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HETEROCYCLIC *ORTHO*-AMINOCARBONYL COMPOUNDS IN THE FRIEDLÄNDER REACTION PROMOTED BY CHLOROTRIMETHYLSILANE

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Abstract – A possibility of introduction of heterocyclic *ortho*-aminoketones into promoted by TMSCl Friedländer reaction with a wide set of α-methylenecarbonyl compounds was studied. A convenient synthetical method to obtain heterofused pyridine systems was elaborated; its scope and limitations were established as well. A set of derivatives of thieno[2,3-*b*]pyridines, [1]benzofuro[3,2-*b*]pyridines, 5*H*-chromeno[2,3-*b*]pyridin-5-ones, pyrido[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-diones was obtained in high preparative yields.

INTRODUCTION

The Friedländer reaction is a facile direct method to obtain the pyridine ring in the quinoline and other heterofused systems.[1] The diversity of α-methyleneketones available nowadays provides a possibility to vary easily the substituents in the formed compounds. In our previous work[2] we described a possibility to use TMSCl[3] in DMF solution as a condensating agent for the synthesis of quinoline derivatives. That let extending the scope of the Friedländer reaction for different *ortho*-aminoketones **I** on α-methyleneketones **II**. During the investigation mentioned a range of diverse derivatives of quinoline **III** was synthesized, that demonstrated a possilbility to introduce different substituents into the quinoline system.

In present paper we report the results of studying the subjection of heterocyclic aminoketones **IV** to the Friedländer reaction using TMSCl/DMF system (Scheme 1).

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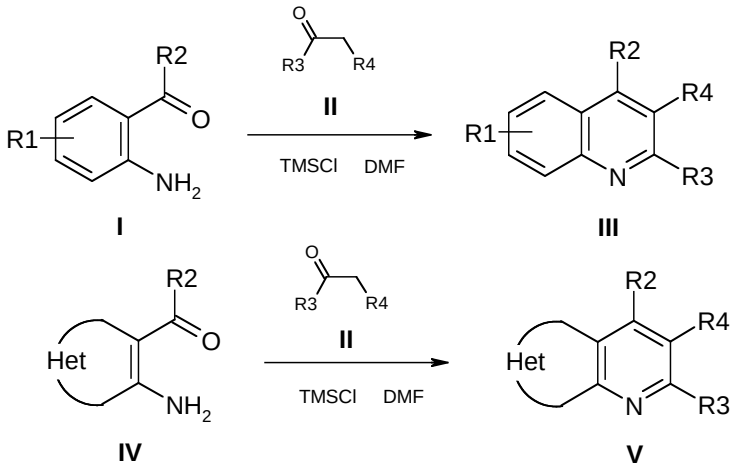
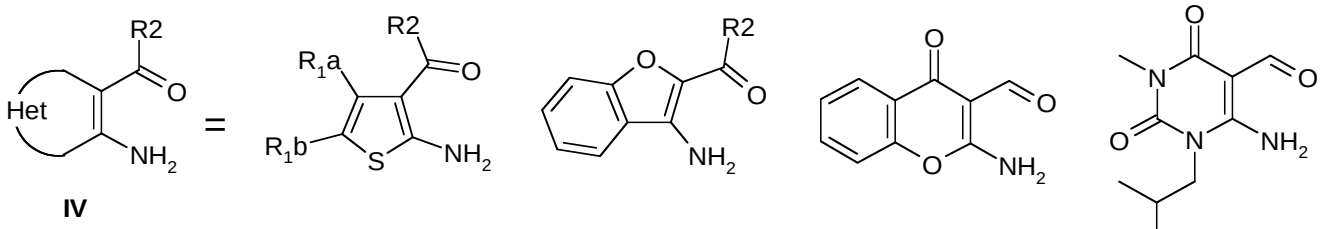


Scheme 1.

The corresponding aminoaldehydes and aminoketones depicted on the Figure 1 were chosen to be model objects for the investigation.



1a: $R_1aR_1b=(CH_2)_4$ R2=Ph **2a:** R2=CH_3

1b: $R_1aR_1b=(CH_2)_3$ R2=Tolyl **2b:** R2=2-Furyl

Figure 1.

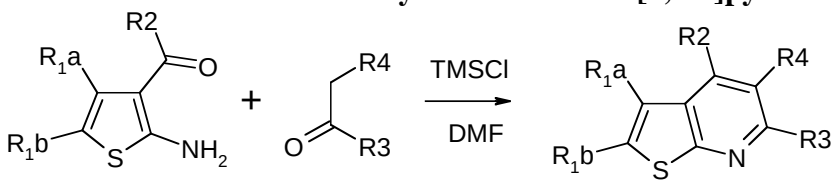
The heterofused systems (**V**) of thieno[2,3-*b*]pyridine, furo[3,2-*b*]pyridine, 5*H*-chromeno[2,3-*b*]pyridin-5-one, pyrido[2,3-*d*]pyridin-2,4(1*H*,3*H*)-dione, which are formed in the reaction of *ortho*-aminocarbonyl compounds with α-methyleneketones (**II**) are common among natural and synthetic chemical substances, and their derivatives exhibit a wide spectra of farmacological activity. The thieno[2,3-*b*]pyridine derivatives are known as specific antagonists of LHRH receptors.[4] Some derivatives of furo[3,2-*b*]pyridine reveal anticonvulsive action.[5] Among the 5*H*-chromeno[2,3-*b*]pyridin-5-one derivatives there are many substances which have found an application as antiallergic and antiulcer drugs.[6] The derivatives of pyrido[2,3-*d*]pyridin-2,4(1*H*,3*H*)-dione exhibit antibacterial,[7a] antitumor,[7b] anticonvulsant[7c] and other therapeutic activities.[7d-h] Till the moment, there is a quite wide range of reagents, systems and conditions for subjecting heterocyclic *ortho*-aminocarbonyl compounds to the Friedländer reaction,[5,8,9,10] however they are not sufficient to cover all the variety of α-methyleneketones which could

be used in this reaction. Therefore, the search for new preparative procedures for the Friedländer reaction and enlarging its scope and limitations by introducing more and more new substances remains still actually.

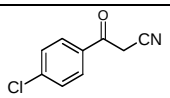
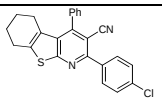
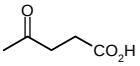
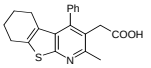
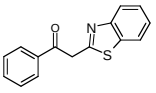
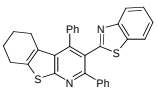
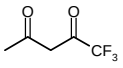
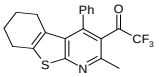
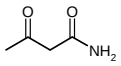
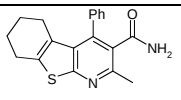
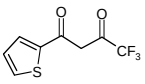
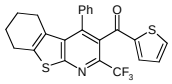
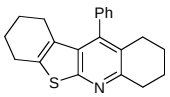
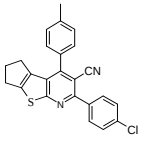
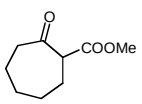
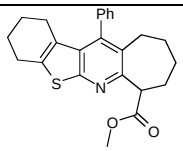
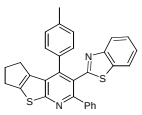
RESULTS AND DISCUSSION

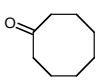
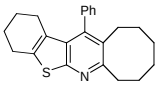
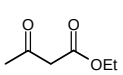
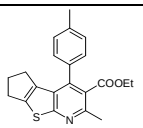
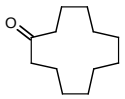
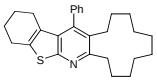
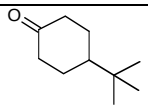
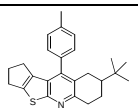
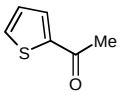
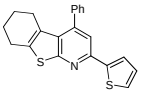
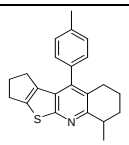
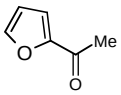
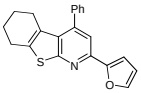
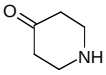
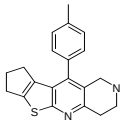
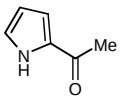
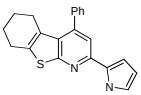
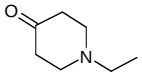
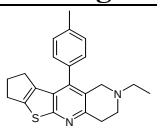
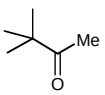
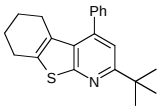
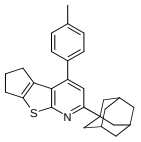
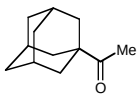
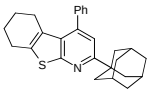
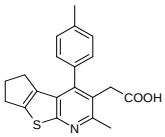
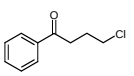
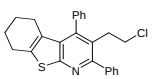
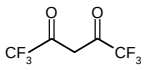
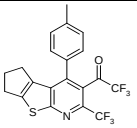
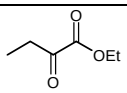
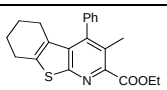
Among the selected model compounds (**IV**), thiophene aminoketones (**1a-b)** are the closest analogues of the aromatic aminoketones (**I**). Therefore, for the elucidation of the possibility of using 2-aminothiophenes as substrates for the Friedländer reaction in TMSCl/DMF system, we used the conditions found to be the best for *o*-aminoacetophenone. Heating 1 equivalent of aminoketones (**1a-b**) with 1 equivalent of α-methyleneketone (**5-11**) and 4 equivalents of TMSCl at 100 °C led to the formation of a set of thieno[2,3-*b*]pyridines (Table 1).

Table 1. TMSCl Promoted Synthesis of thieno[2,3-*b*]pyridines[a]



1a-b **5-11** **12-18**

Entry	1	Carbonyl compound	Product	Time (h)	Yield[a] (%)	Entry	1	Carbonyl compound	Product	Time (h)	Yield (%)[b]
1	1a	 **5a**	 **12aa**	10	94	15	1a	 **10a**	 **17aa**	14	86
2	1a	 **5b**	 **12ab**	10	89	16	1a	 **11a**	 **18aa**	12	85
3	1a	 **6a**	 **13aa**	10	93	17	1a	 **11b**	 **18ab**	12	81
4	1a	 **7a**	 **14aa**	12	96	18	1b	**5a**	 **12ba**	10	92
5	1a	 **7b**	 **14ab**	12	84	19	1b	**5b**	 **12bb**	10	87

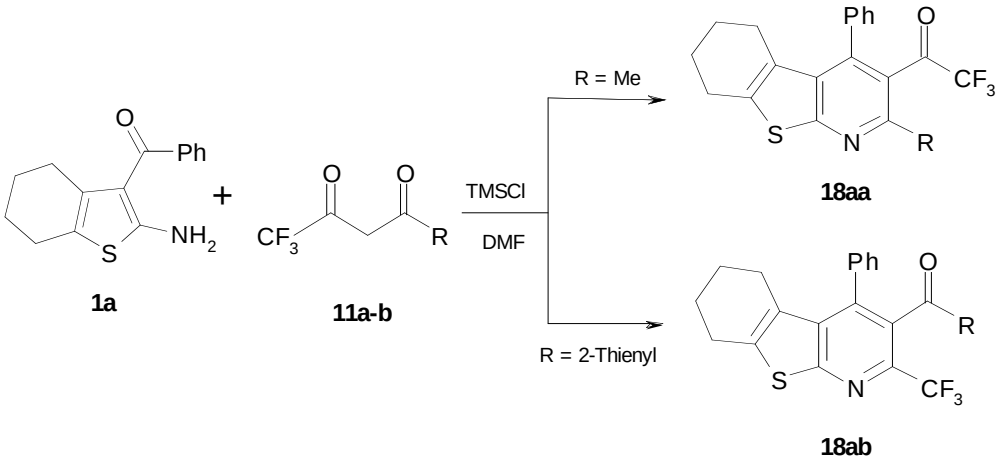
6	**1a**	 **7c**	 **14ac**	**12**	**87**	**20**	**1b**	 **6b**	 **13bb**	**10**	**88**
7	**1a**	 **7d**	 **14ad**	**12**	**88**	**21**	**1b**	 **7e**	 **14be**	**12**	**90**
8	**1a**	 **8a**	 **15aa**	**14**	**79**	**22**	**1b**	 **7f**	 **14bf**	**12**	**87**
9	**1a**	 **8b**	 **15ab**	**14**	**81**	**23**	**1b**	 **7g**	 **14bg**	**12**	**84**
10	**1a**	 **8c**	 **15ac**	**14**	**77**	**24**	**1b**	 **7h**	 **14bh**	**12**	**80**
11	**1a**	 **8d**	 **15ad**	**14**	**86**	**25**	**1b**	**8e**	 **15be**	**14**	**82**
12	**1a**	 **8e**	 **15ae**	**14**	**83**	**26**	**1b**	**10a**	 **17ba**	**14**	**86**
13	**1a**	 **8f**	 **15af**	**14**	**82**	**27**	**1b**	 **11c**	 **18bc**	**12**	**88**
14	**1a**	 **9a**	 **16aa**	**14**	**87**						

[a]Satisfactory microanalysis obtained C ± 0.33; H ± 0.45; N ± 0.25
[b]Yields refer to pure isolated products

Analyzing the results obtained, it should be noted that, in general more drastical conditions are required for aminothiophenes **1a-b** in comparison with *o*-aminoacetophenone for the Friedländer reaction. Thus, even in the case of the most reactive α-methylenecarbonyl compounds such as β-ketonitriles (**5**), β-diketones (**6, 11**) and cyclic ketones (**7**) which were subjected to the similar cyclizations before,[8] the optimal heating time remains to be 10-12 hours. In the case of less active substrates such as acyclic methylketones (**8**),

dialkylketones with additional functional groups (**9-10**), even more prolonged heating time is required (14 hours).

In the reaction of aminothiophene **1a** with unsymmetrical α-CF_3-β-diketones, either thienopyridine **18aa** or **18ab** are formed depending on the substituents, what is in agreement with previously obtained by us results concerning its behavior in the Friedländer reaction with *ortho*-aminobenzophenone[2] (Scheme 2).

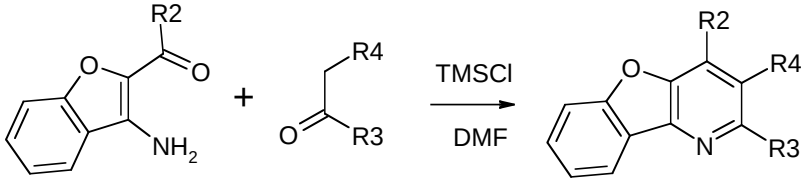


Scheme 2

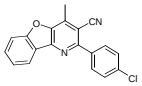
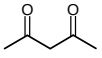
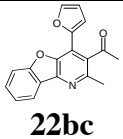
Changing from aminothiophenes to aminoketones of [1]benzofuran **2a-b** led to a significant narrowing the set of α-methylenecarbonyl compounds which could be subjected to the reaction and more drastical reaction conditions.

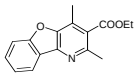
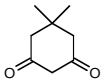
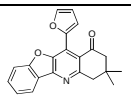
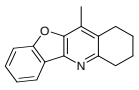
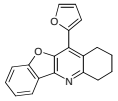
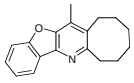
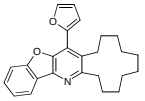
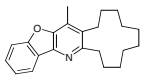
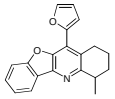
We succeeded in reacting aminoketones **2a-b** with β-ketonitriles (**5**), β-diketones (**6**) and cyclic ketones (**7**) by heating their mixtures in the TMSCl/DMF system for 12-14 hours. An attempt to subject acyclic ketones **8-10** to the same conversion resulted in the formation of only trace amounts of products. All the [1]benzofuro[3,2-b]pyridines obtained are listed in Table 2.

Table 2. TMSCl Promoted Synthesis of [1]benzofuro[3,2-*b*]pyridines[a]



2a-b **5-7** **19-23**

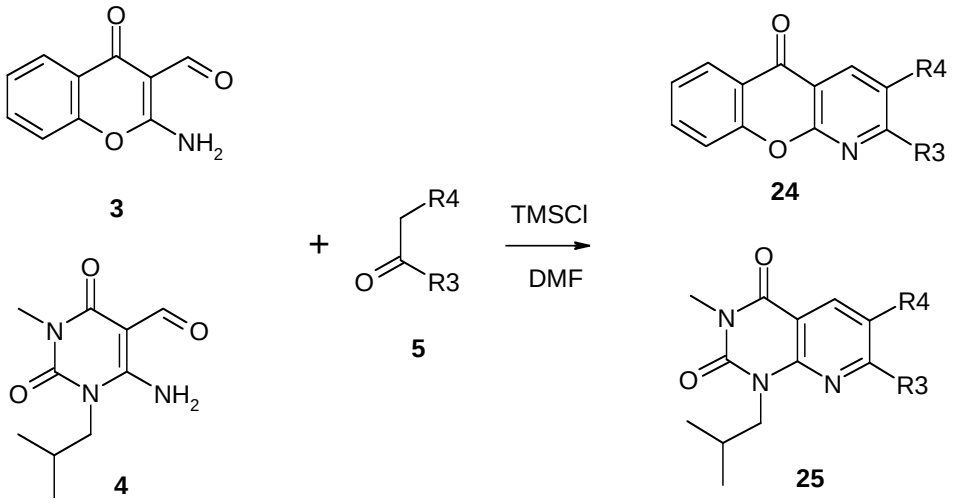
Entry	2	Carbonyl compound	Product	Time (h)	Yield[a] (%)	Entry	2	Carbonyl compound	Product	Time (h)	Yield (%)[b]
28	2a	5a	 19aa	12	90	33	2b	 6c	 22bc	14	88

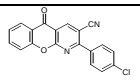
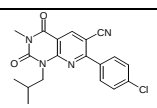
29	**2a**	**6b**	 **20ab**	**14**	**87**	**34**	**2b**	 **6d**	 **22bd**	**14**	**92**
30	**2a**	**7a**	 **21aa**	**14**	**92**	**35**	**2b**	**7a**	 **23aa**	**14**	**90**
31	**2a**	**7c**	 **21ac**	**14**	**83**	**36**	**2b**	**7d**	 **23ad**	**14**	**83**
32	**2a**	**7d**	 **21ad**	**14**	**81**	**37**	**2b**	**7f**	 **23af**	**14**	**86**
[a]Satisfactory microanalysis obtained C ± 0.33; H ± 0.45; N ± 0.25 [b]Yields refer to pure isolated products											

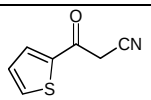
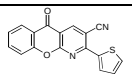
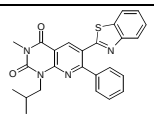
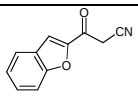
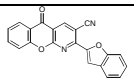
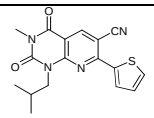
It should be noted that only ethyl acetoacetate was subjected to the Friedländer reaction with [1]benzofuro[3,2-*b*]pyridines before.[5]

The derivatives of 2-amino-3-uracil-carbaldehyde **3** and 2-amino-3-chromone-carbaldehyde **4** appeared to be even less active in the Friedländer reaction using our system in comparison with aminoketones of thiophene and furan. In this case we succeded in reacting only α-methyleneketones **5** with aminoaldehydes **3** and **4** using more prolonged heating (Table 3).

Table 3. TMSCl Promoted Synthesis of 5*H*-chromeno[2,3-*b*]pyridin-5-ones, pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones.[a]



Entry	**3**	**Carbonyl compound**	**Product**	**Time (h)**	**Yield[a] (%)**	**Entry**	**4**	**Carbonyl compound**	**Product**	**Time (h)**	**Yield (%)[b]**
38	**3a**	**5a**	 **24aa**	**16**	**90**	**41**	**4a**	**5a**		**16**	**89**

									25aa		
39	**3a**	 **5c**	 **24ac**	**16**	**86**	**42**	**4a**	**5b**	 **25ab**	**16**	**84**
40	**3a**	 **5d**	 **24ad**	**16**	**83**	**43**	**4a**	**5c**	 **25ac**	**16**	**81**
[a]Satisfactory microanalysis obtained C ± 0.33; H ± 0.45; N ± 0.25 **[b]Yields refer to pure isolated products**											

In conclusion, we described an efficient route for the synthesis of different heteroannelated pyridines using Me_3SiCl as a promoter and water scavenger *via* Friedländer annulation. The methodology is applicable to a wide variety of α-methylene ketones and delivers targeted products in good yields, excellent homogeneity and often in analytically pure form. The procedure is very simple and could be easily adapted to semi-automated solution-phase parallel synthesis of such libraries.

EXPERIMENTAL

General Data: All chemicals were obtained from commercially available sources (Aldrich, Fluka, Enamine Ltd.) and used without further purification. DMF was freshly distilled and dried by standard methods; monitoring of water concentration in solvents (the solvent contained < 0.05%, usually 0.02% of water) was performed using Mettler Toledo DL31 KF Titrator. All solvents for the crystallizations were used without additional purification.

Melting points were measured with a Buchi melting points apparatus and are uncorrected. The ^1H, ^{13}C and ^{19}F NMR spectra (500, 125 and 470 MHz, respectively) were recorded on a Bruker Avance drx 500 with DMSO-d_6 as a solvent, TMS (^1H and ^{13}C) and $CFCl_3$ (^{19}F) were used as internal standards. LC/MS spectra were recorded using chromatography/mass spectrometric system that consists of high-performance liquid chromatograph "Agilent 1100 Series" equipped with diode-matrix and mass-selective detector "Agilent LC/MSD SL". According to HPLC MS data all the synthesized compounds have purity > 95%. BRANSON 2510E-MT ultrasonic bath and autoclave BERGHOF HR-500 were used.

General procedure for the preparation of thieno[2,3-*b*]pyridines, [1]benzofuro[3,2-*b*]pyridines, 5*H*-chromeno[2,3-*b*]pyridin-5-ones, pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (12-25).

An appropriate aminocarbonyl compound **1-4** (1 mmol) and an appropriate carbonyl component **5-11** (1 mmol) were placed in 8 mL pressure tube and dissolved in DMF (2 mL). Chlorotrimethylsilane (4 mmol) was added dropwise to the solution. The tube was thoroughly sealed and heated on a water-bath for a particular time. (For the heating time see Tables 1-3.) After cooling the flask was opened (*caution!*

Excessive pressure inside); the reaction mixture was poured into water (5 mL) and allowed to stand at 20 °C in ultrasonic bath for 1h. The precipitate formed was filtered and washed with small amount of MeOH (or MeCN). Recrystallization from an appropriate solvent yielded the target compound.

2-(4-Chlorophenyl)-4-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridine-3-carbonitrile (12aa)

mp 201 °C. ^{1}H NMR (DMSO-d_6) δ 1.53 (m, 2H), 1.75 (m, 2H), 1.85 (m, 2H), 2.87 (m, 2H), 7.49 (m, 2H), 7.56 (m, 3H), 7.61 (d, J = 7.7 Hz, 2H), 7.92 (d, J = 7.7 Hz, 2H). [M+1]=402. Anal. Calcd for $C_{24}H_{17}ClN_2S$: C, 71.90; H, 4.27; N, 6.99. Found: C, 71.75; H, 4.30; N, 6.90.

3-(1,3-Benzothiazol-2-yl)-2,4-diphenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridine (12ab)

mp 178 °C. ^{1}H NMR (DMSO-d_6) δ 1.49 (m, 2H), 1.72 (m, 4H), 2.86 (m, 2H), 7.2 (m, 5H), 7.28 (m, 3H), 7.37 (t, J = 7.5 Hz, 1H), 7.42 (m, 3H), 7.83 (t, J = 7.5 Hz, 2H). [M+1]=476. Anal. Calcd for $C_{30}H_{22}N_2S_2$: C, 75.92; H, 4.67; N, 5.90. Found: C, 75.86; H, 4.58; N, 6.06.

2-Methyl-4-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridine-3-carboxamide (13aa)

mp 254 °C. ^{1}H NMR (DMSO-d_6) δ 1.45 (m, 2H), 1.69 (m, 4H), 2.57 (s, 3H), 2.77 (m, 2H), 7.29 (m, 3H), 7.39 (m, 3H), 7.67 (s, 1H) ^{13}C NMR (DMSO-d_6) δ = 22.2, 22.5, 22.6, 25.9, 26.1, 127.7, 128.3, 128.6, 128.7, 129.8, 131.1, 136.4, 137.0, 141.7, 149.5, 158.4, 169.2. [M+1]=323. Anal. Calcd for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63; N, 8.69. Found: C, 70.89; H, 5.52; N, 8.54.

11-Phenyl-1,2,3,4,7,8,9,10-octahydro[1]benzothieno[2,3-*b*]quinoline (14aa)

mp 190-191 °C. ^{1}H NMR (DMSO-d_6) δ 1.46 (m, 2H), 1.69 (m, 6H), 1.81 (m, 2H), 2.32 (t, J = 6.2 Hz, 2H), 2.74 (m, 2H), 2.94 (t, J = 6.2 Hz, 2H), 7.21 (m, 2H), 7.47 (m, 3H) . [M+1]=320. Anal. Calcd for $C_{21}H_{21}NS$: C, 78.95; H, 6.63; N, 4.38. Found: C, 78.77; H, 6.57; N, 4.32.

Methyl 12-phenyl-2,3,4,7,8,9,10,11-octahydro-1*H*-[1]benzothieno[2,3-*b*]cyclohepta[*e*]pyridine-7-carboxylate (14ab)

mp 121 °C. ^{1}H NMR (DMSO-d_6) δ 1.43 (m, 1H), 1.49 (m, 2H), 1.51 (m, 1H), 1.75 (m, 8H), 1.98 (m, 1H), 2.39 (m, 1H), 2.73 (m, 2H), 3.67 (s, 3H), 4.31 (m, 1H), 7.21 (m, 2H), 7.45 (m, 3H). [M+1]=393. Anal. Calcd for $C_{24}H_{25}NO_2S$: C, 73.62; H, 6.44; N, 3.58. Found: C, 73.90; H, 6.39; N, 3.68.

13-Phenyl-1,2,3,4,7,8,9,10,11,12-decahydro[1]benzothieno[2,3-*b*]cycloocta[*e*]pyridine (14ac)

mp 243 °C. ^{1}H NMR (DMSO-d_6) δ 1.29 (m, 2H), 1.38 (m, 6H), 1.66 (m, 4H), 1.82 (m, 2H), 2.61 (m, 2H), 2.81 (m, 2H), 3.24 (m, 2H), 7.32 (m, 2H), 7.51 (m, 3H) ^{13}C NMR (DMSO-d_6) δ = 22.3, 22.4, 25.4, 25.6, 25.9, 26.2, 26.9, 30.9, 31.0, 33.3, 128.3, 128.4, 128.8, 129.1, 131.4, 131.7, 137.1, 137.9, 147.3, 153.2, 155.6. [M+1]=349. Anal. Calcd for $C_{23}H_{25}NS$: C, 79.49; H, 7.25; N, 4.03. Found: C, 79.37; H, 7.36; N, 4.11.

17-Phenyl-1,2,3,4,7,8,9,10,11,12,13,14,15,16-tetradecahydro[1]benzothieno[2,3-*b*]cyclododeca[*e*]pyridine (14ad)

mp 175-176 °C. ^{1}H NMR (DMSO-d_6) δ 1.24 (m, 2H), 1.51 (m, 14H), 1.68 (m, 2H), 1.78 (m, 2H), 1.96 (m, 2H), 2.46 (m, 2H), 2.82 (m, 2H), 2.88 (m, 2H), 7.21 (m, 2H), 7.46 (m, 3H) ^{13}C NMR (DMSO-d_6) δ 22.7, 22.8, 23.3, 23.8, 26.1, 26.7, 26.9, 27.3, 27.5, 27.7, 29.3, 32.9, 128.1, 128.3, 129.7, 130.3, 136.1, 138.4, 144.8, 146.6, 155.4, 157.2, 181.9, 208.3, 212.9. [M+1]=405. Anal. Calcd for $C_{27}H_{33}NS$: C, 80.35; H, 8.24; N, 3.47. Found: C, 80.02; H, 8.53; N, 3.58.

4-Phenyl-2-thien-2-yl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridine (15aa)

mp 190 °C. ^{1}H NMR (DMSO-d_6) δ 1.52 (m, 2H), 1.74 (m, 2H), 1.92 (m, 2H), 2.81 (m, 2H), 7.13 (t, J = 3.4 Hz, 1H), 7.42 (m, 2H), 7.48 (m, 3H), 7.63 (d, J = 4.4 Hz 1H), 7.68 (s, 1H), 7.87 (d, J = 2.7 Hz, 1H). [M+1]=349. Anal. Calcd for $C_{21}H_{17}NS_2$: C, 72.58; H, 4.93; N, 4.03. Found: C, 72.44; H, 4.76; N, 4.19.

2-(2-Furyl)-4-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridine (15ab)

mp 199 °C. ^{1}H NMR (DMSO-d_6) δ 1.52 (m, 2H), 1.74 (m, 2H), 1.94 (m, 2H), 2.82 (m, 2H), 6.65 (m, 1H), 7.22 (d, J = 3 Hz, 1H), 7.42 (m, 2H), 7.48 (m, 4H), 7.82 (s, 1H). [M+1]=332. Anal. Calcd for $C_{21}H_{17}NOS$: C, 76.10; H, 5.17; N, 4.23. Found: C, 76.32; H, 5.05; N, 4.39.

4-Phenyl-2-(1*H*-pyrrol-2-yl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridine (15ac)

mp 215 °C. ^{1}H NMR (DMSO-d_6) δ 1.51 (m, 2H), 1.73 (m, 2H), 1.91 (m, 2H), 2.79 (m, 2H), 6.14 (s, 1H), 6.89 (s, 2H), 7.40 (s, 2H), 7.49 (s, 3H), 11.75 (s, 1H). [M+1]=331. Anal. Calcd for $C_{21}H_{18}N_2S$: C, 76.33; H, 5.49; N, 8.48. Found: C, 76.21; H, 5.63; N, 8.37.

2-*tert*-Butyl-4-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridine (15ad)

mp 120 °C. ^{1}H NMR (DMSO-d_6) δ 1.35 (s, 9H), 1.51 (m, 2H), 1.74 (m, 2H), 1.93 (m, 2H), 2.87 (m, 2H), 7.12 (s, 1H), 7.36 (m, 2H), 7.44 (m, 3H). [M+1]=322. Anal. Calcd for $C_{21}H_{23}NS$: C, 78.46; H, 7.21; N, 4.36. Found: C, 78.37; H, 7.30; N, 4.29.

2-(1-Adamantyl)-4-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridine (15ae)

mp 181 °C. ^{1}H NMR (DMSO-d_6) δ 1.50 (m, 2H), 1.72 (m, 8H), 1.97 (m, 8H), 2.03 (m, 3H), 2.49 (m, 2H), 7.04 (s, 1H), 7.33 (m, 2H), 7.43 (m, 3H). [M+1]=401. Anal. Calcd for $C_{27}H_{29}NS$: C, 81.16; H, 7.32; N, 3.51. Found: C, 81.05; H, 7.77; N, 3.41.

3-(2-Chloroethyl)-2,4-diphenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridine (15af)

Mp 146-147 °C. ^{1}H NMR (DMSO-d_6) δ 1.48 (m, 2H), 1.71 (m, 4H), 2.79 (m, 2H), 2.88 (m, 2H), 3.22 (m, 2H), 7.41 (m, 2H), 7.52 (m, 8H). [M+1]=405. Anal. Calcd for $C_{25}H_{22}ClNS$: C, 74.33; H, 5.49; N, 3.47. Found: C, 74.45; H, 5.65; N, 3.32.

Ethyl 3-methyl-4-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridine-2-carboxylate (16aa)

mp 130 °C. ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 7.2 Hz, 3H), 1.47 (m, 2H), 1.80 (m, 4H), 2.54 (s, 3H), 2.80 (m, 2H), 3.92 (q, J = 7.2 Hz, 2H), 7.24 (m, 2H), 7.45 (m, 3H). ^{13}C NMR (DMSO-d_6) δ 13.8, 22.4, 22.5,

22.7, 25.9, 26.2, 61.3, 126.8, 128.0, 128.2, 128.3, 128.9, 129.4, 136.2, 137.7, 142.2, 149.8, 160.5, 168.1. [M+1]=352. Anal. Calcd for $C_{21}H_{21}NO_2S$: C, 71.77; H, 6.02; N, 3.99. Found: C, 71.58; H, 6.15; N, 4.13.

(2-Methyl-4-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridin-3-yl)acetic acid (17aa)

mp 276 °C. ^{1}H NMR (DMSO-d_6) δ 1.43 (m, 2H), 1.44 (m, 4H), 2.54 (s, 3H), 2.75 (m, 2H), 3.42 (s, 2H), 7.17 (m, 2H), 7.41 (m, 3H). [M+1]=338. Anal. Calcd for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68; N, 4.15. Found: C, 71.35; H, 5.47; N, 4.26.

2,2,2-Trifluoro-1-(2-methyl-4-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridin-3-yl)ethanone (18aa)

mp 111 °C. ^{1}H NMR (DMSO-d_6) δ 1.50 (m, 2H), 1.71 (m, 2H), 1.82 (m, 2H), 2.49 (s, 3H), 2.83 (m, 2H), 7.29 (m, 2H), 7.49 (m, 3H). ^{13}C NMR (DMSO-d_6) δ 22.35, 22.44, 22.7, 26.0, 26.4, 114.9 (q, $^1J_{CF}$ = 292.7 Hz), 126.5, 128.2, 128.36, 128.40, 129.9, 130.3, 134.2, 139.0, 142.8, 149.0, 162.5, 189.9 (q, $^2J_{CF}$ = 37.2 Hz). ^{19}F NMR (DMSO-d_6) δ -76.3. [M+1]=376. Anal. Calcd for $C_{20}H_{16}F_3NOS$: C, 63.99; H, 4.30; N, 3.73. Found: C, 64.12; H, 4.24; N, 3.62.

4-Phenyl-2-(trifluoromethyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*b*]pyridin-3-yl](thien-2-yl)methanone (18ab)

mp 210 °C. ^{1}H NMR (DMSO-d_6) δ 1.51 (m, 2H), 1.71 (m, 3H), 1.90 (m, 1H), 2.91 (m, 2H), 7.08 (m, 1H), 7.15 (m, 2H), 7.21 (m, 1H), 7.33 (m, 2H), 7.47 (d, J = 5.1 Hz, 1H), 7.97 (d, J = 5.1 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 22.25, 22.28, 26.0, 26.4, 122.1 (q, $^1J_{CF}$ = 275.6 Hz), 127.5, 128.0, 128.9, 129.2, 129.3, 130.0, 130.3, 130.5, 133.3, 134.2, 137.5, 137.6, 143.8 (q, $^2J_{CF}$ = 33.0 Hz), 144.6, 160.1, 185.9. ^{19}F NMR (DMSO-d_6) δ -62.0. [M+1]=445. Anal. Calcd for $C_{23}H_{16}F_3NOS_2$: C, 62.29; H, 3.64; N, 3.16. Found: C, 62.43; H, 3.57; N, 3.26.

2-(4-Chlorophenyl)-4-(4-methylphenyl)-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*b*]pyridine-3-carbonitrile (12ba)

mp 216 °C. ^{1}H NMR (DMSO-d_6) δ 2.18 (m, 2H), 2.24 (m, 2H), 2.42 (s, 3H), 3.01 (m, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H) 7.63 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H). [M+1]=402. Anal. Calcd for $C_{24}H_{17}ClN_2S$: C, 71.90; H, 4.27; N, 6.99. Found: C, 71.76; H, 4.15; N, 6.85.

3-(1,3-Benzothiazol-2-yl)-4-(4-methylphenyl)-2-phenyl-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*b*]pyridine (12bb)

mp 250 °C. ^{1}H NMR (DMSO-d_6) δ 2.06 (m, 2H), 2.22 (m, 5H), 2.99 (m, 2H), 7.06 (d, J = 7.3 Hz, 2H), 7.17 (m, 5H), 7.32(t, J = 8 Hz, 1H), 7.41 (m, 3H), 7.86 (t, J = 8 Hz, 2H). [M+1]=476. Anal. Calcd for $C_{30}H_{22}N_2S_2$: C, 75.92; H, 4.67; N, 5.90. Found: C, 76.06; H, 4.53; N, 5.82.

Ethyl 2-methyl-4-(4-methylphenyl)-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*b*]pyridine-3-carbo-

xylate (13bb)

mp 99 °C. ^{1}H NMR (DMSO-d_6) δ 0.96 (t, J = 7.2 Hz, 3H), 2.18 (m, 2H), 2.29 (m, 2H), 2.46 (s, 3H), 2.61 (s, 3H), 3.01 (m, 2H), 3.99 (q, J = 7.2 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H) ^{13}C NMR (DMSO-d_6) δ 13.9, 21.3, 22.8, 27.1, 29.8, 29.9, 61.4, 125.9, 126.2, 128.7, 129.2, 133.0, 137.4, 138.2, 141.9, 142.8, 150.0, 165.8, 168.2. [M+1]=352. Anal. Calcd for $C_{21}H_{21}NO_2S$: C, 71.77; H, 6.02; N, 3.99. Found: C, 71.64; H, 6.18; N, 4.09.

8-*tert*-Butyl-10-(4-methylphenyl)-2,3,6,7,8,9-hexahydro-1*H*-cyclopenta[4,5]thieno[2,3-*b*]quinoline (14be)

mp 193 °C. ^{1}H NMR (DMSO-d_6) δ 0.85 (s, 9H), 1.44 (m, 2H), 1.97 (m, 1H), 2.05 (m, 2H), 2.21 (m, 3H), 2.49 (s, 3H), 2.51 (m, 1H), 2.92 (m, 3H), 3.07 (m, 1H), 7.06 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H). ^{13}C NMR (DMSO-d_6) 21.3, 24.2, 27.0, 27.4, 28.2, 29.4, 29.9, 32.6, 33.8, 44.5, 126.6, 126.8, 126.9,.128.9, 129.0, 134.2, 137.2, 137.4, 140.7, 143.7, 163.0. [M+1]=377. Anal. Calcd for $C_{25}H_{29}NS$: C, 79.95; H, 7.78; N, 3.73. Found: C, 80.05 H, 7.63; N, 3.65.

6-Methyl-10-(4-methylphenyl)-2,3,6,7,8,9-hexahydro-1*H*-cyclopenta[4,5]thieno[2,3-*b*]quinoline (14bf)

mp 179 °C. ^{1}H NMR (DMSO-d_6) δ 1.36 (d, J = 4.7 Hz, 3H), 1.60 (m, 2H), 1.72 (m, 1H), 1.95 (m, 3H), 2.14 (m, 2H), 2.37 (s, 3H), 2.45 (m, 2H), 2.87 (m, 2H), 3.06 (m, 1H), 7.11 (m, 2H), 7.27 (m, 2H). ^{13}C NMR (DMSO-d_6) 20.4, 21.3, 21.8, 27.0, 27.6, 29.3, 29.9, 31.0, 35.9, 126.5, 127.0, 129.01, 129.05, 129.1, 134.2, 137.1, 137.5, 141.4, 157.0, 169.5. [M+1]=335. Anal. Calcd for $C_{22}H_{23}NS$: C, 79.23; H, 6.95; N, 4.20. Found: C, 79.17 H, 7.04; N, 4.33.

10-(4-Methylphenyl)-2,3,4,7,8,9-hexahydro-1*H*-cyclopenta[4,5]thieno[2,3-*b*]-1,6-naphthyridine (14bg)

mp 258-259 °C. ^{1}H NMR (DMSO-d_6) δ 2.02 (m, 2H), 2.17 (m, 2H), 2.40 (s, 3H) 2.92 (m, 2H), 3.25 (m, 2H), 3.46 (m, 2H), 3.99 (m, 2H), 7.19 (d, J = 7.3 Hz, 2H), 7.35 (d, J = 7.3 Hz, 2H). [M+1]=321. Anal. Calcd for $C_{20}H_{20}N_2S$: C, 74.96; H, 6.29; N, 8.74. Found: C, 75.15 H, 6.34; N, 8.56.

2-Ethyl-10-(4-methylphenyl)-2,3,4,7,8,9-hexahydro-1*H*-cyclopenta[4,5]thieno[2,3-*b*]-1,6-naphthyridine (14bh)

mp 239-240 °C. ^{1}H NMR (DMSO-d_6) δ 1.21 (m, 3H), 2.03 (m, 2H), 2.17 (m, 2H), 2.40 (s, 3H), 2.91 (m, 2H), 3.02 (m, 2H), 3.23 (m, 4H), 4.09 (m, 2H), 7.53 (m, 2H), 7.35 (m, 2H), 8.94 (br s, 1H), 11.69 (br s, 1H). [M+1]=350. Anal. Calcd for $C_{22}H_{24}N_2S$: C, 75.82; H, 6.94; N, 8.04. Found: C, 75.87 H, 6.81; N, 7.80.

2-(1-Adamantyl)-4-(4-methylphenyl)-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*b*]pyridine (15be)

mp 195 °C. ^{1}H NMR (DMSO-d_6) δ 1.71 (m, 6H), 2.03 (m, 11H), 2.21 (m, 2H), 2.38 (s, 3H) 2.94 (m, 2H),

7.17 (d, *J* = 7.3 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 2H). [M+1]=401. Anal. Calcd for $C_{27}H_{29}NS$: C, 81.16; H, 7.32; N, 3.51. Found: C, 80.98 H, 7.51; N, 3.42.

[2-Methyl-4-(4-methylphenyl)-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*b*]pyridin-3-yl]acetic acid (17ba)

mp 141 °C. ^{1}H NMR (DMSO-d_6) δ 1.92 (m, 2H), 2.05 (m, 2H), 2.38 (s, 3H), 2.52 (s, 3H), 2.87 (m, 2H), 3.44 (s, 2H), 7.06 (d, *J* = 7.0 Hz, 2H), 7.28 (d, *J* = 7.0 Hz, 2H), 12.30 (br s, 1H). [M+1]=338. Anal. Calcd for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68; N, 4.15. Found: C, 71.28 H, 5.53; N, 4.28.

2,2,2-Trifluoro-1-[4-(4-methylphenyl)-2-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*b*]pyridin-3-yl]ethanone (18bc)

mp 147 °C. ^{1}H NMR (DMSO-d_6) δ 2.18 (m, 2H), 2.24 (m, 2H), 2.39 (s, 3H), 3.07 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (DMSO-d_6) δ 21.4, 27.2, 29.5, 30.6, 114.7 (q, $^1J_{CF}$ = 292.8 Hz), 118.7, 121.6 (q, $^1J_{CF}$ = 274.6 Hz), 129.2, 129.6, 129.8, 130.4, 138.0, 140.1, 143.3 (q, $^2J_{CF}$ = 32.6 Hz), 143.5, 150.8, 166.7, 186.6 (q, $^2J_{CF}$ = 38.9 Hz). ^{19}F NMR (DMSO-d_6) δ -76.3, -62.3. [M+1]=430. Anal. Calcd for $C_{20}H_{13}F_6NOS$: C, 55.95; H, 3.05; N, 3.26. Found: C, 56.16 H, 3.23; N, 3.16.

2-(4-Chlorophenyl)-4-methyl[1]benzofuro[3,2-*b*]pyridine-3-carbonitrile (19aa)

mp 220-221 °C. ^{1}H NMR (DMSO-d_6) δ 2.73 (s, 3H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.78 (t, *J* = 7.3 Hz, 1H), 7.91 (m, 3H), 8.23 (d, *J* = 7.3 Hz, 1H). [M+1]=320. Anal. Calcd for $C_{19}H_{11}ClN_2O$: C, 71.59; H, 3.48; N, 8.79. Found: C, 71.45 H, 3.58; N, 8.65.

Ethyl 2,4-dimethyl[1]benzofuro[3,2-*b*]pyridine-3-carboxylate (20ab)

mp 167 °C. ^{1}H NMR (DMSO-d_6) δ 1.35 (t, *J* = 7.3 Hz, 3H), 2.54 (s, 3H), 3.63 (s, 3H), 4.45 (q, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 8.21 (d, *J* = 7.5 Hz, 1H) . [M+1]=270. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.25 H, 5.50; N, 5.15.

11-Methyl-1,2,3,4-tetrahydro[1]benzofuro[3,2-*b*]quinoline (21aa)

mp 284 °C. ^{1}H NMR (DMSO-d_6) δ 1.86 (m, 4H), 2.87 (s, 3H), 2.87 (m, 2H), 3.19 (m, 2H), 7.56 (t, 1H , *J* = 7.2 Hz), 7.75 (t, 1H , *J* = 7.2 Hz), 7.88 (d, 1H , *J* = 7.2 Hz), 8.53 (m, 1H). [M+1]=238. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.06 H, 6.52; N, 5.98.

6-Methyl-7,8,9,10,11,12-hexahydro[1]benzofuro[3,2-*b*]cycloocta[*e*]pyridine (21ac)

mp 268 °C. ^{1}H NMR (DMSO-d_6) δ 1.29 (m, 2H), 1.41 (m, 2H), 1.71 (m, 2H), 1.83 (m, 2H), 2.69 (s, 3H), 3.32 (m, 2H), 3.33 (m, 2H), 7.57 (t, 1H , *J* = 7.3 Hz), 7.76 (t, 1H , *J* = 7.3 Hz), 7.91 (d, 1H , *J* = 7.3 Hz), 8.60 (m, 1H). [M+1]=266. Anal. Calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28. Found: C, 81.59 H, 7.10; N, 5.35.

6-Methyl-7,8,9,10,11,12,13,14,15,16-decahydro[1]benzofuro[3,2-*b*]cyclododeca[*e*]pyridine (21ad)

mp 265 °C. ^{1}H NMR (DMSO-d_6) δ 1.7 (m, 6H), 1.53 (m, 8H), 1.84 (m, 2H), 2.79 (s, 3H), 2.96 (m, 2H), 2.97 (m, 2H), 7.45 (t, 1H , *J* = 7.5 Hz), 7.65 (t, 1H , *J* = 7.5 Hz), 7.79 (d, 1H , *J* = 7.5 Hz), 8.50 (br s, 1H). [M+1]=322. Anal. Calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.06 H, 8.31; N, 4.24.

1-[4-(2-Furyl)-2-methyl[1]benzofuro[3,2-*b*]pyridin-3-yl]ethanone (22bc)

mp 245 °C. ^{1}H NMR (DMSO-d_6) δ 2.51 (s, 3H), 2.59 (s, 3H), 6.87 (s, 1H), 7.52 (t, *J* = 8.2 Hz, 1H), 7.58 (s, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 8.04 (s, 1H), 8.26 (d, *J* = 7.4 Hz, 1H). [M+1]=292. Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.11 H, 4.45; N, 4.93.

11-(2-Furyl)-3,3-dimethyl-3,4-dihydro[1]benzofuro[3,2-*b*]quinolin-1(2*H*)-one (22bd)

mp 220 °C. ^{1}H NMR (DMSO-d_6) δ 1.07 (s, 6H), 2.19 (s, 2H), 2.56 (s, 2H), 6.86 (m, 1H), 7.42 (t, *J* = 7.8 Hz, 1H),7.63 (t, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.91 (m, 1H), 8.17 (m, 1H) . [M+1]=332. Anal. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.28 H, 5.04; N, 4.38.

11-(2-Furyl)-1,2,3,4-tetrahydro[1]benzofuro[3,2-*b*]quinoline (23aa)

mp 266 °C. ^{1}H NMR (DMSO-d_6) δ 1.84 (m, 4H), 3.08 (m, 2H), 3.17(m, 2H), 6.87 (m, 1H), 7.49 (m, 2H), 7.68 (m, 1H), 7.78 (m, 1H), 8.13 (m, 1H), 8.45 (m, 1H), 8.96 (br s, 1H). [M+1]=290. Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.77 H, 5.15; N, 4.94.

6-(2-Furyl)-7,8,9,10,11,12,13,14,15,16-decahydro[1]benzofuro[3,2-*b*]cyclododeca[*e*]pyridine (23ad)

mp 160 °C. ^{1}H NMR (DMSO-d_6) δ 1.35 (m, 6H), 1.50 (m, 8H), 1.86 (m, 2H), 2.94 (m, 2H), 3.00 (m, 2H), 6.78 (m, 1H), 7.19 (d, *J* = 3.0 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.76 (d, *J* = 7.3 Hz, 1H), 8.00 (s, 1H), 8.11 (d, *J* = 7.3 Hz, 1H). [M+1]=375. Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.40; H, 7.29; N, 3.75. Found: C, 80.52 H, 7.18; N, 3.62.

11-(2-Furyl)-4-methyl-1,2,3,4-tetrahydro[1]benzofuro[3,2-*b*]quinoline (23af)

mp 252 °C. ^{1}H NMR (DMSO-d_6) δ 1.50 (d, *J* = 6.5 Hz, 3H), 1.71 (m, 1H), 1.87 (m, 2H), 2.02 (m, 1H), 3.04 (m, 1H), 3.16 (m, 1H), 3.47 (m, 1H), 6.87 (s, 1H), 7.51 (s, 2H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 8.13 (s, 1H), 8.59 (s, 1H). [M+1]=304. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.01 H, 5.56; N, 4.74.

2-(4-Chlorophenyl)-5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (24aa)

mp 266 °C. ^{1}H NMR (DMSO-d_6) δ 7.24 (m, 3H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.83 (d, *J* = 6.0 Hz, 2H), 8.33 (d, *J* = 7.2 Hz, 1H), 9.05 (s, 1H). [M+1]=334. Anal. Calcd for $C_{19}H_9ClN_2O_2$: C, 68.58; H, 2.73; N, 8.42. Found: C, 68.43 H, 2.80; N, 8.39.

5-Oxo-2-thien-2-yl-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (24ac)

mp 260 °C. ^{1}H NMR (DMSO-d_6) δ 7.33 (m, 1H), 7.53 (t, J = 7.3 Hz, 1H), 7.72 (d, J = 7.3 Hz, 1H), 7.91 (t, J = 7.3 Hz, 1H) 8.00 (m, 1H), 8.15 (d, J = 7.3 Hz, 1H), 8.34 (m, 1H), 8.94 (s, 1H). [M+1]=305. Anal. Calcd for $C_{17}H_8N_2O_2S$: C, 67.09; H, 2.65; N, 9.20. Found: C, 67.21 H, 2.79; N, 9.15.

2-(1-Benzofuran-2-yl)-5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (24ad)

mp 295 °C. ^{1}H NMR (DMSO-d_6) δ 7.38 (d, J = 7.2 Hz, 1H), 7.54 (m, 2H), 7.72 (m, 2H), 7.86 (m, 1H), 7.93 (m, 1H), 8.05 (m, 1H), 8.19 (d, J = 7.2 Hz, 1H), 9.00 (s, 1H). [M+1]=339. Anal. Calcd for $C_{21}H_{10}N_2O_3$: C, 74.55; H, 2.98; N, 8.28. Found: C, 74.43 H, 2.77; N, 8.17.

7-(4-Chlorophenyl)-1-isobutyl-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (25aa)

mp 222 °C. ^{1}H NMR (DMSO-d_6) δ 0.90 (d, J = 9.6 Hz, 6H), 2.25 (m, 1H), 3.32 (s, 3H), 4.11 (m, 2H), 7.71 (m, 2H), 7.98 (d, J = 6.9 Hz, 2H), 8.85 (s, 1H). [M+1]=370. Anal. Calcd for $C_{19}H_{17}ClN_4O_2$: C, 61.88; H, 4.65; N, 15.19. Found: C, 61.76 H, 4.73; N, 15.26.

6-(1,3-Benzothiazol-2-yl)-1-isobutyl-3-methyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (25ab)

mp 220 °C. ^{1}H NMR (DMSO-d_6) δ 0.92 (d, J = 9.6 Hz, 6H), 2.07 (m, 1H), 3.35 (s, 3H), 4.13 (d, J = 10.0 Hz, 2H), 7.52 (m, 7H), 7.99 (m, 2H), 8.83 (s, 1H). [M+1]=444. Anal. Calcd for $C_{25}H_{22}N_4O_2S$: C, 67.85; H, 5.01; N, 12.66. Found: C, 67.73 H, 4.92; N, 12.78.

1-iso-Butyl-3-methyl-2,4-dioxo-7-thien-2-yl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (25ac)

mp 200 °C. ^{1}H NMR (DMSO-d_6) δ 0.95 (d, J= 6.3 Hz, 6H), 2.15 (m, 1H), 3.31 (s, 3H), 4.07 (d, J = 7.2 Hz, 2H), 7.35 (t, J = 4.1 Hz, 1H), 8.29 (d, J = 4.1 Hz, 1H), 8.04 (d, J = 4.1 Hz, 1H), 8.70 (s, 1H). [M+1]=341. Anal. Calcd for $C_{17}H_{16}N_4O_2S$: C, 59.98; H, 4.74; N, 16.46. Found: C, 59.86 H, 4.84; N, 16.53.

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