3. Results and Discussion

The research work carried out towards achieving the proposed plan has been discussed under the following two main headings:

3.1 Chemical studies

3.2 Biological evaluation

3.1 Chemical studies

3.1.1 Synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one intermediates (**4a-c** & **6a-c**)

- Synthesis of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**4a**)
- Synthesis of 3-isocyanato-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**6a**)
- Synthesis of 8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**4b**)
- Synthesis of 3-isocyanato-8-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**6b**)
- Synthesis of 7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**4c**)
- Synthesis of 7-chloro-3-isocyanato-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**6c**)

3.1.2 Synthesis of (4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea derivatives (**Series I**)

- Synthesis of (4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea derivatives
- Synthesis of 8-methyl-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea derivatives
- Synthesis of 7-chloro-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea derivative

3.1.3 Synthesis of *N*-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(pyridin-2-yl)piperazine-1-carboxamide derivatives (**Series II**)

- Synthesis of *N*-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(pyridin-2-yl)-piperazine-1-carboxamide derivatives
- Synthesis of *N*-(8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(pyridin-2-yl)piperazine-1-carboxamide derivatives
- Synthesis of *N*-(7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(pyridin-2-yl)piperazine-1-carboxamide derivatives

3.1.4 Synthesis of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carbamate derivatives (**Series III**)

- Synthesis of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carbamate derivatives

- Synthesis of 8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carbamate derivatives
- Synthesis of 7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carbamate derivatives

3.1.5 Synthesis of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carboxamide derivatives (**Series IV**)

- Synthesis of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carboxamide derivatives

- Synthesis of 8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carboxamide derivatives
- Synthesis of 7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carboxamide derivatives
- Synthesis of 7-(4-methoxyphenyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbox-amide intermediates
- Synthesis of 7-(4-methoxyphenyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbox-amides derivatives

Compounds belonging to these individual categories have been synthesized by following six major schemes as described below:

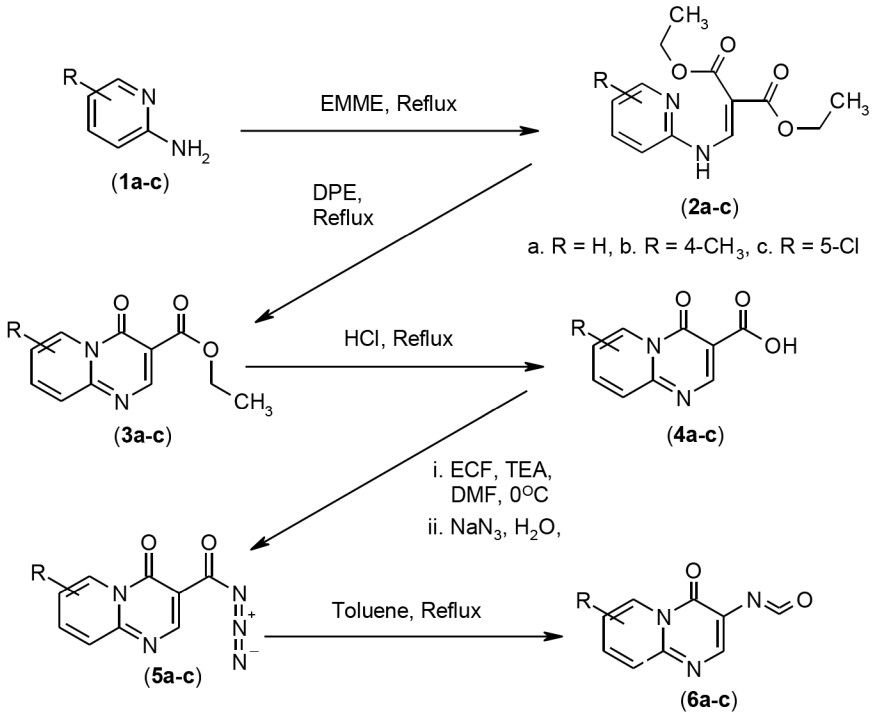
3.1.1 Synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one intermediates (**4a-c** & **6a-c**)

The acids (**4a-c**) and the isocyanates (**6a-c**) are the key intermediates in the preparation of the targeted compounds. Their synthesis was accomplished by following the key steps i) Gould and Jacob reaction ii) cyclization, iii) hydrolysis and iv) Curtius rearrangement reaction. Synthesis of theses intermediates is accomplished by following the reaction sequence as outlined in the Scheme-1.

- **Synthesis of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (4a)**

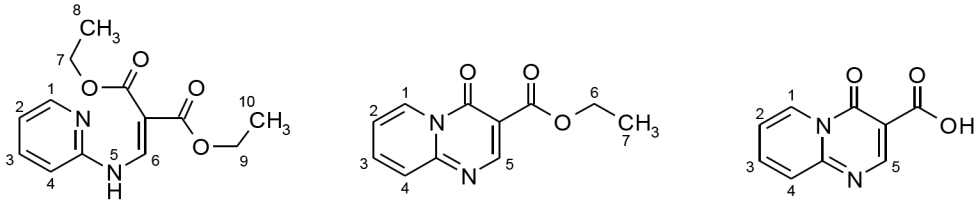
2-Aminopyridine (**1a**) was reacted with diethyl ethoxymethylene-malonate affording the diethyl 2-pyridylaminomethylenemalonate (**2a**). Compound (**2a**) offered characteristic peaks at 3274 (N-H str.), 1686 (C=O, str.) and 1248 cm^{-1} (C-O, str.) in its IR spectrum. The compound (**2a**) displayed

characteristic signals at δ 1.22-1.29 (m, 6H, C$H_{3(8/10)}$), 4.12-4.18 (q, 2H, C$H_{2(7/9)}$), 4.20-4.25 (q, 2H, C$H_{2(7/9)}$), 7.14-7.17



Scheme 1

(m, 1H, Ar-$H_{(2)}$), 7.39-7.41 (d, 1H, Ar-$H_{(4)}$), 7.79-7.83 (m, 1H, Ar-$H_{(3)}$), 8.36-8.37 (d, 1Ar-$H_{(1)}$), 9.05-9.08 (d, 1H, Ar-$H_{(6)}$) and 10.76-10.80 (d, 1H, N$H_{(5)}$) in its NMR spectrum. The (M^++1) peak was observed at (*m/z*) 265 in its mass spectrum.



(**2a**) (**3a**) (**4a**)

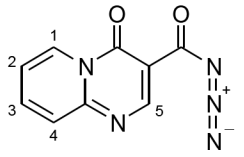
The diester (**2a**) was refluxed in diphenyl ether to get the cyclized product ethyl 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**3a**). Its IR spectrum displayed characteristic peaks at 1730 (C=O str.) and 1103 cm^{-1} (C-O str.). The cyclized product showed characteristic signals at δ 1.29-1.32 (3H, C$H_{3(7)}$) and 4.25-4.30 (m, 2H, C$H_{2(6)}$), 7.56-7.59 (m, 1H, Ar-$H_{(2)}$), 7.84-7.87 (d,

1H, Ar-$H_{(4)}$), 8.19-8.23 (m, 1H, Ar-$H_{(3)}$), 8.87 (s, 1H, Ar-$H_{(5)}$) and 9.16-9.18 (d, 1H, Ar-$H_{(1)}$) in its NMR spectrum. The (M^++1) peak was obtained at (*m/z*) 219 in its mass spectrum.

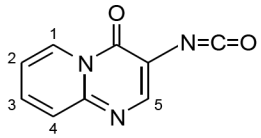
4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**4a**) was prepared by acid catalyzed ester hydrolysis of the compound (**3a**) using concentrated hydrochloric acid. Characteristic peaks were displayed at 3091 (O-H str.) and 1757 cm^{-1} (C=O str.) in its IR spectrum. The ^{1}H-NMR displayed characteristic signals at δ 7.67-7.71 (m, 1H, Ar-$H_{(2)}$), 7.97-8.00 (d, 1H, Ar-$H_{(4)}$), 8.31-8.35 (m, 1H, Ar-$H_{(3)}$), 8.96 (s, 1H, Ar-$H_{(5)}$) and 9.22-9.23 (d, 1H, Ar-$H_{(1)}$). The (M^++1) peak was observed in its mass spectrum at (*m/z*) 191.

- **Synthesis of 3-isocyanato-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (6a)**

The carbonyl azide (**5a**) was prepared by reacting the acid (**4a**) with ethyl chloroformate to get the mixed anhydride which was treated *in situ* with aqueous sodium azide offering 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonylazide (**5a**). Characteristic absorption bands were observed at 2140 for the azide and 1724 cm^{-1} (C=O, str.) in its IR spectrum. The ^{1}H-NMR showed peaks at δ 7.61-7.64 (m, 1H, Ar-$H_{(2)}$), 7.87-7.91 (d, 1H, Ar-$H_{(4)}$), 8.24-8.35 (m, 1H, Ar-$H_{(3)}$), 8.94 (s, 1H, Ar-$H_{(5)}$) and 9.10-9.28 (d, 1H, Ar-$H_{(1)}$). The mass spectrum of the compound (**5a**) showed (M^+-1) peak at (*m/z*) 214.



(**5a**)



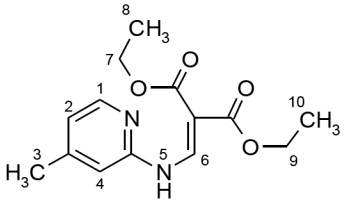
(**6a**)

The azide (**5a**) was refluxed in toluene to get the Curtius rearrangement product 3-isocyanato-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**6a**). Characteristic peaks were observed at 2140 (N=C=O str.) and 1687 cm^{-1} (C=O str.) in its IR spectrum. The mass spectrum displayed (M^++1) peak at (*m/z*) 188.

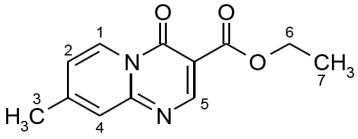
- **Synthesis of 8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (4b)**

Similarly, diethyl (4-methyl-2-pyridylamino)methylenemalonate (**2b**) was prepared by reacting compound (**1b**) with diethyl ethoxymethylenemalonate

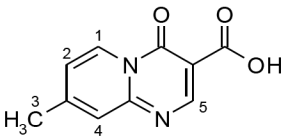
as described above for compound (**2a**). It gave strong characteristic absorption bands at 1682 (C=O str.) and 1218 cm^{-1} (C-O str.) in its IR spectrum. The mass spectrum displayed (M^++1) peak at (*m/z*) 279.



(**2b**)



(**3b**)



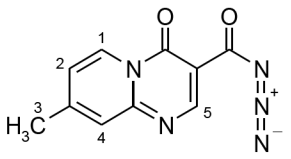
(**4b**)

Ethyl 8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**3b**) was prepared from compound (**2b**) as described above for compound (**3a**). Strong characteristic peaks were observed at 1689, (C=O str.) and 1143 cm^{-1} (C-O str.) in its IR spectrum. Its ^{1}H-NMR displayed signals of the ethyl ester groups at δ 1.30 (t, 3H, C$H_{3(7)}$), 2.51 (s, 3H, C$H_{3(3)}$), 4.23-4.29 (m, 2H, $CH_{2(6)}$), 7.42-7.44 (m, 1H, Ar-$H_{(2)}$), 7.67 (s, 1H, Ar-$H_{(4)}$), 8.82 (s, 1H, Ar-$H_{(5)}$), 9.04-9.05 (d, 1H, Ar-$H_{(1)}$). The mass spectrum showed (M^++1) peak at (*m/z*) 233.

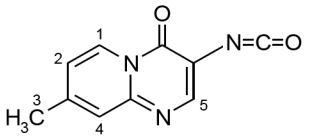
8-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**4b**) was obtained on acidic hydrolysis of the ester (**3b**). It gave characteristic absorption bands at 2645 (O-H str.) and 1764 cm^{-1} (C=O str.) in its IR spectrum. ^{1}H-NMR displayed characteristic signals for methyl group at δ 2.62 (s, 3H, C$H_{3(3)}$) and acid at 10.90 (b, 1H, COO*H*). The aromatic protons were observed at δ 7.62-7.64 (m, 1H, Ar-$H_{(2)}$), 7.89 (s, 1H, Ar-$H_{(4)}$), 8.88-8.90 (d, 1H, Ar-$H_{(5)}$) and 9.14-9.16 (d, 1H, Ar-$H_{(1)}$). The compound gave (M^+-1) peak at (*m/z*) 203 in its mass spectrum.

- **Synthesis of 3-isocyanato-8-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (6b)**

The synthesis of 8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonylazide (**5b**) was accomplished by treating (**4b**) with ethyl chloroformate and sodium azide as outlined in (Scheme 1). Characteristic IR peaks were observed at 2142 (azide str.) and 1712 cm^{-1} (C=O str.) in its IR spectrum. Its ^{1}H-NMR signals appeared at δ 2.56 (s, 3H, C$H_{3(3)}$), 7.49-7.51 (d, 1H, Ar-$H_{(2)}$), 7.75 (s, 1H, Ar-$H_{(4)}$), 8.84 (s, 1H, Ar-$H_{(5)}$) and 9.09-9.13 (d, 1H, Ar-$H_{(1)}$). The mass spectrum showed (M^++1) signal at (*m/z*) 230.



(**5b**)

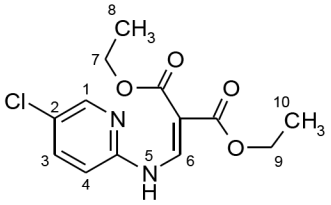


(**6b**)

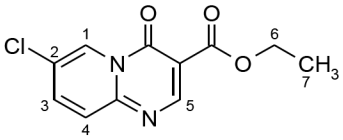
The acid azide (**5b**) was refluxed in toluene as described above for (**6a**) yielding 3-isocyanato-8-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**6b**). Strong absorption bands were observed at 2223 (N=C=O str.) and 1670 cm^{-1} (C=O str.) in its IR spectrum. The mass showed (M^{+}+1) peak at (*m/z*) 201.

- **Synthesis of 7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (4c)**

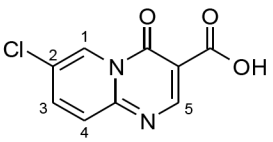
Diethyl (5-chloro-2-pyridylamino)methylenemalonate (**2c**) was synthesized by reacting compound (**1c**) with diethyl ethoxymethylenemalonate as described above for compound (**2a**). Its IR spectrum showed strong absorption bands at 1676 (C=O



(**2c**)



(**3c**)



(**4c**)

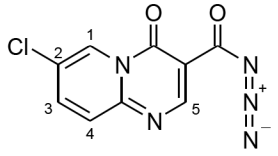
str.) and 1219 cm^{-1} (C-O str.). The characteristic NMR signals were displayed at δ 1.11-1.29 (m, 6H, C$H_{3(8/10)}$), 4.13-4.26 (m, 4H, C$H_{2(7/9)}$), 7.47-7.49 (d, 1H, Ar-$H_{(3)}$), 7.91-7.94 (m, 1H, Ar-$H_{(4)}$), 8.41 (s, 1H, Ar-$H_{(1)}$), 8.94-8.97 (d, 1H, Ar-$H_{(6)}$) and 10.79-10.82 (d, 1H, N$H_{(5)}$). Molecular ion peak (M^{+}+1) was observed at (*m/z*) 299 in its mass spectrum.

Ethyl 7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**3c**) was prepared from compound (**2c**) as described above for compound (**3a**). Strong peaks were observed in its IR spectrum at 1681 (C=O str.) and 1222 cm^{-1} (C-O str.). The mass spectrum displayed a prominent (M^{+}+1) peak at (*m/z*) 253.

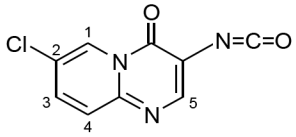
7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**4c**) was prepared from compound (**3c**) as described above for compound (**4a**). Characteristic IR bands were observed at 3063 (O-H str.), 1756 cm^{-1} (C=O str.) in its IR spectrum. The mass spectrum showed (M^++1) peak at (*m/z*) 225.6.

- **Synthesis of 7-chloro-3-isocyanato-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (6c)**

Reaction of compound (**4c**) with ethyl chloroformate and sodium azide was done as described above for compound (**5a**) to get 7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonylazide (**5c**). Its IR spectrum showed absorption bands at 2158 (azide str.) and 1732 cm^{-1} (C=O str.). A prominent (M^++1) peak was observed at (*m/z*) 250.6 in its mass spectrum.



(**5c**)



(**6c**)

7-Chloro-3-isocyanato-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**6c**) was synthesized as described above for compound (**6a**). It displayed characteristics peaks at 2243 (N=C=O str.) and 1668 cm^{-1} (C=O str.) in its IR spectrum. The mass spectrum showed (M^++1) peak at 222.6.

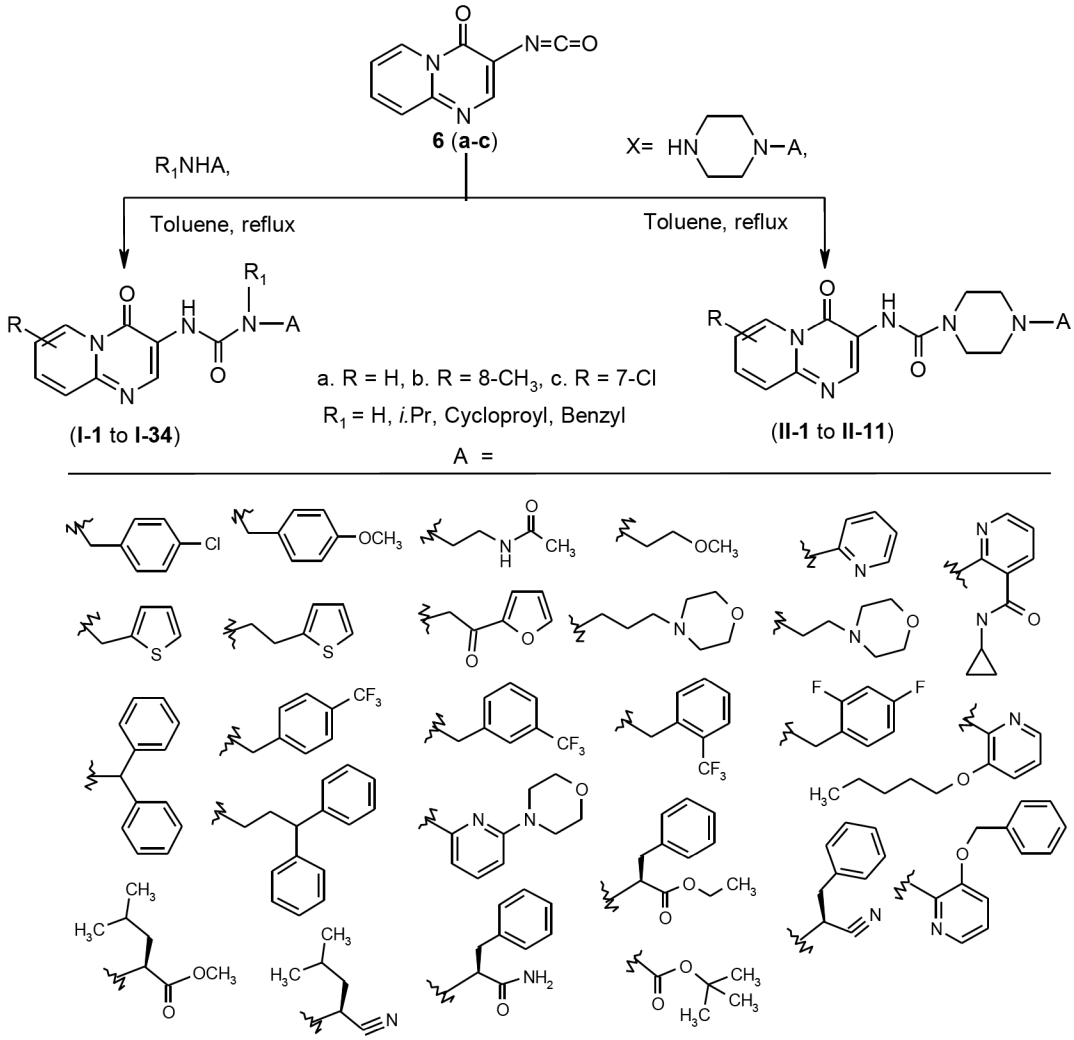
3.1.2 Synthesis of substituted (4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea derivatives (Series I)

The ureas **Series-I** (**I-1** to **I-34**) were prepared by coupling of suitable isocyanate **(6a-c**) with amine derivatives of type $\mathbf{R_1NHA}$ in toluene under reflux conditions following the procedure as depicted in **Scheme 2** or **Scheme 3**.

- **Synthesis of (4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea derivatives**

The synthesis of 1-(4-chlorobenzyl)-3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea (**I-1**) has been carried out by refluxing the isocyanate derivative (**6a**) (Scheme 1) and 4-chlorobenzylamine in toluene as depicted in Scheme 2 to get the compound (**I-1**). Its IR spectrum showed characteristic peaks

at 3318 (N-H str.) and 1693 cm^{-1} (C=O str.). The ^{1}H-NMR displayed characteristic signals at δ 4.39-4.41 (d, 2H, C$H_{2(8)}$), 7.26-7.28 (m, 1H, Ar-$H_{(2)}$),

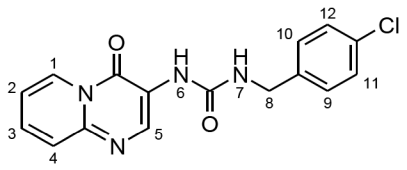


Scheme 2

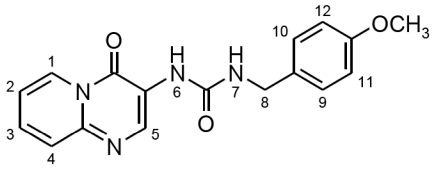
7.30-7.35 (m, 2H, Ar-$H_{(9,10)}$), 7.41-7.47 (m, 2H, Ar-$H_{(11,12)}$), 7.56 (t, 1H, N$H_{(7)}$), 7.61-7.64 (d, 1H, Ar-$H_{(4)}$), 7.68-7.71 (m, 1H, Ar-$H_{(3)}$), 8.55 (s, 1H, N$H_{(6)}$), 8.85-8.87 (d, 1H, Ar-$H_{(1)}$) and 9.16 (s, 1H, Ar-$H_{(5)}$). The mass spectrum displayed molecular ion peak (M^+) at 328.9 and (M^++2) at (*m/z*) 330.8 characteristic of the chloro compound.

1-(4-Methoxybenzyl)-3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea (**I-2**) was prepared by reacting the isocyanate (**6a**) with 2-methoxyethylamine as

described above for compound (**I-1**). Characteristic signals appeared at 3361 (N-H str.), 1639 (C=O str.) and 1180 cm^{-1} (C-O str.) in its IR spectrum. ^{1}H-NMR spectrum showed peaks at δ 3.73 (s, 3H, OC$H_{3(13)}$), 4.24–4.25 (d, 2H, C$H_{2(8)}$), 6.89–6.91 (d, 2H, Ar-$H_{(9,10)}$), 7.22–7.27 (m, 3H, Ar-$H_{(11,12)}$ & Ar-$H_{(2)}$), 7.40–7.43 (t, 1H, N$H_{(7)}$), 7.61–7.63 (d, 1H, Ar-$H_{(4)}$), 7.68–7.72 (m, 1H, Ar-$H_{(3)}$), 8.39 (s, 1H, N$H_{(6)}$), 8.84–8.86 (d, 1H, Ar-$H_{(1)}$) and 9.18 (s, 1H, Ar-$H_{(5)}$). A molecular ion peak (M^++1) was observed at (*m/z*) 325 in its mass spectrum.

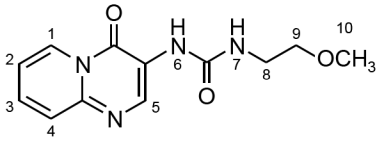


(**I-1**)

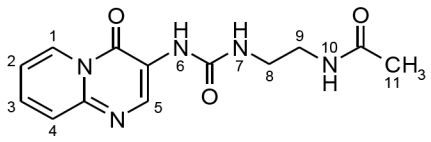


(**I-2**)

The synthesis of 1-(2-methoxyethyl)-3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea (**I-3**) was accomplished by reacting the isocyanate derivative (**6a**) with 2-methoxyethylamine as described above for compound (**I-1**). It gave characteristic IR absorption bands at 3362 (N-H str.), 1639 (C=O str.) and 1099 cm^{-1} (C-O str.). Its ^{1}H-NMR showed characteristic signals at δ 3.25-3.28 (m, 5H, OC$H_{3(10)}$ & C$H_{2(9)}$), 3.70-3.39 (t, 2H, C$H_{2(8)}$), 7.16-7.17 (m, 1H, N$H_{(7)}$), 7.23-7.27, (m, 1H, Ar-$H_{(2)}$), 7.60-7.63 (d, H, Ar-$H_{(4)}$), 7.67-7.72 (m, 1H, Ar-$H_{(3)}$), 8.41 (s, 1H, N$H_{(6)}$), 8.45-8.86 (d, 1H, Ar-$H_{(1)}$) and 9.16 (s, 1H, Ar-$H_{(5)}$). The mass spectrum displayed (M^++1) peak at (*m/z*) 263.



(**I-3**)

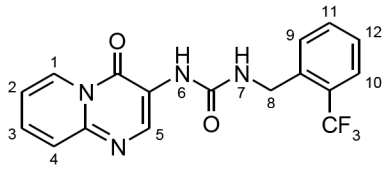


(**I-4**)

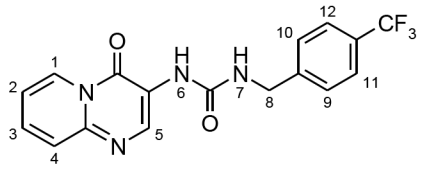
The isocyanate (**6a**) was reacted with 2-acetamidoethylamine as described above for compound (**I-1**) affording *N*-{2-[3-(4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ureido]ethyl}acetamide (**I-4**). It showed characteristic peaks at 3317 (N-H str.), 1633 cm^{-1} (C=O str.) in its IR spectrum. The characteristic peaks were observed at δ 1.81 (s, 3H, C$H_{3(11)}$), 3.11-3.16 (m, 4H, C$H_{2(8,9)}$), 7.09-7.11 (m, 1H, N$H_{(7)}$), 7.23-7.27 (m, 1H, Ar-$H_{(2)}$), 7.61-7.63 (d, 1H, Ar-$H_{(4)}$), 7.68-7.72 (m, 1H, Ar-$H_{(3)}$), 7.94 (b, 1H, N$H_{(10)}$), 8.35 (s, 1H, N$H_{(6)}$), 8.84-8.86 (d, 1H, Ar-$H_{(1)}$)

and 9.17 (s, 1H, Ar-$H_{(5)}$) in its NMR spectrum. The compound (**I-4**) offered (M^++1) peak at (*m/z*) 290 in its mass spectrum.

1-(4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3-(2-trifluoromethylbenzyl)-urea (**I-5**) was prepared by reacting the isocyanate (**6a**) with 2-trifluoromethyl-benzylamine as described above for compound (**I-1**). The compound showed strong peaks at 3315 (N-H str.) and 1667 cm^{-1} (C=O str.) in its IR spectrum. The characteristic signals were displayed at δ 4.51-4.52 (d, 2H, C$H_{2(8)}$), 7.25-7.28 (m, 1H, Ar-$H_{(2)}$), 7.47-7.51 (m, 1H, N$H_{(7)}$), 7.56-7.64 (m, 3H, Ar-$H_{(4,11,12)}$), 7.68-7.74 (m, 3H, Ar-$H_{(3,9,10)}$), 8.59 (s, 1H, N$H_{(6)}$), 8.86-8.88 (d, 1H, Ar-$H_{(1)}$) and 9.17 (s, 1H, Ar-$H_{(5)}$) in its NMR spectrum. The compound gave (M^++1) peak at (*m/z*) 363 in its mass spectrum.



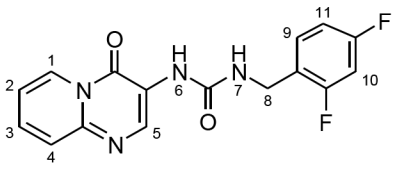
(**I-5**)



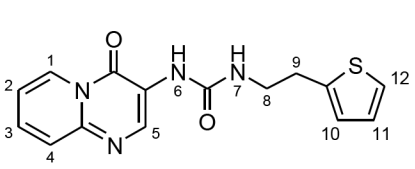
(**I-6**)

1-(4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3-(4-trifluoromethylbenzyl)-urea (**I-6**) displayed characteristic peaks at 3328 (N-H str.), 3048 (Ar-H str.) and 1670 cm^{-1} (C=O str.) in its IR spectrum. The NMR spectrum displayed characteristic signals at δ 4.42-4.44 (d, 2H, C$H_{2(8)}$), 7.25-7.28 (m, 1H, Ar-$H_{(2)}$), 7.51-7.54 (d, 2H, Ar-$H_{(9,10)}$), 7.59-7.64 (m, 2H, Ar-$H_{(3,4)}$), 7.69-7.73 (m, 3H, Ar-$H_{(11,12)}$ & N$H_{(7)}$), 8.50 (s, 1H, N$H_{(6)}$), 8.86-8.87 (d, 1H, Ar-$H_{(1)}$) and 9.16 (s, 1H, Ar-$H_{(5)}$). The (M^+-1) peak was observed at (*m/z*) 361 in its mass spectrum.

The compound 1-(2,4-difluorobenzyl)-3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea (**I-7**) showed characteristic IR signals at 3328 (N-H str.) and 1676 cm^{-1} (C=O str.). The ^{1}H-NMR displayed characteristic peaks at δ 4.35-



(**I-7**)



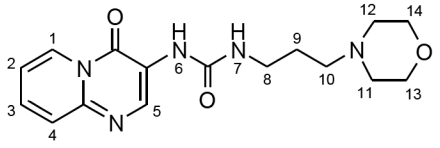
(**I-8**)

4.37 (d, 2H, C$H_{2(8)}$), 7.14-7.20 (m, 2H, Ar-$H_{(9,11)}$), 7.24-7.28 (m, 2H, Ar-$H_{(2,10)}$), 7.52-7.55 (t, 1H, N$H_{(7)}$), 7.62-7.64 (d, 1H, Ar-$H_{(4)}$), 7.69-7.74 (m, 1H , Ar-$H_{(3)}$),

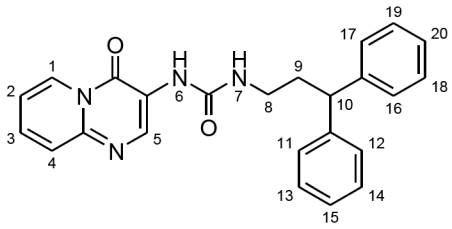
8.50 (s, 1H, N$H_{(6)}$), 8.85-8.87 (d, 1H, Ar-$H_{(1)}$) and 9.14 (s, 1H, , Ar-$H_{(5)}$). The molecular ion (M^++1) peak was observed at (*m/z*) 331 in its mass spectrum.

1-(4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3-[2-(thiophen-2-yl)ethyl]-urea (**I-8**) showed characteristic IR signals at 3213 of urea (N-H str.), 3033 (Ar-H str.) and 1656 cm^{-1} (C=O str.). The compound gave the signals at δ 2.97-3.01 (t, 2H, $CH_{2(9)}$), 3.37-3.4 (t, 2H, C$H_{2(8)}$), 6.92-6.93 (b, 1H, Ar-$H_{(10)}$), 6.97-6.99 (m, 1H, Ar-$H_{(11)}$), 7.15-7.18 (t, 1H, N$H_{(7)}$), 7.23-7.27 (m, 1H, Ar-$H_{(2)}$), 7.35-7.37 (d, 1H, Ar-$H_{(12)}$), 7.61-7.63 (d, 1H, Ar-$H_{(4)}$), 7.68-7.72 (m, 1H, Ar-$H_{(3)}$), 8.41 (s, 1H, N$H_{(6)}$), 8.84-8.85 (d, 1H, Ar-$H_{(1)}$) and 9.19 (s, 1H, Ar-$H_{(5)}$) in its NMR spectrum. The mass spectrum showed (M^++1) peak at (*m/z*) 315.

The compound 1-[3-(morpholin-4-yl)propyl]-3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea (**I-9**) displayed characteristic peaks at 3297 (N-H str.) and 3072 (Ar-H str.), 1663 (C=O str.) and 1118 cm^{-1} (C-O str.) in its IR spectrum. The signals were displayed at δ 1.55–1.62 (m, 2H, C$H_{2(9)}$), 2.28–2.32 (m, 2H, C$H_{2(10)}$), 2.34 (b, 4H, C$H_{2(11/12)}$), 3.10–3.15 (m, 2H, C$H_{2(8)}$), 3.56–3.58 (t, 4H, C$H_{2(13/14)}$), 7.01–7.04 (m, 1H, N$H_{(7)}$), 7.23–7.27 (m, 1H, Ar-$H_{(2)}$), 7.60–7.63 (d, 1H, Ar-$H_{(4)}$), 7.67–7.71 (t, 1H, Ar-$H_{(3)}$), 8.29 (s, 1H, N$H_{(6)}$), 8.84–8.86 (d, 1H, Ar-$H_{(1)}$) and 9.17 (s, 1H, Ar-$H_{(5)}$) in its NMR spectrum. The compound gave (M^++1) peak at (*m/z*) 332 in its mass spectrum.



(**I-9**)

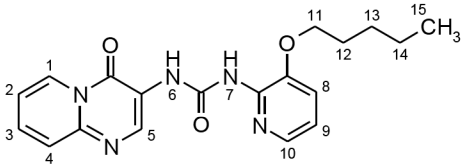


(**I-10**)

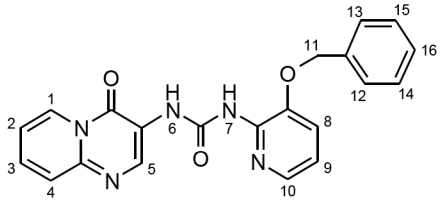
1-(3,3-Diphenyl)propyl-3-(4-oxo-4H-pyrido[1,2-*a*]pyrimidin-3-yl)urea (**I-10**) displayed strong IR signals at 3324 (N-H str.) and 1664 cm^{-1} (C=O Str.). The signals were observed at δ 2.18-2.23 (m, 2H, C$H_{2(9)}$), 2.97-3.05 (m, 2H, C$H_{2(8)}$), 4.01-4.05 (t, 1H $CH_{(10)}$), 7.11-7.34 (m, 12H, Ar-$H_{(2,11-20)}$ & N$H_{(7)}$), 7.60-7.63 (d, 1H, Ar-$H_{(4)}$), 7.67-7.74 (m, 1H, Ar-$H_{(3)}$), 8.32 (s, 1H, N$H_{(6)}$), 8.85-8.92 (d, 1H, Ar-$H_{(1)}$) and 9.15 (s, 1H, Ar-$H_{(5)}$) in its ^{1}H-NMR spectrum. The (M^++1) peak was displayed at (*m/z*) 399 in the mass spectrum.

The IR spectrum of the compound 1-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3-[3-(*n*.pentyloxy)pyridin-2-yl]urea (**I-11**) displayed characteristic bands at 3350 (N-H str.), 1665 (C=O str.) and 1220 cm^{-1} (C-O Str.). The ^{1}H-NMR signals were displayed at δ 0.90-0.94 (t, 3H, C$H_{3(15)}$), 1.32-1.47 (m, 4*H,* C$H_{2(13,14)}$), 1.78-1.85 (m, 2H*,* C$H_{2(12)}$), 4.07-4.11 (t, 2H*,* C$H_{2(11)}$), 7.05-7.08 (m, 1H, Ar-$H_{(9)}$), 7.30-7.34 (m, 1H, Ar-$H_{(2)}$), 7.44-7.46 (d, 1H, Ar-$H_{(8)}$), 7.67-7.69 (d, 1H, Ar-$H_{(4)}$), 7.76-7.81 (m, 1H, Ar-$H_{(3)}$), 7.89-7.91 (dd, 1H, Ar-$H_{(10)}$), 8.35 (s, 1H, N$H_{(6)}$), 8.92-8.94 (d, 1H, Ar-$H_{(1)}$), 9.29 (s, 1H, Ar-$H_{(5)}$) and 12.15 (s, 1H, N$H_{(7)}$). The compound gave (M^++1) peak at (*m/z*) 368 in its mass spectrum.

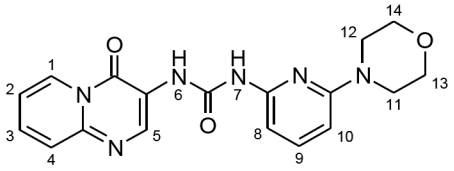
Characteristic peaks were displayed in the IR spectrum of 1-[3-(benzyloxy)pyridin-2-yl]-3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea (**I-12**) at 3436 (N-H str.), 1675 (C=O str.) and 1229 cm^{-1} (Ar-O str.). ^{1}H-NMR signals appeared at δ 5.29 (s, 2H, C$H_{2(11)}$), 7.07 (m, 1H, Ar-$H_{(9)}$), 7.33-7.42 (m, 3H, Ar-$H_{(14-16)}$), 7.51-7.57 (m, 3H, Ar-$H_{(2,12,13)}$), 7.70-7.76 (m, 1H, Ar-$H_{(4)}$), 7.77-7.79 (m, 1H, Ar-$H_{(3)}$), 7.91-7.92 (d, 1H, Ar-$H_{(8)}$), 8.46 (s, 1H, N$H_{(6)}$), 8.90-8.94 (m, 1H, Ar-$H_{(10)}$), 9.22-9.28 (d, 1H, Ar-$H_{(1)}$), 9.52 (s, 1H, Ar-$H_{(5)}$) and 12.06 (s, 1H, N$H_{(7)}$). The compound offered (M^++1) peak at (*m/z*) 388 in its mass spectrum.



(**I-11**)



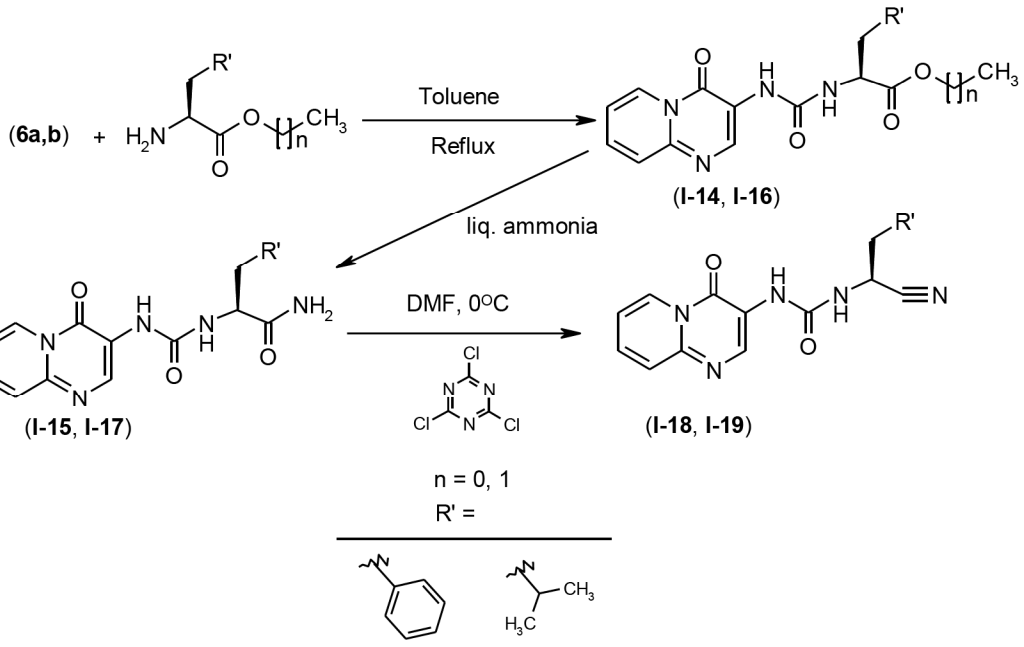
(**I-12**)



(**I-13**)

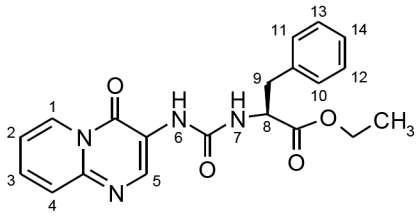
1-[6-(Morpholin-4-yl)pyridin-2-yl]-3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea (**I-13**) displayed characteristic Ibands at 3118 (N-H str.), 1688 (C=O str.) and 1229 cm^{-1} (C-O str.). Its NMR spectrum showed characteristic signals at δ 3.66-3.68 (b, 4H, Ar-$H_{(11,12)}$), 3.95-3.97 (b, 4H, Ar-$H_{(13,14)}$), 6.17-6.20 (d, 1H, Ar-$H_{(10)}$), 6.29-6.31 (d, 1H, Ar-$H_{(8)}$) and 11.48 (s, 1H, N$H_{(7)}$). The mass spectrum showed (M^++1) peak at (*m/z*) 367.

To study the binding pattern in the P1 and P2 pocket, some additional compounds bearing esters (**I-14**), (**I-19**), amides (**I-15**), (**I-17**) and nitriles (**I-18**), (**I-19**) were also synthesized. The esters, amide and nitriles have been reported to show good binding affinity for FPs. Hence compounds (**I-14** to **I-19**) were synthesized by following the reaction sequence as outlined in the **Scheme 3**.

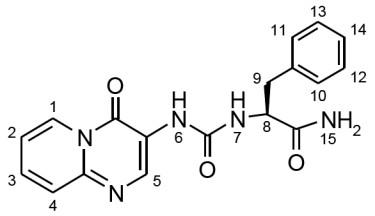


Scheme 3

Ethyl (2*S*)-2-{[(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)carbamoyl]amino}-3-phenylpropanoate (**I-14**) was prepared by reacting compound (**6a**) with *L*-phenylalanine ethyl ester, afforded compound (**I-14**). The IR spectrum showed characteristic peaks at 3338 (N-H str.), 3032 (Ar-H str.) and 1733, 1629 cm^{-1} (C=O str.). The mass spectrum displayed the (M^++1) at (*m/z*) 381.



(**I-14**)

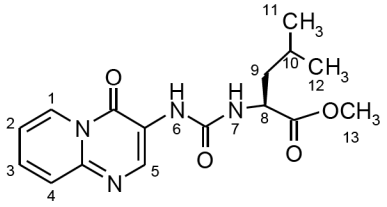


(**I-15**)

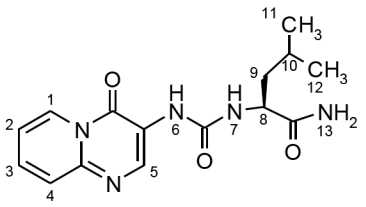
(2*S*)-2-{[(4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)carbamoyl]amino}-3-phenylpro-panamide (**I-15**) was prepared by reacting compound (**I-14**) with

ammonia solution yielding the compound (**I-15**). Its IR spectrum showed peaks at 3329 (N-H str,) and 1634 cm^{-1} (C=O str.). The mass spectrum displayed (M^++1) signal at (*m/z*) 352.

Methyl (2*S*)-4-methyl-2-{[(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)carbamoyl]amino}*n*.pentanoate (**I-16**) was obtained by reacting the compound (**6a**) with *L*-leucine methyl ester. Its IR spectrum showed characteristic peaks at 3325 (N-H str.) and 1745, 1657 cm^{-1} (C=O str.). The peak (M^++1) was observed at (*m/z*) 333 in its mass spectrum.



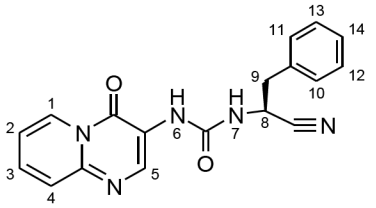
(**I-16**)



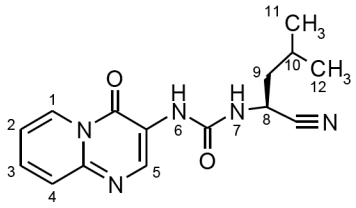
(**I-17**)

(2*S*)-4-Methyl-2-{[(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)carbamoyl]amino}*n*.pentanamide (**I-17**) was prepared by treating the compound (**I-16**) with ammonia solution affording the compound (**I-17**). Its IR spectrum displayed characteristic peaks at 3361 (N-H str.) and 1672, 1628 (C=O str.). The compound offered (M^++1) peak at (*m/z*) 318 in its mass spectrum.

Dehydration of the amide compound (**I-16**) was done using cyanuric chloride in dimethylformamamide to get the nitrile product 1-[(1*S*)-1-(cyano-2-phenyl)ethyl]-3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea (**I-18**). Characteristic peaks at δ 3.09-3.19 (m, 2H, C$H_{2(9)}$), 4.92-4.98 (m, 1H, C$H_{(8)}$), 7.26-7.34 (m, 2H, Ar-$H_{(2,14)}$), 7.36-7.37 (m, 4H, Ar-$H_{(10-13)}$), 7.63-7.67 (m, 2H, Ar-$H_{(4)}$ & N$H_{(7)}$), 7.72-7.77 (t, 1H, Ar-$H_{(3)}$), 8.58 (s, 1H, N$H_{(6)}$), 8.85-8.87 (d, 1H, Ar-$H_{(1)}$) and 9.10 (s, 1H, Ar-$H_{(5)}$) were observed in its PMR. The mass spectrum showed (M^++1) peak at (*m/z*) 334.

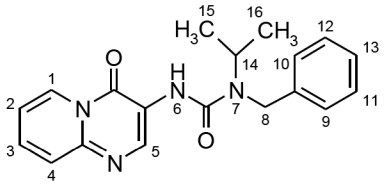


(**I-18**)



(**I-19**)

1-[(1*S*) 1-(Cyano-3-methyl)butyl]-3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea (**I-19**) was obtained by the dehydration of the compound (**I-17**) using cyanuric chloride affording the compound (**I-19**). The ^{1}H-NMR gave peaks at δ 0.91-0.96 (m, 6H, C$H_{3(11,12)}$), 1.64-1.80 (m, 3H, C$H_{2(9)}$ & C$H_{(10)}$), 4.65-4.71 (m, 1H, C$H_{(8)}$), 7.27-7.31 (m, 1H, N$H_{(2)}$), 7.65-7.67 (d, 2H, Ar-H$_{(4)}$ & N$H_{(7)}$), 7.73-7.77 (m, 1H, Ar-$H_{(3)}$), 8.49 (s, 1H, N$H_{(6)}$), 8.86-8.88 (d, 1H, Ar-$H_{(1)}$) and 9.12 (s, 1H, Ar-$H_{(5)}$). The mass spectrum gave (M^{+}+1) peak at (*m/z*) 300.



(**I-20**)

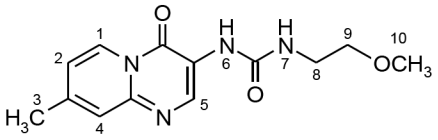
1-Benzyl-1-isopropyl-3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea (**I-20**) showed strong signals at 3373 (N-H str.) and 1641 cm^{-1} (C=O str.) in its IR spectrum. Characteristic NMR peaks appeared at δ 1.14-1.16 (d, 6H, C$H_{3(15,16)}$), 4.51-4.52 (m, 1H, C$H_{(14)}$), 4.55 (s, 2H, C$H_{2(8)}$), 7.25-7.29 (m, 2H, Ar-$H_{(2,13)}$), 7.36-7.37 (d, 4H, Ar-$H_{(9\text{-}12)}$), 7.50 (s, 1H, N$H_{(6)}$), 7.63-7.65 (d, 1H, Ar-$H_{(4)}$), 7.73-7.77 (m, 1H, Ar-$H_{(3)}$), 8.78-8.80 (d, 1H, Ar-$H_{(1)}$) and 8.96 (s, 1H, Ar-$H_{(5)}$). The compound offered (M^{+}+1) peak at (*m/z*) 337 in its mass spectrum.

- **Synthesis of 8-methyl-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea derivatives**

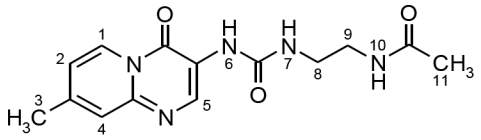
1-(2-Methoxyethyl)-3-(8-methyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidin-3-yl)urea (**I-21**) showed characteristic peaks at 3305 (N-H str.), 1633 (C=O str.) and 1228 cm^{-1} (C-O str.) in its IR spectrum. Characteristic signals appeared at δ 2.39 (s, 3H, C$H_{3(3)}$), 3.22-3.36 (m, 7H, C$H_{2(8,9)}$ & OC$H_{3(10)}$), 7.09-7.7.11 (m, 2H, Ar-$H_{(2)}$ & , N$H_{(7)}$), 7.41(s, 1H, Ar-$H_{(4)}$), 8.30 (s, 1H, N$H_{(6)}$), 8.73-8.75 (d, 1H, Ar-$H_{(1)}$) and 9.06 (s, 1H, Ar-$H_{(5)}$) in its ^{1}HNMR. The compound displayed (M^{+}-1) peak at (*m/z*) 277 in its mass spectrum.

N-{2-[3-(8-Methyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidin-3-yl)ureido]ethyl}-acetamide (**I-22**) gave strong IR signals at 3356 (N-H str.) and 1633 cm^{-1} (C=O str) in its IR spectrum. The characteristic signals were displayed at δ 1.81 (s, 3H, C$H_{3(11)}$), 2.41 (s, 3H, C$H_{3(3)}$), 3.1-3.15 (m, 4H, C$H_{2(8,9)}$), 7.03-7.06 (t, 1H, N$H_{(7)}$),

7.11-7.13 (dd, 1H, Ar-$H_{(2)}$), 7.43 (s, 1H, Ar-$H_{(4)}$), 7.93-7.94 (t, 1H, N$H_{(10)}$), 8.26 (s, 1H, N$H_{(6)}$), 8.76-8.78 (d, 1H, Ar-$H_{(1)}$) and 9.09 (s, 1H, Ar-$H_{(5)}$) in its NMR. The mass showed the (M^++1) peak at (*m/z*) 304.

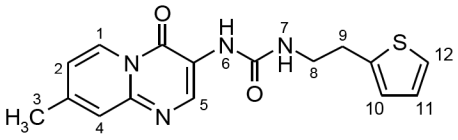


(**I-21**)

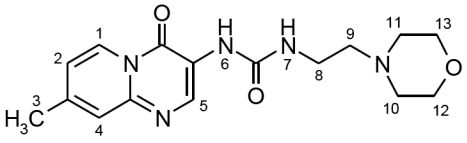


(**I-22**)

The characteristic IR signals of 1-(8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3-[2-(thiophen-2-yl)ethyl]urea (**I-23**) appeared at 3278 (N-H str) and 1634 cm^{-1} (C=O str.). The characteristic peaks at δ 2.41 (s, 3H, C$H_{3(3)}$), 2.95-2.98 (m, 4H, C$H_{2(8,9)}$), 6.92 (s, 1H, Ar-$H_{(10)}$), 6.98 (b, 1H, Ar-$H_{(11)}$), 7.11-7.12 (m, 2H, Ar-$H_{(2)}$ & N$H_{(7)}$), 7.35-7.37 (d, 1H, Ar-$H_{(12)}$), 7.43 (s, 1H, Ar-$H_{(4)}$), 8.32 (s, 1H, N$H_{(6)}$), 8.75-8.77 (d, 1H, Ar-$H_{(1)}$) and 9.11 (s, 1H, Ar-$H_{(5)}$) in its NMR spectrum. The mass spectrum displayed the (M^++1) peak at (*m/z*) 329.



(**I-23**)

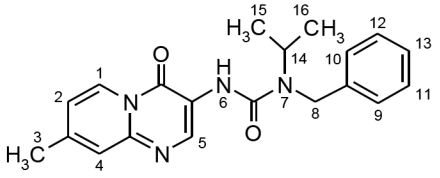


(**I-24**)

The IR spectrum of 1-(8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3-[2-(morpholin-4-yl)ethyl]urea (**I-24**) showed characteristic peaks at 3334 (N-H str.), 1632, (C=O str.) and 1145 cm^{-1} (C-O str.). The ^{1}H-NMR displayed peaks at δ 2.37-2.41 (m, 9H, C$H_{3(3)}$ & $CH_{2(9,10,11)}$), 3.21-3.24 (m, 2H, C$H_{2(8)}$), 3.58-3.59 (b, 4H, C$H_{2(12,13)}$), 6.98-6.99 (m, 1H N$H_{(7)}$), 7.11-7.12 (d, 1H Ar-$H_{(2)}$), 7.42 (s, 1H Ar-$H_{(4)}$), 8.37 (s, 1H N$H_{(6)}$), 8.76-8.78 (d, 1H Ar-$H_{(1)}$) and 9.08-9.09 (d, 1H Ar-$H_{(5)}$). The mass spectrum displayed (M^++1) peak at (*m/z*) 332.

1-Benzyl-1-isopropyl-3-(8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea (**I-25**) gave characteristic bands at 3353 (N-H str.) and 1642 cm^{-1} (C=O str.) in its IR spectrum. The characteristic ^{1}HNMR peaks were observed at δ 1.13-1.15 (d, 6H, C$H_{3(15,16)}$), 2.41 (s, 3H, C$H_{3(3)}$), 4.49-4,51 (m, 1H, C$H_{(14)}$), 4.54 (s, 2H, C$H_{2(8)}$), 7.13-7.15 (d, 1H, Ar-$H_{(2)}$), 7.25- 7.26 (m, 1H, Ar-$H_{(13)}$), 7.35-7.36 (d, 4H, Ar-$H_{(9-12)}$), 7.45 (b, 2H, N$H_{(6)}$ & Ar-$H_{(4)}$), 8.70-8.72 (d, 1H, Ar-$H_{(1)}$) and 8.87

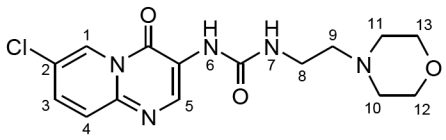
(s, 1H, Ar-$H_{(5)}$). The compound displayed (M^++1) peak at (*m/z*) 351 in its mass spectrum.



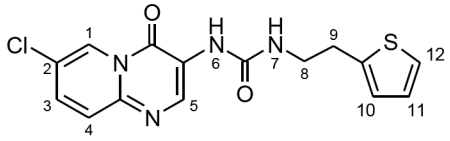
(**I-25**)

- **Synthesis of 7-chloro-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)urea derivatives**

IR spectrum of 1-(7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3-[2-(morpholin-4-yl)ethyl] urea (**I-26**) gave characteristic peaks at 3285 (N-H str.), 1729, 1646 (C=O str.) and 1284 cm^{-1} (C-O str.). The signals appeared at δ 2.39 (b, 6H, C$H_{2(9,10,11)}$), 3.23-3.24 (m, 2H, C$H_{2(8)}$), 3.60 (b, 4H, C$H_{2(12,13)}$), 7.08 (b, 1H, N$H_{(7)}$), 7.63-7.65 (d, 1H, Ar-$H_{(4)}$), 7.70-7.73 (dd, 1H, Ar-$H_{(3)}$), 8.57 (s, 1H, N$H_{(6)}$), 8.84 (s, 1H, Ar-$H_{(1)}$) and 9.17 (s, 1H, Ar-$H_{(5)}$) in its ^{1}H-NMR. The compound showed (M^+) peak at 352.1 and (M^++2) at (*m/z*) 354.1 in its mass spectrum.



(**I-26**)

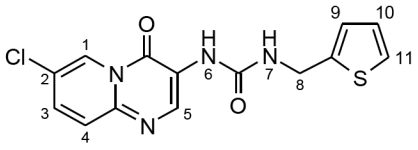


(**I-27**)

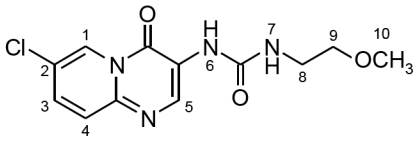
1-(7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3-[2-(thiophen-2-yl)ethyl]urea (**I-27**) in its IR spectrum showed characteristic signals at 3387 (N-H str.) and 1651 cm^{-1} (C=O str.). ^{1}H-NMR displayed the peaks at δ 2.97-3.00 (t, 2H, C$H_{2(9)}$), 3.37-3.40 (t, 2H, C$H_{2(8)}$), 6.92-6.93 (d, 1H, Ar-$H_{(10)}$), 6.97-6.99 (m, 1H, Ar-$H_{(11)}$), 7.18-7.20 (m, 1H, N$H_{(7)}$), 7.35-7.37 (m, 1H, Ar-$H_{(12)}$), 7.63-7.66 (d, 1H, Ar-$H_{(4)}$), 7.71-7.74 (dd, 1H, Ar-$H_{(3)}$), 8.51 (s, 1H, Ar-$H_{(6)}$), 8.83-8.84 (d, 1H, Ar-$H_{(1)}$) and 9.19 (s, 1H, Ar-$H_{(5)}$). The mass spectrum showed the molecular ion peak (M^+) at 349 and (M^++2) at (*m/z*) 350.9.

The IR spectrum of 1-(7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3-(thiophen-2-yl)methylurea (**I-28**) gave characteristics IR signals at 1702, 3272 (N-H str.) and 1652 cm^{-1} (C=O str.). The compound showed peaks at δ 4.49-4.50

(d, 2H, C$H_{2(8)}$), 6.97-6.98 (m, 1H, Ar-$H_{(10)}$), 7.00 (b, 1H, Ar-$H_{(9)}$), 7.40-7.41 (d, 1H, Ar-$H_{(11)}$), 7.56 (b, 1H, N$H_{(7)}$), 7.64-7.66 (d, 1H, Ar-$H_{(4)}$), 7.72-7.74 (d, 1H, Ar-$H_{(3)}$), 8.51 (s, 1H, N$H_{(6)}$), 8.89 (s, 1H, Ar-$H_{(1)}$) and 9.18 (s, 1H, Ar-$H_{(5)}$) in its NMR spectrum. The compound showed (M^+) peak at (*m/z*) 335.34 and (M^++2) at (*m/z*) 337.38 in its mass spectrum.



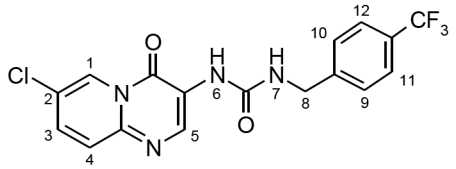
(**I-28**)



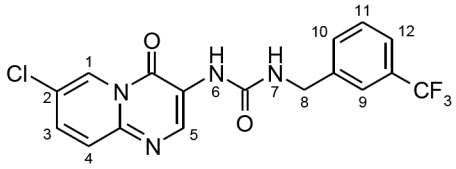
(**I-29**)

1-(7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3-(2-methoxyethyl)urea (**I-29**) displayed characteristic peaks 3370 (N-H str.), 1649 (C=O str.) and 1229 cm^{-1} (C-O str.) in its IR spectrum. NMR spectrum displayed characteristic peaks at δ 3.24-3.39 (m, 7H, C$H_{2(8,9)}$ & C$H_{3(10)}$), 7.19-7.21 (t, 1H, N$H_{(7)}$), 7.63-7.65 (d, 1H, Ar-$H_{(4)}$), 7.70-7.73 (dd, 1H, Ar-$H_{(3)}$), 8.51 (s, 1H, N$H_{(6)}$), 8.83-8.84 (b, 1H, Ar-$H_{(1)}$) and 9.16 (s, 1H, Ar-$H_{(5)}$). The mass spectrum gave (M^+) peak at (*m/z*) 297 and (M^++2) at (*m/z*) 299.

1-(7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3-(4-trifluoromethyl)benzylurea **(I-30**) gave characteristic peaks at 3397 (N-H str.) and 1692, 1656 cm^{-1} (C=O str.) in its IR spectrum. Characteristic signals appeared at δ 4.42-4.44 (d, 2H, C$H_{2(8)}$), 7.57-7.66 (m, 6H, N$H_{(7)}$ & Ar-$H_{(4,9\text{-}12)}$), 7.72- 7.75 (dd, 1H, Ar-$H_{(3)}$), 8.58 (s, 1H, N$H_{(6)}$), 8.84-8.85 (d, 1H, Ar-$H_{(1)}$) and 9.16 (s, 1H, Ar-$H_{(5)}$) in its NMR spectrum. The compound offered (M^+) at (*m/z*) 397.34 and (M^++1) at (*m/z*) 399.38.



(**I-30**)

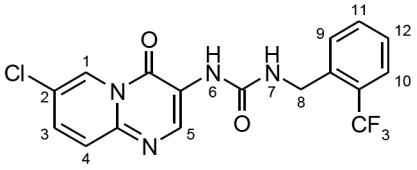


(**I-31**)

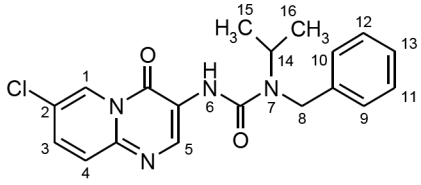
1-(7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3-(3-trifluoromethyl)benzylurea (**I-31**) displayed characteristic peaks at 3312 (N-H str.) and 1677, 1646 cm^{-1} (C=O str.) in its IR spectrum. ^{1}HNMR spectrum signals appeared at δ 4.42-4.43 (d, 2H, C$H_{2(8)}$), 7.51-7.53 (d, 2H, Ar-$H_{(4,10)}$), 7.61-7.63 (m, 2H, N$H_{(7)}$ & Ar-$H_{(11)}$), 7.70-7.75 (m, 3H, Ar-$H_{(3,9,12)}$), 8.60 (s, 1H, N$H_{(6)}$), 8.84-8.85 (d, 1H,

Ar-$H_{(1)}$) and 9.17 (s, 1H, Ar-$H_{(5)}$). The compound gave (M^+) peak at (*m/z*) 397.34 and (M^++2) at (*m/z*) 399.32.

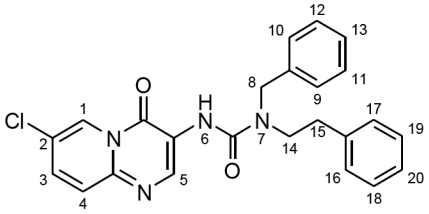
Characteristic IR signals of 1-(7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3-(2-trifluoromethylbenzyl)urea (**I-32**) appeared at 3362 (N-H str.) and 1707, 1622 cm^{-1} (C=O str.). NMR spectrum showed peaks at δ 4.51-4.52 (d, 2H, C$H_{2(8)}$), 7.47-7.51 (m, 1H, Ar-$H_{(11)}$), 7.59-7.75 (m, 6H, Ar-$H_{(3,4,9\text{-}12)}$ & N$H_{(7)}$), 8.68 (s, 1H, N$H_{(6)}$), 8.85 (b, 1H, Ar-$H_{(1)}$) and 9.17 (s, 1H, Ar-$H_{(5)}$). The compound showed (M^+) peak at (*m/z*) 397.34 and (M^++2) at (*m/z*) 399.32 in its mass spectrum.



(**I-32**)



(**I-33**)



(**I-34**)

1-Benzyl-3-(7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-1-isopropylurea (**I-33**) displayed IR bands at 3447 (N-H str.) and 1663, 1630 cm^{-1} (C=O str.). Its mass spectrum showed (M^+) peak at (*m/z*) 371.42 and (M^++2) at (*m/z*) 373.41.

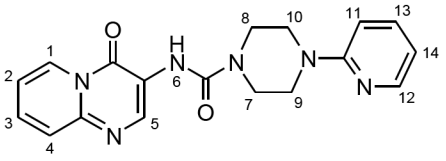
1-Benzyl-3-(7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-1-phenethylurea (**I-34**) showed characteristic IR signals at 3345 (N-H str.) 1647 cm^{-1} (C=O str.). NMR peaks were displayed at 2.85-2.89 (t, 2H, C$H_{2(15)}$), 3.35-3.59 (t, 2H, C$H_{2(14)}$), 4.58 (s, 2H, C$H_{2(8)}$), 7.14-7.38 (m, 10H, Ar-$H_{(9\text{-}13,16\text{-}20)}$), 7.68-7.71 (d, 1H, Ar-$H_{(4)}$), 7.81-82 (m, 2H, Ar-$H_{(3)}$, N$H_{(6)}$), 8.88 (b, 1H, Ar-$H_{(1)}$) and 8.92 (s, 1H, Ar-$H_{(5)}$). The compound showed ($M^+$) peak at (*m/z*) 433.42 and (M^++2) at (*m/z*) 435.41.

3.1.3 Synthesis of *N*-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(pyridin-2-yl)piperazine-1-carboxamide derivatives (Series II)

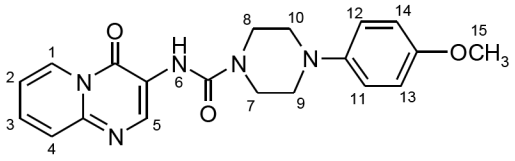
Synthesis of *N*-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(pyridin-2-yl)piperazine-1-carboxamide derivatives (piperazine urea analogs) of the **Series-II** (**II-1** to **II-11**) were synthesized by coupling of isocyanate **(6a-c**) with suitably substituted piperazine derivatives under reflux conditions in toluene as depicted in **Scheme 2**.

- **Synthesis of *N*-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(pyridin-2-yl)piperazine-1-carboxamide derivatives**

The synthesis of compound *N*-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(pyridin-2-yl)piperazine-1-carboxamide (**II-1**) was done by reacting compound (**6a**) with 4-(2-pyridyl)piperazine as described for compound (**I-1**). Characteristic IR peaks were observed at 3393 (N-H str.) and 1659 cm^{-1} (C=O) str.). The NMR spectrum showed characteristic peaks at δ 3.57-3.58 (b, 8H, C$H_{2(7\text{-}10)}$), 6.65-6.69 (m, 1H, Ar-$H_{(14)}$), 6.86-6.88 (d, 1H, Ar-$H_{(11)}$), 7.31-7.35 (m, 1H, Ar-$H_{(2)}$), 7.54-7.58 (m, H, Ar-$H_{(13)}$), 7.67-7.69 (d, 1H, Ar-$H_{(4)}$), 7.80-7.84 (m, 1H, Ar-$H_{(3)}$), 8.08 (s, 1H, N$H_{(6)}$), 8.13-8.14 (d, 1H, Ar-$H_{(12)}$), 8.77 (s, 1H, Ar-$H_{(5)}$) and 8.90-8.93 (d, 1H, Ar-$H_{(1)}$). The compound displayed (M^++1) peak at (*m/z*) 351 in its mass spectrum.



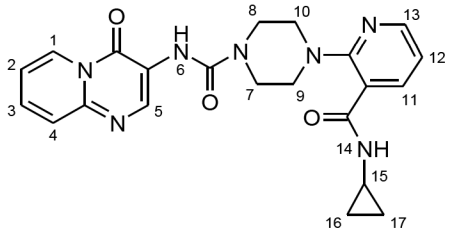
(**II-1**)



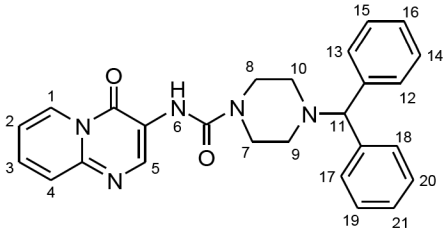
(**II-2**)

The IR spectrum of 4-(4-methoxyphenyl)-*N*-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)piperazine-1-carboxamide (**II-2**) showed characteristic bands at 3396 (N-H str.), 1649 (C=O str.) and 1229 cm^{-1} (C-O str.). The characteristic signals appeared at δ 2.99 (b, 4H $CH_{2(9,10)}$), 3.61(b, 4H C$H_{2(7,8)}$), 3.81 (s, 3H, OC$H_{3(15)}$), 6.87-7.01 (m, 4H, Ar-$H_{(11\text{-}14)}$), 7.32-7.35 (m, 1H, Ar-$H_{(2)}$), 7.67-7.69 (d, 1H, Ar-$H_{(4)}$), 7.80-7.84 (t, 1H, Ar-$H_{(3)}$), 8.06 (s, 1H, N$H_{(6)}$), 8.77 (s, 1H, Ar-$H_{(5)}$) and 8.91-8.93 (d, 1H, Ar-$H_{(1)}$) in its NMR spectrum. The (M^++1) peak was observed at (*m/z*) 380 in its mass spectrum.

N-(4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-[3-(*N*-cyclopropylcarboxamido)pyridine-2-yl]piperazinecarboxamide (**II-3**) offered the peaks at 3296 (N-H str.) and 1654 cm^{-1} (C=O str.). The ^{1}H-NMR gave characteristic signals at δ 0.55-0.58 (m, 2H, $CH_{2(16/17)}$), 0.69-0.72 (m, 2H, $CH_{2(16/17)}$), 2.82-2.83 (m, 1H, $CH_{(15)}$), 3.31-3.36 (t, 4H, $CH_{2(9,10)}$), 3.57-3.59 (t, 4H, $CH_{2(7,8)}$), 6.89-6.92 (m, 1H, Ar-$H_{(12)}$), 7.32-7.36 (m, 1H, Ar-$H_{(2)}$), 7.65-7.67 (m, 2H, Ar-$H_{(4,11)}$), 7.81-7.85 (m, 1H, Ar-$H_{(3)}$), 8.08 (s, 1H, N$H_{(6)}$), 8.23-8.25 (dd, 1H, Ar-$H_{(13)}$), 8.51-8.53 (d, 1H, N$H_{(14)}$), 8.76 (s, 1H, Ar-$H_{(5)}$) and 8.91-8.93 (d, 1H, Ar-$H_{(1)}$). The (M^++1) peak was observed at (*m/z*) 434 in its mass spectrum.



(**II-3**)



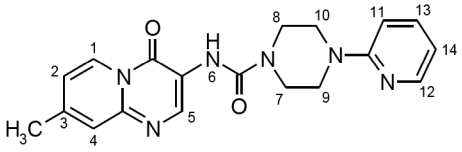
(**II-4**)

4-Benzhydryl-1-[*N*-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)]carboxamidopiperazine (**II-4**) displayed characteristic signals at 3403 (N-H str.) and 1657 cm^{-1} (C=O Str.). The ^{1}H-NMR displayed characteristic peaks at δ 2.33-2.36 (b, 4H, $CH_{2(9,10)}$), 3.48-3.49 (b, 4H, $CH_{2(7,8)}$), 4.35 (s, 1H, $CH_{(11)}$), 7.19-7.22 (m, 2H, Ar-$H_{(16,21)}$), 7.30-7.34 (m, 5H, Ar-$H_{(2,14,15,19,20)}$), 7.45-7.47 (d, 4H, Ar-$H_{(14,15,19,20)}$), 7.66-7.68 (d, 1H, Ar-$H_{(4)}$), 7.79-7.83 (m, 1H, Ar-$H_{(3)}$), 7.93 (s, 1H, N$H_{(6)}$), 8.74 (s, 1H, Ar-$H_{(5)}$) and 8.88-8.90 (d, 1H, Ar-$H_{(1)}$). The compound gave (M^++1) peak at (*m/z*) 440 in its mass spectrum.

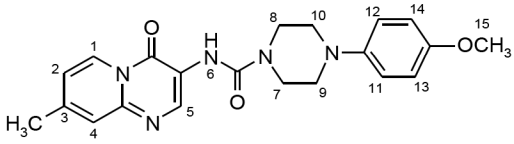
- **Synthesis of *N*-(8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(pyridin-2-yl)piperazine-1-carboxamide derivatives**

N-(8-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(pyridin-2-yl)-piperazine-1-carboxamide (**II-5**) offered characteristic bands at 3395 (N-H str.) and 1654 cm^{-1} (C=O str.) in its IR spectrum. Characteristic peaks appeared at δ 2.45 (3H, $CH_{3(3)}$), 3.57 (b, 8H, $CH_{2(7\text{-}10)}$), 6.65-6.68 (t, 1H, Ar-$H_{(14)}$), 6.86-6.88 (d, 1H, Ar-$H_{(11)}$), 7.20-7.22 (d, 1H, Ar-$H_{(2)}$), 7.50 (s, 1H, Ar-$H_{(4)}$), 7.54-7.58 (m, 1H, Ar-$H_{(13)}$), 8.05 (s, 1H, N$H_{(6)}$), 8.13-8.14 (d, 1H, Ar-$H_{(12)}$), 8.66 (s, 1H, Ar-$H_{(5)}$) and

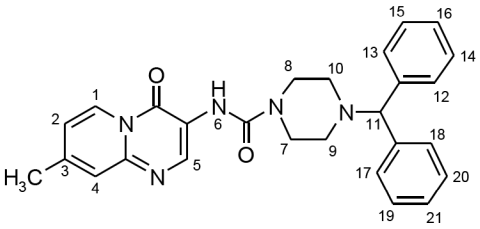
8.82-8.84 (d, 1H, Ar-$H_{(1)}$) in its NMR spectrum. The mass spectrum displayed the (M^++1) peak at (*m/z*) 365.



(**II-5**)



(**II-6**)



(**II-7**)

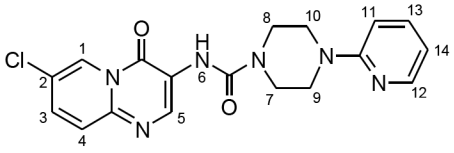
N-(8-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-[(4-methoxy-phenyl)]piperazine-1-carboxamide (II-6) gave characteristic IR signals at 3393 (N-H str.), 1648 cm^{-1} (C=O str.) and 1241 (C-O str.). Its PMR spectra displayed characteristic peaks at δ 2.44 (s, 3H, C$H_{3(3)}$), 2.97-2.99 (b, 4H, $CH_{2(9,10)}$), 3.58-3.61 (b, 4H, C$H_{2(7,8)}$), 3.80 (s, 3H, OC$H_{3(15)}$), 6.87-7.00 (m, 4H, Ar-$H_{(11\text{-}14)}$), 7.19-7.22 (dd, 1H, Ar-$H_{(2)}$), 7.50 (s, 1H, Ar-$H_{(4)}$), 8.00 (s, 1H, N$H_{(6)}$), 8.66 (s, 1H, Ar-$H_{(5)}$), 8.82-8.84 (d, 1H, Ar-$H_{(1)}$) in its NMR spectrum**.** The mass spectrum displayed (M^++1) peak at (*m/z*) 394.

N-(8-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-benzhydrylpip-erazine-1-carboxamide (**II-7)** displayed characteristic IR bands at 3390 (N-H str.), 1644 cm^{-1} (C=O str.). The compound displayed characteristic signals at 2.32-2.34 (b, 4H, C$H_{2(9,10)}$), 2.43 (s, 3H, C$H_{3(3)}$), 3.46-3.48 (b, 4H, C$H_{2(7,8)}$), 4.34 (s, 1H, C$H_{(11)}$), 7.18-7.22 (m, 3H, Ar-$H_{(2\ \&\ diphenyl)}$), 7.29-7.33 (m, 4H, Ar-$H_{(diphenyl)}$), 7.44-7.48 (m, 5H, Ar-$H_{(4\ \&\ diphenyl}$), 7.87 (s, 1H, N$H_{(6)}$), 8.63 (s, 1H, Ar-$H_{(5)}$) and 8.79-8.81 (d, 1H, Ar-$H_{(1)}$) in its NMR spectrum. The (M^++1) peak was observed at (*m/z*) 454 in its mass spectrum.

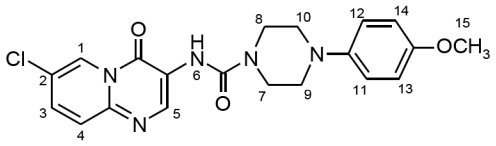
- **Synthesis of *N*-(7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(pyridin-2-yl)piperazine-1-carboxamide derivatives**

N-[(7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(pyridin-2-yl)piperazine]-1-carboxamide (**II-8**) was prepared by refluxing compound (**6c**)

with 4-(pyridin-2-yl)piperazine as depicted in **Scheme 1**. Characteristic peaks were observed in its IR spectrum at 3397 (N-H str.) and 1729, 1643 cm^{-1} (C=O str.). Characteristic signals were observed at δ 3.57-3.58 (m, 8H, C$H_{2(7\text{-}10)}$), 6.65-6.68 (m, 1H, Ar-$H_{(14)}$), 6.86-6.88 (d, 1H, Ar-$H_{(11)}$), 7.54-7.58 (m, 1H, Ar-$H_{(13)}$), 7.69-7.71 (d, 1H, Ar-$H_{(4)}$), 7.83-7.86 (dd, 1H, Ar-$H_{(3)}$), 8.13-8.14 (d, 1H, Ar-$H_{(12)}$), 8.16 (s, 1H, N$H_{(6)}$), 8.82 (s, 1H, Ar-$H_{(5)}$) and 8.89-8.90 (d, 1H, Ar-$H_{(1)}$) in its NMR spectrum. The compound gave (M^+) peak at (*m/z*) 384.8 and (M^++2) at (*m/z*) 386.5.



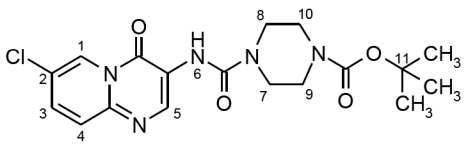
(**II-8**)



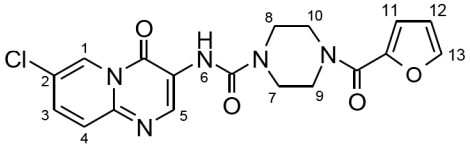
(**II-9**)

N-[(7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(4-methoxyphenyl) piperazine]-1-carboxamide (**II-9**) was synthesized by reacting (**6c**) with 4-(4-methoxyphenyl)piperazine. The compound offered characteristic IR peaks at 3393 (N-H str.), 1665 (C=O str.) and 1236 cm^{-1} (C-O str.). Characteristic signals were observed at δ 2.97-2.99 (b, 4H, C$H_{2(9,10)}$), 3.60-3.61 (b, 4H, C$H_{2(7,8)}$), 3.80 (s, 3H, OC$H_{3(15)}$), 6.87-7.00 (m, 4H, Ar-$H_{(11,14)}$), 7.69-7.71 (d, 1H, Ar-$H_{(4)}$), 7.83-7.86 (m, 1H, Ar-$H_{(3)}$), 8.13 (s, 1H, N$H_{(6)}$), 8.89 (s, 1H, Ar-$H_{(5)}$) and 8.90 (s, 1H, Ar-$H_{(1)}$) in its NMR spectrum. The mass spectrum displayed (M^+) peak at 414.4 and (M^++1) at (*m/z*) 416.2 in its mass spectrum.

N-[(7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-(4-*tert*-butyloxycarbonyl)piperazine]-1-carboxamide (**II-10**) gave strong absorption bands at 3393 (N-H str.), 1691, 1650 cm^{-1} (C=O str.). NMR spectrum displayed characteristic peaks at δ 1.42 (s, 9H, C$H_{3(11)}$), 3.39 (b, 4H, C$H_{2(9,10)}$), 3.44-3.45 (b, 4H, C$H_{2(7,8)}$), 7.68-7.71 (d, 1H, Ar-$H_{(4)}$), 7.83-7.85 (d, 1H, Ar-$H_{(3)}$), 8.13 (s, 1H, N$H_{(6)}$), 8.78 (s, 1H, Ar-$H_{(5)}$) and 8.88-8.89 (d, 1H, Ar-$H_{(1)}$). The compound gave (M^+) peak at (*m/z*) 408.41 and (M^++2) at (*m/z*) 410.39 in its mass spectrum.



(**II-10**)

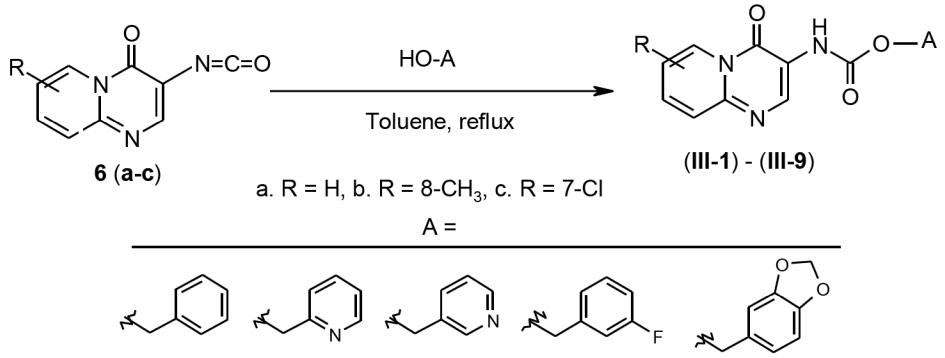


(**II-11**)

N-[(7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-4-(furan-2-carbonyl)-piperazine]-1-carboxamide (**II-11**) displayed peaks at 3446 (N-H str.) and 1626 cm^{-1} (C=O str.) in its IR spectrum. ^{1}HNMR peaks were displayed at δ 3.57-3.58 (b, 4H, C$H_{2(9,10)}$), 3.74 (b, 4H, C$H_{2(7,8)}$), 6.65 (b, 1H, Ar-$H_{(11)}$), 7.04-7.05 (m, 1H, Ar-$H_{(12)}$), 7.69-7.71 (d, 1H, Ar-$H_{(4)}$), 7.83-7.86 (m, 1H, Ar-$H_{(3)}$), 7.87 (s, 1H, Ar-$H_{(13)}$), 8.18 (s, 1H, N$H_{(6)}$), 8.80 (s, 1H, Ar-$H_{(5)}$) and 8.89 (b, 1H, Ar-$H_{(1)}$). The compound gave molecular ion (M^{+}) peak at (*m/z*) 402.37 in its mass spectrum.

3.1.4 Synthesis of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carbamate derivatives (Series III)

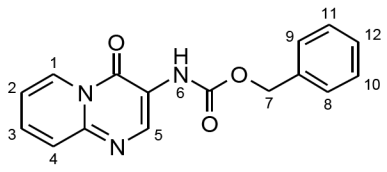
Synthesis of the carbamate derivatives of **Series-III** (**III-1** to **III-9**) have been accomplished by reaction of the isocyanate (**6a-c**) and suitable alcohol derivative (**A-HO**) in toluene under reflux conditions following the procedure as outlined in **Scheme 4**.



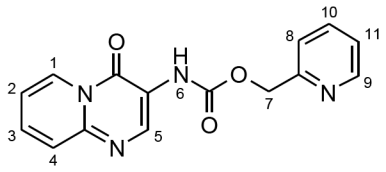
Scheme 4

- **Synthesis of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carbamate derivatives**

The isocyanate derivative (**6a**) and benzyl alcohol were refluxed in toluene offering the compound benzyl (4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)carbamate (**III-1**). The compound (**III-1**) displayed characteristic peaks at 3239 (N-H str.), 1718, 1650 cm^{-1} (C=O str.) and 1116 cm^{-1} (C-O str.) in its IR spectrum. The ^{1}H-NMR showed characteristic peaks at δ 5.17 (s, 2H C$H_{2(7)}$), 7.32-7.44 (m, 6H, Ar-$H_{(2,8-12)}$), 7.69-7.71 (d, 1H Ar-$H_{(4)}$), 7.84-7.89 (m, 1H Ar-$H_{(3)}$), 8.70 (b, 1H, Ar-$H_{(5)}$), 8.92-8.94 (d, 1H Ar-$H_{(1)}$) and 9.05 (b, 1H, N$H_{(6)}$). The mass spectrum showed (M^{+}+1) peak at (*m/z*) 296.



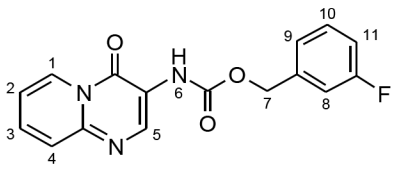
(**III-1**)



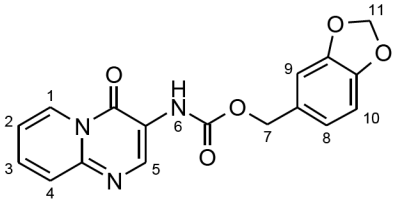
(**III-2**)

The compound pyridin-2-ylmethyl (4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)carbamate (**II-2**) displayed characteristic bands at 3245 (N-H str.), 1713, 1666 (C=O str.) and 1234 cm^{-1} (C-O str.) in its IR spectrum. The ^{1}H-NMR showed characteristic signals at δ 5.22 (s, 2H, C$H_{2(7)}$), 7.32-7.37 (m, 2H, Ar-$H_{(2,11)}$), 7.51-7.53 (d, 1H, Ar-$H_{(4)}$), 7.69-7.72 (d, 1H, Ar-$H_{(8)}$) , 7.83-7.89 (m, 2H, Ar-$H_{(3,10)}$), 8.55-8.56 (d, 1H, Ar-$H_{(9)}$), 8.72 (s, 1H, Ar-$H_{(5)}$), 8.94-8.95 (d, 1H, Ar-$H_{(1)}$) and 9.21 (b, 1H, N$H_{(6)}$) in its NMR spectrum. The (M^++1) peak was observed in the mass spectrum at (*m/z*) 297.

3-Fluorobenzyl (4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)carbamate (**III-3**) was obtained by reacting isocyanate derivative (**6a**) with 3-fluorobenzyl alcohol as described above for compound (**III-1**). Characteristic absorption bands were observed at 3416 (N-H str.), 1716, 1659 (C=O str.) and 1234 cm^{-1} (C-O str.) in its IR spectrum. The NMR signals appeared at δ 5.19 (s, 2H, C$H_{2(7)}$), 7.14-7.19 (m, 1H, Ar-$H_{(10)}$), 7.27-7.37 (m, 3H, Ar-$H_{(2,9,11)}$), 7.41-7.47 (m, 1H, Ar-$H_{(8)}$), 7.69-7.71 (d, 1H, Ar-$H_{(4)}$), 7.85-7.89 (m, 1H, Ar-$H_{(3)}$), 8.72 (b, 1H, Ar-$H_{(5)}$), 8.93-8.95 (d, 1H, Ar-$H_{(1)}$) and 9.16 (b, 1H, N$H_{(6)}$). The mass spectrum gave (M^++1) signal at (*m/z*) 314.



(**III-3**)



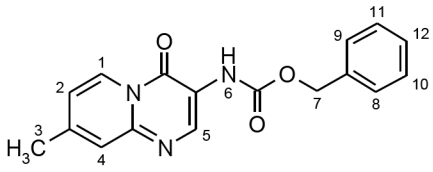
(**III-4**)

The IR spectrum of 3,4-methylenedioxybenzyl(4-oxo-4*H*-pyrido[1,2-*a*]pyrimdin-3-yl)carbamate (**III-4**) showed characteristic peaks at 3242 (N-H str.), 1717, 1666 (C=O str.) and 1235 cm^{-1} (C-O str.). The compound (**III-4**) displayed characteristic signals at δ 5.06 (s, 2H, $CH_{2(7)}$), 6.02 (s, 2H, C$H_{2(11)}$), 6.92 (s, 2H, Ar-$H_{(8,10)}$), 7.02 (s, 1H, Ar-$H_{(9)}$), 7.33-7.37 (m, 1H, Ar-$H_{(2)}$), 7.69-7.71 (d, 1H, Ar-

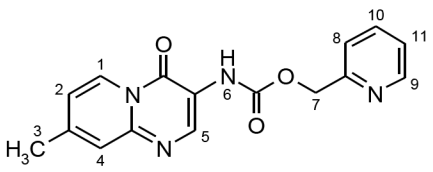
$H_{(4)}$), 7.84-7.89 (m, 1H, Ar-$H_{(3)}$), 8.70 (b, 1H, Ar-$H_{(5)}$), 8.92-8.94 (d, 1H, Ar-$H_{(1)}$) and 9.01 (b, 1H, N$H_{(6)}$) in its NMR spectrum. The mass spectrum showed (M^++1) peak at (*m/z*) 340.

- **Synthesis of 8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carbamate derivatives**

Benzyl (8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)carbamate (**III-5**) gave characteristic signals at 3242 (N-H str.), 1717, 1635 (C=O str.) and 1224 cm^{-1} (C-O str). The compound (**III-5**) offered characteristic peaks at δ 2.45 (s, 3*H*, C$H_{3(3)}$), 5.15 (s, 2H, C$H_{2(7)}$), 7.21-7.23 (d, 1H, Ar-$H_{(2)}$), 7.31-7.44 (m, 5H, Ar-$H_{(8-11)}$), 7.52 (s, 1H, Ar-$H_{(4)}$), 8.60 (b, 1H, Ar-$H_{(5)}$), 8.83-8.85 (d, 1H, Ar-$H_{(1)}$) and 8.97 (b, 1H, N$H_{(6)}$) in its NMR spectrum. The (M^++1) peak was observed at (*m/z*) 310 in its mass spectrum.



(**III-5**)



(**III-6**)

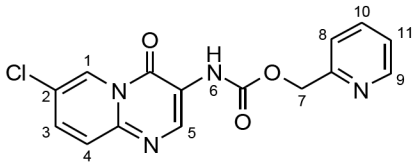
Pyridin-2-ylmethyl (8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)carbamate (**III-6**) displayed characteristic peaks at 3247 (N-H str.), 1721, 1667 (C=O str.) and 1244 cm^{-1} (C-O str) in its IR spectrum. The ^{1}H-NMR displayed characteristic peaks at δ 2.45 (s, 3H, C$H_{3(3)}$), 5.20 (s, 2H, C$H_{2(7)}$), 7.22-7.24 (d, 1H, Ar-$H_{(2)}$), 7.33-7.36 (m, 1H, Ar-$H_{(11)}$), 7.49-7.51 (m, 1H, Ar-$H_{(8)}$), 7.53 (b, 1H, Ar-$H_{(4)}$), 7.83-7.87 (m, 1H, Ar-$H_{(10)}$), 8.55-8.56 (d, 1H, Ar-$H_{(9)}$), 8.62 (b, 1H, Ar-$H_{(5)}$), 8.85-8.87 (d, 1H, Ar-$H_{(1)}$) and 9.14 (b, 1H, N$H_{(6)}$). The mass spectrum showed (M^++1) peak at (*m/z*) 311.

- **Synthesis of 7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carbamate derivatives**

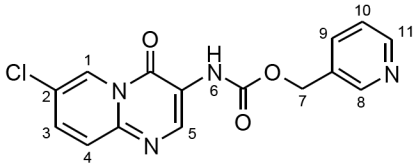
2-Pyridinylmethyl (7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)carbamate (**III-7**) gave characteristic peaks at 3451 (N-H str.), 1724, 1652 (C=O str.) and 1236 cm^{-1} (C-O str) in its IR spectrum. Characteristic signals were appeared at δ 5.23 (s, 2H, C$H_{2(7)}$), 7.33-7.36 (t, 1H, Ar-$H_{(11)}$), 7.51-7.53 (d, 1H,

Ar-$H_{(8)}$), 7.71-7.73 (d, 1H, Ar-$H_{(4)}$), 7.83-7.87 (t, 1H, Ar-$H_{(10)}$), 7.88-7.91 (dd, 1H, Ar-$H_{(3)}$), 8.55-8.56 (d, 1H, Ar-$H_{(9)}$), 8.76 (s, 1H, Ar-$H_{(5)}$), 8.92-8.93 (d, 1H, Ar-$H_{(1)}$) and 9.32 (s, 1H, N$H_{(6)}$) in its NMR spectrum. The compound showed (M^+) peak at (*m/z*) 331.37 and (M^++1) at (*m/z*) 333.35 in its mass spectrum.

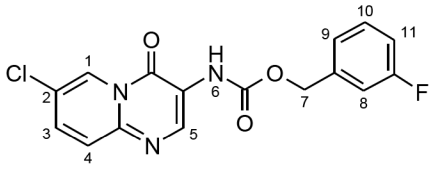
3-Pyridinylmethyl (7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-carbamate (**III-8**) displayed characteristic IR absorption bands at 3431 (N-H str.), 1722, 1664 (C=O str.) and 1232 cm^{-1} (C-O str) in its IR spectrum. The PMR gave peaks at δ 5.22 (s, 2H, C$H_{2(7)}$), 7.41-7.45 (m, 1H, Ar-$H_{(10)}$), 7.70-7.73 (d, 1H, Ar-$H_{(4)}$), 7.86-7.91 (m, 2H, Ar-$H_{(3,9)}$), 8.54-8.55 (d, 1H, Ar-$H_{(11)}$), 8.66 (b, 1H, Ar-$H_{(8)}$), 8.74 (b, 1H, Ar-$H_{(5)}$), 8.91- 8.92 (d, 1H, Ar-$H_{(1)}$) and 9.16 (s, 1H, N$H_{(6)}$). The signals, (M^+) at (*m/z*) 331.37 and (M^++2) at (*m/z*) 333.35 displayed in its mass spectrum.



(**III-7**)



(**III-8**)

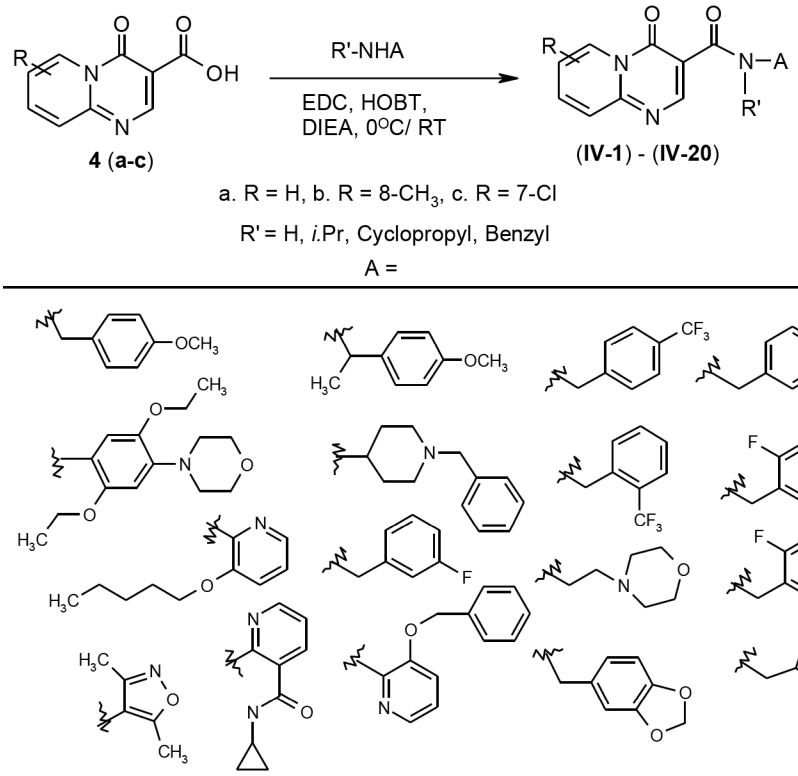


(**III-9**)

3-Fluorobenzyl (7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)carbamate (**III-9**) displayed characteristic bands at 3276 (N-H str.), 1726, 1660 (C=O str.) and 1229 cm^{-1} (C-O str) in its IR spectrum. Its NMR signals were observed at δ 5.15 (s, 2H, C$H_{2(7)}$), 7.20-7.24 (m, 2H, Ar-$H_{(9,10)}$), 7.48-7.51 (m, 2H, Ar-$H_{(8,11)}$), 7.70-7.72 (d, 1H, Ar-$H_{(4)}$), 7.88-7.90 (d, 1H, Ar-$H_{(3)}$), 8.74 (s, 1H, Ar-$H_{(5)}$), 8.91 (s, 1H, Ar-$H_{(1)}$), 9.18 (s, 1H, N$H_{(6)}$). The compound showed (M^+) peak at (*m/z*) 348 and (*m/z*) 350 (M^++2) in its mass spectrum.

3.1.5 Synthesis of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carboxamide derivatives (Series IV)

Synthesis of the amide derivatives of **Series IV** (**IV-1** to **IV-26**) have been accomplished by reacting the acid (**4a-c**) with suitable amine (R'-NHA) using EDC as a coupling agent as outlined in **Scheme 5** and **Scheme 6**.

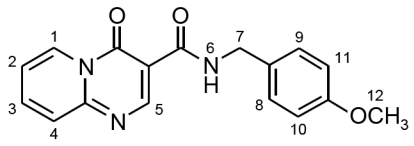


Scheme 5

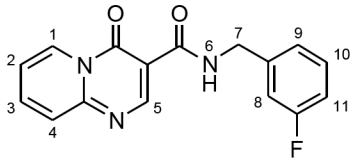
- **Synthesis of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl-carboxamide derivatives**

N-(4-Methoxybenzyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (**IV-1**) was prepared by the carbodimide coupling reaction. The acid derivative (**4a**) was coupled with 4-methoxybenzylamine using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide affording the compound (**IV-1**). Its IR spectrum showed characteristic peaks at 3336 (N-H str.) and 1679 cm^{-1}(C=O str.). The NMR spectrum of the compound (**IV-1**) displayed characteristic peaks at δ 3.80 (3H, OC$H_{3(12)}$), 4.62-4.64 (m, 2H, C$H_{2(7)}$), 6.86-6.90 (d, 2H, Ar-$H_{(8,9)}$) 7.31-7.33 (d, 2H, Ar-$H_{(10,11)}$) 7.34-7.38 (m, 1H, Ar-$H_{(2)}$) 7.84-7.86 (d, 1H, Ar-$H_{(4)}$) 7.92-7.97 (m, 1H, Ar-$H_{(3)}$) 9.19-9.21 (d, 1H, Ar-$H_{(1)}$), 9.30 (b, 1H, N$H_{(6)}$) and 9.38 (s, 1H,Ar-$H_{(5)}$). The mass spectrum displayed (M^++1) peak at (*m/z*) 310.

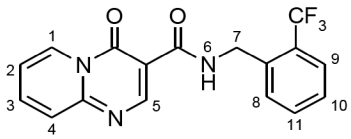
N-(3-Fluorobenzyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-2**) in its IR spectrum displayed peaks at 3327 (N-H str.), 1662 cm^{-1} (C=O str.). The ^{1}H-NMR showed characteristic peaks at δ 4.59-4.61 (d, 2H, C$H_{2(7)}$), 7.06-7.11 (m, 1H, Ar-$H_{(10)}$), 7.15-7.21 (m, 2H, Ar-$H_{(9,11)}$), 7.36-7.41 (m, 1H, Ar-$H_{(8)}$), 7.59-7.63 (m, 1H, Ar-$H_{(2)}$), 7.90-7.92 (d, 1H, Ar-$H_{(4)}$), 8.19-8.23 (m, 1H, Ar-$H_{(3)}$), 9.05 (s, H, Ar-$H_{(5)}$), 9.19-9.21 (d, 1H, Ar-$H_{(1)}$) and 9.43-9.46 (t, 1H, N$H_{(6)}$). The mass spectrum gave (M^++1) peak at (*m/z*) 298.



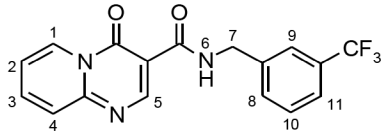
(**IV-1**)



(**IV-2**)



(**IV-3**)



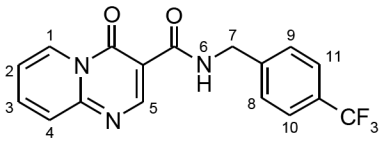
(**IV-4**)

4-Oxo-*N*-[2-(trifluoromethyl)benzyl]-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-3**) displayed characteristic peaks at 3299 (N-H str.), 1695 cm^{-1} (C=O str.) in its IR spectrum. ^{1}H-NMR showed characteristic signals at δ 4.76-4.78 (d, 2H, $CH_{2(7)}$), 7.48-7.52 (m, 1H Ar-$H_{(2)}$), 7.59-7.69 (m, 3H, Ar-$H_{(8,10,11)}$), 7.75-7.77 (d, 1H, Ar-$H_{(9)}$), 7.91-7.93 (d, 1H, Ar-$H_{(4)}$), 8.20-8.24 (m, 1H, Ar-$H_{(3)}$), 9.05 (s, 1H, Ar-$H_{(5)}$), 9.21-9.23 (d, 1H, Ar-$H_{(1)}$) and 9.48-9.51 (t, 1H, N$H_{(6)}$). The mass spectrum displayed the (M^++1) peak at (*m/z*) 348.

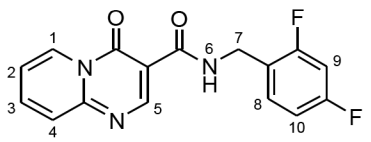
The compound 4-oxo-*N*-[3-(trifluoromethyl)benzyl]-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-4**) displayed characteristic peaks at 3328 (N-H str.), 1691, 1645 and 1490 cm^{-1} (C=O str.). The NMR spectrum of the compound (**IV-4**) displayed characteristic peaks at δ 4.66-4.67 (d, 2H, C$H_{2(7)}$), 7.56-7.63 (m, 3H, Ar-$H_{(2,8,10)}$), 7.66-7.68 (d, 1H, Ar-$H_{(11)}$), 7.72 (s, 1H, Ar-$H_{(9)}$), 7.90-7.92 (d, 1H, Ar-$H_{(4)}$), 8.18-8.23 (m, 1H, Ar-$H_{(3)}$), 9.05 (s, 1H, Ar-$H_{(5)}$), 9.20-9.21 (d, 1H, Ar-$H_{(1)}$) and 9.50-9.53 (t, 1H, N$H_{(6)}$). The mass spectrum showed (M^++1) peak at (*m/z*) 348.

4-Oxo-*N*-[4-(trifluoromethyl)benzyl]-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-5**) displayed characteristic IR signals at 3336 (N-H str.), 1663

(C=O str.) and 1123 cm^{-1} (C-O str.). The compound showed characteristic peaks at δ 4.75-4.76 (d, 2H, C$H_{2(7)}$), 7.38-7.41 (m, 1H, Ar-$H_{(2)}$), 7.49-7.51 (d, 2H, Ar-$H_{(8,9)}$), 7.58-7.60 (d, 2H, Ar-$H_{(10,11)}$), 7.86-7.88 (d, 1H, Ar-$H_{(4)}$), 7.96-8.00 (m, 1H, Ar-$H_{(3)}$), 9.21-9.23 (d, 1H, Ar-$H_{(1)}$), 9.37-9.38 (s, 1H, Ar-$H_{(5)}$) and 9.47 (b, 1H, N$H_{(6)}$) in its NMR spectrum. Its mass spectrum displayed the (M^++1) peak at (*m/z*) 348.

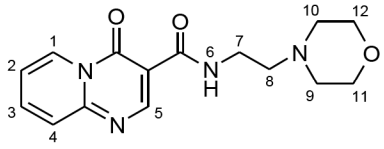


(**IV-5**)

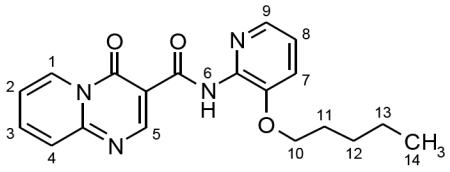


(**IV-6**)

The compound *N*-(2,4-Difluorobenzyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-6**) displayed characteristic IR peaks at 3328 (N-H str.) and 1664 cm^{-1} (C=O str.) in its IR spectrum. The NMR signals appeared at δ 4.60-4.62 (d, 2H, C$H_{2(7)}$), 7.14-7.21 (m, 2H, Ar-$H_{(8,10)}$), 7.24-7.29 (m, 1H, Ar-$H_{(9)}$), 7.59-7.63 (m, 1H, Ar-$H_{(2)}$), 7.89-7.92 (d, 1H, Ar-$H_{(4)}$), 8.19-8.23 (m, 1H, Ar-$H_{(3)}$), 9.03 (s, 1H, Ar-$H_{(5)}$), 9.20-9.23 (d, 1H, Ar-$H_{(1)}$) and 9.42-9.45 (t, 1H, N$H_{(6)}$). The mass spectrum showed (**M**$^+$+1) peak at (*m/z*) 316.



(**IV-7**)



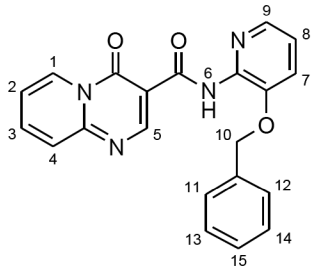
(**IV-8**)

N-[2-(Morpholin-4-yl)ethyl]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-7**) displayed characteristic IR peaks at 3423 (N-H str.), 1690 (C=O str.) and 1115 cm^{-1} (C-O str.). Characteristic ^{1}H-NMR signals were observed at δ 2.43 (b, 4H, C$H_{2(9,10)}$), 2.50-2.51 (m, 2H, C$H_{2(8)}$), 3.45-3.50 (m, 2H, C$H_{2(7)}$), 3.59-3.61 (t, 4H, C$H_{2(11,12)}$), 7.57-7.61 (m, 1H, Ar-$H_{(2)}$), 7.84-7.90 (d, 1H, Ar-$H_{(4)}$), 8.17-8.21 (m, 1H, Ar-$H_{(3)}$), 9.02 (s, 1H, Ar-$H_{(5)}$), 9.15-9.16 (t, 1H, N$H_{(6)}$) and 9.20-9.22 (d, 1H, Ar-$H_{(1)}$). The mass spectrum showed (M^++1) peak at (*m/z*) 303.

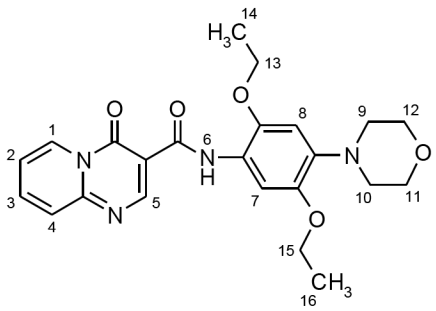
4-Oxo-*N*-[3-(*n*.pentyloxy)pyridin-2-yl]-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-8**) displayed characteristic peaks at 3297 (N-H str.) 1693 (C=O str.) and 1218 cm^{-1} (C-O str.) in its IR spectrum. The ^{1}H-NMR spectrum

displayed characteristic signals at δ 0.89-0.93 (t, 3H, C$H_{3(14)}$), 1.36-1.43 (m, 2H, C$H_{2(13)}$), 1.49-1.57 (m, 2H, C$H_{2(12)}$), 1.78-1.84 (m, 2H, C$H_{2(11)}$), 4.09-4.13 (t, 2H, C$H_{2(10)}$), 7.95-7.97 (d, 2H, Ar-$H_{(4,9)}$), 8.24-8.28 (m, 1H, Ar-$H_{(3)}$), 9.13 (s, 1H, Ar-$H_{(5)}$), 9.21-9.24 (d, 1H, Ar-$H_{(1)}$) and 11.51 (s, 1H, N$H_{(6)}$). The (M^++1) peak appeared in mass spectrum at (*m/z*) 353.

N-[3-(Benzyloxy)pyridin-2-yl]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-9**) IR spectrum showed characteristic peaks at 3480 (N-H str.), 1699 (C=O str.) and 1285 cm^{-1} (Ar-O str.). The characteristic signals were appeared at δ 5.28 (s, 2H, C$H_{2(10)}$), 7.00-7.04 (m, 1H, Ar-$H_{(8)}$), 7.58-7.60 (d, 2H, Ar-$H_{(11,12)}$), 8.16-8.18 (m, 1H, Ar-$H_{(7)}$), 9.27-9.31 (m, 1H, Ar-$H_{(1)}$), 9.49 (s, 1H, Ar-$H_{(5)}$), 11.76 (s, 1H, N$H_{(6)}$) in its NMR spectrum. (M^++1) peak was observed in the mass spectrum at (*m/z*) 373 in its mass spectrum.



(**IV-9**)

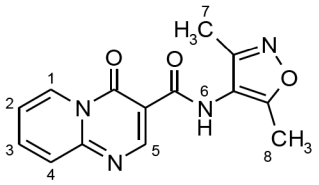


(**IV-10**)

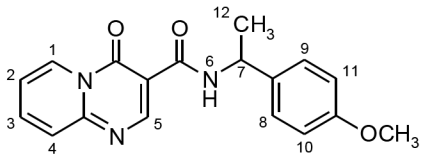
The IR spectrum of *N*-[(2,5-diethoxy)-4-(morpholin-4-yl)phenyl]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (**IV-10**) displayed characteristic peaks at 3263 (N-H str.), 1685 (C=O str.) and 1199 cm^{-1} (C=O str.). Characteristic signals were observed at δ 1.44-1.47 (t, 3H, C$H_{3(14/16)}$) and 1.54-1.58 (3H, C$H_{3(14/16)}$), 3.09-3.10 (t, 4H, C$H_{2(9,10)}$), 3.89-3.91 (t, 4H, C$H_{2(11/12)}$), 6.60 (s, 1H, Ar-$H_{(8)}$), 7.37-7.41 (m, 1H, Ar-$H_{(2)}$), 7.85-7.87 (d, 1H, Ar-$H_{(4)}$), 7.95-7.99 (m, 1H, Ar-$H_{(3)}$), 8.40 (s, 1H, Ar-$H_{(7)}$), 9.33-9.34 (d, 1H, Ar-$H_{(1)}$), 9.42 (s, 1H, Ar-$H_{(5)}$) and 11.49 (s, 1H, N$H_{(6)}$) in its NMR spectrum. The mass showed (M^++1) peak at (*m/z*) 439.

The IR spectrum of *N*-(3,5-Dimethyl-1,2-oxazol-4-yl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-11**) displayed characteristic peaks at 3253 (N-H str.) and 1694 cm^{-1} (C=O str.). The characteristic peaks were displayed at δ 2.15 (s, 3H, C$H_{3(8)}$), 2.33 (s, 3H, C$H_{3(7)}$), 7.65-7.69 (m, 1H, Ar-$H_{(2)}$), 7.95-7.97 (d, 1H, Ar-$H_{(4)}$), 8.24-8.29 (m, 1H, Ar-$H_{(3)}$), 9.09 (s, 1H, Ar-$H_{(5)}$), 9.26-9.27

(d, 1H, Ar-$H_{(1)}$) and 10.20 (s, 1H, N$H_{(6)}$) in its NMR spectrum. The (M^++1) peak at (*m/z*) 285 was present in its mass spectrum.



(**IV-11**)

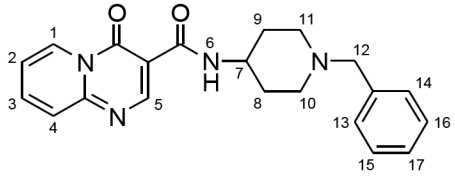


(**IV-12**)

N-[1-(4-Methoxyphenyl)ethyl]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-12**) gave peaks at 3315 (N-H str.), 1667 (C=O str.), 1240 (C-O str.) and 1025 cm^{-1} in its IR spectrum. Characteristic peaks were displayed δ 1.61-1.66 (m, 3H, C$H_{3(12)}$), 3.79 (s, 3H, OC$H_{3(13)}$) and 5.28-5.35 (m, 1H, C$H_{(7)}$), 6.87-6.91(d, 2H, Ar-$H_{(8,9)}$), 7.34-7.38 (m, 3H, Ar-$H_{(2,10,11)}$), 7.83-7.86 (d, 1H, Ar-$H_{(4)}$), 7.92-7.97 (m, 1H, Ar-$H_{(3)}$), 9.20-9.22 (d, 1H, Ar-$H_{(1)}$) and 9.36 (s, 1H, Ar-$H_{(5)}$, N$H_{(6)}$) in its NMR spectrum. The mass spectrum showed (M^++1) peak at (*m/z*) 324.

The IR spectrum of *N*-(1-benzylpiperidin-4-yl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-13**) showed characteristic peaks at 3288 (N-H str.) and 1695 cm^{-1} (C=O str.). Characteristic signals appeared at δ 1.52-1.58 (m, 2H, C$H_{2(8,9)}$), 1.89-1.92 (b, 2H, C$H_{2(8,9)}$), 2.18-2.22 (t, 2H, C$H_{2(10,11)}$), 2.70 (b, 2H, C$H_{2(10,11)}$), 3.50 (s, 2H, C$H_{2(12)}$), 3.88 (b, 1H, C$H_{(7)}$) and 9.20-9.22 (d, 1H, N$H_{(6)}$) in its NMR. The (M^++1) signal was displayed at (*m/z*) 363 in mass spectrum.

N-(3,4-Methylenedioxybenzyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (**IV-14**) IR spectrum displayed 3260 (N-H str.), 1666 (C=O str.) and 1224 cm^{-1}(C-O str.). Characteristic peaks were observed at δ 4.46-4.48 (d, 2H, C$H_{2(7)}$), 5.98 (s, 2H, C$H_{2(11)}$), 6.82-6.88 (m, 2H, Ar-$H_{(8,10)}$), 6.93 (s, 1H, Ar-$H_{(9)}$), 7.58-7.62 (m, 1H, Ar-$H_{(2)}$), 7.89-7.91 (d, 1H, Ar-$H_{(4)}$), 8.17-8.22 (m, 1H, Ar-$H_{(3)}$), 9.05 (s, 1H, Ar-$H_{(5)}$), 9.17-9.19 (d, 1H, Ar-$H_{(1)}$) and 9.27-9.33 (t, 1H, N$H_{(6)}$). in its NMR spectrum. Its mass spectrum showed (M^++1) peak at (*m/z*) 324.



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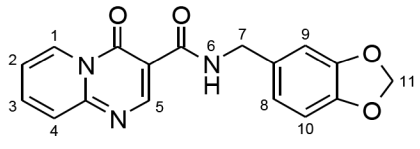
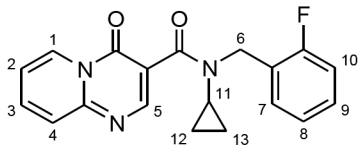


(**IV-14**)

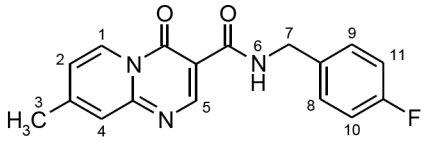


(**IV-15**)

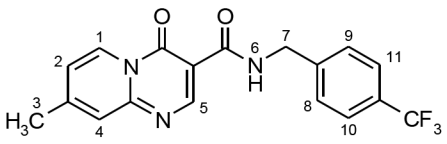
N-Cyclopropyl-*N*-(2-fluorobenzyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-15**) displayed characteristic peaks at 1669, 1636 cm^{-1} (C=O, str.) in its IR spectrum. The ^{1}H-NMR at δ 0.58-0.61 (d, 4H, C$H_{2(12,13)}$), 3.06 (b, 1H, C$H_{(11)}$) and 4.93 (s, 2H, C$H_{2(6)}$). The mass spectrum showed (M^++1) peak at (*m/z*) 338.

- **Synthesis of 8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide derivatives**

N-(4-Fluorobenzyl)-8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-16**) was prepared by treating (**4b**) with 4-fluorobenzylamine as described above for compound (**IV-1**) yielding (**IV-16**). IR spectrum of the compound displayed characteristic peaks at 3287 (N-H str.) and 1677 cm^{-1} (C=O str.). The ^{1}H-NMR displayed characteristic peaks at δ 2.58 (s, 3H, C$H_{3(3)}$), 4.65-4.66 (d, 2H, C$H_{2(7)}$), 7.00-7.04 (t, 2H, Ar-$H_{(8,9)}$), 7.18-7.21 (m, 1H, Ar-$H_{(2)}$), 7.34-7.37 (m, 2H, Ar-$H_{(10,11)}$), 7.63 (s, 1H, Ar-$H_{(4)}$), 9.08-9.09 (d, 1H, Ar-$H_{(1)}$), 9.33 (s, 1H, Ar-$H_{(5)}$) and 9.35 (b, 1H, N$H_{(6)}$). The mass spectrum showed the (M^++1) peak at (*m/z*) 312.



(**IV-16**)

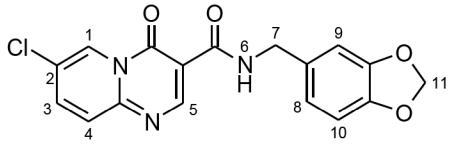


(**IV-17**)

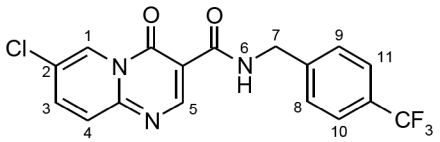
The IR spectrum of *N*-(4-trifluorobenzyl)-8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-17**) displayed characteristic peaks at 3414 (N-H str.), 1695 (C=O str.) cm^{-1}. Its ^{1}H-NMR showed characteristics peaks at δ 2.55 (s, 3H, C$H_{(3)}$), 4.65-4.67 (d, 2H, C$H_{(7)}$), 7.46-7.49 (dd, 1H, Ar-$H_{(2)}$), 7.55-7.57 (d, 2H, Ar-$H_{(8,9)}$), 7.69-7.73 (m, 3H, Ar-$H_{(4,10,11)}$), 9.00 (s, 1H, Ar-$H_{(5)}$), 9.08-9.10 (d, 1H, Ar-$H_{(1)}$) and 9.45-9.48 (t, 1H, N$H_{(6)}$) The compound gave (M^++1) peak at (*m/z*) 362 in its mass spectrum.

- **Synthesis of 7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide derivatives**

7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**4c**) was reacted with 3,4-methylenedioxy benzylamine) as described above for compound (**IV-1**) yielding the compound (**IV-18**) Characteristic IR peaks were observed at 3300 (N-H str.) and 1672 cm^{-1} (C=O str.). Characteristic NMR signals were present at δ 4.46-4.48 (d, 2H, C$H_{2(7)}$), 5.98 (s, 2H, C$H_{2(11)}$), 6.81-6.87 (m, 2H, Ar-$H_{(8,10)}$), 6.92 (s, 1H, Ar-$H_{(9)}$), 7.90-7.93 (d, 1H, Ar-$H_{(4)}$), 8.24-8.26 (dd, 1H, Ar-$H_{(3)}$), 9.04 (s, 1H, Ar-$H_{(5)}$), 9.15-9.16 (d, 1H, Ar-$H_{(1)}$) and 9.23-9.26 (t, 1H, N$H_{(6)}$). The compound gave molecular ion peak (M^+) at (*m/z*) 358.3 and (M^++2) peak at (*m/z*) 360.4.

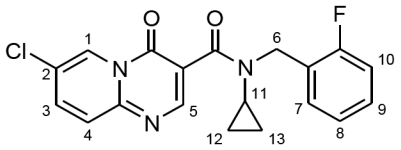


(**IV-18**)



(**IV-19**)

7-Chloro-4-oxo-*N*-[4-(trifluoromethyl)benzyl]-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (**IV-19**) gave characteristic IR signals at 3315 (N-H str.) and 1674 cm^{-1}. The compound (**IV-19**) gave characteristic peaks at δ 4.67-4.68 (d, 2H, C$H_{2(7)}$), 755-7.57 (d, 2H, C$H_{2(8,9)}$), 7.70-7.72 (d, 2H, Ar-$H_{(10,11)}$), 7.92-7.95 (d, 1H, Ar-$H_{(4)}$), 8.26 -8.29 (dd, 1H, Ar-$H_{(3)}$), 9.04 (s, 1H, Ar-$H_{(5)}$), 9.17-9.18 (d, 1H, Ar-$H_{(1)}$) and 9.43-9.46 (t, 1H, N$H_{(6)}$) in its NMR spectrum. The mass spectrum displayed (M^+) at (*m/z*) 382.2 and (M^++2) (*m/z*) 384.2.



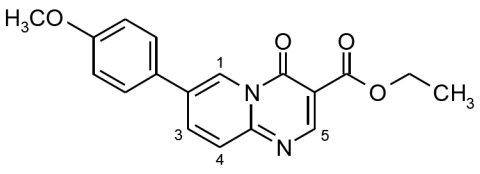
(**IV-20**)

The characteristic signals were displayed in IR spectrum of 7-chloro-*N*-cyclopropyl-*N*-(2-fluorobenzyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (**IV-20**) at 3102 (N-H str.) and 1630 cm^{-1} (C=O str.). The characteristic signals were displayed at δ 0.51-0.55 (d, 4H, C$H_{2(12,13)}$), 2.87 (b, 1H, C$H_{(11)}$), 4.75 (b, 2H, C$H_{2(6)}$), 7.21-7.24 (m, 2H, Ar-$H_{(7,8)}$), 7.33-7.36 (m, 1H, Ar-$H_{(9)}$), 7.63 (b, 1H, Ar-$H_{(4)}$), 7.84-7.87 (d, 1H, Ar-$H_{(3)}$), 8.14-8.17 (dd, 1H, Ar-$H_{(1)}$), 8.47 (s, 1H, Ar-$H_{(5)}$)

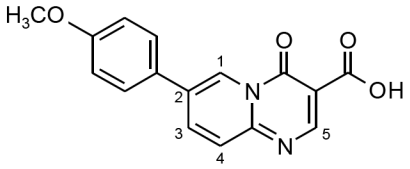
and 9.14 (s, 1H, N$H_{(6)}$) in its NMR spectrum. The mass spectrum displayed (M^++1) peak at (*m/z*) 372.4.

- **7-(4-Methoxyphenyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid intermediate**

The 7-chloro ester (**3c**) was reacted with *p*-methoxyphenylboronic acid through Suzuki coupling offering the ester (**7**) which on acid hydrolysis yielded the acid (**8**). The acid derivative (**8**) was coupled with suitable amines to get the targeted compounds (**IV23 - IV24**) as depicted in **Scheme 6**. Ethyl 7-(4-methoxyphenyl)-4-



(**7**)



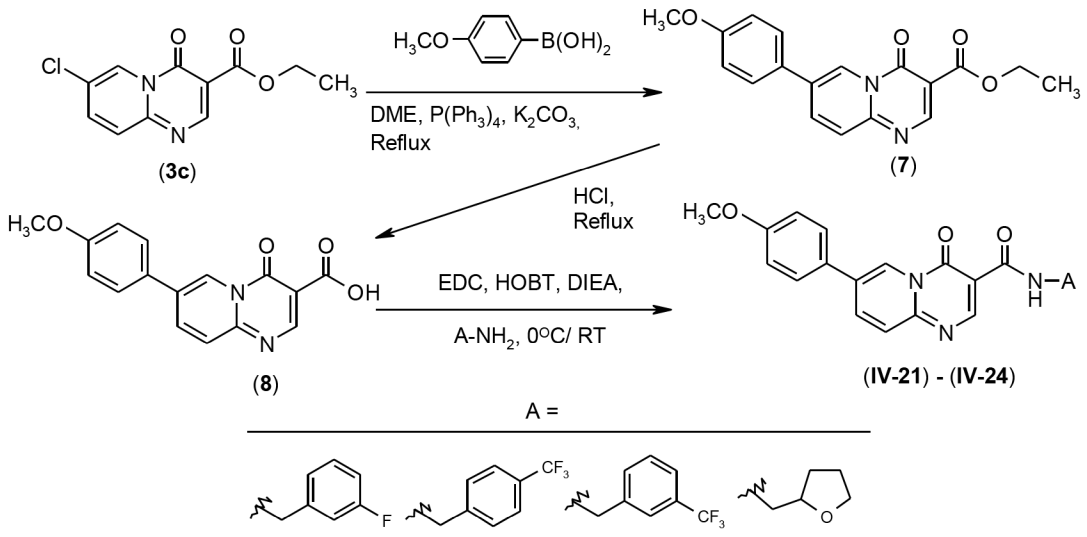
(**8**)

oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**7**) displayed characteristic IR signals at 1744 (C=O str.) and 1113 cm^{-1} (C-O str.) in its IR spectrum. The compound gave (M^++1) peak at (*m/z*) 325 in its mass spectrum.

The ester (**7**) on acidic hydrolysis furnished the free acid (**8**) 7-(4-methoxyphenyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**8**). Its IR spectrum displayed characteristic bands at 3087 (COO-H str.) and 1772 (C=O str.) cm^{-1}. The (M^++1) peak at (*m/z*) 297 was observed in its mass spectrum.

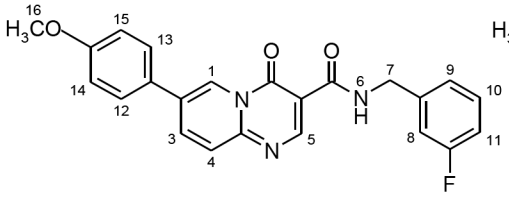
- **Synthesis of 7-(4-methoxyphenyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide derivatives**

In order to study the hydrophobic binding interactions by increasing the steric bulk of the group attached to the B-ring (i.e. pyrido) of the pyridopyrimidine ring, some additional compounds (**IV23 - IV24**) were synthesized. Synthesis of 7-(4-methoxyphenyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide derivatives of (**Series IV)** has been was accomplished by using the intermediates of Scheme 1 and by following the reaction sequence outlined in **Scheme 6**.

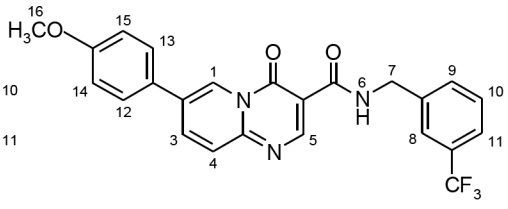


Scheme 6

N-(3-Fluorobenzyl)-7-(4-methoxyphenyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (**IV-21**) was synthesized by reacting compound (**8**) with 3-fluorobenzylamine as described for compound (**IV-1**). Its IR spectrum displayed characteristic peaks at 3319 (N-H str.), 1688 (C=O str.) and 1264 cm^{-1} (C-O str.). The compound gave characteristic signals at δ 3.89 (s, 3H, $OCH_{3(16)}$), 4.60-4.62 (d, 2H, $CH_{2(7)}$), 7.07-7.16 (m, 3H, Ar-$H_{(9\text{-}11)}$), 7.20-7.22 (m, 2H, Ar-$H_{(14,15)}$), 7.37-7.42 (m, 1H, Ar-$H_{(8)}$), 7.79-7.81 (d, 2H, Ar-$H_{(12,13)}$), 7.95-7.98 (d, 1H, Ar-$H_{(4)}$), 8.54-8.57 (dd, 1H, Ar-$H_{(3)}$), 9.04 (s, 1H, Ar-$H_{(5)}$), 9.27-9.28 (d, 1H, Ar-$H_{(1)}$) and 9.45-9.48 (t, 1H, $NH_{(6)}$) in its NMR spectrum. A strong peak (M^{+}-1) peak was observed at (*m/z*) 403 in its mass spectrum.



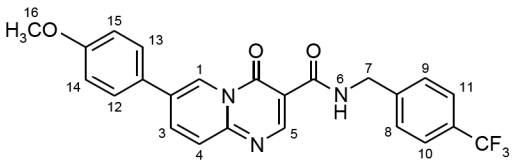
(**IV-21**)



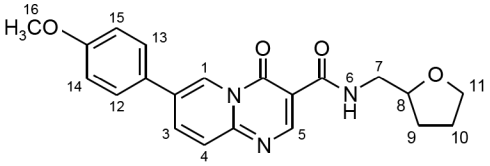
(**IV-22**)

Characteristic bands were observed for the compound *N*-(3-trifluoromethylbenzyl)-7-(4-methoxyphenyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides (**IV-22**) in its IR spectrum displayed characteristic bands at 3414 (N-H str.), 1692 (C=O str.) and 1163 (C-O str.) cm^{-1}. The PMR spectrum gave

characteristic peaks at δ 3.83 (s, 3H, OC$H_{3(16)}$), 4.67-4.68 (d, 2H, C$H_{2(7)}$), 7.11-7.14 (d, 2H, Ar-$H_{(14,15)}$), 7.57-7.64 (m, 2H, Ar-$H_{(9,10)}$), 7.78-7.81 (d, 2H, Ar-$H_{(12,13)}$), 7.67-7.69 (m, 1H, Ar-$H_{(11)}$), 7.72 (b, 1H, Ar-$H_{(8)}$), 7.95-7.97 (d, 1H, Ar-$H_{(4)}$), 8.53-8.56 (dd, 1H, Ar-$H_{(3)}$), 9.04 (s, 1H, Ar-$H_{(5)}$), 9.26 (s, 1H, Ar-$H_{(1)}$) and 9.51-9.54 (t, 1H, N$H_{(6)}$). Its mass spectrum gave (M^++1) peak at (*m/z*) 454.



(**IV-23**)



(**IV-24**)

N-(4-Trifluoromethylbenzyl)-7-(4-methoxyphenyl)-4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidine-3-carboxamide (**IV-23**) gave strong peaks at 3425 (N-H str.), 1689 (C=O str.) and 1263 cm^{-1} (C-O str.) in its IR spectrum. Characteristic peaks were observed in its NMR at δ 3.84 (s, 3H, OC$H_{3(16)}$), 4.68-4.69 (d, 2H, C$H_{2(7)}$), 7.13-7.15 (d, 2H, Ar-$H_{(14,15)}$), 7.57-7.59 (d, 2H, Ar-$H_{(8,9)}$), 7.71-7.73 (d, 2H, Ar-$H_{(10,11)}$), 7.80-7.82 (d, 2H, Ar-$H_{(12,13)}$), 7.96- 7.99 (d, 1H, Ar-$H_{(4)}$), 8.55-8.58 (dd, 1H, Ar-$H_{(3)}$), 9.04 (s, 1H, Ar-$H_{(5)}$), 9.28-9.29 (d, 1H, Ar-$H_{(1)}$) and 9.52-9.55 (t, 1H, N$H_{(6)}$). Its mass spectrum gave (M^++1) signal at (*m/z*) 454.

N-(Tetrahydrofuran-2-ylmethyl)-7-(4-methoxyphenyl)-4-oxo-4*H*-pyrido [1,2-*a*]pyrimidine-3-carboxamide (**IV24**) displayed IR bands at 3453 (N-H str.), 1689 (C=O str.) and 1180 cm^{-1} (C-O str.) in its IR spectrum. Characteristic peaks were appeared at δ 3.84 (s, 3H, OC$H_{3(16)}$), 3.96-3.99 (m, 1H, C$H_{(8)}$), 7.12-7.15 (d, 2H, Ar-$H_{(14,15)}$) and 7.79-7.84 (d, 2H, Ar-$H_{(12,13)}$), 7.91-7.97 (d, 1H, Ar-$H_{(4)}$), 8.54-8.56 (dd, 1H, Ar-$H_{(3)}$), 9.03 (s, 1H, Ar-$H_{(5)}$), 9.17-9.19 (t, 1H, N$H_{(6)}$) and 9.29-9.30 (d, 1H, Ar-$H_{(1)}$) in its NMR spectrum. The compound gave (M^++1) signal at (*m/z*) 380 in its mass spectrum.

3.2 Biological evaluation

The aim of the current study was to develop new antimalarial agents, ideally directed against the targets which were not previously exploited in the antimalarial chemotherapy. Malarial cysteine protease falcipain-2 is such a target. The synthesized compounds were tested for falcipain inhibition-2 (*in vitro* inhibition assay) following the reported procedure.[93]

Compounds were evaluated for their inhibitory activity against recombinant FP-2 using Cbz-Phe-Arg-AMC as a fluorogenic substrate. Preliminary screening was performed at 10 μM concentration. An equivalent concentration of DMSO was used as negative control and the irreversible standard inhibitor of clan CA family C1 cysteine proteases (papain family), namely E-64 was used as positive control. Assays were performed to determine the percentage inhibition of the enzyme at a concentration of 10 μM. FP-2 activity is assessed by cleavage of the fluorogenic substrate Cbz-Phe-Arg-AMC releasing the fluorescent AMC group. Hence decrease in fluorescence intensity in a sample represents inhibition of enzyme activity. The IC_{50} values were determined for those compounds only which showed more than 40 % inhibition at 10 μM concentration.

3.2.1 Assay of falcipain-2 inhibition

The diluted soluble *Plasmodium falciparum* FP-2 (30 nM) was incubated for 10 min at room temperature in 100 mM sodium acetate buffer of *p*H 5.5, 10 mM dithiothreitol (DTT), with a fixed/different concentration of the compounds to be tested or the standard (E64). Compound solutions were prepared from a stock in DMSO. After 10 min incubation, the substrate Z-Phe-Arg-AMC was added to a final concentration of 25 μM. The fluorescence intensity was monitored (excitation 355 nm; emission 460 nm) for 10 min at room temperature with a Synergy^{TM} 4 Multi-Mode Microplate Reader (BioTek). The inhibition rate (%) is calculated using the given equation:

$$\% \text{ Inhibition} = [1 - (F \text{ test} / F \text{ stand.})] \times 100$$

Where (*F test* is the fluorescence intensity of the test compound, *F* standard is the fluorescence intensity of the standard compound (**E64**). All values are the means of three independent determinations and the deviations are <10 % of the mean value. Fluorescence was monitored for 15 min at room temperature in a Labsystems Fluoroskan Ascent spectrofluorometer. IC_{50} values were determined from plots of percents of activity over the compound concentration using Graphpad Prism Software. . The IC_{50} values were determined for those compounds only which showed 40 % or more of enzyme inhibition at 10 μM. The results of the study are summarized in Table 1.

Table 1: ***In vitro*** falcipain-2 inhibition activity data of the test compounds

Comp. No.	Falcipain-2 Inhibition Ratio (%)	IC_{50} (μM)	Comp. No.	Falcipain-2 Inhibition Ratio (%)	IC_{50} (μM)
I-1	38.83	NP	**II-5**	37	NP
I-2	18.35	NP	**II-6**	46.14	**18.87**
I-3	31.11	NP	**II-7**	23.2	NP
I-4	46.37	**16.08**	**II-8**	41.34	**12.16**
I-8	44.43	**14.27**	**II-9**	36.01	NP
I-9	25.12	NP	**III-1**	11.52	NP
I-21	62.51	**6.36**	**III-2**	17.53	NP
I- 22	15.28	NP	**III-5**	30.71	NP
I-23	45.09	**21.16**	**III-6**	41.91	**18.32**
I-24	27.21	NP	**IV-14**	7.4	NP
I-26	67.97	**6.93**	**IV-16**	5.56	NP
I-27	41.81	**23.35**	**IV-18**	23.65	NP
II-1	46.13	**14.84**	**E-64**	92 (2μM)	**0.02**
II-2	42.79	NP	**DMSO**	0	

NP- not performed

The enzyme inhibition data given in **Table 1** shows that the pyrido[1,2-*a*]pyrimidin-4-ones show FP-2 inhibition in micromolar range. Based on the result of evaluated compounds a broad structure activity relationship could be deduced for this series of the compounds. Urea moiety has the potential to provide potent FP-2 inhibitors as the carbamate and carboxamide derivatives are much less active in comparison to the substituted ureas.

Ethylmorpholine (**I-26,** IC_{50} **6.93 μM**) and methoxyethyl (**I-21,** IC_{50} **6.36 μM**) urea derivatives proved to be the most potent compounds. 2-Thiophenethyl (**I-8,** IC_{50} **14.27 μM; IV-23,** IC_{50} **21.16 μM; I-27,** IC_{50} **23.35 μM**), acetamidoethyl (**I-4,** IC_{50} **16.08 μM**) and 4-methoxyphenylpiperazine (**II-5,** IC_{50} **18.87 μM**) were the other groups which gave active compounds when attached to the other end of the urea moiety. 2-Pyridylpiperazine is another moiety which offered quite active compounds (**II-8,** IC_{50} **12.16 μM; II-1,** IC_{50} **14.84 μM**).

In general 8-methyl and 7-chloro substituted derivatives offered more potent compounds indicating that increasing the steric bulk of the group attached to the B-ring (i.e. pyrido) is likely to provide more potent FP-2 inhibitors. An

electron rich environment at the end of the carbon chain attached to the urea nitrogen also seems to be conducive for better activity as indicated by the compounds having morpholine, 2-thiophenenyl, 2-pyridyl, 4-methoxyphenyl, acetamidoethyl and 2-methoxyethyl groupings. But bulky groupings (**II-7**, benzhydrylpiperazine and **I-9,** 4-morpholinopropyl) may not offer potent derivatives.

The above given SAR points have been framed on the basis of available biological data for a limited number of compounds. For the remaining compounds the biological data is yet to be obtained. A detailed structure activity relationship would be framed once the biological data of all the synthesized compounds is available at hand.

With the availability of biological activity for compounds the current work has proved the potential of pyrido[1,2-*a*]pyrimidin-4-one derivatives as potent FP-2 inhibitors. Based on the activity data of the synthesized compounds it could be claimed that pyrido[1,2-*a*]pyrimidin-4-one can serve as a lead series for future investigations. By appropriate structural optimizations the potency of this series of compounds can be improved substantially against FP-2 enzyme which in turn can serve to be potential antimalarial agents. Further optimization of the lead structures and biological screening is in progress in the laboratory.