

# Synthesis and Characterization of Novel (E)-1-(aylideneamino)-6-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile derivatives

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## ABSTRACT

We have described simple facile method for the synthesis of Novel (E)-1-(aylideneamino)-6-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile derivatives by using 1,3-diketone as synthon. All the synthesized compounds were characterized by IR, Mass and <sup>1</sup>H NMR spectroscopy.

**Keywords:** N-amino pyridine; 2-cyanoacetohydrazide; 1,3-diketone

## 1. INTRODUCTION

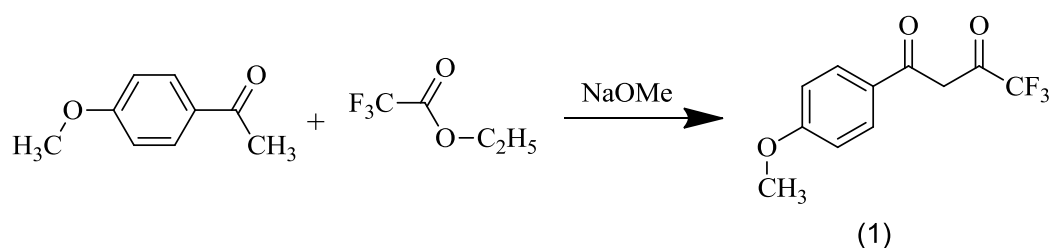
The pyridine skeleton is of great importance to chemists as well as to biologists as it is found in a large variety of naturally occurring compounds and also in clinically useful molecules having diverse biological activities. The pyridine ring systems have emerged as integral backbones of over 7000 existing drugs<sup>[1,2]</sup>. The pyridine ring is also an integral part of anticancer and anti-inflammatory agents<sup>[3]</sup>.

In association with those, Pyridone and their derivatives play an essential role in several biological processes and have considerable chemical and pharmacological importance<sup>[4-6]</sup>. 2-Pyridones represent a unique class of pharmacophore, which are observed in various therapeutic agents<sup>[7]</sup> and antibiotics<sup>[8]</sup>. These heterocycles attracted attention because of their applications as bioactive compounds for example as a promising class of HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs)<sup>[9]</sup>, as antibacterial<sup>[10]</sup>, antifungal<sup>[11]</sup>, sedative<sup>[12]</sup> and cardiotoxic agents<sup>[13]</sup>. Moreover, such derivatives have recently become important due to their structural similarity to nucleosides<sup>[14]</sup>. Also, 2-pyridones were used as ligands for the late 3d-metals<sup>[15]</sup>.

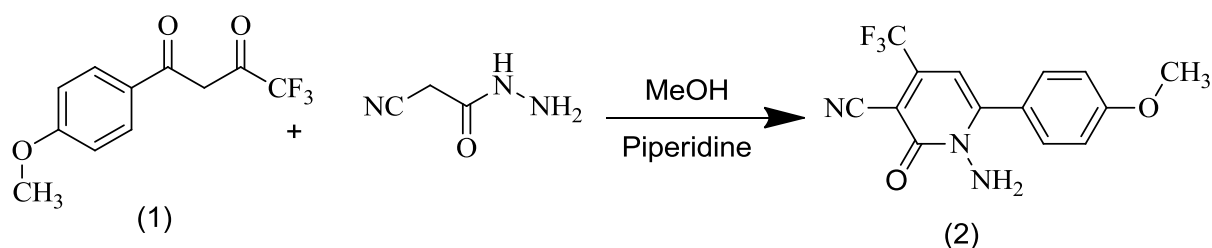
They are also versatile precursors for the construction of complex natural products<sup>[16]</sup>, pyridines<sup>[17]</sup> and larger pyridone systems such as those found in the nitroguanidine insecticide Imidacloprid<sup>[18]</sup> and subtype selective GABAA receptor agonists<sup>[19]</sup>. Consequently, methodologies for the preparation of pyridones have attracted much attention from both industry and academia. 3-Cyano-2-Pyridones are much interest in the anticancer activity of

these compounds owing to different types of biological targets they might interfere with for this effect to occur e.g. PDE3, PIM1 Kinase, and Surviving protein.

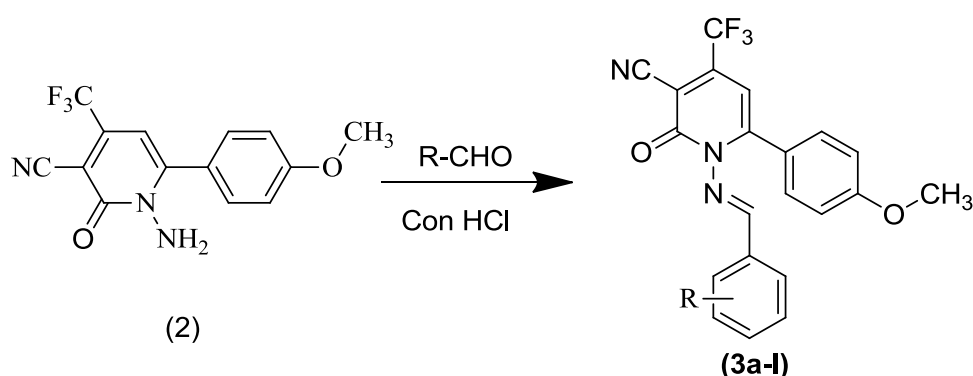
By considering all these advantages based on pyridine nucleus we report here the library of novel substituted pyridine analogues. 4,4,4-trifluoro-1-(4-methoxyphenyl)butane-1,3-dione (1), a trifluoromethylated 1,3-diketone can be easily synthesized from acetophenone and ethyltrifluoroacetate. (Scheme 1). This compound (1) converted in to N-amino pyridine (2) by refluxing with 2-cyanoacetohydrazide in presence of piperidine. (Scheme 2). Intermediate-2 contains N-amino group which behave as nucleophile and is easily reacted with carbonyl group of aldehyde (Scheme 3).



**Scheme 1.** Synthesis of 4,4,4-trifluoro-1-(4-methoxyphenyl)butane-1,3-dione.



**Scheme 2.** Synthesis of 1-amino-6-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile.



**Scheme 3.** (E)-1-(arylidenamino)-6-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile.

## 2. RESULT AND DISCUSSION

In the first step it is very convenient to use sodium methoxide/sodiummethoxide. Here the use of sodium hydride also gives the better result. In step-2 the cyclization rapidly exist if electron donating group present on phenyl ring and further more the presence of electron-withdrawing group at another end also beneficial. The cyclisedpyridone ring with N-amino functionality undergoes nucleophilic addition on carbonyl of various aromatic aldehydes results in to the formation of substituted pyridone derivatives (3a-l). The Various aldehydes used are listed in Table 1 with their M.P.

**Table 1.** Various Aldehydes used

| Compound | Substitution R       | MP °C | Yield % |
|----------|----------------------|-------|---------|
| 3a       | -2,4-Di Cl           | 172   | 70      |
| 3b       | -3-OH                | 164   | 69      |
| 3c       | -4-N,N-dimethylamino | 172   | 75      |
| 3d       | -4-Me                | 170   | 81.6    |
| 3e       | -2-Cl                | 160   | 68      |
| 3f       | -Crotonaldehyde      | 145   | 73      |
| 3g       | -H                   | 165   | 71      |
| 3h       | -Naphthyl            | 173   | 80      |
| 3i       | -3-Br                | 170   | 72      |
| 3j       | -4-OMe               | 145   | 66      |
| 3k       | -3,4-DiOMe           | 155   | 77      |
| 3l       | -3-NO <sub>2</sub>   | 178   | 62      |

## 3. EXPERIMENTAL

Thin-layer chromatography was accomplished on 0.2 mm precoated plates of silica gel G60 F<sub>254</sub> (Merck). Visualization was made with UV light (254 and 365 nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. <sup>1</sup>H (400 MHz) and <sup>13</sup>C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in CDCl<sub>3</sub>.

Chemical shifts are expressed in  $\delta$  ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected.

### Preparation of 4,4,4-trifluoro-1-(4-methoxyphenyl)butane-1,3-dione

To the freshly prepared solution of sodium methoxide (1.7eq) in methanol, 4-methoxy acetophenone (1 eq) was added at 15-20 °C. It was stirred for 30 minutes at 20 °C. Trifluoroethylacetate (1.2 eq) was added into reaction flask by addition funnel within 30 minutes at 20 °C, stirred the reaction mixture for 19 hrs at 70 °C. Completion of reaction was confirmed by TLC. Reaction mixture was poured into 10 % HCl solution and stirred for 15 minutes. Separated solid was filtered and washed with 100 ml water. Product was recrystallized in methanol : water (80 : 20).

### Preparation of 1-amino-6-(4 methoxy phenyl)2-oxo-4-(trifluoro methyl)-1,2-dihydroxy pyridine-3-carbonitrile.

In 100 ml RBF 0.002 mole of 4,4,4-trifluoro-1-(4-methoxyphenyl)butane-1,3-dione and 0.002 moles of 2-cyanoacetohydrazide were mixed together and dissolved in 20 ml methanol. piperidine was added in catalytic amount. Reflux this mixture for 3 hrs. The solvent was removed in vacuum and the residue was cooled to give a solid compound. Solid was filtered and washed with chilled methanol to get pure compound.

### General procedure for the synthesis of (E)-1-(benzylideneamino)-6-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile derivatives.

In 100 ml RBF 1-amino-6-(4 methoxy phenyl)2-oxo-4-(trifluoro methyl)-1,2-dihydroxy pyridine-3-carbonitrile and 1.1 equivalent of different substituted aldehydes were dissolved in minimum quantity of methanol. Then one drop of HCl was added in this mixture. Shake the mixture vigorously. The reaction mixture was heated at 60-70 °C for 5 hrs. Completion of reaction was confirmed by TLC. The reaction mixture was kept in ice bath. Separated solid was filtered and wash with chilled methanol.

## 2. 1. Spectroscopic data for the compounds

### (E)-1-((2,4-dichlorobenzylidene)amino)-6-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (3a)

White solid, yield 70 %, mp 172 °C; IR (KBr)  $\text{cm}^{-1}$ : 3032, 1545, 1388, 1274, 1213, 1672, 770, 2297, 1630, 1105, 864, 877;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  ppm 9.41 (s, 1H), 7.90 (s, 1H), 7.75 (d, 1H), 7.58 (d, 1H), 7.56 (d, 2H), 7.03 (d, 2H), 6.88 (s, 1H), 3.81 (s, 3H); MS (m/z): 465 [ $\text{M}^+$ ] Anal. Calcd for  $\text{C}_{21}\text{H}_{12}\text{Cl}_2\text{F}_3\text{N}_3\text{O}_2$ : C, 54.10; H, 2.59; N, 9.01; Found: C, 54.42; H, 2.78; N, 9.12.

### (E)-1-(3-Hydroxybenzylideneamino)-4-(trifluoromethyl)-1,2-dihydro-6-(4-methoxy phenyl)-2-oxopyridine-3-carbonitrile(3b)

White solid, yield 69 %, mp 164 °C; IR (KBr)  $\text{cm}^{-1}$ : 3020, 1600, 1217, 1267, 1662, 3620, 2223, 1604, 1105, 864, 877, 1075;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  ppm 9.89 (s, 1H), 8.92 (s, 1H), 7.55 (d, 2H), 7.35 (t, 1H), 7.17 (d, 1H) 7.15 (s, 1H), 7.04 (d, 2H), 7.03 (m, 1H), 6.85 (s, 1H), 3.79 (s, 3H); MS (m/z): 413 [ $\text{M}^+$ ] Anal. Calcd for  $\text{C}_{21}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_3$ : C, 61.02; H, 3.41; N, 10.17; Found: C, 61.09; H, 3.28; N, 10.32.

### (E)-1-((4-(dimethylamino)benzylidene)amino)-6-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile(3c)

White solid, yield 75 %, mp 172 °C; IR (KBr)  $\text{cm}^{-1}$ : 3016, 1541, 1377, 1263, 1219, 1658, 2225, 1658, 1141, 1219;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  ppm 8.65 (s, 1H), 7.56 (d, 2H), 7.54

(d, 2H), 7.08 (d, 2H), 6.80 (s, 1H), 6.77 (t, 2H), 3.78(s, 3H), 3.02 (s, 6H); MS (m/z): 440 [M<sup>+</sup>]; Anal. Calcd for C<sub>23</sub>H<sub>19</sub>F<sub>3</sub>N<sub>4</sub>O<sub>2</sub>: C, 62.72; H, 4.35; N, 12.72; Found: C, 62.58; H, 4.52; N, 12.64.

**(E)-6-(4-methoxyphenyl)-1-((4-methylbenzylidene)amino)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile(3d)**

White solid, yield 81 %, mp 170 °C; IR (KBr) cm<sup>-1</sup>: 3012, 1552,1379, 1213, 1263, 1660, 2227, 1600, 1143, 680, 830; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ ppm 8.85 (s, 1H), 7.88 (d, 2H), 7.84 (d, 2H), 7.22 (d, 2H), 6.94 (s, 1H), 6.68 (d, 2H), 3.92 (s, 3H), 2.26 (s, 3H); MS (m/z): 411 [M<sup>+</sup>]; Anal. Calcd for C<sub>22</sub>H<sub>16</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>: C, 64.23; H, 3.92; N, 10.21; Found: C, 64.08; H, 4.06; N, 10.36.

**(E)-1-((2-chlorobenzylidene)amino)-6-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (3e)**

White solid, yield 68 %, mp 160 °C; IR (KBr) cm<sup>-1</sup>: 3298, 1599, 1384, 1265, 1193, 1676, 2231, 1676, 1020, 761, 735; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ ppm 9.32 (s, 1H), 7.82(d, 2H), 7.56 (d,1H), 7.46 (d, 1H), 7.44 (d, 2H), 7.12-7.66 (m, 2H), 6.78 (s, 1H), 3.82 (s, 3H); MS (m/z): 427 [M<sup>+</sup>]; Anal. Calcd for C<sub>21</sub>H<sub>13</sub>ClF<sub>3</sub>N<sub>3</sub>O<sub>2</sub>: C, 58.41; H, 3.03; N, 9.73; Found: C, 58.19; H, 2.88; N, 9.98.

**1-((E)-((E)-but-2-en-1-ylidene)amino)-6-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile(3f)**

White solid, yield 73 %, mp 145 °C; IR (KBr) cm<sup>-1</sup>: 3016, 1541, 1377, 1263, 1219, 1658, 2225, 1658, 1141, 2359, 2859; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ ppm 8.42 (s, 1H), 7.48 (d, 2H), 7.12 (d, 2H), 6.76 (s, 1H), 6.62-6.56 (m, 3H), 3.66 (s, 3H), 2.08 (d, 3H); MS (m/z): 361 [M<sup>+</sup>]; Anal. Calcd for C<sub>18</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>: C, 59.83; H, 3.91; N, 11.63; Found: C, 59.83; H, 3.91; N, 11.63.

**(E)-1-(benzylideneamino)-6-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (3g)**

White solid, yield 71 %, mp 165 °C; IR (KBr) cm<sup>-1</sup>: 3070, 1543, 1386, 1263, 1220, 1654, 1780, 2297, 1630, 1105; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ ppm 9.02 (s, 1H), 7.78 (d, 2H), 7.64 (t, 1H), 7.58 (d, 2H), 7.52 (s, 2H), 7.03 (d, 2H), 6.86 (s, 1H), 3.79 (s, 3H); MS (m/z): 397 [M<sup>+</sup>]; Anal. Calcd for C<sub>21</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>: C, 63.48; H, 3.55; N, 10.58; Found: C, 63.43; H, 3.61; N, 10.48.

**(E)-1-((naphthalen-1-yl)methyleneamino)-4-(trifluoromethyl)-1,2dihydro-6-(4-methoxyphenyl)-2-oxopyridine-3-carbonitrile(3h)**

White solid, yield 80 %, mp 173 °C; IR (KBr) cm<sup>-1</sup>: 3074, 1545, 1388, 1274, 1213, 1672, 2297, 1630, 1105; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ ppm 9.67 (s, 1H), 8.47 (t, 1H), 8.22 (d, 1H), 8.08 (t, 1H), 7.96 (d, 1H), 7.63 (d, 2H), 7.66 (m, 3H), 7.03 (d, 2H), 6.91 (s, 1H), 3.76 (s, 3H); MS (m/z): 447 [M<sup>+</sup>]; Anal. Calcd for C<sub>25</sub>H<sub>16</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>: C, 67.11; H, 3.60; N, 9.39; Found: C, 67.17; H, 3.55; N, 9.46.

**(E)-1-((3-bromobenzylidene)amino)-6-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (3i)**

White solid, yield 72 %, mp 170 °C ; IR (KBr) cm<sup>-1</sup>: 3016, 1541, 1377, 1263, 1219, 1658, 2225, 1658, 1141, 680, 780; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ ppm 9.05 (s, 1H), 7.94 (s, 1H),

7.81 (d,1H), 7.74 (d, 1H), 7.57 (d, 2H), 7.51 (t, 1H), 7.02 (d, 2H), 6.80 (s, 1H), 3.80 (s, 3H); MS (m/z): [M<sup>+</sup>] MS (m/z): 475 [M<sup>+</sup>] Anal. Calcd for C<sub>21</sub>H<sub>13</sub>BrF<sub>3</sub>N<sub>3</sub>O<sub>2</sub>: C, 52.96; H, 2.75; N, 8.82; Found: C, 53.03; H, 2.73; N, 8.76.

**(E)-1-((4-methoxybenzylidene)amino)-6-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile(3j)**

White solid, yield 66 %, mp 145 °C; IR (KBr) cm<sup>-1</sup>: 3007, 1386, 1265, 1217, 1660, 2227, 1660, 1101, 1143, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ ppm 8.78 (s, 1H), 7.72 (d, 2H), 7.76(d, 2H), 7.26 (d, 2H), 7.18 (d, 2H), 6.53 (s, 1H), 3.78 (s, 3H), 3.85 (s, 3H); MS (m/z): 427 [M<sup>+</sup>] Anal. Calcd for C<sub>22</sub>H<sub>16</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>: C, 61.83; H, 3.77; N, 9.83; Found: C, 61.80; H, 3.68; N, 9.69.

**(E)-1-((3,4-dimethoxybenzylidene)amino)-6-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (3k)**

White solid, yield 77 %, mp 155 °C; IR (KBr) cm<sup>-1</sup>: 3005, 1545, 1380, 1273, 1222, 1651, 2225, 1658, 1145, 1022, 835, 758 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ ppm 8.74 (s, 1H), 7.74 (d, 2H), 7.68 (d,1H), 7.63 (s, 1H), 7.36 (d, 1H), 7.17 (d, 2H), 6.59 (s, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H); MS (m/z): [M<sup>+</sup>] MS (m/z): 427 [M<sup>+</sup>] Anal. Calcd for C<sub>23</sub>H<sub>18</sub>F<sub>3</sub>N<sub>3</sub>O<sub>4</sub>: C, 60.39; H, 3.97; N, 9.19; Found: C, 60.28; H, 4.06; N, 9.28.

**(E)-6-(4-methoxyphenyl)-1-((3-nitrobenzylidene)amino)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile(3l)**

White solid, yield 62 %, mp 178 °C; IR (KBr) cm<sup>-1</sup>: 3300, 1599, 1357, 1298, 1261, 1666, 2229, 1527, 1024, 1357 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ ppm 9.44 (s, 1H), 8.17 (m, 1H), 8.02 (s, 1H), 7.96 (d, 1H), 7.89 (d, 1H), 7.70 (d, 2H), 7.38 (d, 2H), 6.76 (s, 1H); MS (m/z): [M<sup>+</sup>] MS (m/z): 442 [M<sup>+</sup>] Anal. Calcd for C<sub>21</sub>H<sub>13</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub>: C, 57.02; H, 2.96; N, 12.67; Found: C, 56.96; H, 2.98; N, 12.72.

#### 4. CONCLUSION

Pyridone compounds when it bearing different functional group it is very important in its class. We have reported here the novel trifluoromethylated N-arylidine amino pyridone library which can be utilised in the field of organo-pharmaceutical chemistry.

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#### References

- [1] Li, A. H.; Moro, S.; Forsyth, N.; Melman, N.; Ji, X. D.; Jacobsen, K. A. *J. Med. Chem.* 42 (1999) 706.
- [2] Vacher, B.; Bonnand, B.; Funes, F.; Jubault, N.; Koek, W.; Assie, M. B.; Cosi, C.; Kleven, M. *J. Med. Chem.* 42 (1999) 1648.

- [3] (a) Son, J. K.; Zhao, L. X.; Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Jeong, T. C.; Jeong, B. S.; Lee, C. S.; Lee, E. S., *Eur. J. Med. Chem.* 43 (2008) 675.  
(b) Amr, A. G.; Abdulla, M. M.; *Bioorg. Med. Chem.* 14 (2006) 4341.
- [4] Choi, W.; Houpis, I. N.; Charchil, H. R. O.; Molina, A.; Lynch, J. E.; Volante, R. P.; Reider, P. J.; King, A. O. *Tetrahedron* 36 (1995) 4571.
- [5] Bhupathy, M.; Conlon, D. A.; Wells, K. M.; Wells, M.; Nolson, J. R.; Reider, P. J.; Rossen, K.; Sager, J.W.; Volante, R. P. *J. Heterocyclic Chem.* 32 (1995) 1283.
- [6] Kappe, O. C.; Kappe, T. *Monatshefte fur Chemie* 120 (1989) 1095.
- [7] (a) Saiki, A. Y. C.; Shen, L. L.; Chen, C. M.; Baranowski, J.; Lerner, C. G. *Antimicrob. Agents Chemother.* 43 (1999) 1574;  
(b) Li, Q.; Mitscher, L. A.; Shen, L. L. *Med. Res. Rev.* (2000) 231.
- [8] Brickner, S. *Chem. Ind.* (1997) 131.
- [9] (a) Goldman, M. E.; Nunberg, J. H.; O'Brien, J. A.; Quintero, J. C.; Schleif, W. A.; Freund, K. F.; Gaul, S. L.; Saari, W. S.; Wai, J. S.; Hoffman, J. M.; Anderson, P. S.; Hupe, D. J.; Emini, E. A.; Stern, A. M. *Proc. Natl. Acad. Sci.* 88 (1991) 6863;  
(b) Medina-Franco, J. L.; Martínez-Mayorga, K.; Juárez-Gordiano, C.; Castillo, R. *Chem. Med. Chem.* 2 (2007) 1141.
- [10] (a) Li, Q.; Mitscher, L. A.; Shen, L. L. *Med. Res. Rev.* 20 (2000) 231;  
(b) Holzgrabe, U. *Pharm. Unserer Zeit.* 30 (2001) 446.
- [11] Gupta, A. K.; Plott, T. *Int. J. Dermatol.* 43 (2004) 3.
- [12] Collins, I.; Moyes, C.; Davey, W.; Rowley, M.; Bromidge, F.; Quirk, K.; Atack, J.; McKernan, R.; Thompson, S. A.; Wafford, K.; Dawson, G.; Pike, A.; Sohal, B.; Tsou, N.; Bull, R.; Castro, J. *J. Med. Chem.* 45 (2002) 1887.
- [13] (a) Endoh, M.; Hori, M. *Exp. Opin. Pharmacother.* 7 (2006) 2179;  
(b) Robert, N.; Verrier, C.; Hoarau, C.; Celanire, S.; Marsais, F. *Arkivoc* 7 (2008) 92;  
(c) Presti, E. L.; Boggia, R.; Feltrin, A.; Menozzi, G.; Dorigo, P.; Mosti, L. *Il Farmaco* 54 (1999) 465.
- [14] Sollogoub, M.; Fox, K. R.; Powers, V. E. C.; Brown, T., *Tetrahedron Lett.* 43 (2002) 3121;  
(b) Seidel, A.; Brunner, S.; Seidel, P.; Fritz, G. I.; Herbarth, O., *British J. Cancer* 2006, 94, 1726; (c) Sun, Z.; Ahmed, S.; McLaughlin, L. W., *J. Org. Chem.* 71 (2006) 2922;  
(d) Yang, Z.; Hutter, D.; Sheng, P.; Sismour, A. M.; Benner, S. A. *Nucl. Acids Res.* 34 (2006) 6095;  
(e) Rajeswaran, M.; Srikrishnan, T. *Nucleosides, Nucleotides and Nucleic Acids* 27 (2008) 1113.
- [15] Parsons, S.; Winpenny, R. E. P. *Acc. Chem. Res.* 30 (1997) 89.
- [16] Kawato, Y.; Terasawa, H. *Prog. Med. Chem.* 34 (1997) 69.

- [17] Murray, T.; Zimmerman, S. *Tetrahedron Lett.* 36 (1995) 7627.
- [18] Werbitzky, O.; Studer, P. *U.S. Patent* 6,022,974, Feb 9, 2000.
- [19] Harrison, T.; Moyes, C. R.; Nadin, A.; Owens, A. P.; Lewis, R. T. *PCT WO* 98/50384.

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