (20 mL) was heated under reflux for 7-8 hr. The reaction mixture was poured onto crushed ice, neutralized with 1N sodium hydroxide solution and the solid obtained was filtered off, washed with water, dried and recrystallized from toluene or a mixture of DMF-EtOH (6:4) to give the title compounds.

Method B: A mixture of 5,7-disubstituted 3-amino-4-imino-7H-pyrrolo[2,3-d]pyrimidine (**7**, 0.01 mole) in formic acid (15 mL) was heated under reflux for 3-4 hr. The cold reaction mixture was poured onto crushed ice, treated with 1N sodium hydroxide solution and the solid obtained was filtered, washed with water, dried and recrystallized to give the identical compounds **4**.

7-(4-Chorophenyl)-9-phenyl-7H-triazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (4a): Yield: 69 % (Method A), 57 % (Method B); mp: 256-58°C, IR: 1616, 1504 (C=C, C=N ring); ¹H-NMR (DMSO-d₆): 8.4-7.3 (m, 11H, ArH), 9.12 (s, 1H, H at C₂); MS: 346 (M⁺); Anal. Calcd. for C₁₉H₁₂ClN₅: C 65.99, H 3.50, N 20.26 %, found: C 66.17, H 3.30, N 20.01 %.

7-Phenyl-9-(4-methoxyphenyl)triazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (4b): Yield: 55 % (Method A), 62 % (Method B); mp: 225-26°C; IR: 1616, 1498 (C=C, C=N ring); ¹H-NMR (DMSO-d₆): 3.82 (s, 3H, OCH₃), 8.3-6.95 (m, 11H, ArH), 9.1 (s, 1H, H at C₂); MS: 341 m/z (M⁺); Anal. Calcd. for C₂₀H₁₅N₅O: C 72.42, H 4.56, N 20.51 %, found: C 72.09, H 4.36, N 20.31 %.

7,9-Di(4-methoxyphenyl)triazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (4c): Yield: 85 % (Method A), 75 % (Method B); mp: 204-05°C; IR: 1608, 1496 (C=C, C=N ring); ¹H-NMR (DMSO-d₆): 3.8 (s, 6H, OCH₃), 8.2-7.0 (m, 10H, ArH), 9.1 (s, 1H, H at C₂); MS: 371 m/z (M⁺); Anal. Calcd. for C₂₁H₁₇N₅O₂: C 67.91, H 4.62, N 18.86 %, found: C 67.71, H 4.50, N 18.66 %.

7-(4-Phenyl)-9-(4-chlorophenyl)-7H-triazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (4d): Yield: 70 % (Method A), 72 % (Method B); mp: 240-42°C; IR: 1616, 1500 (C=C, C=N ring); ¹H-NMR (DMSO-d₆): 8.3-7.3 (m, 11H, ArH), 9.12 (s, 1H, H at C₂); MS: 346 m/z (M⁺); Anal. Calcd. for C₁₉H₁₂ClN₅: C 65.99, H 3.50, N 20.26 %, found: C 66.17, H 3.66, N 20.06 %.

7,9-Di(4-chlorophenyl)-7H-triazolo[1,5-c]-7H-pyrrolo[3,2-e]pyrimidine (4e): Yield: 85 % (Method A), 82 % (Method B); mp: 237-39°C; IR: 1616, 1500 (C=C, C=N ring); ¹H-NMR (DMSO-d₆): 8.3-7.2 (m, 10H, ArH), 9.15 (s, 1H, H at C₂); MS: 380 m/z (M⁺); Anal. Calcd. for C₁₉H₁₁Cl₂N₅: C 60.01, H 2.92, N 18.42 %, found: C 60.11, H 3.08, N 18.31 %.

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