# Synthesis and anti-HIV Activity of New Fused Chromene Derivatives Derived from 2-Amino-4-(1-naphthyl)-5-oxo-4*H*,5*H*-pyrano[3,2*c*]chromene-3-carbonitrile

Najim A. Al-Masoudi<sup>a</sup>, Hamid H. Mohammed<sup>b,c</sup>, Aws M. Hamdy<sup>b</sup>, Omer A. Akrawi<sup>b</sup>, Nadi Eleya<sup>b</sup>, Anke Spannenberg<sup>d</sup>, Christophe Pannecouque<sup>e</sup>, and Peter Langer<sup>b,d</sup>

- <sup>a</sup> Department of Chemistry, College of Science, University of Basrah, Basrah, Iraq. Present address: Am Tannenhof 8, 78464 Konstanz, Germany
- <sup>b</sup> Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
- <sup>c</sup> Department of Chemistry, College of Science, University of Al-Mustansiryah, Baghdad, Iraq
- <sup>d</sup> Leibniz-Institut für Katalyse an der Universität Rostock e.V., Albert-Einstein-Str. 29a, 18059 Rostock, Germany
- <sup>e</sup> Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium

Reprint requests to Prof. Peter Langer. E-mail: peter.langer@uni-rostock.de or Najim A. Al-Masoudi. najim.al-masoudi@gmx.de

*Z. Naturforsch.* **2013**, 68b, 229 – 238 / DOI: 10.5560/ZNB.2013-2297 Received November 17, 2012

A new series of pyrano-chromene and pyrimido pyrano-chromene derivatives were synthesized starting from 2-amino-4-(1-naphthyl)-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile (6). The structures of the synthesized compounds were elucidated by spectral data. Compounds 6-11, 13-15 and 18 have been selected for an inhibitory activity screening against HIV-1 and HIV-2 in MT-4 cells.

*Key words:* Anti-HIV Activity, Chromenes, Pyrano-chromenes, Reverse Transcriptase Inhibitors (NNRTIs)

### Introduction

Chromenes and coumarins [1] have been the subject of considerable chemical interest in the past decades. They occur widely in nature and exhibit important biological as well as pharmacological activities [2-5]. Among chromene derivatives are biologically interesting compounds showing antimicrobial [6-10] and antifungal activities [11, 12], inhibitors of influenza virus silidoses [13, 14], compounds with antihypertensive [15] and anti-allergic activity [16] and hair growth stimulant properties [17]. However, the chromenes are also well known for their biocidal [18, 19], wound healing [20], anti-inflammatory [21], and antiulcer [22] activities.

Some fused chromene derivatives were found useful as antiviral [23], antiproliferation [24], antioxidative [25, 26], antileishmanial [27], antitumor [28], and anti-HIV agents [29], show central nervous system (CNS) activities [30], and find application in the treatment of Alzheimer's disease [31] and Schizophrenia disorder [32]. Satyanarayana et al. [33] reported the synthesis and antifungal screening of new Schiff bases of chromenes under conventional and microwave conditions. Furthermore, Lee et al. [34] have synthesized 3'R, 4'R-di-(O)-(-)-camphanoyl-2', 2'-dimethyldihydropyrano[2,3-f]chromone (DCP) (1) as a potent *in vitro* inhibitor of HIV-1 replication in H9 lymphocyte cells with an EC<sub>50</sub> of  $6.78 \times 10^{-4} \mu$ M. The family of 4-aryl-4*H*-chromenes has been recently reported to possess anti-cancer activity. These compounds, which are potent apoptosis inducers (e.g. compound 2), were found to be highly active in the growth inhibition MTT with the concentration causing 50% cell growth inhibition (IC<sub>50</sub>) values in the low nanomolar range [35]. Geiparvarin (3), a naturally occurring compound bearing a coumarin residue, has been shown to possess a significant inhibitory activity

© 2013 Verlag der Zeitschrift für Naturforschung, Tübingen · http://znaturforsch.com



against a variety of cell lines including sarcoma 180, *Lewis* lung carcinoma, P-388 lymphocytic leukaemia, and *Walker* 256 carcinosarcoma [36].

In the present paper, we report the synthesis of new chromene derivatives and their *in vitro* activity on the replication of HIV-1 and HIV-2.

# **Results and Discussion**

A number of synthetic strategies have been reported for the construction of chromenes, for example, construction of the chromene ring by a twostep sequence, typically involving prefunctionalization of the arene (*e. g.*, halogenation at the 2position) followed by Heck-type cyclization [37-41]. In the present study, we report on the synthesis of 2-amino-4-(naphthalen-1-yl)-5-oxo-4H,5H- pyrano[3,2-*c*]chromene-3-carbonitrile (6) *via* reaction of (1-naphthylmethylene)malononitrile (4) and 4-hydroxycoumarin (5). Compound 6 was selected as a key intermediate for the synthesis of new fused and non-fused chromene derivatives, aiming at an evaluation of their anti-HIV activity. Thus, treatment of 6 with triethyl orthoformate in acetic anhydride gave the corresponding formimidate derivative 7 in 69% yield. Benzoylation of 6 with benzoyl chloride afforded the pyrimido derivative 10 (60%), while treatment of 7 with hydrazine hydrate or methyl amine at room temperature afforded the anthracene derivatives 8 and 9 in 50 and 52% yield, respectively. The reactions are summarized in Scheme 1.

The structures of 7-10 were confirmed by their <sup>1</sup>H, <sup>13</sup>C NMR and mass spectra and by elemental analyses. The chromene and aromatic protons showed a simi-



Scheme 1. Synthesis of chromene-3-nitrile (6), chromen-2-yl-formimidate (7), 8,9-dihydrochromeno-pyrimidin-6-one (8) and (9), and phenylchromeno-pyrimidin-6,8-dione (10) derivatives.

lar pattern. In the <sup>1</sup>H NMR spectrum of 7, the singlet at  $\delta = 9.01$  ppm was assigned to the CH=N proton, while the singlets at  $\delta = 5.80$ , 5.82, 5.88, and 5.49 ppm were attributed to 5-H of compounds 7-10. The  ${}^{13}C$  NMR spectra of 7–10 contained similar resonance signals of the coumarin and aromatic carbon atoms. In the <sup>13</sup>C NMR spectrum of 7, C-2 resonated at  $\delta = 162.3$  ppm, while the resonances at  $\delta = 154.9$ , 154.0 and 152.1 ppm were assigned to EtOHC = N, C-11a and C-6a carbon atoms. The chemical shifts at  $\delta = 116.6, 116.4, 112.9$  and 103.7 ppm were attributed to CN, C-7, C-10a and C-4a, respectively, while the resonance at  $\delta = 83.2 \text{ ppm}$  was assigned to C-3. In the  ${}^{13}C$  NMR spectra of **8**–**10**, the chemical shifts between  $\delta = 160.0$  and 161.0 ppm were assigned to the C=O carbon atom of the coumarin moiety (C-6), while the resonances at  $\delta = 158.0$  ppm were assigned to C=NH carbon atom. C-7a, C-12a and C-13a appeared in the ranges  $\delta = 141.7 - 138.3$ , 154.0 and 152.0-151.1 ppm. The signal at  $\delta = 157.0$  ppm was assigned to C-2 of 10, whereas the signals at  $\delta = 133.3$ and 135.3 ppm were attributed to the same atom of 8 and 9, respectively. C-5 appeared at  $\delta = 31.4, 30.1$  and 39.4 ppm, respectively. The signals of the other carbon atoms were fully analyzed (cf. Experimental Section).

Compound 9 has been selected for further NMR studies. From the gradient selected HMBC [42] spectrum, 5-H at  $\delta_{\rm H} = 5.80$  ppm showed two  ${}^{2}J_{\rm C,H}$  couplings: one with C-4a at  $\delta_{\rm C} = 75.0$  ppm, and the other with C-5a at  $\delta_{\rm C} = 105.0$  ppm. Additionally, 5-H showed two  ${}^{3}J_{\rm C,H}$  couplings wih C=O at  $\delta_{\rm C} = 161.0$  ppm and C=NH at  $\delta_{\rm C} = 158.0$  ppm.



Fig. 1. Molecular structure of ethyl N-(3-cyano-4-(naphthalene-1-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromen-2-yl)-formimidate (7) in the crystal. Displacement ellipsoids are drawn at the 30% probability level.

The structure of **7** was independently confirmed by a single-crystal X-ray diffraction analysis (Fig. 1 and Experimental Section).

Next, treatment of **6** with acetic anhydride in dry pyridine for 3 h afforded the monoacetyl derivative **12**, while the reaction with acetic anhydride in the presence of sulfuric acid for 10 h led to the pyrimidine derivative **13** in 55 and 75% yield, respectively. An attempt to construct a third heterocyclic ring condensed with coumarin was successful *via* reaction of



Scheme 2. Synthesis of [1,2,4]triazolo[1,5-a]quinoline-11-carbonitrile (11), chromen-2-yl-acetamide (12), and chromeno-[3',4':5,6]pyrano[2,3-d]pyrimidine-dione (13) derivatives.



Scheme 3. Synthesis of chromene-9-dicarboxylate (14–17) and 2-(4-methoxybenzylideneamino)-chromene-3-carbonitrile (18) derivatives.

**6** with semicarbazide hydrochloride in refluxing dry pyridine to give triazolo[1,5-*a*]quinolone **11** in 75% yield (Scheme 2).

The mass spectral data were consistent with the structures of the synthesized compounds 11-13. The structures of 11-13 were assigned by the IR, <sup>1</sup>H, <sup>13</sup>C NMR and mass spectra. In the case of compounds 11 and 12, the <sup>1</sup>H NMR spectra were characterized by the presence of 4-H signals at  $\delta = 5.49$ and 5.77 ppm, while the <sup>13</sup>C NMR spectra exhibited signals at  $\delta = 119.1$  and 116.5 ppm, attributed to the CN carbons, respectively. The <sup>13</sup>C NMR spectrum of 13 exhibited a signal at  $\delta = 161.6$  ppm, attributed to the carbonyl group (C4=O) of the pyrimidine residue, with disappearance of the CN group signal, which supported the formation of a pyrimidine ring in 13. The signals at  $\delta = 31.5$ and 29.2 ppm were attributed to C-4 of 11 and 12, respectively, while the signal at  $\delta = 30.0$  ppm was assigned to C-5 of 13. The signals of the chromene and aromatic carbon atoms were fully analyzed (cf. Experimental Section). The structure of 13 was further confirmed by the gradient selected HMBC spectrum [42]. 5-H at  $\delta = 5.75$  ppm showed  ${}^{3}J_{C,H}$  couplings with the carbonyl groups of the pyrimidine ring (C4=O) and the chromene residue at  $\delta = 161.9$  and 159.8 ppm, respectively. Further,  ${}^{2}J_{C,H}$  couplings of H-5 with C-4a and C-5a at  $\delta = 102.3$  and 106.4 ppm, respectively, were observed.

When mixtures of **6** and various  $\beta$ -ketoesters in toluene were stirred under reflux in the presence of SnCl<sub>4</sub> as a Lewis acid catalyst, the fused ring products **14–17** were obtained in 54, 53, 53, and 56% yield, respectively. Treatment of **6** with *p*-anisaldehyde in a dioxane-piperidine mixture gave the 2-(4-methoxybenzylideneamino)chromene-3carbonitrile derivative **18** in 56% yield (Scheme 3).

The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of 14-17were in agreement with the suggested structures. The <sup>1</sup>H NMR spectra were characterized by the presence of the 5-H signal in the range  $\delta = 6.07 - 6.02$  ppm, whereas the <sup>13</sup>C NMR spectra exhibited signals in the range  $\delta = 39.5 - 36.5$  ppm, attributed to C-5. Compound 15 was selected for further NMR experiments. From a gradient HMBC NMR spectrum, a  ${}^{3}J_{C,H}$  coupling between OCH<sub>2</sub> protons at  $\delta = 4.23$  ppm and the carbonyl carbon atom at  $\delta = 168.0$  ppm of the ester moiety at C-3, was observed. Further, the protons of the 2-methyl group at  $\delta = 2.49$  ppm showed a  ${}^{3}J_{C,H}$ coupling with C-3 at  $\delta = 114.0$  ppm, the same protons revealved a  ${}^{2}J_{C,H}$  coupling with C-2 at  $\delta = 139.2$  ppm. Similarly, 5-H at  $\delta = 6.02$  ppm showed two  ${}^{2}J_{C,H}$  couplings with carbon atoms 4a and 5a at  $\delta = 116.6$  and 80.0 ppm, respectively, while the same proton demonstrated two  ${}^{3}J_{C,H}$  couplings with carbon atom 4 and carbonyl carbon atom C-6 at  $\delta = 155.3$  and 161.0 ppm, respectively (Fig. 2). The mass spectra of the prepared compounds showed the correct molecular ions suggested by their molecular formulas.



Fig. 2.  $J_{C,H}$  correlations in the HMBC NMR spectrum of **15**.

The <sup>1</sup>H and <sup>13</sup>C NMR spectra of **18** showed patterns similar to those of **12**; the OMe, 5-H and HC=N protons appeared as three singlets at  $\delta = 3.90$ , 6.09 and 9.41 ppm, respectively. The <sup>13</sup>C NMR spectrum of **18** was characterized by the presence of signal at  $\delta = 161.0$  ppm, assigned to HC=N together with the aromatic carbon atom (*C*-OMe).

#### In vitro anti-HIV activity

Compounds 6–11, 13–15 and 18 were tested for their *in vitro* anti-HIV-1 (strain  $III_B$ ) and HIV-2 (strain ROD) activity in human (MT-4) cells. based on an MTT assay [43]. The results are summarized in Table 1, in which the data for nevirapine (BOE/BIRG587) [44] and azidothymidine (DDN/AZT) [45] are included for comparison purposes.

Compounds 7, 8 and 13 were found to be the only compounds in the series inhibiting HIV-1 and HIV-

2 replication in cell cultures with  $EC_{50}$  of > 2.27, > 4.84, and  $> 3.64 \,\mu g \,m L^{-1}$ , respectively, and a selectivity index of < 1.

In conclusion, the structure-activity relationship (SAR) suggested that the potency of compound 7 could be attributed to the presence of the cyano and formimidate groups in the 3- and 4-positions, respectively, of the pyrane ring. However, the anti-HIV activity and the selectivity of these compounds are too limited to perform extensive mode-of-action studies, and 7 might be considered as a new lead in the development of antiviral agents as a non-nucleoside reverse transcriptase inhibitor.

# Conclusion

In this paper we have reported the synthesis and anti-HIV-1 and anti-HIV-2 evaluation of some pyranochromene and pyrimido pyrano-chromene derivatives. The preliminary *in vitro* anti-HIV data have demonstrated that the ethyl *N*-(3-cyano-4-(naphthalene-yl)-5oxo-4,5-dihydropyrano[3,2-*c*]chromen-2-yl) formimidate (**7**) is more active than other chromene derivatives. The synthesis of new analogs of these derivatives could lead to the discovery of more potent and selective compounds that will allow the elucidation of their molecular mode of action.

#### **Experimental Section**

General

Melting points are uncorrected and were determined on a Micro heating table HMK 67/1825 Kuestner (Büchi Appa-

Entry	HIV-1 (III <sub>B</sub> )	HIV-2 (ROD)	$CC_{50}^d$	SI <sup>e</sup>	SI <sup>e</sup>
•	$EC_{50}^{c} (\mu g m L^{-1})$	$EC_{50}^{c} (\mu g m L^{-1})$	$(\mu g \mathrm{mL}^{-1})$	$(III_B)$	(ROD)
6	> 9.92	> 9.92	9.92	< 1	< 1
7	> 2.27	> 0.76	> 2.27	< 1	$\leq 3$
8	> 4.84	> 4.84	4.84	< 1	< 1
9	> 80.20	> 80.20	> 80.20	< 1	< 1
10	> 125.0	> 125.0	> 125.0	< 1	< 1
11	> 10.73	> 10.73	10.73	< 1	< 1
13	> 3.63	> 3.63	3.63	< 1	< 1
14	> 58.83	> 58.83	58.83	< 1	< 1
15	> 50.0	> 50.0	> 50.0	< 1	< 1
18	> 6.82	> 6.82	6.82	< 1	< 1
Nevirapine	0.050	> 4.00	> 4.00	> 80	< 1
AZT	0.0022	0.00094	> 25	> 11363	> 26596

Table 1. In vitro anti-HIV-1<sup>a</sup> and HIV-2<sup>b</sup> activity of some new chromene derivatives.

<sup>a</sup> Anti-HIV-1 activity measured with strain III<sub>B</sub>; <sup>b</sup> anti-HIV-2 activity measured with strain ROD; <sup>c</sup> compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1 and 2-induced cytopathogenic effect; <sup>d</sup> compound concentration that reduces the viability of mockinfected MT-4 cells by 50%; <sup>e</sup> SI: selectivity index ( $CC_{50}/EC_{50}$ ). ratus), and a Leitz Labolux 12 Pol with heating table Mettler FP 90. FT-IR spectra were recorded on a Nicolet 205 FT-IR and Nicolet Protége 460 FT-IR instruments using the KBr technique. <sup>1</sup>H NMR (300 MHz) and <sup>13</sup>C NMR (75.5 MHz) spectra were measured on Bruker AC 250, Bruker ARX 300 and Bruker ARX 500 instruments in [D<sub>6</sub>]DMSO as a solvent. Mass spectra (MS) were run on AMD MS40, Varian MAT CH 7, MAT 731 (EI, 70 eV), Intecta AMD 402, (EI, 70 eV and CI), and Finnigan MAT 95 (CI, 200 eV) spectrometers. High-resolution mass spectrometry (HRMS) was performed on Varian MAT 311 and Intecta AMD 402 instruments.

# (1-Naphthylmethylene)malononitrile (1) and 2-amino-4-(naphthalen-1-yl)-5-oxo-4H,5H-pyrano-[3,2-c]chromene-3-carbonitrile (6)

These compounds were synthesized according to method described previously [46].

# *Ethyl N-(3-cyano-4-(naphthalen-1-yl)-5-oxo-4,5dihydropyrano[3,2-c]chromen-2-yl)formimidate (7)*

A mixture of 6 (0.36 g, 1.0 mmol), triethyl orthoformate (2 mL) and acetic anhydride (10 mL) was heated under reflux for 8 h (TLC control). The reaction mixture was left to cool overnight, and the solid formed was recrystallized from dioxane to give 7 (0.29 g, 69%) as a pale-yellow solid, m. p.  $282 - 283 \degree C. - FT-IR$  (KBr, cm<sup>-1</sup>): v = 3050, 2984(w), 2215 (m), 1715, 1666, 1608 (s). – <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 1.38$  (t, 3H, CH<sub>3</sub>), 4.42 (q, 2H, CH<sub>2</sub>), 5.80 (s, 1H, 4-H), 7.50-7.95 (m, 8H, Ar-H), 8.03 (d, 1H, J = 8.0 Hz, Ar-H), 8.31 (d, 1H, J = 7.7 Hz, Ar-H), 8.57 (d, 1H, J = 7.6 Hz, Ar-H), 9.01 (s, 1H, CH=N). – <sup>13</sup>C NMR (75.5 MHz,  $[D_6]DMSO$ ):  $\delta = 13.8$  (CH<sub>3</sub>), 39.4 (C-4), 64.2 (CH<sub>2</sub>), 83.2 (C-3), 103.7 (C-4a), 112.9 (C-10a), 116.4 (C-7), 116.6 (CN), 123.5, 124.7, 125.8, 125.9, 126.4, 128.0, 128.5, 131.0, 133.1, 133.2 (Carom), 152.1 (C-6a), 154.0 (C-11a), 154.9 (HC=N), 159.5 (C=O), 162.3 (C-2). – MS ((+)-FAB):  $m/z = 423 [M+H]^+$ . – GC-MS (EI, 70 eV): m/z (%) = 422 (68) [M]<sup>+</sup>, 365 (12), 295 (100), 267 (16), 239 (89), 121 (36). - C<sub>26</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub> (422.42): calcd. C 73.92, H 4.29, N 6.63; found C 73.71, H, 4.16, N 6.45.

# 9-Amino-8-imino-7-(naphthalen-1-yl)-8,9-dihydrochromeno[3',4':5,6]pyrano[2,3-d]pyrimidin-6-one (8)

To a solution of **7** (0.40 g, 1.0 mmol) in EOH (25 mL) a solution of hydrazine hydrate (5 mL) was added, and the mixture was stirred for 1 h, then allowed to stand overnight. The precipitate formed was filtered, dried and recrystallized from dioxane to afford **8**, 0.20 g (50%), as a yellow solid, m. p. 256–258 °C. – FT-IR (KBr, cm<sup>-1</sup>): v = 3308, 3342, 3268, 3064, 3043 (w), 1730, 1664, 1606 (s), 1587, 1564. – <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 5.64$  (s, 2H, NH<sub>2</sub>), 5.82 (s, 1H, 5-H), 7.40–7.58 (m, 6H, Ar-H), 7.67–7.80

(m, 3H, Ar-H), 7.91 (d, 1H, J = 7.5 Hz, Ar-H), 8.01 (d, 1H, J = 7.9 Hz, Ar-H), 8.17 (s, 1H, CH=N), 8.81 (br s., 1H, NH). – <sup>13</sup>C NMR (75.5 MHz, [D<sub>6</sub>]DMSO):  $\delta = 31.4$  (C-5), 70.0 (C-4a), 104.6 (C-5a), 116.6 (C-11a), 119.1 (C-8), 122.4, 123.4, 124.7, 125.7, 125.8, 126.1, 127.4, 128.4, 130.9, 133.0 (C<sub>arom</sub>), 133.3 (C-2), 140.7 (C-7a), 152.1 (C-13a), 154.0 (C-12a), 158.0 (C=NH), 160.0 (C=O). – MS ((+)-FAB): m/z = 409 [M+H]<sup>+</sup>. – GC-MS (EI, 70 eV): m/z (%) = 408 (100) [M]<sup>+</sup>, 392 (52), 365 (21), 266 (58), 239 (15), 121 (19). – C<sub>24</sub>H<sub>17</sub>N<sub>4</sub>O<sub>3</sub> (408.12): calcd. C 70.58, H 3.95, N 13.72; found C 70.37, H 3.52, N 13.40.

### 8-Imino-9-methyl-7-(naphthalen-1-yl)-8,9-dihydrochromeno[3',4':5,6]pyrano[2,3-d]pyrimidin-6-one (9)

To a solution of 7 (0.40 g, 1.0 mmol) in EtOH (25 mL) a solution of methylamine (0.03 g, 1.0 mmol) was added and the mixture stirred for 1 h. Then it was allowed to stand overnight. The precipitate formed was filtered, dried and recrystallized from dioxane to afford 9 (0.21 g, 52%), m. p. > 300 °C. – FT-IR (KBr, cm<sup>-1</sup>): v = 3336, 3056, 2940(w), 1718, 1659 (s), 1608, 1577 (m). – <sup>1</sup>H NMR (300 MHz,  $[D_6]DMSO$ :  $\delta = 3.28$  (s, 3H, CH<sub>3</sub>), 5.80 (s, 1H, 5-H), 7.48-7.66 (m, 6H, Ar-H), 7.81-8.08 (m, 5H, Ar-H), 8.27 (s, 1H, CH=N), 8.89 (br s., 1H, NH). - <sup>13</sup>C NMR (75.5 MHz,  $[D_6]DMSO$ :  $\delta = 30.1$  (CH<sub>3</sub>), 39.4 (C-5), 75.0 (C-4a), 105.0 (C-5a), 116.6 (C-11a), 120.1 (C-8), 122.0, 123.4, 124.9, 125.7, 125.8, 126.0, 127.4, 128.5, 130.9, 132.9 (C<sub>arom</sub>), 135.3 (C-2), 141.0 (C-7a), 152.1 (C-13a), 154.0 (C-12a), 158.0 (C=NH), 161.0 (C=O). – MS ((+)-FAB): m/z = 408 $[M+H]^+$ . – C<sub>25</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</sub> (407.13): calcd. C 73.70, H 4.21, N 10.31; found C 73.39, H 3.95, N 10.01.

#### 7-(Naphthalen-1-yl)-10-phenylchromeno[3',4' : 5,6]pyrano-[2,3-d]pyrimidin-6,8(7H,9H)-dione (**10**)

A mixture of 6 (0.36 g, 1.0 mmol) and benzoyl chloride (0.15 g, 1.0 mmol) in pyridine (20 mL) was refluxed for 12 h (TLC control). The obtained product was recrystallized from dioxane to give 10 (0.28 g, 60%) as a yellow solid, m.p.  $370 \,^{\circ}\text{C.} - \text{FT-IR} \text{ (KBr, cm}^{-1}\text{): } v = 3416, 3054, 2940 \text{ (w)},$ 1713, 1660, 1605 (s), 1549 (m). - <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 5.88$  (s, 1H, 5-H), 7.40–7.76 (m, 10H, Ar-H), 7.81–7.87 (m, 3H, Ar-H), 7.97 (d, 1H, J = 7.76 Hz, Ar-H), 8.52 (d, 2H, Ar-H), 8.79 (br s., 1H, NH). - <sup>13</sup>C NMR (75.5 MHz, [D<sub>6</sub>]DMSO):  $\delta = 39.4$  (C-5), 80.0 (C-4a), 104.6 (C-5a), 116.6 (C-11a), 119.1 (C-8), 122.4, 122.9, 123.4, 124.0, 124.7, 125.7, 125.8, 126.0, 127.4, 128.4, 130.9, 133.9 (Carom), 138.3 (C-7a), 152.0 (C-13a), 154.0 (C-12a), 157.0 (C-2) 158.0 (C=NH), 160.0 (C=O). – MS ((+)-FAB):  $m/z = 469 \text{ [M-H]}^+$ . – GC-MS (EI, 70 eV): m/z (%) = 470 (1) [M]<sup>+</sup>, 444 (89), 427 (5), 366 (2), 317 (100), 239 (12), 189 (4). –  $C_{30}H_{17}N_2O_4$  (470.13): calcd. C 76.59, H 3.86, N 5.95; found C 76.20, H 3.45, N 5.63.

10-Amino-12-(naphthalen-1-yl)-2-oxo-3,12-dihydro-2H-pyrano[3,2-c][1,2,4]triazolo[1,5-a]quinoline-11-carbonitrile (11)

To a solution of 6 (0.36 g, 1.0 mmol) in pyridine (20 mL), semicarbazide hydrochloride (0.11 g, 1.0 mmol) was added, and the mixture was heated under reflux for 6 h (TLC control). After cooling, the mixture was poured into cold water with stirring. The solid crude product was filtered, dried and recrystallized from dioxane to give 11 (0.30 g, 75%), as an orange solid; m. p. 246-248 °C. - FT-IR (KBr, cm<sup>-1</sup>): v = 3291, 3257, 3176, 3056, 2959 (w), 2193, 1719, 1673 (s), 1597 (m).  $-{}^{1}$ H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 5.49$ (s, 1H, 4-H), 7.34-7.64 (m, 9H, NH<sub>2</sub> + Ar-H), 7.72-8.00 (m, 4H, NH + Ar-H), 8.45 (d, 1H, J = 8.0 Hz, Ar-H). – <sup>13</sup>C NMR (75.5 MHz, [D<sub>6</sub>]DMSO):  $\delta = 31.5$  (C-4), 58.5 (C-3), 100.0 (C-4a), 112.9 (C-13a), 116.6 (C-10), 119.1 (CN), 122.4, 123.4, 124.7, 125.7, 125.8, 126.0, 127.4, 128.4, 130.9, 132.9, 133.2 (Carom), 140.7 (C-9a), 152.1 (C-14a), 153.8 (C-5a), 157.8 (C-2), 163.0 (C=O). – MS ((+)-FAB): m/z = 405 $[M]^+$ . – GC-MS (EI, 70 eV): m/z (%) = 405 (1)  $[M]^+$ , 404 [M–H]<sup>+</sup> (5), 378 (25), 366 (5), 302 (100), 153 (71), 121 (88). - C<sub>24</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub> (405.12): calcd. C 71.10, H 3.73, N 17.27; found C 70.82, H 3.42, N 16.98.

# *N-(3-Cyano-4-(naphthalen-1-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromen-2-yl)acetamide* (12)

To a solution of 6 (0.36 g, 1.0 mmol) in dry pyridine (1.0 mL) was added acetic anhydride (3 mL), and the mixture was refluxed for 3 h (TLC monitoring). On cooling, a precipitate was separated and washed with EtOH. Recrystallization from dioxane afforded 12 (0.22 g, 55%) as a brown solid; m. p.  $160 - 162 \degree C. - FT-IR$  (KBr, cm<sup>-1</sup>): v = 3201, 3055,2957, 2223 (w), 1719 (s), 1675 (m), 1636 (w), 1608 (m). -<sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 2.35$  (s, 3H, CH<sub>3</sub>), 5.77 (s, 1H, 4-H), 7.30-7.57 (m, 5H, Ar-H), 7.61-7.89 (m, 3H, Ar-H), 7.93 (d, 1H, J = 8.1 Hz, Ar-H), 8.03 (d, 1H, J = 7.6 Hz, Ar-H), 8.71 (d, 1H, J = 7.6 Hz, Ar-H), 12.61 (br s., 1H, NH). – <sup>13</sup>C NMR (75.5 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 20.9 (CH<sub>3</sub>), 29.2 (C-4), 57.0 (C-3), 102.3 (C-4a), 106.4 (C-10a), 116.5 (CN), 122.6, 124.8, 125.0, 125.5, 125.6, 126.0, 127.1, 127.4, 127.9, 131.4, 132.8 (Carom), 151.9 (C-2), 154.1 (C-6a), 159.3 (C-11a), 160.1 (C=O), 162.0 (MeCO). - MS ((+)-FAB):  $m/z = 408 \text{ [M]}^+$ . – GC-MS (EI, 70 eV): m/z $(\%) = 408 (35) [M]^+$ , 366, (18), 342 (33), 314 (50), 299  $(33), 239 (100), 152 (40), 121 (50). - C_{25}H_{16}N_2O_4 (408.11):$ calcd. C 73.52, H 3.95, N 6.86; found C 73.21, H 3.52, N 6.45.

# Methyl-7-(naphthalen-1-yl) chromeno[3,4:5,6]pyrano-[2,3-d]pyrimidin-6,8-dione (13)

A solution of **6** (0.36 g, 1.0 mmol) in acetic anhydride (10 mL) containting conc.  $H_2SO_4$  (5 mL) was heated un-

der reflux for 10 h. A precipitate was formed after keeping the mixture at room temperature for 24 h, which was filtered and washed with water and EtOH. The product was recrystallized from EtOH to give 13 (0.30 g, 75%) as a colorless solid; m. p.  $160-162 \degree C. - FT-IR$  (KBr, cm<sup>-1</sup>): v = 3116, 3034, 3003, 2938, 2847 (w), 1737 (s), 1662 (s), 1595 (m).  $^{-1}$ H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 2.35$  (s, 3H, CH<sub>3</sub>), 5.75 (s, 1H, 5-H), 7.29-7.57 (m, 5H, Ar-H), 7.61-7.79 (m, 3H, Ar-H), 7.90 (d, 1H, J = 7.9 Hz, Ar-H), 8.01 (d, 1H, J = 7.6 Hz, Ar-H), 8.70 (d, 1H, J = 8.0 Hz, Ar-H), 12.60 (br s., 1H, NH). – <sup>13</sup>C NMR (75.5 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 20.9 (CH<sub>3</sub>), 30.0 (C-5), 102.3 (C-4a), 106.4 (C-5a), 116.5 (C-11a), 122.5, 124.8, 125.0, 125.5, 125.6, 126.0, 127.1, 127.4, 127.9, 131.4, 132.8, 132.8 (Carom), 151.9 (C-7a), 154.1 (C-2), 159.1 (C-12a), 159.3 (C-13a), 159.8 (C=O), 161.9 (C4=O). – MS ((+)-FAB):  $m/z = 408 [M]^+$ . – GC-MS (EI, 70 eV): m/z (%) = 408 (30) [M]<sup>+</sup>, 281 (100), 240 (9), 128 (10). - C<sub>25</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> (408.11): calcd. C 73.52, H 3.95, N 6.86; found C 73.20, H 3.51, N 6.44.

# *General preparation of alkyl 8-amino-(naphthalen-1-yl)-6-oxo-10-alkyl-6,7-dihydro-[3',4' : 5,6]pyrano[2,3-b]pyridine-9-carboxylate* **14–17**

To a stirred solution of ester (1.0 mmol) in dry toluene (20 mL) were added **6** (0.36 g, 1.0 mmol) and SnCl<sub>4</sub> (2 mL). The reaction mixture was stirred under argon at room temperature for 30 min and then heated under reflux for 6 h (TLC control). After cooling, the mixture was dispersed into water and adjusted to pH = 12 - 13 with a saturated aq. solution of Na<sub>2</sub>CO<sub>3</sub>. The mixture was filtered, and the filterate was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried and evaporated to dryness to give a crude product. Recrystallization from dioxane afforded the desired product.

# *Ethyl 8-amino-7-(naphthalen-1-yl)-6-oxo-10-propyl-6,7-dihydrochromeno[3',4' : 5,6]pyrano[2,3-b]pyridine-9-carboxylate (14)*

From propyl 3-oxopentanoate (0.16 g). Yield: 0.27 g (54%) as a yellow solid, m. p. 187–189 °C. – FT-IR (KBr, cm<sup>-1</sup>): v = 3475, 3307, 3055, 2960 (w), 1719 (s), 1677, 1651, 1605 (m). – <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 1.00$  (t, 3H, J = 7.1 Hz, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.25 (m, 5 H, OCH<sub>2</sub>CH<sub>3</sub>), 4.26 (q, 2H, J = 7.3 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 5.95 (br s., 2H, NH<sub>2</sub>), 6.07 (s, 1H, 5-H), 7.47–7.79 (m, 6H, Ar-H), 7.86 (d, 2H, Ar-H), 7.99 (d, 2H, Ar-H), 8.16 (d, 1H, J = 8.0 Hz, Ar-H). – <sup>13</sup>C NMR (75.5 MHz, [D<sub>6</sub>]DMSO):  $\delta = 13.0$ , 13.2 (2 × CH<sub>3</sub>), 22.4 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 28.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 39.5 (C-5), 60.1 (OCH<sub>2</sub>CH<sub>3</sub>), 70.0 (C-5a), 110.0 (C-3), 113.0 (C-4a), 115.6 (C-8), 121.3 (C-11a), 122.5, 123.2, 124.4, 124.7, 125.0, 127.2, 127.6, 128.2, 128.3, 130.2,

131.3 (C<sub>arom</sub>), 139.2 (C-2); 151.5 (C-4), 154.3 (C-7a), 154.3 (C-13a), 155.0 (C-12a), 162.2 (C=O), 167.0 (CO<sub>2</sub>Et). – MS ((+)-FAB): m/z = 506 [M]<sup>+</sup>. – GC-MS (EI, 70 eV): m/z (%) = 506 (9) [M<sup>+</sup>], 478 (45), 406 (95), 379 (100), 333 (60), 315 (21), 278 (22), 207 (44). – C<sub>31</sub>H<sub>27</sub>N<sub>2</sub>O<sub>5</sub> (506.18): calcd. C 73.50, H,5.17, N 5.53; found C 73.18, H 4.88, N 5.20.

# *Ethyl 8-amino-10-methyl-7-(naphthalen-1-yl)-6-oxo-6,7dihydrochromeno[3',4' : 5,6]pyrano [2,3-b]pyridine-9-carboxylate (15)*

From methyl 3-oxopentanoate (0.13 g). Yield: 0.25 g (53%) as a colorless solid, m. p. 260-262 °C. - FT-IR (KBr,  $cm^{-1}$ ): v = 3500, 3399, 3055, 2970 (w), 1709, 1650(s), 1607 (m).  $-{}^{1}$ H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 1.24$  (t, 3H, J = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.49 (s, 3H, CH<sub>3</sub>), 4.23 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 6.02 (s, 1H, 5-H), 6.10 (br s., 2H, NH<sub>2</sub>), 7.39–7.75 (m, 7H, Ar-H), 7.82 (d, 1H, J = 7.7 Hz, Ar-H), 7.94 (d, 1H, J = 8.1 Hz, Ar-H), 8.10 (d, 1H, J = 8.0 Hz, Ar-H), 8.83 (d, 1H, J = 8.0 Hz, Ar-H). – <sup>13</sup>C NMR (75.5 MHz,  $[D_6]DMSO$ :  $\delta = 14.1$  (OCH<sub>2</sub>CH<sub>3</sub>), 26.7 (CH<sub>3</sub>), 36.4 (C-5), 61.1 (OCH<sub>2</sub>CH<sub>3</sub>), 80.0 (C-5a), 114.0 (C-3), 116.6 (C-4a + C-8), 122.3 (C-11a), 123.4, 124.3, 125.7, 126.0, 127.5, 128.7, 129.4, 131.2, 132.3 (Carom), 139.2 (C-2); 155.2 (C-4), 155.3 (C-7a), 155.9 (C-13a), 160.0 (C-12a), 161.0 (C=O), 168.0 (CO<sub>2</sub>Et). – MS ((+)-FAB):  $m/z = 478 \text{ [M]}^+$ . – GC-MS (EI, 70 eV): m/z (%) = 478 (32) [M]<sup>+</sup>, 404 (7), 351 (100), 305 (67), 216 (3). - C<sub>29</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>(478.15): calcd. C 72.79, H 4.63, N 5.85; found C 72.50, H 4.22, N 5.43.

# *Methyl 8-amino-10-ethyl-7-(naphthalen-1-yl)-6-oxo-6,7-dihydrochromeno[3',4' : 5,6]pyrano[2,3-b]pyridine-9-carboxylate (16)*

From ethyl 3-oxobutanoate (0.13 g). Yield: 0.25 g (53%) as a colorless solid, m. p.  $166 - 168 \circ C. - FT-IR (KBr, cm^{-1})$ : *v* = 3484, 3311, 3075, 3041, 2974, 2947, 2876 (w), 1719 (s), 1681 (m), 1651 (s), 1605 (m). - <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 1.23$  (t, 3H, J = 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.76 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.76 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 5.93 (s, 2H, NH<sub>2</sub>), 6.05 (s, 1H, 5-H), 7.44-7.76 (m,7H, Ar-H), 7.85 (d, 1H, J = 7.4 Hz, Ar-H), 7.97 (d, 1H, J = 7.7 Hz, Ar-H), 8.12 (d, 1H, J = 7.5 Hz, Ar-H), 8.88 (br s., 1H, Ar-H). -<sup>13</sup>C NMR (75.5 MHz, [D<sub>6</sub>]DMSO):  $\delta = 13.5$  (CH<sub>2</sub>CH<sub>3</sub>), 29.4 (CH<sub>2</sub>CH<sub>3</sub>), 38.8 (C-5), 52.1 (CO<sub>2</sub>CH<sub>3</sub>), 100.8 (C-5a), 109.7 (C-3), 113.5 (C-4a), 116.5 (C-8), 122.8 (C-11a), 123.5, 124.8, 125.8, 126.0, 127.0, 127.9, 128.1, 128.7, 131.1, 132.8, 133.0 (Carom), 139.9 (C-2), 153.1 (C-4), 154.6 (C-7a), 155.1 (C-13a), 160.0 (C=O), 160.8 (C-12a), 167.1 (CO<sub>2</sub>Me). -MS ((+)-FAB):  $m/z = 478 \text{ [M]}^+$ . – GC-MS (EI, 70 eV): m/z $(\%) = 478 (32) [M]^+, 418 (6), 351 (100), 319 (50), 207 (8),$ 127 (5). –  $C_{29}H_{22}N_2O_5$  (478.15): calcd. C 72.79, H 4.63, N 5.85; found C 72.52, H 4.20, N 5.41.

# *Methyl* 8-amino-10-methyl-7-(naphthalen-1-yl)-6-oxo-6,7-dihydrochromeno[3',4' : 5,6]pyrano[2,3-b]pyridine-9-carboxylate (**17**)

From methyl 3-oxobutanoate (0.13 g). Yield: 0.26 g (56%) as a colorless solid, m. p. 313-315 °C. - FT-IR (KBr,  $cm^{-1}$ ): v = 3489, 3317, 3055, 2996, 2948 (w), 1720 (s), 1678, 1651, 1605 (m). – <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 2.47$  (s, 3H, CH<sub>3</sub>), 3.73 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 6.01 (s, 1H, 5-H), 6.09 (s, 2H, NH<sub>2</sub>), 7.41-7.57 (m, 3H, Ar-H), 7.63-7.96 (m, 6H, Ar-H), 8.10 (d, 1H, J = 7.5 Hz, Ar-H), 8.83 (br s., 1H, Ar-H). – <sup>13</sup>C NMR (75.5 MHz, [D<sub>6</sub>]DMSO):  $\delta = 24.4$ (CH<sub>3</sub>), 38.6 (C-5), 51.9 (CO<sub>2</sub>CH<sub>3</sub>), 60.0 (C-3), 109.1 (C-3), 113.5 (C-4a), 116.5 (C-8), 122.8 (C-11a), 124.9, 125.81, 126.7, 128.0, 128.2, 128.7, 131.4, 132.9 (Carom), 138.7 (C-2), 153.7 (C-4), 154.6 (C-7a), 154.9 (C-13a), 157.15 (C=O), 160.0 (C-12a), 167.3 (CO<sub>2</sub>CH<sub>3</sub>). - MS ((+)-FAB):  $m/z = 465 [M+H]^+$ . – GC-MS (EI, 70 eV): m/z (%) = 464 (49) [M]<sup>+</sup>, 404 (15), 351 (26), 337 (100), 319 (14), 305 (52), 278 (7), 250 (6), 216 (6), 127 (12). - C<sub>28</sub>H<sub>21</sub>N<sub>2</sub>O<sub>5</sub>(464.14): calcd. C 72.14, H 4.34, N 6.03; found C 71.85, H 4.01, N 5.70.

# (Z)-2-((4-Methoxybenzylidene)amino)-4-(naphthalen-1-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (18)

A solution of 6 (0.36 g, 1.0 mmol) in dioxane (20 mL) and piperidine (0.5 mL) was treated with *p*-anisaldehyde (0.30 g, 1.0 mmol) and refluxed for 2 h. The mixture was poured onto ice/water, and the solid obtained was collected and recrystallized from diethyl ether to give 18 (0.27 g, 56%) as an orange solid, m. p.  $103 - 105 \degree$ C. – FT-IR (KBr, cm<sup>-1</sup>): v = 3200, 3027, 2982, 2219 (w), 2219 (s), 1713, 1674 (w), 1603 (s). -<sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 3.90 (s, 3H, OCH<sub>3</sub>), 6.09 (s, 1H, 4-H), 7.22-7.50 (m, 4H, Ar-H), 7.73-7.84 (m, 3H, Ar-H), 8.01-8.43 (m, 8H, Ar-H), 9.41 (s, 1H, CH=N). - <sup>13</sup>C NMR (75.5 MHz, [D<sub>6</sub>]DMSO):  $\delta = 39.5$  (C-4), 55.9 (OCH<sub>3</sub>), 76.9 (C-3), 113.2 (C-4a + C<sub>arom</sub>), 114.8 (C-10a), 115.2 (C-7), 115.4 (CN), 123. 8, 124.1, 125.4, 126.9, 127.2, 128.1, 128.1, 128.7, 128.9, 129.0, 130.8, 133.0, 133.4, 134.1, 135.3 (Carom), 150.0 (C-6a), 160.3 (C-11a), 160.4 (C=O), 161.0 (HC=N +C-OMe), 164.4 (C-2). - MS ((+)-FAB):  $m/z = 484 \text{ [M]}^+$ . – GC-MS (EI, 70 eV): m/z (%) = 484 (20) [M]<sup>+</sup>, 377 (18), 357 (30), 299 (100), 279 (32), 249 (23), 184 (42). - C31H20N2O4 (484.14): calcd. C 76.85, H 4.16, N 5.78; found C 76.43, H 3.87, N 5.36.

#### Crystal structure determination of 7

Data were collected on a Bruker APEX II Duo diffractometer. The structure was solved by Direct Methods and refined by full-matrix least-squares procedures on  $F^2$  with the SHELXTL software package [47]. Hydrogen atoms were placed in idealized positions and included as constrained into the refinement while all other atoms were refined with anisotropic displacement parameters.

*Crystal structure data*: C<sub>26</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>,  $M_r$  = 422.42, colorless plates, crystal dimensions = 0.5 × 0.2 × 0.1 mm<sup>3</sup>, orthorhombic, space group *Pbca*, *a* = 15.9428(3), *b* = 12.3953(2), *c* = 20.5395(4) Å, *Z* = 8, *D*<sub>calcd</sub> = 1.38 g cm<sup>-3</sup>,  $\mu$ (Mo $K_{\alpha}$ ) = 0.1 mm<sup>-1</sup>, *F*(000) = 1.760 e, *T* = 150(2) K.

- G. P. Ellis in *Chromenes, Chromanones and Chromones*, (Eds.: A. Weissberger, E. Taylor), John Wiley & Sons, New York, **1977**, pp. 1–10.
- [2] W. C. Cutting, R. H. Dreisbach, M. Azima, B. J. Neff, B. J. Brown, J. Wray, *Stanford Med. Bull.* **1951**, *9*, 236–242.
- [3] C. Mentzer, P. Meunier, J. Lecocq, D. Billet, D. Xuong, Bull. Soc. Chim. Fr. 1945, 12, 430–437.
- [4] J. S. G. Cox, Nature (London) 1967, 216, 1328-1329.
- [5] T. S. C. Orr, M. C. Pollard, J. Gwilliam, J. S. G. Cox, *Clin. Exp. Immunol.* **1970**, *7*, 745–757.
- [6] A. M. El Agrody, M. S. Abd El Latif, N. A. El Hady, A. H. Fakery, A. H. Badair, *Molecules* 2001, *6*, 519-527.
- [7] A. H. Badair, N. A. El Hady, M. S. Abd El Latif, A. H. Fakery, A. M. El Agrody, *Farmaco* 2000, 55, 708-714.
- [8] A. M. El Agrody, M. H. El Hakim, M. S. Abd El Latif, A. H. Faker, E. S. El Sayed, K. A. El Ghareab, *Acta Pharm.* 2000, *50*, 111–120.
- [9] M. C. Yimdjo, A. G. Azebaze, A. E. Nkengfack, A. M. Michele, B. Bodo, Z. T. Fomum, *Phytochemistry* 2004, 65, 2789–2795.
- [10] V. Jeso, K. C. Nicolaou, *Tetrahedron Lett.* 2009, 50, 1161–1163.
- [11] T. Mouri, T. Yano, S. Kochi, T. Ando, M. Hori, J. Pestic. Sci. 2005, 30, 209–213.
- [12] S. Sardari, Y. Mori, K. Horita, R. G. Micetich, S. Nishibe, M. Daneshtalab, *Bioorg. Med. Chem.* 1999, 7, 1933–1940.
- [13] W. P. Smith, L. S. Sollis, D. P. Howes, C. P. Cherry, D. I. Starkey, N. K. Cobley, *J. Med. Chem.* **1998**, *41*, 787–797.
- [14] R. N. Taylor, A. Cleasby, O. Singh, T. Sharzynski, J. A. Wonacott, W. P. Smith, L. S. Sollis, D. P. Howes, C. P. Cherry, R. Bethell, P. Colman, J. Med. Chem. 1998, 41, 798-807.
- [15] D. A. Quagliato, US Patent 5171857, 1993.
- [16] D. R. Buckle, S. Harry, US Patent 4263299, 1981.
- [17] H. Koga, H. Nabata, H. Nishina (Chugai Seiyaku K. K., Japan), PCT Int. Appl. WO 9214439, **1992**.

Mo *K*<sub>α</sub> radiation,  $\lambda = 0.71073$  Å, 56177 collected refls. (*hkl* -21/20, ±16, ±27), 5261 unique refls. (*R*<sub>int</sub> = 0.062), 290 refined parameters, *R*1 / *wR*2 = 0.0771 / 0.1363 (all data), GOF = 1.023,  $\Delta\rho_{\text{fin}}$  (max / min) = 0.39 / -0.21 e Å<sup>-3</sup>.

CCDC 918360 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data\_request/cif.

- [18] M. Weidenbörner, H. Hindrof, H. C. Jha, P. Tsotsonos, H. Egg, *Phytochemistry* **1990**, *29*, 1103–1105.
- [19] M. Weidenbörner, H. C. Jha, Pestic. Sci. 1993, 38, 347–351.
- [20] R. H. Davis, J. J. Donato, G. M. Hartman, R. C. Haas, J. Am. Podiatr. Med. Assoc. 1994, 84, 77-81.
- [21] T. Hirata, T. Suga, Bull. Chem. Soc. Jap. 1978, 51, 842–849.
- [22] D. Womble, J. H. Helderman, Int. J. Immunopharmac. 1988, 10, 967–974.
- [23] C. Conti, N. Desideri, *Bioorg. Med. Chem.* 2009, *17*, 3720–372; and refs. cited therein.
- [24] C. P. Dell, C. W. Smith, Eur. Pat. Appl. 537 949, 1993.
- [25] S. V. Jovanovic, S. Steenken, M. Tosic, B. Marjanovic, M. G. Simic, J. Am. Chem. Soc. 1994, 116, 4846–4851.
- [26] T. Symeonidis, M. Chamilos, D. J. Hadjipavlou-Litina, M. Kallitsakis, K. E. Litinas, *Bioorg. Med. Chem. Lett.* 2009, 19, 1139–1142.
- [27] T. Narender, S. S. Gupta, *Bioorg. Med. Chem. Lett.* 2009, 14, 3913–3916.
- [28] D. O. Moon, C. Park, M. S. Heo, Y. M. Park, Y. H. Choi, G. H. Kim, *Int. Immunopharmacol.* 2007, 7, 36-45.
- [29] Y. A. Al-Soud, I. A. Al-Masoudi, S. Saeed, U. Beifuß, N. A. Al-Masoudi, *Chem. Heterocyc. Comp.* **2006**, 467, 669–676.
- [30] F. Eiden, F. Denk, Arch. Pharm. (Weinheim) 1991, 324, 353-354.
- [31] C. Bruhlmann, F. Ooms, P.-A. Carrupt, B. Testa, M. Catto, F. Leonetti, C. Altomare, A. Carotti, *J. Med. Chem.* 2001, 44, 3195–3208.
- [32] S. R. Kesten, T. G. Heffner, S. G. Johnson, T. A. Pugsley, J. L. Wright, D. L. Wise, *J. Med. Chem.* **1999**, *42*, 3718–3725.
- [33] V. S. V. Satyanarayana, P. Sreevani, A. Sivakumar, V. Vijayakumar, *Arkivoc* 2008, *17*, 221–233.
- [34] D. Yu, A. Brossi, N. Kilgore, C. Wild, G. Allaway, K.-H. Lee, *Bioorg. Med. Chem. Lett.* 2003, 13, 1575-1576.

6299-6310.
[36] T. Fujiwara, A. Sato, M. El-Farrash. K. Miki, K. Kabe, Y. Isaka, M. Kodama, Y. M. Wu, L. B. Chen, H. Harada, M. Sugimoto, M. Hatanaka, Y. Hinuma, *Antimicrob. Agents Chemother.* 1998, 42, 1340-1345.

S. Kasibhatla, S. X. Cai, J. Med. Chem. 2004, 47,

- [37] S. J. Pastine, S. W. Youn, D. Same, Org. Lett. 2003, 5, 1055-1058.
- [38] C. Hardouin, L. Burgaud, A. Valleix, E. Doris, *Tetrahedron Lett.* 2003, 44, 435–437.
- [39] S. Caddick, W. Kofie, *Tetrahedron Lett.* **2002**, *43*, 9347–9350.
- [40] N. Shezad, A. A. Clifford, C. M. Rayner, *Tetrahedron Lett.* 2001, 42, 323–325.
- [41] L. Shi, C. K. Narula, K. T. Mak, L. Kao, Y. Xu, R. F. Heck, J. Org. Chem. 1983, 48, 3894–3900.

- [42] W. Willker, D. Leibfritz, R. Kressebaum, W. Bermel, Mag. Reson. Chem. 1993, 31, 287–292.
- [43] R. Pauwels, J. Balzarini, M. Baba, R. Snoeck, D. Schols, P. Herdewijn, J. Desmyter, E. De Clercq, J. Virol. Methods 1988, 20, 309–321.
- [44] K. D. Hargrave, J. R. Proudfoot, K. G. Grozinger, E. Cullen, S. R. Kapadia, U. R. Patel, V. U. Fuchs, S. C. Mauldin, J. Vitous, M. L. Behnke, J. M. Klunder, K. Pal, J. W. Skiles, D. W. McNeil, J. M. Rose, G. C. Chow, M. T. Skoog, J. C. Wu, G. Schmidt, W. W. Engel, W. G. Eberlein, T. D. Saboe, S. J. Campbell, A. S. Rosenthal, J. Adams, J. Med. Chem. 1991, 34, 2231–2241.
- [45] H. Mitsuya, K. J. Weinhold, P. A. Furman, M. H. St. Clair, S. N. Lehrmann, R. Gallo, D. Bolognesi, D. W. Barry, S. Broder, *Proc. Natl. Acad. Sci. USA* 1985, 82, 7096–7100.
- [46] V. Nesterov, D. Weinenfeld, S. Nesterova, L. Daniels, J. Chem. Crystallogr. 2005, 35, 917–922.
- [47] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112–122.