A New Aspect of the Pfitzinger Reaction: Microwave-assisted Synthesis of the New Heterocyclic Ring System 6-Arylbenzo[4,5]imidazolo[2,1-*b*]quino[4,3-*e*]-1,3-thiazin-14-one

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We report herein on the utility of the Pfitzinger reaction in a facile two-step synthesis of the new heterocyclic ring system 6-arylbenzo[4,5]imidazolo[2,1-*b*]quino[4,3-*e*]-1,3-thiazin-14-one using microwave irradiation (MWI) and/or conventional heating. Microwave irradiation was used for a rapid and efficient synthesis of quinoline-4-carboxylic acids **6a** – **d** from the reaction of isatin with 2-(1*H*-benzimidazol-2-ylthio)-1-arylethanones **3a** – **d**. Cyclization of cinchoninic acids **6a** – **d** afforded the fused title compounds **7a** – **d**.

Key words: Quinolines, Antibiotics, Cyclization, Pfitzinger Reaction, Microwave Irradiation (MWI)

Introduction

Quinolines are an important class of heterocycles found in numerous natural products [1, 2] and medicinal structures [3, 4] such as ciprofloxacin, norfloxacin and pefloxacin [5], which are amongst the most effective broad-spectrum agents developed to date as potent antibiotics. They are now frequently the drugs of choice for treating infections of the urinary and genital tracts. On the other hand, quinoline-containing compounds, such as quinine, chloroquine and mefloquine [6 – 9] have long been used for treatment of malaria, one of the most devastating infectious diseases in the world. In addition, quinoline is the backbone of the antiarrythmic drug quinidine [2, 10] and the antiulcer agent rebamipide [11]. Furthermore, quinoline-4-carboxylic acids and their analogs have interesting antiviral, analgesic, tranquillizer, antitumor, and antitubercular activities [12 – 15].

Consequently, the efficient construction of quinolines has received significant attention [16]. One of the powerful methods for the synthesis of these compounds involves the Pfitzinger reaction. The formation of 4-quinolinecarboxylic (cinchoninic) acid derivatives as a result of the reaction of isatin or its derivatives with ketones containing the $-CH_2CO-$ group in the presence of sodium hydroxide or potassium hydroxide was first discovered at the end of the nineteenth century by Pfitzinger [17] and is known in organic chemistry as the Pfitzinger reaction.

The first successful use of keto ethers or keto thioethers in the Pfitzinger reaction was made by Calaway *et al*. in the middle of the last century [18 – 21]. Recently, the first attempt to use microwave irradiation (MWI) for performing the Pfitzinger reaction has been reported by El Ashry [22]. Although many strategies for the construction of substituted quinolines or their fused systems have been explored depending on the Pfitzinger reaction [16], a convergent synthesis of fused quinolines from Pfitzinger reaction products with a thioether substituent at C3 has not yet emerged.

In the course of our research efforts towards the preparation of new biologically active heterocyles [23 – 30], we report herein on the utility of keto thioethers in the Pfitzinger reaction in a facile two-step synthesis of the title compounds using microwave irradiation (MWI) and/or conventional heating. The latter two-component Pfitzinger reaction was utilized as a convenient method to generate the quinolines that undergo subsequent cyclization to afford the title compounds with expected interesting biological activity.

Results and Discussion

Microwave irradiation has been used for a rapid and efficient synthesis of quinoline-4-carboxylic acids **6a** – **d** from the reaction of isatin with 2-(1*H*-benz-

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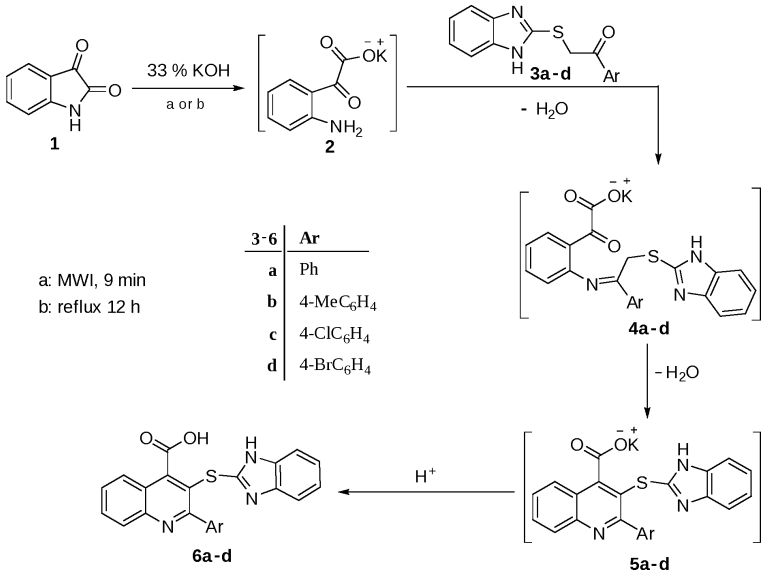
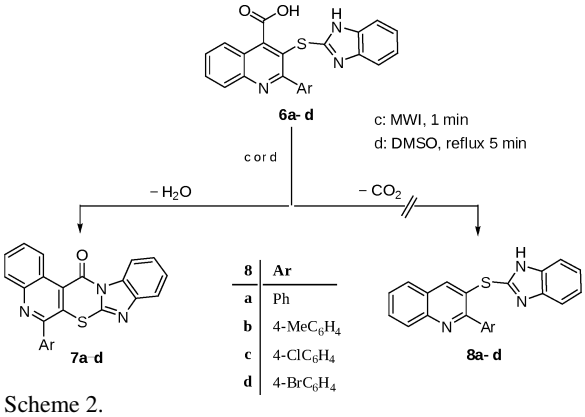


Scheme 1.

imidazol-2-ylthio)-1-arylethanones **3a – d** in aqueous potassium hydroxide solution (Scheme 1). Thus, under conventional heating, the reaction required refluxing for 12 h to afford 63 – 68 % yield, but MWI accelerated the condensation of isatin with compounds **3a – d** where the reaction time was dramatically reduced to 9 min, and slightly higher yields (77 – 85 %) were observed.

The structures of **6a – d** were elucidated on the basis of their spectra (^{1}H NMR, ^{13}C NMR, IR, and MS) and microanalyses. For example, the ^{1}H NMR spectra of the latter compounds showed a D_2O-exchangeable NH proton signal at δ = 6.23 – 6.9 ppm in addition to the D_2O-exchangeable signal of the OH proton at δ = 10.45 – 10.62 ppm. The mass spectra of **6a – d** were also consistent with their assigned structures. In addition to the molecular ion peak, they revealed peaks at *m/z* corresponding to $[M–18]^+$.

Surprisingly, upon attempts to decarboxylation of cinchoninic acids **6a – d** to afford compounds **8a – d**, cyclization of the latter acids occurred to afford the fused compounds **7a – d** *via* loss of a water molecule (Scheme 2). Thus, during solvent-free heating of the solid acids **6a – d** under MWI, the material melted and solidified within 1 min to afford compounds **7a – d**. The conventional heating of acids **6a – d** in DMSO for 5 min gave the same results and approximately, in each case, the same yield. Furthermore, acids **6a – d** were also cyclized upon solvent-free conventional heating for 5 min. Generally, the decarboxylated quinolines



Scheme 2.

of the Pfitzinger reaction have melting points lower than the acids from which they are derived [18, 19]. In our case, the cyclized compounds **7a – d** have melting points higher than their corresponding acyclic compounds **6a – d**.

Although all attempts to get crystals of **7a – d** for X-ray diffraction analysis failed, the spectra of **7a – d** (^{1}H NMR, ^{13}C NMR, IR, and MS) and their microanalyses were sufficient to establish, beyond doubt, the assigned structures. The IR and ^{1}H NMR spectra of **7a – d** were lacking the NH and OH signals, which were characteristic of the starting substrates **6a – d**. The mass spectra of **7a – d** showed, in each case, a peak corresponding to their molecular ions.

In summary, a rapid and efficient synthesis of a new ring system, 6-arylbenzo[4,5]imidazolo[2,1-*b*]-

quino[4,3-*e*]-1,3-thiazin-14-one, with expected biological activity was described.

Experimental Section

Melting points were taken on an Electrothermal IA 9000 series digital melting point apparatus. Elemental analyses were obtained from the microanalytical unit, Cairo University, Cairo, Egypt. The results were found to be in good agreement with the calculated values. The IR spectra (KBr) were recorded on a Shimadzu CVT-04 spectrophotometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H Spectra were run at 300 MHz in deuterated dimethylsulfoxide, [D_6]DMSO. Mass spectra were measured on a Varian MAT CH-5 spectrometer (70 eV). Irradiation was achieved using a domestic microwave oven (800 W output power). 1-Aryl-2-(1*H*-benzimidazol-2-ylthio) ethanones **3a – d** were synthesized according to the reported method [31].

*General procedure for the synthesis of 2-aryl-3-(1H-benzimidazol-2-ylthio)quinoline-4-carboxylic acids **6a – d***

Method A: To a solution of isatin (1.47 g, 10.0 mmol) in 33 % aqueous potassium hydroxide solution (15 mL), the appropriate 1-aryl-2-(1*H*-benzimidazol-2-ylthio)ethanone **3a – d** (10.0 mmol) was added, and the mixture was irradiated by MWI for 9 min. The resulting dark solution was filtered. The clarified solution was poured into an ice-water mixture (100 mL) and acidified with acetic acid. The pale-yellow solid which separated was filtered, washed with water, and dried to afford compounds **6a – d** in 77 – 85 % yield. The latter compounds were used directly in the next reaction without further purification.

Method B: To a solution of isatin (1.47 g, 10.0 mmol) in 33 % aqueous potassium hydroxide solution (15 mL), the appropriate 1-aryl-2-(1*H*-benzimidazol-2-ylthio)ethanone **3a – d** (10.0 mmol) was added, and the mixture was heated under reflux for 12 h. The treatment of the resulting solution was carried out as mentioned above in method A to afford compounds **6a – d** in 63 – 68 % yield.

*3-(1H-Benzimidazol-2-ylthio)-2-phenylquinoline-4-carboxylic acid (**6a**)*

Pale-yellow powder; yield (%/method): 85/A, 68/B. – M. p. 205 – 207 °C. – IR (KBr): ν = 3417 (NH), 2745 (OH), 1623 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 6.23 (s, D_2O-exchangeable, 1H, NH), 7.05 – 7.08 (m, 2H, Ar-H), 7.26 – 7.33 (m, 5H, Ar-H), 7.55 – 7.58 (m, 2H, Ar-H), 7.80 (dd, *J* = 6.6, 1.2 Hz, 1H, Ar-H), 7.89 – 7.97 (m, 2H, Ar-H), 8.20 (d, *J* = 8.4 Hz, 1H, Ar-H), 10.52 (s, D_2O-exchangeable, 1H, OH). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 113.9, 116.5, 121.5, 122.9, 125.2, 127.3, 128.2, 128.3, 128.9, 129.4, 131.8, 139.4, 147.3, 148.3, 149.4, 161.9, 165.3, 166.8. – MS (EI, 70 eV): *m/z* (%) = 398 (21.5) [M+1]$^+$, 397 (43.6) [M]$^+$, 379 (12.2), 235 (28.4), 134 (27.8), 89 (29.7), 77 (50.8), 51 (100.0). – $C_{23}H_{15}N_3O_2S$: calcd. C 69.50, H 3.80, N 10.57, S 8.07; found C 69.32, H 3.77, N 10.52, S 8.12.

*3-(1H-Benzimidazol-2-ylthio)-2-(4-tolyl)quinoline-4-carboxylic acid (**6b**)*

Pale-yellow powder; yield (%/method): 84/A, 63/B. – M. p. 218 – 219 °C. – IR (KBr): ν = 3389 (NH), 2737 (OH), 1612 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 2.42 (s, 3H, CH_3), 6.25 (s, D_2O-exchangeable, 1H, NH), 7.11 – 7.27 (m, 5H, Ar-H), 7.53 – 8.18 (m, 3H, Ar-H), 8.26 (d, *J* = 8.0 Hz, 2H, Ar-H), 8.31 (d, *J* = 7.4 Hz, 1H, Ar-H), 9.12 (d, *J* = 6.8 Hz, 1H, Ar-H), 10.27 (s, D_2O-exchangeable, 1H, OH). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 20.8, 113.9, 116.4, 121.3, 122.9, 125.1, 127.3, 128.1, 128.3, 128.9, 129.4, 131.7, 139.3, 147.3, 148.3, 149.3, 161.9, 165.4, 166.8. – MS (EI, 70 eV): *m/z* (%) = 412 (21.6) [M+1]$^+$, 411 (100.0) [M]$^+$, 393 (19.5), 321 (46.3), 249 (32.7), 77 (71.6). – $C_{24}H_{17}N_3O_2S$: calcd. C 70.05, H 4.16, N 10.21, S 7.79; found C 70.15, H 4.03, N 10.01, S 7.68.

*3-(1H-Benzimidazol-2-ylthio)-2-(4-chlorophenyl)quinoline-4-carboxylic acid (**6c**)*

Pale-yellow powder; yield (%/method): 84/A, 68/B. – M. p. 228 – 229 °C. – IR (KBr): ν = 3418 (NH), 2767 (OH), 1625 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 6.90 (s, D_2O-exchangeable, 1H, NH), 7.42 – 7.20 (m, 7H, Ar-H), 8.46 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.75 (d, 1H, *J* = 8.2 Hz, Ar-H), 9.47 (d, *J* = 8.3 Hz, 1H, Ar-H), 10.62 (s, D_2O-exchangeable, 1H, OH). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 114.1, 116.6, 121.3, 122.9, 125.2, 127.3, 128.3, 128.5, 129.1, 129.6, 131.8, 139.3, 147.6, 148.5, 149.4, 161.0, 165.5, 166.9. – MS (EI, 70 eV): *m/z* (%) = 433 (13.5) [M+2]$^+$, 432 (37.3) [M+1]$^+$, 431 (72.2) [M]$^+$, 413 (24.3), 385 (24.3), 269 (38.1), 102 (27.0), 64 (100.0). – $C_{23}H_{14}ClN_3O_2S$: calcd. C 63.96, H 3.27, N 9.73, S 7.42; found C 63.92, H 3.12, N 9.58, S 7.40.

*3-(1H-Benzimidazol-2-ylthio)-2-(4-bromophenyl)quinoline-4-carboxylic acid (**6d**)*

Pale-yellow powder; yield (%/method): 77/A, 65/B. – M. p. 237 – 239 °C. – IR (KBr): ν = 3418 (NH), 3752 (OH), 1632 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 6.35 (s, D_2O-exchangeable, 1H, NH), 7.21 – 7.63 (m, 6H, Ar-H), 8.01 (d, 1H, Ar-H), 8.12 (d, *J* = 8.3, 2H, Ar-H), 8.36 (d, *J* = 7.7, 1H, Ar-H), 9.11 (d, *J* = 8.4 Hz, 1H, Ar-H), 10.45 (s, D_2O-exchangeable, 1H, OH). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 113.9, 116.5, 121.3, 122.8, 125.2, 127.3, 128.3, 128.4, 129.1, 129.5, 131.7,

139.2, 147.6, 148.5, 149.2, 161.1, 165.4, 166.8. – MS (EI, 70 eV): *m/z* (%) = 478 (9.7) $[M+2]^+$, 477 (14.7) $[M+1]^+$, 476 (34.2) $[M]^+$, 458 (22.7), 234 (22.7), 123 (18.2), 89 (36.4), 62 (100.0). – $C_{23}H_{14}BrN_3O_2S$: calcd. C 57.99, H 2.96, N 8.82, S 6.73; found C 57.83, H 3.03, N 8.73, S 6.66.

*General procedure for the synthesis of 6-arylbenzo[4,5]-imidazolo[2,1-b]quino[4,3-e]-1,3-thiazin-14-ones **7a – d***

Method A: On heating of the appropriate compound **6a – d** (1.0 mmol) in a microwave oven for 1 min the solid material melted and solidified. It was then left to cool, taken up in ethanol, filtered off, washed with ethanol, dried, and crystallized from DMSO to afford compounds **7a – d**, respectively.

Method B: A solution of the appropriate compound **6a – d** (1.0 mmol) in DMSO (10 mL) was refluxed for 5 min and then left to cool. The solid which separated was filtered off, washed with ethanol, dried, and crystallized from DMSO to afford compounds **7a – d**, respectively.

Method C: On heating of the appropriate compound **6a – d** (1.0 mmol) in a sand bath for 5 min at a temperature, in each case, over the melting point by 10 °C, the solid substance melted and solidified within 1 – 3 min. It was then left to cool, taken up in ethanol, filtered off, washed with ethanol, dried, and crystallized from DMSO to afford compounds **7a – d**, respectively.

Due to the limited solubility of products **7c** and **7d** in common ^{13}C NMR solvents, the ^{13}C NMR spectra were recorded for **7a** and **7b** only as representative examples of the series prepared.

*6-Phenylbenzo[4,5]imidazolo[2,1-b]quino[4,3-e]-1,3-thiazin-14-one (**7a**)*

Greenish-yellow fine needles; yield (%/method): 92/A, 94/B, 90/C. – M. p. 296 – 298 °C. – IR (KBr): ν = 1692 (C=O) cm^{-1}. – ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 7.52 – 7.82 (m, 9H, Ar-H), 8.21 (dd, J = 6.3, 3.1 Hz, 1H, Ar-H), 8.63 (dd, J = 6.6, 3.0 Hz, 1H, Ar-H), 9.74 (dd, J = 6.6, 3.6 Hz, 1H, Ar-H). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 113.8, 116.5, 121.5, 122.8, 125.2, 127.2, 128.2, 128.3, 128.9, 129.3, 131.8, 139.7, 147.3, 148.1, 149.3, 161.8, 165.3, 176.2. – MS (EI, 70 eV): *m/z* (%) = 380 (31.0) $[M+1]^+$, 379 (100.0) $[M]^+$, 350 (51.2), 235 (15.5), 189 (21.4), 64 (9.3), 51 (7.9). – $C_{23}H_{13}N_3OS$: calcd. C 72.80, H 3.45, N 11.07, S 8.45; found C 72.83, H 3.42, N 10.87, S 8.34.

*6-(4-Tolyl)benzo[4,5]imidazolo[2,1-b]quino[4,3-e]-1,3-thiazin-14-one (**7b**)*

Pale-yellow powder; yield (%/method): 85/A, 87/B, 85/C. – M. p. 337 – 339 °C. – IR (KBr): ν = 1692 (C=O) cm^{-1}. – ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 2.45 (s, 3H, CH_3), 7.42 – 8.21 (m, 8H, Ar-H), 8.28 (d, J = 8.3 Hz, 2H, Ar-H), 8.42 (d, J = 6.4 Hz, 1H, Ar-H), 8.98 (d, J = 6.6 Hz, 1H, Ar-H). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 20.7, 113.7, 116.5, 121.3, 122.7, 125.2, 127.3, 128.0, 128.3, 129.1, 129.3, 131.6, 139.4, 147.4, 147.8, 149.0, 161.7, 165.3, 176.0. – MS (EI, 70 eV): *m/z* (%) = 394 (37.5) $[M+1]^+$, 393 (70.3) $[M]^+$, 293 (100.0), 248 (26.1), 204 (13.5), 124 (16.2), 63 (21.6). – $C_{24}H_{15}N_3OS$: calcd. C 73.26, H 3.84, N 10.68, S 8.15; found C 73.11, H 3.81, N 10.64, S 8.01.

*6-(4-Chlorophenyl)benzo[4,5]imidazolo[2,1-b]quino-[4,3-e]-1,3-thiazin-14-one (**7c**)*

Pale-yellow fine needles; yield (%/method): 92/A, 90/B, 92/C. – M. p. 322 – 324 °C. – IR (KBr): ν = 1694 (C=O) cm^{-1}. – ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 7.53 – 8.74 (m, 7H, Ar-H), 8.21 (d, J = 8.0 Hz, 2H, Ar-H), 8.53 – 8.65 (m, 2H, Ar-H), 9.74 (d, J = 6.6 Hz, 1H, Ar-H). – MS (EI, 70 eV): *m/z* (%) = 415 (16.2) $[M+2]^+$, 414 (43.2) $[M+1]^+$, 413 (78.4) $[M]^+$, 385 (24.3), 269 (27.0), 176 (27.0), 102 (27.0), 64 (100.0), 51 (91.9). – $C_{23}H_{12}ClN_3OS$: calcd. C 66.75, H 2.92, N 10.15, S 7.75; found C 66.67, H 2.90, N 10.00, S 7.72.

*6-(4-Bromophenyl)benzo[4,5]imidazolo[2,1-b]quino-[4,3-e]-1,3-thiazin-14-one (**7d**)*

Pale-yellow fibers; yield (%/method): 86/A, 84/B, 86/C. – M. p. 334 – 336 °C. – IR (KBr): ν = 1693(C=O) cm^{-1}. – ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 7.40 – 8.26 (m, 8H, Ar-H), 8.31 (d, J = 8.2 Hz, 2H, Ar-H), 8.61 (d, J = 6.3 Hz, 1H, Ar-H), 9.28 (d, J = 6.6 Hz, 1H, Ar-H). – MS (EI, 70 eV): *m/z* (%) = 460 (12.3) $[M+2]^+$, 459 (32.5) $[M+1]^+$, 458 (38.2) $[M]^+$, 359 (79.4), 312 (29.4), 233 (41.2), 188 (47.1), 93 (100.0), 64 (26.5), 51 (50.0). – $C_{23}H_{12}BrN_3OS$: calcd. C 60.27, H 2.64, N 9.17, S 7.00; found C 60.18, H 2.57, N 9.01, S 6.88.

[1] Y. Morimoto, F. Matsuda, H. Shirahama, *Synlett* **1991**, 202.

[2] R. B. Woodward, W. V. Doering, *J. Am. Chem. Soc.* **1945**, *67*, 860.

[3] A. A. Alhaider, M. A. Abdelkader, E. J. Lien, *J. Med. Chem.* **1985**, *28*, 1394.

[4] X. Y. Yu, J. M. Hill, G. Yu, Y. Yang, A. F. Kluge, D. Keith, J. Finn, P. Gallant, J. Silverman, A. Lim, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 541.

[5] G. C. Crumplin, *The 4-Quinolones: Antibacterial Agents In-vitro*, Springer-Verlag, London, **1990**.

[6] P. B. Madrid, J. Sherrill, A. P. Liou, J. L. Weisman, J. L. DeRisib, R. K. Guy, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1015.

[7] P. M. O'Neill, A. Mukhtar, P. A. Stocks, L. E. Randle, S. Hindley, S. A. Ward, R. C. Storr, J. F. Bickley, I. A. O'Neil, J. L. Maggs, R. H. Hughes, P. A. Winstanley, P. G. Bray, B. K. Park, *J. Med. Chem*. **2003**, *46*, 4933.
[8] R. G. Ridley, W. Hofheinz, H. Matile, C. Jaquet, A. Dorn, R. Masciadri, S. Jolidon, W. F. Richter, A. Guenzi, M. A. Girometta, H. Urwyler, W. Huber, S. Thaithong, W. Peters, *Antimicrob. Agents Chemother*. **1996**, *40*, 1846.
[9] P. A. Stocks, K. J. Raynes, P. G. Bray, B. K. Park, P. M. O'Neill, S. A. Ward, *J. Med. Chem*. **2002**, *45*, 4975.
[10] J. Guutzwiller, M. Uskokovic, *J. Am. Chem. Soc*. **1970**, *92*, 204.
[11] P. B. Madrid, N. T. Wilson, J. L. DeRisi, R. K. Guy, *J. Comb. Chem*. **2004**, *6*, 437.
[12] H. P. David, *U. S. Pat*. 4,680,299, **1987**.
[13] M. Foley, L. Tilley, *Pharmacol. Ther*. **1998**, *79*, 55.
[14] M. C. Dubroeucq, G. Lefur, C. Renault, *Eur. Pat*. 112776, **1984**.
[15] G. J. Atwell, C. D. Bos, B. C. Baguley, W. A. Denny, *J. Med. Chem*. **1988**, *31*, 1048.
[16] M. G. A. Shvekhgeimer, *Chem. Heterocyclic Compds*. **2004**, *40*, 257.
[17] W. Pfitzinger, *J. Prakt. Chem*. a) **1886**, *33*, 100; b) **1888**, *38*, 582; c) **1897**, *56*, 283.
[18] P. K. Calaway, H. R. Henze, *J. Am. Chem. Soc*. **1939**, *61*, 1355.
[19] J. A. Knight, Jr., H. K. Porter, P. K. Calaway, *J. Am. Chem. Soc*. **1944**, *66*, 1893.
[20] O. Newell, P. K. Calaway, *J. Am. Chem. Soc*. **1947**, *69*, 116.
[21] A. M. Dowell, Jr., H. S. Mccullough, P. K. Calaway, *J. Am. Chem. Soc*. **1948**, *70*, 226.
[22] E. H. El Ashry, E. Ramadan, H. Abdel-Hamid, M. Hagar, *Synth. Commun*. **2005**, *35*, 2243.
[23] H. A. Abdel-Aziz, A. M. Gamal-Eldeen, N. A. Hamdy, I. M. I. Fakhr, *Arch Pharm*. **2009**, *342*, 230.
[24] B. F. Abdel-Wahab, H. A. Abdel-Aziz, E. M. Ahmed, *Eur. J. Med. Chem*. **2009**, *44*, 2632.
[25] B. F. Abdel-Wahab, H. A. Abdel-Aziz, E. M. Ahmed, *Arch. Pharm*. **2008**, *341*, 734.
[26] H. A. Abdel-Aziz, N. A. Hamdy, A. M. Farag, I. M. I. Fakhr, *J. Heterocyclic Chem*. **2008**, *45*, 1.
[27] N. A. Hamdy, H. A. Abdel-Aziz, A. M. Farag, I. M. I. Fakhr, *Monatsh. Chem*. **2007**, *138*, 1001.
[28] K. M. Dawood, A. M. Farag, H. A. Abdel-Aziz, *Heteroatom Chem*. **2007**, *18*, 294.
[29] A. S. Shawali, S. M. Gomha, *Tetrahedron* **2002**, *58*, 8559.
[30] A. S. Shawali, S. M. Gomha, *J. Prakt. Chem*. **2000**, *342*, 599.
[31] J. J. D'Amico, R. H. Campbell, E. C. Guinn, *J. Org. Chem*. **1961**, *29*, 865.