TRIFLUOROMETHYLATED PYRIMIDINES STARTING FROM β-TRIFLUOROACETYL-LACTAMS, -LACTONE AND -CYCLANONE

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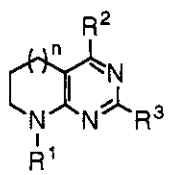
Dedicated to Prof. A. Katritzky on the occasion of his 65th birthday.

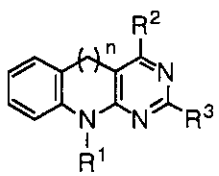
Abstract-A synthesis of trifluoromethylated pyrimidines from β-trifluoroacetyl-lactams and -benzolactams is accomplished by reaction with benzamidine as bis-nucleophile. This condensation is also extended to cyclic trifluoromethylated 1,3-diketones and 3-aroyl-2-pyrrolidinones.

The synthesis of pyrrolo[2,3-*d*]pyrimidines (7-deazapurines),[1a] their 5,6-dihydro derivatives[1a] (**1**) (n=0) and the corresponding benzoannulated analogs (**2**) (n=1, 5-deazaflavines)[1b] has been a topic of continuing interest because of their structural similarity with purines and flavines and the interesting biological activities associated with them.



1

n = 0, 1, 2
R^1 = H, alkyl, aryl
R^2 = H, alkyl, vinyl, OH
R^3 = H, alkyl, aryl, OH SH, NH_2



2

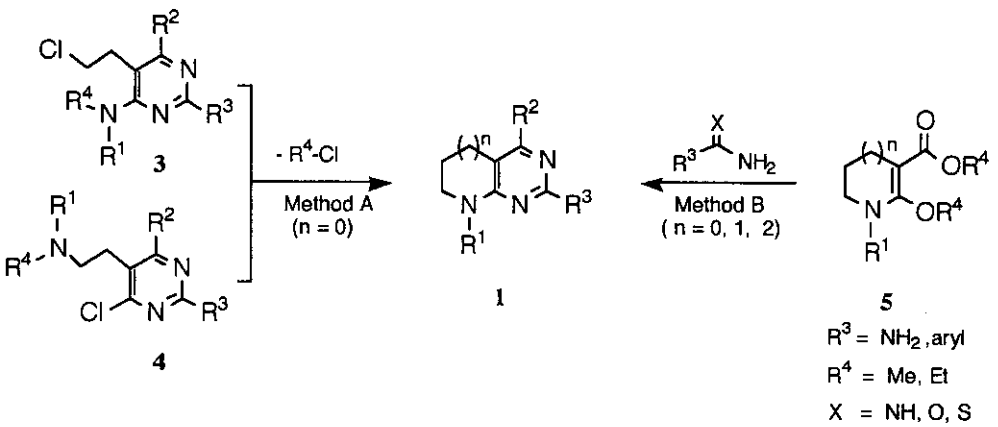
n = 1, 2
R^1 = H, alkyl, sugar residue
R^2 = H, OH
R^3 = H, OH, SH, NH_2

Scheme 1

In fact, certain important antibiotics such as tubercidine, toyocamycine and sangivamycine possess a pyrrolo[2,3-*d*]pyrimidine substructure[1c-d] whereas 2,4-dioxopyrimido[4,5-*b*]-quinoline constitutes the framework of NADPH cofactors.[1e]

Nevertheless, only few methods leading to these compounds have been described so far in the literature. Thus pyrrolo[2,3-*d*]pyrimidines (**1**) (n=0) are obtained by dechloroalkylation of either **3**[2a,b] or **4**[3a,b] (Scheme 2, Method A).

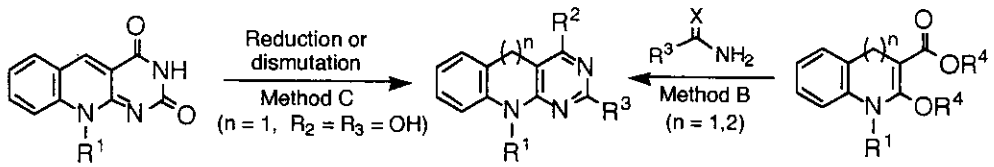
Another approach uses a condensation between cyclic ketene *N,O*-acetal esters (**5**) (which are derived from the corresponding lactams) and 1,3-bis-nucleophiles such as urea, thiourea, amidines and guanidines[4a,b] (Scheme 2, Method B).



Scheme 2

In addition to the rather general methods outlined in Scheme 2, one can also quote a one-pot synthesis of 5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine by heating a mixture of pyrrolidone, formamide and $POCl_3$[5] as well as the rearrangement of 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*d*]azepines into 4-vinyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidines.[6]

As far as the benzoannulated analogs (**2**) (n=1,2) are concerned, they can be obtained from **7** in complete analogy to Method B.[7] Dihydro-5-azaflavines (**2**) (n=1) are also prepared by reduction of 5-dezaflavines (**6**) using $NaBH_4$[1b] or via an enzymatic process.[8] A dismutation reaction of **6** has also been described[9a,b] (Scheme 3, Method C).



6 **2** **7**

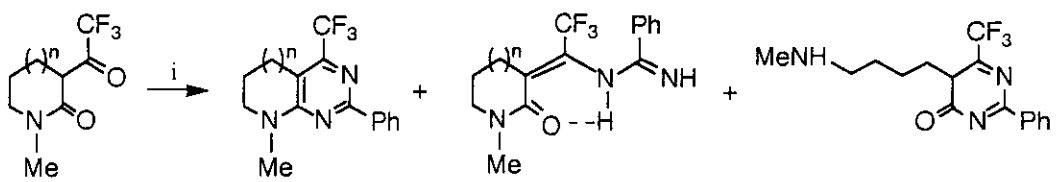
R^3 = NH_2
R^4 = Me, Et
X = NH, O, S

Scheme 3

This shows that the number of methods to access **1** and **2** are quite limited. Furthermore, the starting materials must be highly functionalized which severely limits the scope of these reactions.

Owing to the fact that 3-trifluoroacetyl-lactams (**8**) and -benzolactams (**9**) have become readily available[10] and they cyclize with bis-nucleophiles,[11] we have developed a practical one-step synthesis of trifluoromethylated pyrimidines using benzamidine. This condensation was also extended to other cyclic trifluoromethylated 1,3-diketones and 3-aroyl-2-pyrrolidinones.

The first attempts to cyclize **8a,b,c** with benzamidine hydrochloride failed but as it turned out, heating neat **8a,b,c** with benzamidine base at 100-120°C for a few hours led to the new [2,3-*d*]pyrimidines (**10a,b**) (Scheme 4, Table 1). Intermediates (**11a,c**) and product (**12**) were also obtained.



8a,b,c
n = 1,2,3

10a,b **11a,c** **12**

i : benzamidine, Δ, neat, 100 - 120°C

Scheme 4

Lactam[ref]	n	Conv. (%)	Yield **10** (%)[a]	Yield **11** (%)[a]	Yield **12** (%)[a]
8a[10]	0	49	28	7[b]	-
8b[10]	1	80	51	-	-
8c[10]	2	100	-	31	41

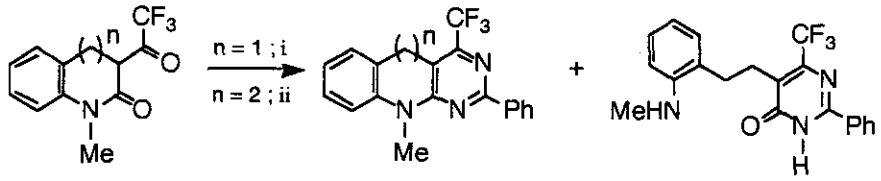
a) chromatography on silica gel (ether/MeOH); b) detected by ^{1}H and ^{13}C nmr

Table 1

These results show that the nature of condensation products depends strongly on the ring size. Also, the non-cyclized *N*-vinyl amidines (**11a,c**) (detected from **8a** and isolated from **8c**) are most probably the reaction intermediates.[5] Accordingly, **11c** cyclizes into **10c** when heated with $POCl_3$ (Scheme 6). 3-Trifluoroacetyl-ε-caprolactam (**8c**) gave mainly compound (**12**) (41% vs 31% of **11c**). It derives probably from intermediate (**11c**) followed by subsequent ring-opening of the lactam moiety. Nevertheless, it is surprising that no elimination of water occurs which would lead to the formation of pyrimidine (**10c**) as observed for **8a** and **8b** (Scheme 4 - Table 1).

The above heterocyclisation could not be extended either to acetamidine or to S-methylthiourea.

In order to define the scope of the heterocyclisation and in view of interesting biological activities of benzolactams,[1e,12] we have studied the behaviour of benzoannulated lactams (**9a,b**). 3,4-Dihydro-2*H*-quinolin-2-one (**9a**) affords a fair yield of the expected product (**13a**), whereas benzocaprolactam (**9b**) gives predominantly the ring-opening compound (**14**) (Scheme 5, Table 2).



9a,b **13a,b** **14**

i : benzamidine, Ph-Me, reflux
ii : benzamidine, Δ, neat, 100 - 120°C

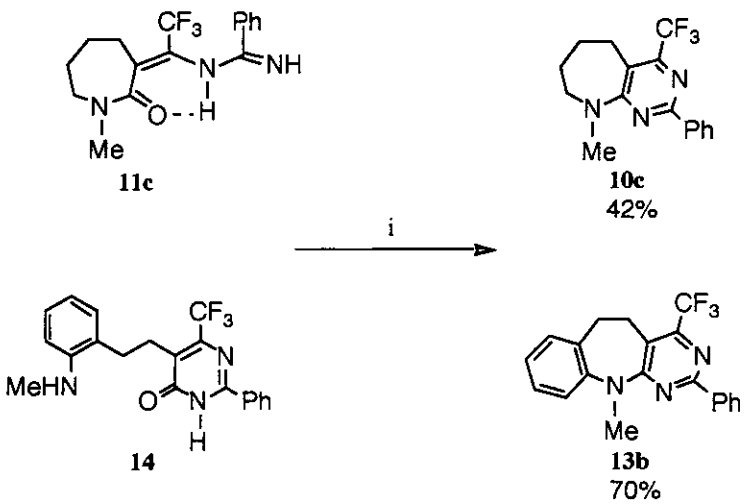
Scheme 5

Benzolactam[ref]	n	Conv. (%)	Yield **13** (%)[a)]	Yield **14** (%)[a)]
9a[10]	1	100	60	-
9b[10]	2	92	12	35

a) chromatography on silica gel (pet. ether/ether)

Table 2

The condensation of amidines followed by ring-opening has already been noticed in the cases of 3-benzoyl-3,4-dihydro-1-thiacoumarin[13a] and 7*H*-furo-[3,2-*g*]-benzopyranes.[13b] Similarly to **11c**, **14** is converted to **13b** by treatment with $POCl_3$ (Scheme 6).

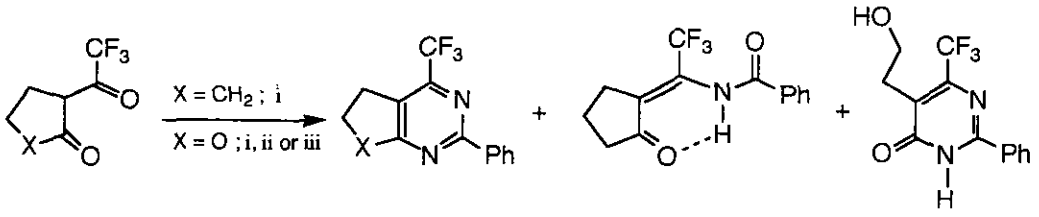


i : $POCl_3$ excess, reflux, 1 h

Scheme 6

Next we have examined the heterocyclisation with benzamidine and trifluoroacetyl-cyclopentanone (**15a**), -butyrolactone (**15b**) and 3-aroyl-2-pyrrolidinones (**17a,b**). Although **15a** and **15b** are known,[14a,b] we developed an improved procedure of their preparation.[10]

As we found, **15a** affords modest yields of pyrimidine (**18a**) and benzamidoenamine (**19**) whereas lactone (**16**) undergoes partly or entirely a ring-opening leading to 2-hydroxy-ethylpyrimidinone (**20**) (Scheme 7, Table 3).



15 a,b **18a,b** **19** **20**

i : benzamidine, cat APTS, Ph–Me, reflux
ii : benzamidine, Δ, neat, 100 - 140 °C
iii : 1) EtONa, EtOH, 25°C ; 2) benzamidine, EtOH, reflux

Scheme 7

Substrat[ref]	X	Method[a)]	Yield **18** (%)	Yield **19** (%)	Yield **20** (%)
15a[14a]	CH_2	i	34	18	-
15b[14b]	O	i	19	-	18
		ii	19	-	35
		iii	-	-	25

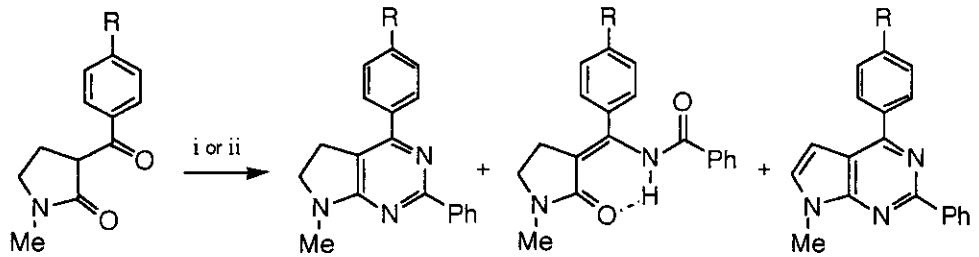
a) Chromatography on silica gel (pet. ether/ether)

Table 3

It should be noted that heterocyclisations with 3-acyllactones generally proceed with ring-opening of the lactone moiety.[15,16a,b] Accordingly, **18b** should be formed *via* 2-hydroxyethylpyrimidine (**20**) which is the only product when the lactone ring is opened using sodium ethoxide (Table 3, method iii). Similar sequences are frequently used in heterocyclic chemistry.[15,17] Compound (**20**) has an enolisable amide function and under favourable experimental conditions (Scheme 7, Table 3 : method i or ii), recyclisation leads to a small amount (19 %) of **18b**. This process, however little efficient, takes place under mild conditions. Generally, cyclodehydration into pyrimidines takes place only when concentrated H_2SO_4, $POCl_3$ or $SOCl_2$ is applied.[18a-c]

We have also studied the heterocyclisation of 3-aroyl-2-pyrrolidinones (**17a,b**). Although the product (**17a**) has already been described in the literature,[19] we synthesized the precursors (**17a,b**) using a Claisen condensation.[20] Their cyclisation proceeds in complete

analogy with **8,9,15a,b** to give pyrrolo[2,3-*d*]pyrimidines but the yields of **21a,b** and **23** are very low (Scheme 8, Table 4). Even when starting materials are heated without solvent for a few hours the conversion is lower than 50 %.



17a,b **21a,b** **22a,b** **23**

i : benzamidine,cat APTS, Ph–Me, reflux
ii : benzamidine, Δ, neat, 120 - 150°C

Scheme 8

pyrrolidinone[ref]	R	Method	Conv. (%)	Yield **21** (%)	Yield **22** (%)	Yield **23** (%)
17a[20]	H	i[a)]	19	5	8	-
		ii[a)]	90[b)]	-	-	-
17b[20]	CF_3	i[c)]	18	-	-	5
		ii[a)]	48	7[d)]	13[d)]	-

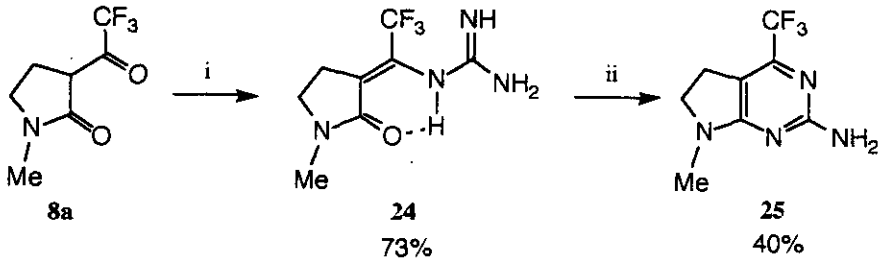
a) chromatography on silica gel (ether/MeOH); b) fragmentation; c) chromatography on silica gel (pet. ether/ether); d) detected by ^1H and ^{19}F nmr but not isolated

Table 4

Non-cyclic *N*-benzoylenamides (**22a,b**) are also present and two new features are observed. Namely, **21b** oxidizes spontaneously to 7-deazapurine (**23**) (Table 4 : R = CF_3, method i) and a fragmentation to 3-(phenylaminomethylene) pyrrolidone accompanies the process (Table 4 : R = H, method ii). Similar observations have been done during condensations of 3-trifluoroacetyllactams with various nucleophiles.[21]

In order to extend the reaction to other 1,3-bis-nucleophiles we also tried guanidine which was prepared from its carbonate and sodium ethoxide. Its treatment with **8a** leads to

guanidyl enamine (**24**). This compound is isolated in a good yield and can be cyclized to **25** using $POCl_3$ (Scheme 9).



8a **24** 73% **25** 40%

i : 1) EtONa, EtOH, 25°C ; 2) guanidine carbonate, EtOH, reflux
ii : $POCl_3$ excess, reflux, 1 h

Scheme 9

In conclusion, we have prepared a series of new trifluoromethylated pyrimidines in one step *via* an original procedure. Several reaction intermediates could be isolated, characterized and in some cases (**11c, 14** and **24**) cyclized into pyrimidines upon treatment with phosphorus oxychloride. The cyclization with guanidines (Scheme 9) could be extended to other β-trifluoroacetyl-lactams and -benzolactams.

EXPERIMENTAL

Mp were taken using a Dr. Tottoli apparatus and are uncorrected. Ir and mass spectra were measured on a Perkin-Elmer 1710 and A Finnigan Mat TSQ 70 apparatus, respectively. The ^1H, ^{13}C and ^{19}F nmr spectra were run on a Bruker AM 500 spectrometer at 500.13 MHz (^1H) and 125.77 MHz (^{13}C) or with Varian VXR-200 and Gemini-200 spectrometers at 200 MHz (^1H), 188.2 MHz (^{19}F) and 50.3 MHz (^{13}C), using 5 mm probes. The TMS signal was taken as an internal reference for the ^1H and ^{13}C spectra, while $CFCl_3$ was used as an internal reference for the ^{19}F spectra. Most of the ^{13}C nmr spectra were obtained from proton coupled or proton noise decoupled spectra. For molecules (**14**) and (**21a**), unambigous assignments were obtained by use of the two-dimensional ^1H-^{13}C heteronuclear chemical shift correlation spectroscopy.[22,23] For the ^1J connectivities, we have assumed an average one bond carbon-proton coupling constant of

about 135 Hz (fixed delays durations : Δ_1 = 1/2 ($^1J_{CH}$) = 3.6 Msec; Δ_2 = 1/4 ($^1J_{CH}$) = 1.8 Msec). For the long-range ^1H-^{13}C connectivities, we have chosen averaged ^{13}C-^1H coupling constant of about 12.5 Hz (fixed delays : Δ_1 = 1/2 ($^nJ_{CH}$) = 40 Msec; Δ_2 = 1/4 ($^nJ_{CH}$) = 20 Msec. The two-dimensional data matrix were submitted to a Lorentz-Gauss transformation[22,23] in the t_1 dimension and to a sinusoïdal multiplication[22,23] in the t_2 dimension prior to Fourier transformation ("power" spectrum calculation in all cases). We have also used the double-quantum filtered correlation spectroscopy (DQF-COSY)[22-24] to verify or to assign some of the ^1H resonances. The DQF-COSY experiments have been acquired using the TPPI (Time-Proportional Phase Incrementation)[22,23,25] and transformed in the phase-sensitive mode.[22,23,25] Chemical shifts are in ppm on the δ scale and coupling constants J are given in Hz.

Free benzamidine base was obtained from the commercial hydrochloride using 1N NaOH in CH_2Cl_2 and drying over $MgSO_4$.

*General Procedure for Pyrimidines (**10a,b; 13b; 18b and 21b.**)* A stirred liquid mixture of 1,3-dicarbonyl compound (**8a-c, 9b, 15b** or **17b** - 10 mmol, 1 eq.) and an excess of benzamidine (2-4 eq.) is heated up to 100-150°C during 4-10 hours. Ether and some methanol are added to the cooled product. The solution is washed twice with brine, dried over $MgSO_4$ and evaporated. The resulting oil is purified on silica gel to give the above mentioned products and also the by-products (**11a,c**; **12**; **14** and **20**).

*1-Methyl-7-phenyl-5-trifluoromethylpyrrolo[2,3-d]pyrimidine (**10a**).* mp > 240°C. Ir (KBr) : 3062, 3036, 2962, 2938, 2899, 1608, 1576, 1505, 1482, 1379, 1038. Ms (m/z) : 279, 233, 149, 98, 69. ^1H Nmr (DMSO-d_6; 500 MHz; 30°C) : δ 2.9-3.0 (m, 2H), 3.08 (s, 3H), 3.57 (t, 2H, J = 6.0 Hz), 7.3-7.4 (m, 1H), 7.5-7.6 (m, 1H), 8.26 (dd, 1H, J = 7.9 and 2.3 Hz). ^{13}C Nmr (DMSO-d_6; 500 MHz; 30°C) : δ 22.7 (tm, ^4J_F = 2.3 and ^1J_H = 135.7 Hz), 39.0, 49.8 (tm, ^1J_H = 141.3 Hz), 113.7 (sm, ^3J_F = 2.4 Hz), 122.6 (qs, ^1J_F = 276.6 Hz), 127.1 (dddd, ^1J_H = 161.5, ^3J_H = 6.0, 6.0 and ^2J_H = 1.6 Hz), 127.6 (ddm, ^1J_H = 160.5 and ^3J_H = 6.8 Hz), 128.7 (dt, ^1J_H = 163.8 and ^3J_H = 6.0 Hz), 138.9 (st, ^3J_H = 4.4 Hz), 148.3 (qm, ^2J_F = 28.2 Hz), 162.0 (sm), 165.2 (sm). ^{19}F Nmr (DMSO-d_6; 25°C) : δ -63.5 (s).

*3-(1-Benzamidino-2,2,2-trifluoroethylidene)-1-methyl-2-pyrrolidinone (**11a**).* ^{1}H Nmr (DMSO-d_6; 500 MHz; 30°C) : δ 7.3-7.4 (m, 2H), 7.5-7.6 (m, 2H), 7.6-7.7 (m, 1H). ^{13}C Nmr (DMSO-d_6; 500 MHz; 30°C) : δ 20.9, 43.9, 46.9, 112.7, 127.9 (dm, $^{1}J_H$ = 158.8 Hz), 129.1 (dt, $^{1}J_H$ = 160.0 and $^{3}J_H$ = 7.9 Hz), 129.5 (sm), 131.5 (dm, $^{1}J_H$ = 162.8 Hz), 171.8 (sm), 174.3 (sm). ^{19}F Nmr (DMSO-d_6; 25°C) : δ -63.8 (s).

*1-Methyl-7-phenyl-5-trifluoromethylpiperidino[2,3-d]pyrimidine (**10b**).* mp 105-107°C. Ir (KBr) : 3054, 3010, 2960, 2942, 2967, 1581, 1553, 1524, 1454, 1175. Ms (m/z) : 293, 264, 121, 105, 77, 51. ^{1}H Nmr ($CDCl_3$) : δ 1.99 (q_t, 2H, J = 5.9 Hz), 2.89 (tm, 2H, J = 5.8 Hz), 3.31 (s, 3H), 3.48 (tm, 2H, J = 5.9 Hz), 7.4-7.5 (m, 3H), 8.3-8.4 (m, 2H). ^{13}C Nmr ($CDCl_3$) : δ 19.8 (ttm, $^{1}J_H$ = 130.7 and $^{2}J_H$ = 4.1 Hz), 21.9 (tm, $^{4}J_F$ = 2.7 and $^{1}J_H$ = 131.4 Hz), 36.2 (qt, $^{6}J_F$ = 1.5, $^{1}J_H$ = 138.5 and $^{3}J_H$ = 1.7 Hz), 48.8 (tm, $^{1}J_H$ = 139.5 Hz), 110.1 (stm, $^{3}J_F$ = 1.1 and $^{2}J_H$ = 5.9 Hz), 122.1 (qs, $^{1}J_F$ = 276.4 Hz), 127.7 (ddd, $^{1}J_H$ = 163.9, $^{3}J_H$ = 6.6 and $^{2}J_H$ = 2.4 Hz), 127.9 (dm, $^{1}J_H$ = 161.7 Hz), 130.0 (dtt, $^{1}J_H$ = 160.2, $^{3}J_H$ = 7.9 and $^{2}J_H$ = 1.3 Hz), 137.6 (st, $^{3}J_H$ = 4.4 Hz), 148.6 (qt, $^{2}J_F$ = 32.5 and $^{3}J_H$ = 3.0 Hz), 160.3 (sm), 160.9 (sm). ^{19}F Nmr ($CDCl_3$) : δ -66.0 (s). Anal. Calcd for $C_{15}H_{14}N_3F_3$: C, 61.43; H, 4.81; N, 14.33. Found C, 61.18; H, 4.75; N, 14.09.

*3-(1-Benzamidino-2,2,2-trifluoroethylidene)-1-methyl-2-caprolactam (**11c**).* mp 195-198°C. Ir (KBr) : 3440-3410, 2954, 2939, 1589, 1574, 1559, 1521, 1506, 1451, 1163. Ms (m/z) : 326, 325, 282, 254, 104, 84, 57, 44. ^{1}H Nmr (DMSO-d_6; 500 MHz; 30°C) : δ 1.60 (q_t, 2H, J = 7.6 Hz), 1.73 (q_t, 2H, J = 6.8 Hz), 2.58 (m, 2H), 2.64 (s, 3H), 2.96 (t, 2H, J = 6.5 Hz), 5.3-5.9 (br s, NH_2), 7.3-7.4 (m, 3H), 8.29 (dd, 2H, J = 6.6 and 2.1 Hz). ^{13}C Nmr (DMSO-d_6; 500 MHz; 30°C) : δ 23.6 (tm, $^{4}J_F$ = 2.2 and $^{1}J_H$ = 131.9 Hz), 25.3 (tm, $^{1}J_H$ = 126.3 Hz), 25.7 (tm, $^{1}J_H$ = 126.2 Hz), 33.8 (qt, $^{1}J_H$ = 139.1 and $^{3}J_H$ = 2.2 Hz), 48.9 (tm, $^{1}J_H$ = 138.5 Hz), 119.8 (sm, $^{3}J_F$ = 1.2 Hz), 122.9 (qs, $^{1}J_F$ = 276.6 Hz), 127.7 (ddd, $^{1}J_H$ = 161.2, $^{3}J_H$ = 5.4 and $^{3}J_H$ = 5.4 Hz), 127.8 (ddm, $^{1}J_H$ = 160.7 and $^{3}J_H$ = 6.8 Hz), 129.3 (dt, $^{1}J_H$ = 159.9 and $^{3}J_H$ = 8.0 Hz), 138.8 (st, $^{3}J_H$ = 6.5 Hz), 148.6 (qt, $^{2}J_F$ = 31.0 and $^{3}J_H$ = 4.5 Hz), 161.6 (sm), 175.0 (st, $^{3}J_H$ = 4.8 Hz). ^{19}F Nmr (DMSO-d_6; 25°C) : δ -62.5 (s).

*5-(4-Methylaminobutyl)-2-phenyl-6-trifluoromethylpyrimidin-5H-(4)-one (**12**).* mp 91-92°C. Ir (KBr) : 3205, 3072, 3056, 2976, 2938, 1618, 1588, 1570, 1519, 1450, 1122. Ms (m/z) : 325, 256, 254, 103, 77, 69. ^{1}H Nmr ($CDCl_3$) : δ 1.6-1.9 (m, 4H), 2.5-2.8 (m, 4H), 2.90 (s, 3H), 3.7-4.0 (m, 2H), 7.0-7.3 (m, 3H), 8.1-8.2 (d, 2H, J = 7.7 Hz). ^{13}C Nmr ($CDCl_3$) : δ 22.0 (tm, $^{4}J_F$ = 2.0 and $^{1}J_H$ = 131.8 Hz), 22.5 (tm, $^{1}J_H$ = 125.7 Hz), 27.0 (tm, $^{1}J_H$ = 125.8 Hz), 39.5 (dm, $^{1}J_H$= 136.8 Hz), 50.0 (qt, $^{6}J_F$ = 2.0, $^{1}J_H$ = 140.5 and $^{3}J_H$ = 2.0 Hz), 52.2 (tm, $^{1}J_H$ = 138.1 Hz), 122.7 (qs, $^{1}J_F$ = 276.6 Hz), 127.2 (dm, $^{1}J_H$ = 161.2 Hz), 128.4 (dm, $^{1}J_H$ = 160.4 Hz), 129.2 (sm), 131.3 (dm, $^{1}J_H$ = 160.1 Hz), 149.6 (qm, $^{2}J_F$ = 29.2 Hz), 161.9 (sm), 165.1 (sm). ^{19}F Nmr ($CDCl_3$) : δ -64.7 (s).

*11H-5,6-Dihydro-2-phenyl-11-methyl-4-trifluoromethylpyrimido[4,5-b]benzo[f]azepine (**13b**).* mp 110-112°C. Ir (KBr) : 3068, 2977, 2944, 2928, 1555, 1533, 1497, 1480, 1436, 1412, 1390, 1224. Ms (m/z) : 356, 355, 341, 340, 286, 103, 91, 77. ^{1}H Nmr ($CDCl_3$) : δ 3.0-3.5 (m, 4H), 3.73 (s, 3H), 7.1-7.3 (m, 4H), 7.4-7.5 (m, 3H), 8.4-8.6 (m, 2H). ^{13}C Nmr ($CDCl_3$) : δ 28.6 (tm, $^{5}J_F$ = 1.3 and $^{1}J_H$ = 128.6 Hz), 29.1 (tm, $^{4}J_F$ = 2.9 and $^{1}J_H$ = 132.2 Hz), 39.6 (qs, $^{1}J_H$ = 139.8 Hz), 113.8 (sm, $^{3}J_F$ = 2.6 Hz), 120.6 (qs, $^{1}J_F$ = 276.9 Hz), 121.1 (ddd, $^{1}J_H$ = 158.9, $^{3}J_H$ = 7.1 and $^{2}J_H$ = 1.4 Hz), 123.9 (dm, $^{1}J_H$ = 160.1 Hz), 125.7 (ddd, $^{1}J_H$ = 161.0, $^{3}J_H$ = 7.3 and $^{2}J_H$ = 1.8 Hz), 126.4 (dm, $^{1}J_H$ = 161.7 Hz), 126.5 (dm, $^{1}J_H$ = 162.0 Hz), 126.9, 129.2 (dtm, $^{1}J_H$ = 161.8 and $^{3}J_H$ = 7.6 Hz), 135.4 (sm), 135.6 (sm), 143.4 (sm), 151.0 (qm, $^{2}J_F$ = 31.1 Hz), 158.0 (sm), 159.8 (sm). ^{19}F Nmr ($CDCl_3$) : δ -66.2 (s).

*5-(o-Methylaminophenylethyl)-2-phenyl-6-trifluoromethylpyrimidin-4-one (**14**).* mp 241-242°C. Ir (KBr) : 3458, 3066, 3013, 2935, 1660, 1606, 1585, 1560, 1512, 1204. Ms (m/z) : 374, 373, 253, 210, 120, 91, 77. ^{1}H Nmr (DMSO-d_6; 500 MHz; 40°C) : δ 2.5-2.6 (m, 2H), 2.7-2.8 (m, 2H), 2.81 (s, 3H), 4.0-7.0 (br s, NH_2), 6.5-6.6 (m, 2H), 6.96 (dd, 1H, J = 7.5 and 1.3 Hz), 7.07 (ddd, 1H, J = 7.7, 7.7 and 1.4 Hz), 7.54 (dd, 2H, J = 7.8 and 6.5 Hz), 7.60 (tt, 1H, J = 7.2 and 1.0 Hz), 8.14 (d, 2H, J = 7.3 Hz). ^{13}C Nmr (DMSO-d_6; 500 MHz; 40°C) : δ 24.6 (tm, $^{1}J_H$ = 128.5 Hz), 29.88 (tm, $^{1}J_H$ = 124.2 Hz), 29.95 (qs, $^{1}J_H$ = 134.8 Hz), 108.9 (dd, $^{1}J_H$ = 155.6 and $^{3}J_H$ = 7.8 Hz), 115.4 (dd, $^{1}J_H$ = 160.4 and $^{3}J_H$ = 7.7 Hz), 119.5 (qs, $^{1}J_F$ = 276.5 Hz), 124.0 (sm), 125.7 (sm), 127.3 (ddd, $^{1}J_H$ = 156.9, $^{3}J_H$ = 7.6 and

^2J_H = 1.1 Hz), 127.7 (ddd, ^1J_H = 161.5, ^3J_H = 7.3 and 5.7 Hz), 128.3 (ddtd, ^1J_H = 154.1, ^3J_H = 8.0, 5.2 and ^2J_H = 2.0 Hz), 128.6 (dd, ^1J_H = 162.5 and ^3J_H = 7.6 Hz), 131.3 (st, ^3J_H = 7.7 Hz), 132.0 (dt, ^1J_H = 162.1 and ^3J_H = 7.5 Hz), 146.7 (qt, ^2J_F = 32.3 and ^3J_H = 4.4 Hz), 147.1 (sm), 155.3 (sm), 164.2 (st, ^3J_H = 5.5 Hz). ^{19}F Nmr (DMSO-d_6) : δ -65.2 (s). Anal. Calcd for $C_{20}H_{18}N_3OF_3$: C, 64.34; H, 4.86; N, 11.25. Found C, 63.95; H, 4.78; N, 11.22.

*5,6-Dihydro-4-trifluoromethylfurano[2,3-d]pyrimidine (**18b**).* mp 182°C. Ir (KBr) : 3032, 2986, 2935, 1614, 1597, 1574, 1483, 1456, 1443, 1431, 1396, 1388, 1139, 973. Ms (m/z) : 267, 266, 247, 216, 197, 170, 140, 115, 103, 77, 69. ^{1}H Nmr ($CDCl_3$) : δ 3.49 (t, 2H, J = 8.5 Hz), 4.81 (t, 2H, J = 8.6 Hz), 7.4-7.6 (m, 3H), 8.45 (dm, 2H, J = 7.7 Hz). ^{13}C Nmr (DMSO-d_6; 500 MHz; 40°C) : δ 25.3 (t, ^1J_H = 138.8 Hz), 71.1 (t, ^1J_H = 155.5 Hz), 115.8 (sm), 120.9 (qs, ^1J_F = 274.4 Hz), 127.7 (ddd, ^1J_H = 161.0, ^3J_H = 7.3 and 5.7 Hz), 128.6 (dd, ^1J_H = 161.5 and ^3J_H = 6.9 Hz), 131.2 (dt, ^1J_H = 161.2 and ^3J_H = 7.6 Hz), 135.6 (st, ^3J_H = 7.0 Hz), 148.1 (qt, ^2J_F = 35.8 and ^3J_H = 2.2 Hz), 163.6 (sm), 177.1 (stt, ^3J_H = 2.8 and 2.7 Hz). ^{19}F Nmr (DMSO-d_6) : δ -66.7 (s).

*5-(2-Hydroxyethyl)-2-phenyl-6-trifluoromethylpyrimidin-4-one (**20**).* mp 223°C. Ir (KBr) : 3371, 3175, 3079, 3056, 2962, 2952, 1654, 1605, 1578, 1557, 1402. ^{1}H Nmr (DMSO-d_6) : δ 2.78 (td, 2H, J = 7.2 and 1.6 Hz), 3.52 (t, 2H, J = 7.2 Hz), 7.33 (br s, NH or OH), 7.43 (t, 1H, J = 7.8 Hz), 7.52 (dd, 2H, J = 7.7 and 7.6 Hz), 7.94 (br s, OH or NH), 8.11 (dd, 2H, J = 7.8 and 1.6 Hz). ^{13}C Nmr (DMSO-d_6) : δ 29.0 (tm, ^1J_H = 130.2 and ^4J_F = 1.9 Hz), 59.4 (ttd, ^1J_H= 142.5, ^2J_H = 6.2 and 1.5 Hz), 122.1 (qs, ^1J_F = 276.7 Hz), 122.3 (sm, ^3J_F= 0.9 Hz), 127.8 (dm, ^1J_H = 161.7 Hz), 128.7 (ddd, ^1J_H = 162.0, ^3J_H = 7.2 and ^2J_H = 1.7 Hz), 131.7 (dt, ^1J_H = 161.5 and ^3J_H = 7.5 Hz), 132.9 (st, ^3J_H = 7.4 Hz), 147.8 (qt, ^2J_F= 31.8 and ^3J_H = 4.7 Hz), 156.7 (stq, ^3J_H = 3.7 and ^4J_F = 1.2 Hz), 165.8 (st, ^3J_H = 5.2 Hz). ^{19}F Nmr (CD_3OD) : δ -64.1 (s).

*General Procedure for Pyrimidines (**13a; 18a,b; 21a and 23**).* A solution of 1,3-dicarbonyl compound (**9a**; **15a,b**; **17a** or **17b**) (10 mmol, 1 eq.), benzamidine (10-30 mmol, 1-3 eq.) and a catalytic amount of *p*-toluenesulfonic acid is refluxed during 10-20

hours. The solution is then cooled, diluted with ether and washed with water. The aqueous phase is saturated with NaCl and extracted twice with ether. The combined organic phase is washed with brine, dried over $MgSO_4$ and evaporated. A chromatography on silica gel gives pyrimidines (**13a**; **18a,b**; **21a** or **23**). By-products (**19**; **20** and **22a**) are also isolated and characterized.

*1-Methyl-2-phenyl-4-trifluoromethyltetrahydropyrimido[4,5-b]quinoline (**13a**).* mp 172-173°C. Ir (KBr) : 3072, 3041, 2970, 2930, 1603, 1587, 1574, 1551, 1482, 1444, 1417, 1397, 1179. Ms (m/z) : 342, 341, 340, 322, 272, 217, 123, 103, 77. ^{1}H Nmr ($CDCl_3$) : δ 3.70 (s, 3H), 4.24 (s, 2H), 7.0-7.1 (m, 2H), 7.2-7.3 (m, 2H), 7.4-7.5 (m, 3H), 8.4-8.5 (m, 2H). ^{13}C Nmr ($CDCl_3$) : δ 26.6 (tm, ^4J_F = 2.7 and ^1J_H = 133.3 Hz), 30.9 (qs, ^6J_F = 2.2 and ^1J_H = 139.7 Hz), 110.0 (st, ^3J_F = 1.3 and ^2J_H = 6.9 Hz), 113.8 (ddm, ^1J_H = 159.9 and ^3J_H = 7.9 Hz), 121.0 (sm), 121.9 (qs, ^1J_F = 276.6 Hz), 123.0 (ddd, ^1J_H = 162.8, ^3J_H = 7.1 and ^2J_H = 1.1 Hz), 127.8 (m), 128.1 (m), 128.6 (m), 130.8 (dt, ^1J_H = 162.3 and ^3J_H = 7.5 Hz), 137.0 (sm), 139.7 (sm), 150.5 (qm, ^2J_F= 32.9 Hz), 159.7 (sm), 161.5 (sm). ^{19}F Nmr ($CDCl_3$) : δ -66.6 (s). Anal. Calcd for $C_{19}H_{14}N_3F_3$: C, 66.85; H, 4.13; N, 12.31. Found C, 66.13; H, 3.95; N, 12.28.

*2-Phenyl-6-trifluoromethylcyclopenta[d]pyrimidine (**18a**).* mp 106-107°C. Ir (KBr) : 2981, 2966, 2931, 2909, 1595, 1575, 1558, 1457, 1422, 1387, 1186. Ms (m/z) : 265, 264, 245, 236, 216, 195, 169, 104, 103, 77, 69. ^{1}H Nmr ($CDCl_3$; 500 MHz) : δ 2.22 (qt, 2H, J = 7.7 Hz), 3.13 (dd, 2H, J = 8.1 and 7.7 Hz), 3.17 (tq, 2H, J = 7.5 and ^5J_F = 1.8 Hz), 7.4-7.5 (m, 3H), 8.47 (dm, 2H, J = 7.1 Hz). ^{13}C Nmr ($CDCl_3$) : δ 22.0 (ttt, ^1J_H = 132.4, ^2J_H =3.2 and 3.2 Hz), 28.3 (tm, ^4J_F = 1.6 and ^1J_H = 133.1 Hz), 34.1 (ttt, ^1J_H = 132.2, ^2J_H = 5.6 and ^3J_H = 2.8 Hz), 121.5 (qs, ^1J_F = 275.5 Hz), 128.3 (ddd, ^1J_H = 161.0, ^3J_H = 7.2 and ^2J_H = 2.4 Hz), 128.5 (ddd, ^1J_H = 160.7, ^3J_H = 7.0 and ^2J_H = 2.2 Hz), 129.3 (sm, ^3J_F = 1.4 Hz), 130.9 (dt, ^1J_H = 160.4 and ^3J_H = 7.7 Hz), 136.7 (st, ^3J_H = 7.0 Hz), 150.0 (qm, ^2J_F = 36.1 Hz), 163.5 (sm), 179.2 (sm). ^{19}F Nmr ($CDCl_3$) : δ -68.6 (s). Anal. Calcd for $C_{14}H_{11}N_2F_3$: C, 63.63; H, 4.20; N, 10.60. Found C, 63.84; H, 4.41; N, 10.53.

*2-(1-Benzamido-2,2,2-trifluoroethylidene)cyclopentanone (**19**).* mp 161-162°C. Ir (KBr) 3266, 2973, 1722, 1695, 1672, 1602, 1585, 1538, 1509, 1490, 1365, 1120. Ms (m/z) : 284, 283, 263, 214, 163, 106, 105, 77. ^{1}H Nmr (CD_3OD) : δ 2.0-3.0 (m, 6H), 7.5-7.7 (m, 3H), 7.90 (dd, 2H, J = 7.1 and 1.5 Hz). ^{13}C Nmr (DMSO-d_6) : δ 22.0 (ttt, $^{1}J_H$ = 132.0, $^{2}J_H$ = 3.3 and 3.3 Hz), 31.1 (tm, $^{1}J_H$ = 132.0 Hz), 35.7 (tt, $^{1}J_H$ = 133.4 and $^{2}J_H$ = 3.0 Hz), 122.4 (qd, $^{1}J_F$ = 271.8 and J_H = 4.5 Hz), 125.4 (qm, $^{2}J_F$ = 32.6 Hz), 128.6 (dm, $^{1}J_H$ = 162.3 Hz), 128.7 (dm, $^{1}J_H$ = 163.3 Hz), 132.0 (st, $^{3}J_H$ = 7.6 Hz), 133.3 (dtt, $^{1}J_H$ = 162.3, $^{3}J_H$ = 7.6 and $^{2}J_H$ = 1.2 Hz), 144.6 (sm, $^{3}J_F$ = 4.3 Hz), 166.3 (sm), 168.4 (sm). ^{19}F Nmr (CD_3OD) : δ -63.4 (s).

*1-Methyl-5,7-diphenylpyrrolo[2,3-d]pyrimidine (**21a**).* mp 172-173°C. Ir (KBr) : 3072, 2912, 2869, 1601, 1567, 1537, 1492, 1449, 1411, 1378, 1251. Ms (m/z) : 288, 287, 286, 248, 183, 140, 104, 98, 77, 44. ^{1}H Nmr (DMSO-d_6; 500 MHz; 35°C) : δ 3.03 (s, 3H), 3.31 (t, 2H, J = 8.3 Hz), 3.63 (t, 2H, J = 8.3 Hz), 7.4-7.5 (m, 4H), 7.52 (ddd, 2H, J = 7.7, 7.7 and 1.5 Hz), 8.03 (dd, 2H, J = 7.6 and 1.5 Hz), 8.44 (dd, 2H, J = 7.5 and 1.7 Hz). ^{13}C Nmr (DMSO-d_6; 500 MHz; 35°C) : δ 25.3 (tm, $^{1}J_H$ = 135.4 Hz), 30.9 (qs, $^{1}J_H$ = 137.5 Hz), 50.5 (ttq, $^{1}J_H$ = 142.9, $^{2}J_H$ = 3.2 and $^{3}J_H$ = 3.2 Hz), 114.6 (stt, J_H = 2.4 and 1.8 Hz), 127.5 (dddd, $^{1}J_H$= 159.8, $^{3}J_H$ = 7.2, 7.2 and $^{2}J_H$ = 1.8 Hz), 127.7 (ddd, $^{1}J_H$ = 159.5, $^{3}J_H$ = 6.8 and 6.8 Hz), 128.1 (ddd, $^{1}J_H$ = 160.9, $^{3}J_H$ = 7.5 and $^{2}J_H$ = 1.1 Hz), 128.4 (dd, $^{1}J_H$ = 160.5 and $^{3}J_H$ = 7.5 Hz), 129.1 (dt, $^{1}J_H$ = 160.9 and $^{3}J_H$ = 7.5 Hz), 129.8 (dt, $^{1}J_H$ = 160.5 and $^{3}J_H$ = 7.9 Hz), 137.7 (st, $^{3}J_H$ = 7.4 Hz), 138.3 (st, $^{3}J_H$ = 6.1 Hz), 152.9 (sm), 161.7 (sdd, $^{3}J_H$ = 3.9 and 3.3 Hz), 168.3 (sm). Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found C, 79.17; H, 5.82; N, 14.60.

*3-(1-Benzamido-1-phenylmethylene)-1-methyl-2-pyrrolidinone (**22a**).* mp > 240°C. Ir (KBr) : 3300-3100, 3057, 2931, 2883, 1685, 1651, 1598, 1520, 1498, 1485, 1466, 1444, 1404, 1291. Ms (m/z) : 307, 306, 201, 105, 86, 84, 77. ^{1}H Nmr ($CDCl_3$) : δ 2.66 (t, 2H, J = 7.4 Hz), 2.97 (s, 3H), 3.40 (t, 2H, J = 7.3 Hz), 7.3-7.5 (m, 8H), 8.00 (dd, 2H, J = 7.8 and 1.5 Hz), 12.3 (br s, NH). ^{13}C Nmr ($CDCl_3$) : δ 22.6 (tdd, $^{1}J_H$ = 135.4, $^{2}J_H$ = 6.0 and 6.0 Hz), 29.8 (qt, $^{1}J_H$ = 138.5 and $^{3}J_H$ = 3.0 Hz), 46.8 (tm, $^{1}J_H$ = 142.5 Hz), 111.3 (sm), 127.2 (dm, $^{1}J_H$ = 160.5 Hz), 127.5 (dm, $^{1}J_H$ = 159.9 Hz), 128.0 (ddd, $^{1}J_H$ = 159.8, $^{3}J_H$ = 6.6 and

^2J_H = 2.7 Hz), 128.1 (dm, ^1J_H = 160.6 Hz), 128.5 (dm, ^1J_H = 160.5 Hz), 131.7 (dt, ^1J_H = 160.4 and ^3J_H = 7.8 Hz), 134.0 (sm), 135.8 (sm), 142.7 (sm), 164.0 (sm), 170.5 (sm).

2-Phenyl-4-(p-trifluoromethylphenyl)-7-methylpyrrolo[2,3-d]pyrimidine (23). mp 172-174°C. Ir (KBr) : 3195, 3057, 3028, 2924, 2855, 1605, 1573, 1541, 1503, 1486, 1350, 1273. Ms (m/z) : 353, 311, 309, 281, 268, 234, 104, 103, 77. ^{1}H Nmr (DMSO-d_6) : δ 6.2-6.3 (m, 1H), 7.2-7.7 (m, 8H), 8.30 (d, 2H, J = 7.5 Hz). ^{13}C Nmr (DMSO-d_6) : δ 39.8 (qs, ^1J_H = 140.0 Hz), 68.4 (dm, ^1J_H = 155.9 Hz), 126.2 (dm, ^3J_F = 3.5 and ^1J_H = 158.1 Hz), 127.0 (sm), 127.5 (ddm, ^1J_H = 160.5 and ^3J_H = 6.5 Hz), 128.0, 128.3, 128.5 (ddd, ^1J_H = 160.2, ^3J_H = 7.4 and ^2J_H =1.4 Hz), 130.1 (sm), 132.1, 133.2 (sm), 137.3 (qm, ^2J_F = 31.2 Hz), 144.1 (sm), 159.1 (sm), 159.3 (sm). ^{19}F Nmr (DMSO-d_6) : δ -60.5 (s).

3-(1-Guanidino-2,2,2-trifluoroethylidene)-1-methyl-2-pyrrolidinone (24). Guanidine carbonate (0.90 g, 5 mmol, 1 eq.) is added to a stirred mixture of 0.44 g (18 mmol, 3.6 eq.) NaH (60 %) in 20 ml of dry methanol. After 15 min, **8a** (0.98 g, 5 mmol, 1 eq.) in 10 ml of methanol is added and the mixture is refluxed during 12 h. Water (10 ml) is added and the precipitated solid is collected, washed with water and dissolved in boiling methanol. This solution is dried over $MgSO_4$ and evaporated. Yield of **24** : 0.86 g (73 %). The product is used as such for the preparation of **25**.

mp > 220°C. Ir (KBr) : 3419, 3365, 2929, 2887, 1659, 1594, 1507, 1386, 1288. Ms (m/z) : 236, 195, 187, 131, 126, 69, 44. ^{1}H Nmr (DMSO-d_6; 500 MHz; 40°C) : δ 2.50 (s, 3H), 2.5-2.7 (m, 2H), 3.2-3.4 (m, 2H and NH_2), 6.9 (br s, NH_2). ^{13}C Nmr (DMSO-d_6; 500 MHz; 40°C) : δ 21.0 (tm, ^4J_F = 2.1 and ^1J_H= 134.6 Hz), 29.1 (qs, ^1J_H = 137.2 Hz), 46.9 (tm, ^1J_H = 140.5 Hz), 92.5 (sm, ^3J_F = 1.9 Hz), 120.9 (qs, ^1J_F = 286.8 Hz), 157.2 (qm, ^2J_F = 32.5 Hz), 157.9 (sm), 173.6 (sm). ^{19}F Nmr (DMSO-d_6; 25°C) : δ -70.9 (s).

Cyclization of Intermediates (11c, 14, 24) by means of $POCl_3$. Azapropenylidene lactam (10 mmol, 1 eq.) is refluxed in 30 ml $POCl_3$ for 1 h. The resulting mixture is evaporated, the residue is diluted with ether, washed twice with water and dried over $MgSO_4$. A chromatography on silica gel using ether/methanol (**10c** : 25/75, **25** : 95/5) or pet. ether/ether (**13b** : 30/70) as eluent gives pyrimidines (**10c**, **13b** and **25**), respectively.

7-Amino-1-methyl-5-trifluoromethylpyrrolo[2,3-d]pyrimidine (25). mp > 220°C. Ir (KBr) : 3450, 3026, 2973, 2950, 1593, 1521, 1338, 1135. Ms (m/z) : 219, 218, 150, 122, 83, 69. ^{1}H Nmr (CD_3OD) : δ 2.99 (s, 3H), 3.0-3.2 (m, 2H), 3.44 (t, 2H, J = 6.3 Hz). ^{13}C Nmr (CD_3OD) : δ 24.9 (tt, $^{4}J_F$ = 3.3, $^{1}J_H$ = 134.0 and $^{2}J_H$ = 3.0 Hz), 30.1 (qs, $^{6}J_F$ = 1.5 and $^{1}J_H$ = 138.8 Hz), 45.0 (tm, $^{5}J_F$ = 1.5 and $^{1}J_H$= 141.6 Hz), 116.5 (sm, $^{3}J_F$ = 1.9 Hz), 120.5 (qt, $^{1}J_F$ = 274.1 and $^{4}J_H$ = 3.7 Hz), 120.6 (qt, $^{2}J_F$ = 38.7 and $^{3}J_H$ = 2.0 Hz), 134.5 (sm), 164.0 (st, $^{3}J_H$ = 2.9 Hz). ^{19}F Nmr (CD_3OD) : δ -65.3 (t, 3F, J = 3.7 Hz).

A two-step Synthesis of Pyrimidine (20) (Scheme 7, Table 3, Method iii). 3-Trifluoroacetyl-γ-butyrolactone **16** (0.72 g, 4 mmol, 1 eq.) is added to a stirred solution of 0.10 g (4 mmol, 1 eq.) of Na in 5 ml of ethanol. After 30 min at room temperature (0.49 g, 4 mmol, 1 eq.) of a benzamidine are added portionwise. The solution is refluxed for 3 h, then evaporated and dissolved in 10 ml of water. This mixture is extracted twice with ether and the extract is washed with brine, dried over $MgSO_4$ and evaporated. Chromatography (silica gel, ether then 95 ether/5 methanol) gives 0.28 g (25 %) of **20**.

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