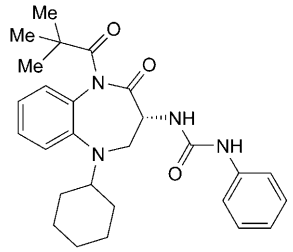
A Facile and Efficient Synthesis of Arylsulfonamido-Substituted 1,5-Benzodiazepines and *N*-[2-(3-Benzoylthioureido)aryl]-3-oxobutanamide Derivatives

by **Abdolali Alizadeh*** and **Nasrin Zohreh**

Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran (phone: +98-21-88006631; fax: +98-21-88006544; e-mail: abdol_alizad@yahoo.com and aalizadeh@modares.ac.ir)

A facile and efficient synthesis of 1,5-benzodiazepines with an arylsulfonamido substituent at C(3) is described. 1,5-Benzodiazepine, derived from the condensation of benzene-1,2-diamine and diketene, reacts with an arylsulfonyl isocyanate *via* an enamine intermediate to produce the title compounds of potential synthetic and pharmacological interest in good yields (*Scheme 1*). In addition, reaction of benzene-1,2-diamine and diketene in the presence of benzoyl isothiocyanate leads to *N*-[2-(3-benzoylthioureido)aryl]-3-oxobutanamide derivatives (*Scheme 2*). This reaction proceeds *via* an imine intermediate and ring opening of diazepine. The structures were corroborated spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by elemental analyses. A plausible mechanism for this type of cyclization is proposed (*Scheme 3*).

1. Introduction. – Benzodiazepines [1] have been important pharmacophores in the pharmaceutical industry. Therapeutically, benzodiazepines have found applications as vasopressin antagonists [2a], HIV reverse-transcriptase inhibitors [2b], and cholecystokinin antagonists [2c]. In this class of compounds, the 1,5-benzodiazepin-2-one scaffolds possess a privileged substructure exhibiting a range of biological activities. They exhibit interleukin-1β converting enzyme inhibition, delayed rectifier potassium current blocking [3], antiarrhythmic [4], and CCK receptor antagonist (compound **1**) [5] activities. They are also found in compounds active against a variety of target types such as protease inhibitors and 7-TM receptors [6–8]. Significantly less research has been undertaken on the 1,5-benzodiazepin-2-ones, compared to the 1,4-benzodiazepin-2-ones. Therefore, development of a synthetic method that could be used to prepare a variety of these templates remains an important task.



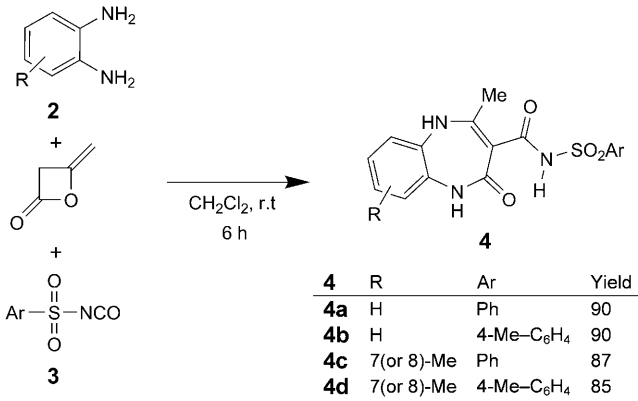
1 (CCK2 receptor antagonist)

Due to the broad spectrum of biological activities of heterocycles with a sulfonamido unit, including antibacterial, antiviral, antidiabetic, diuretic, and antithyroid activities [9], they are an interesting class of compounds. Thus, synthesis of 1,5-benzodiazepines bearing a sulfonamido group is synthetically challenging and of biological interest.

2. Results and Discussion. – Some of our previous works included the synthesis of heterocycles from the reaction of various enamines and arylsulfonyl isocyanates [10]. In continuation, we describe in this article the synthesis of arylsulfonamido-substituted 1,5-benzodiazepines *via* diketene-based multicomponent reaction [11].

Our new synthetic method is outlined in *Scheme 1*. The reaction of 1,5-benzodiazepin-2-one **7**, which is formed *in situ* from the condensation of benzene-1,2-diamine (**2**) and diketene (*cf. Scheme 3*) with arylsulfonyl isocyanate **3** proceeds in CH_2Cl_2 at ambient temperature to give compounds **4a**–**4e** in good yield (*Scheme 1*).

Scheme 1



4	R	Ar	Yield [%]
4a	H	Ph	90
4b	H	4-Me–C_6H_4	90
4c	7(or 8)-Me	Ph	87
4d	7(or 8)-Me	4-Me–C_6H_4	85
4e	6(or 9)-Me	4-Me–C_6H_4	85

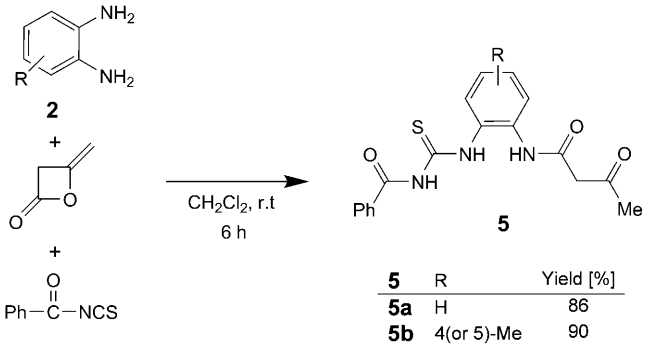
When benzene-1,2-diamines and diketene in dry CH_2Cl_2 were allowed to react in the presence of benzoyl isothiocyanate (PhCONCS) at room temperature, compounds **5** was formed in nearly quantitative yield as yellow powder. This product type was identified as *N*-[2-(3-benzoylthioureido)aryl]-3-oxobutanamide **5** (*Scheme 2*).

The structures of **4a**–**4e**, and **5a** and **5b** were deduced from their elemental analysis, and IR, and ^{1}H- and ^{13}C-NMR spectra.

The mass spectrum of **4a** showed the molecular-ion peak at *m*/*z* 357. Three sharp bands in the IR spectrum (KBr) of **4a** at 3315, 3270, and 3050 cm^{-1} are due to the three NH groups. The ^{1}H-NMR spectrum of **4a** exhibited four sharp *singlet*s readily recognized as arising from the Me group at the seven-membered ring (2.30 ppm) and three NH groups (8.45, 8.10, and 12.31 ppm). The Ph moiety gave rise to characteristic signals in the aromatic region of the spectrum, and 15 distinct signals in the ^{1}H-decoupled ^{13}C-NMR spectrum of **4a** are in agreement with the proposed structure.

The best evidences for the opening of the diazepine ring and formation of compounds **5** are the appearance of a *singlet* at 3.62 ppm in the ^{1}H-NMR spectrum of

Scheme 2



5	R	Yield [%]
5a	H	86
5b	4(or 5)-Me	90

5a (related to CH_2), and three signals at 49.59, 182.53, and 204.61 ppm in the ^{13}C-NMR spectrum of **5a** attributed to CH_2, C=S, and *C*OMe, respectively. It is important to note that diazepine **7a** (R = H) has been synthesized and characterized by its ^{1}H-NMR spectrum[1]).

Although the mechanism of the reaction between **2**, diketene, and arylsulfonyl isocyanate **3** or benzoyl isothiocyanate has not yet been established in an experimental manner, a proposal is presented in *Scheme 3*.

First, the reaction of benzene-1,2-diamine and diketene produces intermediate **6** that is readily converted to 1,5-benzodiazepine **7** *via* a condensation reaction. Probably, 1,5-benzodiazepine **7** reacts with arylsulfonyl isocyanate **3** *via* enamine intermediate **8** to produce **9**. Subsequently, benzodiazepine **9** is converted to the product **4** by H shift. On the other hand, the imine N-atom of **7** reacts with benzoyl isothiocyanate to produce zwitterion **10**, which is then transformed to aminal **11** by uptake of H_2O. Cyclic animal **11** is unstable, and it is converted, by ring opening, to product **5**.

In summary, we have described a simple and efficient method for the synthesis of arylsulfonamido-substituted 1,5-benzodiazepines and *N*-[2-(3-benzoylthioureido)aryl]-3-oxobutanamides. This method is characterized by several unique advantages, such as relatively short reaction times, simplicity in operation under neutral condition, high yields of products, and no need of catalyst. The reaction is also relatively sensitive to the type of cyanate.

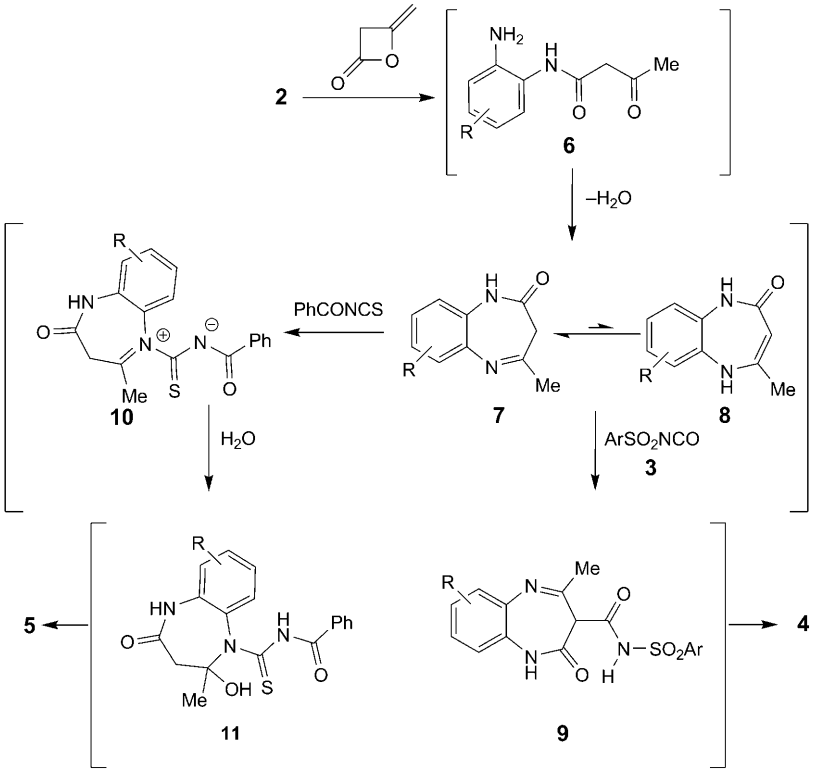
Experimental Part

General. Benzene-1,2-diamines, diketene, arylsulfonyl isocyanates, and benzoyl isothiocyanate were obtained from *Merck* (Germany) and *Fluka* (Switzerland), and were used without further purification. M.p.: *Electrothermal 9100* apparatus. IR Spectra (KBr): *Shimadzu IR-460* spectrometer ($\tilde{\nu}$ in cm^{-1}). ^{1}H- and ^{13}C-NMR spectra: in $CDCl_3$ or (D_6)acetone with a *Bruker DRX-500 AVANCE* spectrometer at 500, and 125 MHz, respectively. MS: *FINNIGAN-MAT 8430* mass spectrometer operating at an ionization potential of 20 eV. Elemental analyses: *Herpes CHN–O–Rapid* analyzer.

---

[1]) *4-Methyl-1,3-dihydro-2*H-*1,5-benzodiazepin-2-one* (**7a**): ^{1}H-NMR (500 MHz, $CDCl_3$): 2.38 (*s*, 3 H); 2.13 (*s*, 2 H); 7.06–7.10 (*m*, 1 H); 7.16–7.18 (*m*, 2 H); 7.31–7.34 (*m*, 1 H); 9.59 (*s*, 1 H).

Scheme 3



Compounds **4a**–**4e**: *General Procedure* (exemplified for **4a**). To a magnetically stirred soln. of *benzene-1,2-diamine* (**2a**; 0.11 g, 1 mmol) and diketene (0.08 g, 1 mmol) in CH_2Cl_2 (5 ml) was added after 1 h *benzenesulfonyl isocyanate* (**3a**; 0.18 g, 1 mmol). After completion of the reaction, the solvent was removed, and the product **4a** precipitated in Et_2O. The product was filtered and washed with cool CH_2Cl_2 for further purification.

2,5-Dihydro-4-methyl-2-oxo-N-*(phenylsulfonyl)-1*H-*1,5-benzodiazepine-3-carboxamide* (**4a**). Yield 320 mg (90%). Yellow powder. M.p. 173–175° (dec.). IR: 3315, 3270, 3050 (3 NH), 1664, 1651 (2 NC=O), 1539, 1471 (2 Ar), 1329, 1153 (2 SO_2). ^{1}H-NMR ((D$_6$)acetone): 2.30 (*s*, 3 H); 7.00–7.05 (*m*, 3 H); 7.13–7.15 (*m*, 1 H); 7.56 (*t*, *J* = 7.3, 2 H); 7.64 (*t*, *J* = 7.5, 1 H); 8.01 (*d*, *J* = 7.3, 2 H); 8.45 (*s*, 1 H); 8.10 (*s*, 1 H); 12.31 (*s*, 1 H). ^{13}C-NMR ((D$_6$)acetone): 25.1; 100.3; 122.2; 122.3; 125.5; 126.8; 128.8; 129.4; 132.8; 133.8; 134.6; 141.6; 165.2; 173.5; 173.6. EI-MS: 357 (8, M^+), 256 (12), 199 (5), 174 (22), 157 (28), 132 (83), 131 (40), 93 (25), 77 (100), 51 (45). Anal. calc. for $C_{17}H_{15}N_3O_4S$ (357.38): C 57.13, H 4.23, N 11.76; found: C 57.19, H 4.26, N 11.75.

2,5-Dihydro-4-methyl-N-*[(4-methylphenyl)sulfonyl]-2-oxo-1*H-*1,5-benzodiazepine-3-carboxamide* (**4b**). Yield 330 mg (90%). Yellow powder. M.p. 198–200°. IR: 3290, 3180, 3020 (3 NH), 1699, 1646 (2 NC=O), 1522, 1408 (2 Ar), 1334, 1149 (2 SO_2). ^{1}H-NMR ((D$_6$)acetone): 2.31 (*s*, 3 H); 2.39 (*s*, 3 H); 7.01–7.05 (*m*, 3 H); 7.13–7.15 (*m*, 1 H); 7.35 (*d*, *J* = 7.9, 2 H); 7.90 (*d*, *J* = 7.8, 2 H); 8.41 (*s*, 1 H); 9.10 (*s*, 1 H); 12.58 (*s*, 1 H). ^{13}C-NMR ((D$_6$)acetone): 21.4; 25.1; 105.4; 122.3; 125.5; 126.9; 128.0; 128.9; 130.0; 133.3; 138.8; 144.5; 165.8; 172.9, 173.0. EI-MS: 371 (5, M^+), 311 (10), 197 (23), 174 (22), 155 (39), 132 (98), 131 (50), 91 (100), 65 (35), 39 (40). Anal. calc. for $C_{18}H_{17}N_3O_4S$ (371.41): C 58.21, H 4.61, N 11.31; found: C 58.29, H 4.64, N, 11.33.

2,5-Dihydro-4,7(or 8)-dimethyl-2-oxo-N-*(phenylsulfonyl)-1*H-*1,5-benzodiazepine-3-carboxamide* (**4c**). Yield 320 mg (87%). Yellow powder. M.p. 197–199° (dec.). IR: 3339, 3270, 3055 (3 NH), 1670, 1651 (2 NC=O), 1512, 1431 (2 Ar), 1327, 1155 (2 SO_2). ^{1}H-NMR ((D$_6$)acetone): 2.29 (*s*, 3 H); 2.81 (*s*, 3 H); 6.97–7.01 (*m*, 3 H); 7.58 (*t*, *J* = 7.6, 2 H); 7.63 (*t*, *J* = 7.5, 1 H); 8.02 (*d*, *J* = 7.3, 2 H); 8.39 (*s*, 1 H); 9.19 (*s*, 1 H); 12.66 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 20.7; 25.1; 100.4; 122.1; 126.0; 126.9; 128.6; 128.8; 129.4; 129.7; 133.8; 138.2; 141.7; 165.3; 172.3; 174.0. EI-MS: 302 (4), 157 (15), 141 (15), 93 (21), 84 (65), 77 (30), 66 (100), 46 (18). Anal. calc. for $C_{18}H_{17}N_3O_4S$ (371.41): C 58.21, H 4.61, N 11.31; found: C 58.27, H 4.66, N 11.29.

2,5-Dihydro-4,7(or 8)-dimethyl-N-*[(4-methylphenyl)sulfonyl]-2-oxo-1*H-*1,5-benzodiazepine-3-carboxamide* (**4d**). Yield 330 mg (85%). Yellow powder. M.p. 160–162° (dec.). IR: 3270, 3195, 3035 (3 NH), 1666, 1638 (2 C=O), 1510, 1439 (2 Ar), 1334, 1153 (2 SO_2). ^{1}H-NMR ((D$_6$)acetone): 2.21 (*s*, 3 H); 2.28 (*s*, 3 H); 2.39 (*s*, 3 H); 6.81–6.85 (*m*, 1 H); 6.90–6.97 (*m*, 2 H); 7.35 (*d*, *J* = 7.9, 2 H); 7.89 (*d*, *J* = 7.8, 2 H); 8.38 (*s*, 1 H); 9.97 (*s*, 1 H); 12.57 (*s*, 1 H). ^{13}C-NMR ((D$_6$)acetone): 20.4; 21.4; 25.1; 99.5; 122.2; 122.6; 126.0; 128.5; 128.9; 129.9; 135.4; 135.2; 138.8; 144.63; 165.24; 173.3; 173.6. EI-MS: 385 (2, M^+), 202 (9), 188 (17), 171 (69), 155 (73), 146 (57), 107 (41), 91 (100), 77 (12), 65 (35). Anal. calc. for $C_{19}H_{19}N_3O_4S$ (385.43): C 59.21, H 4.97, N 10.90; found: C 59.25, H 4.99, N 10.95.

2,5-Dihydro-4,6(or 9)-dimethyl-N-*[(4-methylphenyl)sulfonyl]-2-oxo-1*H-*1,5-benzodiazepine-3-carboxamide* (**4e**). Yield 330 mg (85%). Yellow powder. M.p. 186–189° (dec). IR: 3330, 3295, 3200 (3 NH), 1672, 1647 (2 NC=O), 1571, 1402 (2 Ar), 1324, 1165 (2 SO_2). ^{1}H-NMR ((D$_6$)acetone): 2.24 (*s*, 3 H); 2.30 (*s*, 3 H); 2.37 (*s*, 3 H); 6.81–6.95 (*m*, 3 H); 7.35 (*d*, *J* = 7.9, 2 H); 7.88 (*d*, *J* = 7.82, 2 H); 8.37 (*s*, 1 H); 8.97 (*s*, 1 H); 12.58 (*s*, 1 H). ^{13}C-NMR ((D$_6$)acetone): 20.4; 21.4; 25.1; 100.2; 122.2; 122.5; 126.0; 128.5; 128.90; 129.9; 134.6; 135.4; 138.8; 144.6; 165.2; 173.3; 173.6. EI-MS: 385 (10), 202 (7), 191 (15), 188 (15), 171 (52), 155 (61), 148 (23), 146 (41), 132 (9), 107 (51), 91 (100), 77 (10), 65 (41). Anal. calc. for $C_{19}H_{19}N_3O_4S$ (385.43): C 59.21, H 4.97, N 10.90; found: C 59.27, H 4.96, N 10.91.

N-*({2-[(3-Oxobutanoyl)amino]phenyl}carbamothioyl)benzamide* (**5a**). Yield 300 mg (86%). Yellow powder. M.p. 105–107°. IR: 3235, 3190, 3110 (3 NH), 1710, 1690, 1651 (3 C=O), 1589, 1473 (2 Ar), 1317, 1150 (2 C=S). ^{1}H-NMR ($CDCl_3$): 2.27 (*s*, 3 H); 3.62 (*s*, 2 H); 7.2 (*t*, *J* = 7.5, 1 H); 7.38 (*t*, *J* = 7.5, 1 H); 7.56 (*t*, *J* = 7.7, 2 H); 7.60 (*d*, *J* = 7.4, 1 H); 7.68 (*t*, *J* = 7.4, 1 H); 7.93 (*d*, *J* = 7.7, 2 H); 7.95 (*d*, *J* = 7.8, 1 H); 9.25 (*s*, 1 H); 9.34 (*s*, 1 H); 12.15 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 31.1; 49.6; 124.3; 125.8; 127.1; 127.6; 128.6; 129.2; 131.2; 131.8; 132.7; 133.7; 164.0; 167.9; 182.5; 204.6. EI-MS: 335 (5), 240 (17), 194 (21), 150 (20), 134 (29), 105 (100), 77 (89), 51 (41). Anal. calc. for $C_{18}H_{17}N_3O_3S$ (355.41): C 60.83, H 4.82, N 11.82; found: C 60.87, H 4.90, N 11.81.

N-*({4-(or 5)Methyl-2-[(3-oxobutanoyl)amino]phenyl}carbamothioyl)benzamide* (**5b**). Yield 330 mg (90%). Yellow powder. M.p. 100–102°. IR (KBr): 3230, 3184, 3115 (3 NH), 1713, 1668, 1641 (3 NC=O), 1511, 1412 (2 Ar), 1330, 1166 (2 C=S). ^{1}H-NMR ((D$_6$)acetone): 2.24 (*s*, 3 H); 2.34 (*s*, 3 H); 3.61 (*s*, 2 H); 7.13 (*d*, *J* = 7.8, 1 H); 7.57–7.62 (*m*, 3 H); 7.67–7.72 (*m*, 2 H); 8.08 (*d*, *J* = 7.3, 2 H); 9.21 (*s*, 1 H); 10.32 (*s*, 1 H); 12.31 (*s*, 1 H). ^{13}C-NMR ((D$_6$)acetone): 20.9; 21.37; 49.6; 125.2; 128.2; 128.8; 129.10; 129.6; 131.3; 132.2; 133.3; 134.1; 135.8; 166.0; 168.5; 181.5; 203.4. EI-MS: 369 (9, M^+), 336 (10), 285 (8), 252 (21), 164 (37), 146 (28), 105 (100), 77 (92), 51 (18). Anal. calc. for for $C_{19}H_{19}N_3O_3S$ (369.44): C 61.77, H 5.18, N 11.37; found: C 61.81, H 5.21, N 11.39.

REFERENCES

[1] G. A. Archer, L. H. Sternbach, *Chem. Rev.* **1968**, *68*, 747; L. H. Sternbach, *Prog. Drug Res.* **1978**, *22*, 229.

[2] a) J. D. Albright, M. F. Reich, E. G. D. Santos, J. P. Dusza, F.-W. Sum, A. M. Venkatesan, J. Coupet, P. S. Chan, X. Ru, H. Mazandarani, T. Bailey, *J. Med. Chem.* **1998**, *41*, 2442; b) H. J. Breslin, M. J. Kukla, D. W. Ludovici, R. Mohrbacher, W. Ho, M. Miranda, J. D. Rodgers, T. K. Hitchens, G. Leo, D. A. Gauthier, C. Y. Ho, M. K. Scott, E. De Clercq, R. Pauwels, K. Andries, M. A. C. Janssen, P. A. J. Janssen, *J. Med. Chem.* **1995**, *38*, 771; c) J. L. Castro, H. B. Broughton, M. G. N. Russell, D. Rathbone, A. P. Watt, R. G. Ball, K. L. Chapman, S. Patel, A. J. Smith, G. R. Marshall, V. G. Matassa, *J. Med. Chem.* **1997**, *40*, 2491.

[3] T. F. Herpin, K. G. Van Kirk, J. M. Salvino, S. T. Yu, R. F. Labaudinière, *J. Comb. Chem.* **2000**, *2*, 513.
[4] D. A. Claremon, R. M. Freidinger, N. Liverton, H. G. Selnick, G. R. Smith, PCT Int. Appl. WO 9640656.
[5] I. M. Buck, J. W. Black, T. Cooke, D. J. Dunstone, J. D. Gaffen, E. P. Griffin, E. A. Harper, R. A. D. Hull, S. B. Kalindjian, E. J. Lilley, I. D. Linney, C. M. R. Low, I. M. McDonald, M. J. Pether, S. P. Roberts, N. P. Shankley, M. E. Shaxted, K. I. M. Steel, D. A. Sykes, M. J. Tozer, G. F. Watt, M. K. Walker, L. Wright, P. T. Wright, *J. Med. Chem.* **2005**, *48*, 6803.
[6] M. E. Tranquillini, P. G. Cassarà, M. Corsi, G. Curotto, D. Donati, G. Finizia, G. Pentassuglia, S. Polinelli, G. Tarzia, A. Ursini, F. T. M. van Amsterdam, *Arch. Pharm.* (*Weinheim*, *Ger.*) **1997**, *330*, 353; D. Trist, G. Pentassuglia, M. E. Tranquillini, A. Ursini, PCT Int. Appl. WO 9314075.
[7] M. J. Batchelor, D. Bebbington, G. W. Bemis, W. H. Fridman, R. J. Gillespie, J. M. C. Golec, Y. Gu, D. J. Lauffer, D. J. Livingston, S. S. Matharu, M. D. Mullican, M. A. Murcko, R. Murdoch, P. L. Nyce, A. L. C. Robidoux, PCT Int. Appl. WO 9722619 A2 19970626; G. W. Bemis, J. M. C. Golec, D. J. Lauffer, M. D. Mullican, M. A. Murcko, D. J. Livingston, *PCT Int. Appl.* WO 9535308.
[8] H. G. Selnick, N. J. Liverton, J. J. Baldwin, J. W. Butcher, D. A. Claremon, J. M. Elliott, R. M. Freidinger, S. A. King, B. E. Libby, C. J. McIntyre, D. A. Pribush, D. C. Remy, G. R. Smith, A. J. Tebben, N. K. Jurkiewicz, J. J. Lynch, J. J. Salata, M. C. Sanguinetti, P. K. S. Siegl, D. E. Slaughter, K. Vyas, *J. Med. Chem.* **1997**, *40*, 3865.
[9] T. H. Maren, C. W. Conroy, *J. Biol. Chem.* **1993**, *268*, 26233; A. Scozzafava, T. Owa, A. Mastrolorenzo, C. T. Supuran, *Curr. Med. Chem.* **2003**, *10*, 925; T. Owa, H. Yoshino, T. Okauchi, K. Yoshimatsu, Y. Ozawa, N. H. Sugi, T. Nagasu, N. Koyanagi, K. Kitoh, *J. Med. Chem.* **1999**, *42*, 3789; N. Koyanagi, T. Nagasu, F. Fujita, T. Watanabe, K. Tsukahara, Y. Funahashi, M. Fujita, T. Taguchi, H. Yoshino, K. Kitoh, *Cancer Res.* **1994**, *54*, 1702.
[10] A. Alizadeh, M. Babaki, N. Zohreh, A. Rezvanian, *Synthesis* **2008**, 3793.
[11] A. Alizadeh, N. Zohreh, S. Rostamnia, *Tetrahedron* **2007**, *63*, 8083; A. Alizadeh, N. Zohreh, *Synthesis* **2008**, *3*, 429; A. Alizadeh, N. Zohreh, *Helv. Chim. Acta* **2008**, *91*, 844; A. Alizadeh, N. Zohreh, L.-G. Zhu, *Synthesis* **2008**, *13*, 2073; N. Zohreh, *Synlett* **2008**, 1913; A. Alizadeh, N. Zohreh, L.-G. Zhu, Synthesis **2009**, 464; A. Alizadeh, N. Zohreh, L.-G. Zhu, *Tetrahedron* **2009**, *65*, 2684.

Received October 14, 2009