

Efficient Solvent-Free Synthesis of Benzothiazine-Fused Pyrrolo[3,4-*c*]coumarins: Cycloaddition Reactions between Coumarin-Based Dihydrobenzothiazoles and Isocyanides

by Mehdi Khoobi^{a)}), Ali Ramazani^{*c)}, Mohammad Mahdavi^{d)}, Alireza Foroumadi^{a)}, Saeed Emami^{b)}, Sang Woo Joo^{*e)}, Katarzyna Ślepokura^{f)}, Tadeusz Lis^{f)}, and Abbas Shafiee^{*d)}

^{a)} Drug Design & Development Research Center, Tehran University of Medical Sciences, Tehran, Iran

^{b)} Department of Medicinal Chemistry and Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran

^{c)} Department of Chemistry, University of Zanjan, P.O. Box 45195-313, Zanjan, Iran
(phone: +98-241-5152572; fax: +98-241-5152477; e-mail: aliramazani@gmail.com)

^{d)} Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 14176, Iran

^{e)} School of Mechanical Engineering, Yeungnam University, Gyeongsan 712–749, Republic of Korea
(e-mail: swjoo@yu.ac.kr)

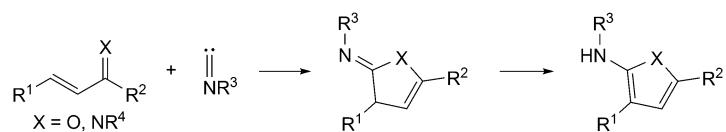
^{f)} Faculty of Chemistry, University of Wrocław, 14 Joliot-Curie St., PL-50-383 Wrocław

A new and unusual synthesis of benzothiazine-fused pyrrolo[3,4-*c*]coumarins, involving the ring-opening of coumarin-based dihydrobenzothiazoles and subsequent [4 + 1] cycloaddition reaction with isocyanides, was described. Thus, simple heating of various 3-(2,3-dihydro-2-methylbenzo[*d*]thiazol-2-yl)coumarins with isocyanides produced the title compounds in good yields under solvent-free conditions.

Introduction. – Cycloaddition reactions are an important route to the formation of cyclic compounds from acyclic substrates. A [4 + 1] cycloaddition reaction of a conjugated 1,3- π system with isocyanides is a straightforward and attractive method for the construction of five-membered compounds, such as furan and pyrrole derivatives ($X = O$ and N , *Scheme 1*) [1]. *Quai et al.* reported the reaction of α,β -unsaturated carbonyl compounds with isocyanides to afford quite unstable furan-2-imines, which are oxidized quickly by *triplet* O_2 leading to 5-hydroxy-*N*-substituted-2*H*-pyrrole-2-ones [2].

Nair and co-workers described the reaction of *in situ* generated quinone methides from 4-hydroxycoumarin with various aldehydes, which underwent reaction with isocyanides to produce furocoumarins [3].

Scheme 1. [4 + 1] Cycloaddition Reaction of Conjugated 1,3- π Systems with Isocyanides



Coumarins (2*H*-1-benzopyran-2-ones) and their annulated derivatives are an important class of compounds, as they display a wide spectrum of biological activities [4]. Especially polycyclic coumarin derivatives have been shown to be potent inhibitors of tumor induction by carcinogenic polycyclic aromatic hydrocarbon [5]. Pyrrolo-annulated benzopyranones were found to possess promising biological features such as antitumor activity, reversal of multidrug resistance (MDR), and HIV-1 integrase inhibition activity [6]. Lamellarins are pyrrolo-annulated benzopyranone alkaloids isolated from mollusks and ascidians. Of the family of lamellarins, Lam-D is one of the most potent lead candidates for cancer chemotherapy. There is substantial evidence that Lam-D is an inhibitor of topoisomerase I and a potent pro-apoptotic agent [7]. In the light of the significance of pyrrolo-annulated coumarin systems and their diverse pharmacological properties, there has been a continuous effort to develop new, convenient, and versatile methods for modification of this class of compounds.

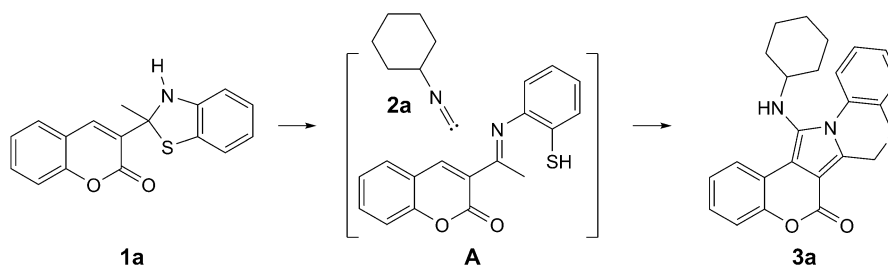
Results and Discussion. – As part of our continuing efforts on the development of efficient routes for the preparation of biologically active coumarin-based compounds [8][9], we have now synthesized new benzothiazine-fused pyrrolo[3,4-*c*]coumarins using a simple reaction between 3-(dihydrobenzothiazol-2-yl)coumarins and isocyanides without using any solvent or catalyst.

Recently, we have studied the synthesis and biological activities of new coumarin derivatives of type **1** containing the 2-methylbenzothiazole motif. These compounds were easily prepared in excellent yields using the standard protocol developed in our laboratory [9].

Considering the ring-opening ability of the dihydrobenzothiazole derivatives **1** and generation of intermediate **A** [10], our attention was directed to develop a [4 + 1] cycloaddition reaction of this 1,3-conjugated system with isocyanides. As far as we know, there is no report on the reaction of 3-imino-substituted coumarin with isocyanides. We initiated our studies with dihydrobenzothiazole **1a**, which, upon treatment with a 1.5 equiv. of cyclohexyl isocyanide **2a**, afforded the product **3a** in 77% yield (Scheme 2).

Product **3a** was characterized on the basis of its spectroscopic data. The IR spectrum showed a strong absorption band at 1721 cm⁻¹, which is characteristic for the coumarin C=O group. In the ¹H-NMR spectrum, the aromatic H-atoms of coumarin and benzene rings appeared at 7–8 ppm and the H–N resonated at 4.93 ppm (exchangeable by D₂O) [3]. Also, two CH₂ H-atoms of the benzothiazine ring were observed as a *singlet*

Scheme 2. Synthesis of Densely Functionalized Pyrrole Derivatives **3a**



at 4.37 ppm. The ^1H -decoupled ^{13}C -NMR spectrum of **3a** exhibited 22 signals. For example, the CH_2 group of the benzothiazine ring which absorbed at 56.5 ppm was confirmed with DEPT spectra. The mass spectrum of **3a** displayed a molecular-ion peak at m/z 402, and a fragmentation peak at m/z 319, indicating the loss of the cyclohexyl group. Furthermore, an X-ray crystallographic study was carried out on compound **3a**, after recrystallization from MeCN (*Fig.*).

Several examples of this prototype reaction which confirm the synthetic utility of this protocol are outlined in the *Table*.

To explain the formation of the products, we propose a reaction mechanism, which is outlined in *Scheme 3*. On the basis of the well-established chemistry of isocyanides [11], it is reasonable to assume that cycloaddition of the initially generated intermediate **A** and isocyanide **2** leads to compound **B**. The formation of the benzothiazine scaffold certainly involves a complex multistep sequence of events and probably proceeds by intramolecular addition of the SH group to alkene. It is conceivable that compound **B** can tautomerize under the reaction condition to an intermediate **C**. In the next step, the intramolecular addition of SH to the exocyclic group $\text{C}=\text{C}$ results in the formation of compounds **D**, which is converted to compound **E** by tautomerization. Finally, compound **3** can be formed after further tautomerization and air oxidation and aromatization.

Conclusions. – We have introduced a new and unusual synthetic procedure to prepare benzothiazine-fused pyrrolo[3,4-*c*]coumarins involving the ring opening of coumarin-based dihydrobenzothiazoles and subsequent $[4+1]$ cycloaddition reaction with isocyanides. The present method offers the advantages that the reaction is

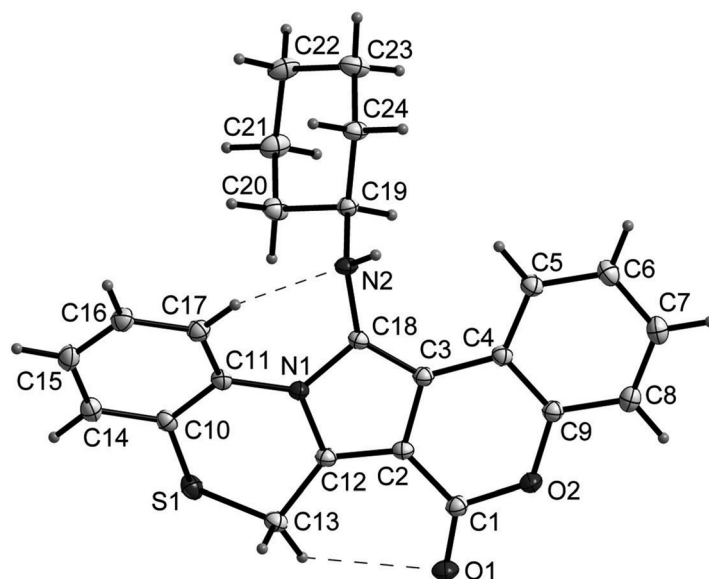
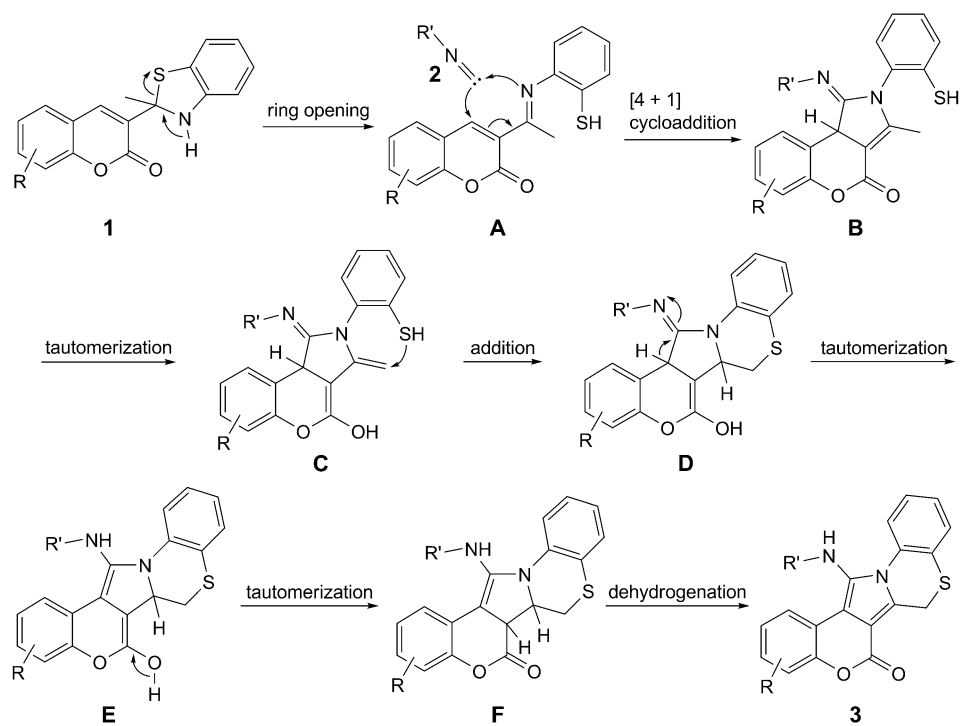


Figure. X-Ray structure of compound **3a** with the atom numbering scheme and the intramolecular $\text{C}-\text{H}\cdots\text{O}/\text{N}$ contacts (dashed lines). Displacement ellipsoids are shown at the 50% probability level.

Table. Synthesis of Benzothiazine-Fused Pyrrolo[3,4-*c*]coumarins **3a–3h**

	1a – 1c	2a – 2c	3a – 3h
Compound	R	R'	Yield [%] ^{a)}
3a	H	Cyclohexyl	77
3b	6-Br	Cyclohexyl	73
3c	8-MeO	Cyclohexyl	74
3d	H	^t Bu	70
3e	8-MeO	^t Bu	77
3f	H	1,1,3,3-Tetramethylbutyl	67
3g	8-MeO	1,1,3,3-Tetramethylbutyl	68
3h	6-Br	1,1,3,3-Tetramethylbutyl	64

^{a)} Yield of isolated product.

Scheme 3. Proposed Mechanism for the Formation of the Title Compounds **3**

performed under neutral conditions and the substances can be mixed under solvent-free conditions, and without any promoters such as acids, *Lewis* acids, or transition-metal complexes. The products are polycyclic molecules of potential synthetic and pharmacological interest.

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Experimental Part

General. IR Spectra: Nicolet FT-IR Magna 550 spectrometer; KBr disks; $\tilde{\nu}$ in cm^{-1} . ^1H -NMR Spectra: Bruker 400 or 500 MHz instruments; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: HP 5937, mass selective detector (Agilent technologies); in m/z . Elemental analyses: CHN-Rapid Heraeus elemental analyzer, the results of elemental analyses (C, H, N) were within $\pm 0.4\%$ of the calculated values.

General Procedure. A mixture of 3-(2-methyl-2,3-dihydrobenzo[*d*]thiazol-2-yl)-2H-chromen-2-ones **1** (2 mmol) and the appropriate isocyanide **2** (3 mmol) was stirred at 130° for 3 h in a sealed tube. The mixture was cooled to r.t. and the residue was purified by column chromatography (CC) with hexane/AcOEt 1:2. The product was recrystallized from hexane/AcOEt 1:1.

14-(Cyclohexylamino)[1]benzopyrano[3',4':3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (3a). Red solid. M.p. $217-219^\circ$. IR: 3332 (NH), 1721 (C=O). ^1H -NMR (CDCl_3): 0.90–1.03 (*m*, 5 H); 1.37–1.58 (*m*, 5 H); 2.54 (*m*, 1 H); 4.37 (*s*, 2 H); 4.93 (*s*, 1 H); 7.29–7.32 (*m*, 4 H); 7.42 (*t*, $J = 7.7$, 1 H); 7.60 (*d*, $J = 7.7$, 1 H); 8.30 (*d*, $J = 7.3$, 1 H); 8.46 (*d*, $J = 8.2$, 1 H). ^{13}C -NMR (CDCl_3): 23.8; 24.1; 25.2; 32.6; 56.5; 100.0; 112.0; 116.7; 117.0; 122.6; 123.5; 124.1; 126.6; 126.7; 127.1; 127.7; 129.4; 129.8; 130.7; 133.8; 150.3; 158.1. ESI-MS: 402 (85, M^+), 319 (100), 305 (51), 280 (48). Anal. calc. for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$ (402.50): C 71.62, H 5.51, N 6.96; found: C 71.41, H 5.86, N 6.69.

2-Bromo-14-(cyclohexylamino)[1]benzopyrano[3',4':3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (3b). Yellow solid. M.p. $222-224^\circ$. IR: 3328 (NH), 1720 (C=O). ^1H -NMR (CDCl_3): 0.87–0.97 (*m*, 5 H); 1.39–1.54 (*m*, 5 H); 2.09 (*s*, 1 H); 4.36 (*s*, 2 H); 5.13 (*s*, 1 H); 7.26 (*d*, $J = 8.5$, 1 H); 7.33 (*t*, $J = 7.5$, 1 H); 7.44 (*t*, $J = 7.5$, 1 H); 7.48 (*d*, $J = 8.5$, 1 H); 7.62 (*d*, $J = 7.5$, 1 H); 8.42 (*d*, $J = 8.5$, 1 H); 8.48 (*s*, 1 H). Anal. calc. for $\text{C}_{24}\text{H}_{21}\text{BrN}_2\text{O}_2\text{S}$ (481.40): C 59.88, H 4.40, N 5.82; found: C 59.56, H 4.22, N 5.61.

14-(Cyclohexylamino)-4-methoxy[1]benzopyrano[3',4':3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (3c). Yellow solid. M.p. $188-190^\circ$. IR: 3326 (NH), 1723 (C=O). ^1H -NMR (CDCl_3): 0.92–1.04 (*m*, 5 H); 1.34–1.48 (*m*, 5 H); 2.48 (*m*, 1 H); 3.94 (*s*, 3 H); 4.39 (*s*, 2 H); 5.01 (*s*, 1 H); 6.91 (*d*, $J = 7.5$, 1 H); 7.23 (*t*, $J = 7.5$, 1 H); 7.44–7.58 (*m*, 5 H); 8.44 (*d*, $J = 8.5$, 1 H). Anal. calc. for $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$ (432.53): C 69.42, H 5.59, N 6.48; found: C 69.21, H 5.80, N 6.69.

14-[(tert-Butyl)amino][1]benzopyrano[3',4':3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (3d). Yellow solid. M.p. $231-233^\circ$. IR: 3332 (NH), 1715 (C=O). ^1H -NMR (CDCl_3): 0.81 (*s*, 9 H); 4.06 (*d*, $J = 1.5$, 1 H); 4.67 (*d*, $J = 1.5$, 1 H); 4.80 (*s*, 1 H); 7.28–7.32 (*m*, 4 H); 7.40 (*t*, $J = 7.6$, 1 H); 7.62 (*d*, $J = 7.6$, 1 H); 8.36 (*d*, $J = 8.0$, 1 H); 8.50 (*d*, $J = 7.6$, 1 H). Anal. calc. for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ (376.47): C 70.19, H 5.35, N 7.44; found: C 70.34, H 5.13, N 7.18.

14-[(tert-Butyl)amino]-4-methoxy[1]benzopyrano[3',4':3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (3e). Yellow solid. M.p. $204-206^\circ$. IR: 3330 (NH), 1722 (C=O). Anal. calc. for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$ (406.50): C 67.96, H 5.46, N 6.89; found: C 67.73, H 5.71, N 6.66.

14-[(1,1,3,3-Tetramethylbutyl)amino][1]benzopyrano[3',4':3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (3f). Yellow solid. M.p. $169-171^\circ$. IR: 3335 (NH), 1720 (C=O). ^1H -NMR (CDCl_3): 0.86 (*s*, 9 H); 0.95 (*s*, 6 H); 1.40 (*s*, 2 H); 4.04 (*d*, $J = 1.5$, 1 H); 4.62 (*s*, 1 H); 4.68 (*d*, $J = 1.5$, 1 H); 7.29–7.33 (*m*, 4 H); 7.42 (*t*, $J = 7.3$, 1 H); 7.62 (*d*, $J = 7.3$, 1 H); 8.31 (*d*, $J = 7.8$, 1 H); 8.48 (*d*, $J = 7.3$, 1 H). ^{13}C -NMR (CDCl_3): 27.2; 28.7; 30.1; 31.5; 55.8; 60.4; 100.1; 114.7; 116.8; 117.3; 123.5; 124.3; 124.5; 126.6; 127.4; 128.5; 128.8; 129.4; 131.5; 134.3; 150.4; 158.2. Anal. calc. for $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_2\text{S}$ (432.58): C 72.19, H 6.52, N 6.48; found: C 72.32, H 6.33, N 6.69.

4-Methoxy-14-[(1,1,3,3-tetramethylbutyl)amino][1]benzopyrano[3',4':3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (**3g**). Yellow solid. M.p. 143–145°. IR: 3328 (NH), 1720 (C=O). Anal. calc. for C₂₇H₃₀N₂O₃S (462.60): C 70.10, H 6.54, N 6.06; found: C 70.33, H 6.21, N 6.27.

2-Bromo-14-[(1,1,3,3-tetramethylbutyl)amino][1]benzopyrano[3',4':3,4]pyrrolo[2,1-c][1,4]benzothiazin-6(7H)-one (**3h**). Yellow solid. M.p. 179–181°. IR: 3334 (NH), 1718 (C=O). Anal. calc. for C₂₆H₂₇BrN₂O₃S (511.47): C 61.05, H 5.32, N 5.48; found: C 61.29, H 5.09, N 5.26.

X-Ray Crystallography. Yellow-brown single crystals of **3a** were obtained from MeCN soln. by slow evaporation at r.t. over several days. The yellow-brown single crystals were filtered, washed with cold MeCN, and dried at r.t. (m.p. 216°). Compound **3a**: C₂₄H₂₂N₂O₂S, *M_r* 402.50; yellow-brown block, crystal dimensions, 0.40 × 0.32 × 0.26 mm³; orthorhombic; space group, *Pbca*; *a* = 7.267(2) Å, *b* = 18.636(4) Å, *c* = 28.259(4) Å, *V* = 3827.1(14) Å³, *T* = 100(2) K, *Z* = 8, *ρ*_{calc} = 11.397 g/cm³, *μ* = 0.19 mm^{−1} (for MoK_α, *λ* = 0.71073 Å); *F*(000) = 1696, reflections collected, 28350; reflections independent, 7480 [*R*_{int} = 0.022]; reflections observed, 6031 [*I* > 2σ(*I*)]; *θ* range, 2.62–38.46°, *h*, *k*, *l* range, −10 ≤ *h* ≤ 11, −28 ≤ *k* ≤ 26, −39 ≤ *l* ≤ 41, full-matrix least-squares on *F*², parameters, 266; restraints, 0; *R*₁ = 0.046, *wR*₂ = 0.115 [*F*² > 2σ(*F*²)], GoF = *S* = 1.09, largest difference in peak and hole, Δ*ρ*_{max} and Δ*ρ*_{min}, 0.54 and −0.36 e/Å³; resp. CCDC-851379 contains supplementary crystallographic data for this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or by e-mailing deposit@ccdc.cam.ac.uk.

The crystallographic measurement was performed on a *κ*-geometry Xcalibur PX four-circle diffractometer with graphite-monochromatized MoK_α radiation (*ω* and *φ* scans). Data were corrected for Lorentz and polarization effects. Data collection, cell refinement, and data reduction and analysis were carried out with the Xcalibur PX software, CRYSLIS CCD, and CRYSLIS RED, resp. (Oxford Diffraction Ltd., Abingdon, England, 2009). Empirical absorption correction was applied to the data with the use of CRYSLIS RED. The structure was solved by direct methods with the SHELXS-97 program, and refined using SHELXL-97 [12] with anisotropic thermal parameters for non-H-atoms. All H-atoms were found in difference Fourier maps, and were refined isotropically. In the final refinement cycles, all C-bonded H-atoms were treated as riding atoms in geometrically optimized positions, with C–H of 0.95–1.00 Å, and with *U*_{iso}(H) = 1.2*U*_{eq}(C). The figure was drawn using DIAMOND program (ver. 3.0d, K. Brandenburg, Crystal Impact GbR, Bonn, Germany, 2005).

REFERENCES

- [1] M. Oshita, K. Yamashita, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2005**, *127*, 761; N. Obata, T. Takizawa, *Tetrahedron Lett.* **1969**, *10*, 3403; Y. Ito, H. Kato, T. Saegusa, *J. Org. Chem.* **1982**, *47*, 741; J. H. Rigby, M. N. Qabar, *J. Am. Chem. Soc.* **1991**, *113*, 8975; G. Kollenz, W. Ott, E. Ziegler, K. Peters, H. G. v. Schnering, H. Quast, *Liebigs Ann. Chem.* **1980**, 1801; W. Ott, C. Kratky, P. Seiler, *Liebigs Ann. Chem.* **1980**, 1711; J. Moskal, A. M. van Leusen, *J. Org. Chem.* **1986**, *51*, 4131.
- [2] M. Quai, S. Frattini, U. Vendrame, M. Mondoni, S. Dossena, E. Cereda, *Tetrahedron Lett.* **2004**, *45*, 1413.
- [3] V. Nair, R. S. Menon, A. U. Vinod, S. Viji, *Tetrahedron Lett.* **2002**, *43*, 2293.
- [4] M. Strzelczyk, H. Matyjewska, H. Strozynski, *Pol. J. Pharmacol. Pharm.* **1990**, *42*, 377; I. Kostova, *Curr. Med. Chem. Anti-Cancer Agents* **2005**, *5*, 29; K. C. Fylaktakidou, D. J. Hadjipavlou-Litina, K. E. Litinas, D. N. Nicolaides, *Curr. Pharm. Des.* **2004**, *10*, 3813.
- [5] R. G. Harvey, C. Cortez, T. P. Ananthanarayan, S. Schmolka, *J. Org. Chem.* **1988**, *53*, 3936.
- [6] Q. Li, J. Jiang, A. Fan, Y. Cui, Y. Jia, *Org. Lett.* **2011**, *13*, 312; H. Fan, J. Peng, M. T. Hamann, J. Hu, *Chem. Rev.* **2008**, *108*, 264; D. Pla, F. Albericio, M. Álvarez, *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 746; S. T. Handy, Y. Zhang, *Org. Prep. Proced. Int.* **2005**, *37*, 411; C. Bailly, *Curr. Med. Chem. Anti-Cancer Agents* **2004**, *4*, 363.
- [7] D. Pla, A. Marchal, C. A. Olsen, A. Francesch, C. Cuevas, F. Albericio, M. Alvarez, *J. Med. Chem.* **2006**, *49*, 3257.
- [8] M. Khoobi, A. Foroumadi, S. Emami, M. Safavi, G. Dehghan, B. H. Alizadeh, A. Ramazani, S. K. Ardestani, A. Shafiee, *Chem. Biol. Drug Des.* **2011**, *78*, 580.

- [9] M. Khoobi, S. Emami, G. Dehghan, A. Foroumadi, A. Ramazani, A. Shafiee, *Arch. Pharm.* **2011**, *344*, 588; M. R. Ganjali, S. Aghabalazadeh, M. Khoobi, A. Ramazani, A. Foroumadi, A. Shafiee, P. Norouzi, *Int. J. Electrochem. Sci.* **2011**, *6*, 52.
- [10] S. H. Mashraqui, R. M. Kellogg, *Tetrahedron Lett.* **1985**, *26*, 1457.
- [11] A. Dömling, *Chem. Rev.* **2006**, *106*, 17; A. Dömling, I. Ugi, *Angew. Chem., Int. Ed.* **2000**, *39*, 3169; I. Ugi, 'Isonitrile Chemistry', Academic, London, 1971; I. Ugi, *Angew. Chem., Int. Ed.* **1982**, *21*, 810; H. M. Walborsky, M. P. Periasamy, 'The Chemistry of Functional Groups, Supplement C', Eds. S. Patai, Z. Rappaport, Wiley, New York, NY, 1983, Chapt. 8.20, pp. 835–837; V. Nair, A. U. Vinod, J. S. Nair, A. R. Sreekanth, N. P. Rath, *Tetrahedron Lett.* **2000**, *41*, 6675.
- [12] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **2008**, *64*, 112.

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