Alkylation of 2,4-(1H,3H)-Quinazolinediones with Dialkyl Carbonates Under Microwave Irradiations

Ignacio Alfredo Rivero 1,2,*, Leticia Guerrero 1, Karla Alejandra Espinoza 3, Martha Cecilia Meza 1 and Jesús Ramón Rodríguez 3

1 Centro de Graduados e Investigación en Química, Instituto Tecnológico de Tijuana. C.P. 1166. Tijuana, B.C. 22000, Mexico
2 Instituto Nacional de Investigaciones Nucleares, Departamento de Química. Carretera México Toluca S/N, La Marquesa, Ocoyoacac, Mexico, D.F. C.P. 52750
3 Facultad de Química, Universidad Autónoma de Baja California, Calzada Tecnológico #14418, Mesa de Otay. Tijuana, B.C, Mexico, C.P. 22390

* Author to whom correspondence should be addressed; E-mail: irivero@tectijuana.mx; Tel.: +52-664-6233772; Fax: +52-664-6234043

Received: 16 March 2009; in revised form: 6 April 2009 / Accepted: 9 April 2009 / Published: 20 May 2009

Abstract: Alkylation is a very important chemical reaction which modifies the biological properties of drugs. Quinazolinedione derivatives are of considerable interest due to their wide array of pharmacological properties. We now report application of a practical alkylation procedure to several quinazolinediones, including pelanserine (5f), which shows antihypertensive properties, 1-methyl-3-(2’-phenylethyl)-1H,3H-quinazoline-2,4-dione (1ab) and 1-methyl-3-[2’-(4’-methoxyphenyl)ethyl]-1H,3H-quinazoline-2,4-dione (1ae), which had been isolated from natural sources. The alkylation was optimized using dimethyl and diethyl carbonates under microwave irradiations.

Keywords: alkylation; quinazoline-2,4-dione; antihypertensive activity; microwaves
Introduction

In general alkylation involves substitution of a hydrogen atom by an alkyl group and is a popular and fundamental process in organic synthesis. Several functional groups such as \( \alpha \)-carbon [1], alcohols [2], amines [3], carboxylic acids [4] and amides-NH [5] are protected by alkylation reactions. These modifications change the physical and biological properties of such compounds. Our group has been working on the synthesis of quinazolinone and quinazolinedione derivatives, which are of considerable interest because of their wide array of pharmacological properties [6-20]. We have synthesized heterocycles containing the quinazoline-2,4-dione backbone, which are known to exhibit potential anti-hypertensive properties [21-25]. We have described the synthesis of pelanserine (5f), a potent anti-hypertensive agent [26], and several quinazoline-2,4-diones with amino acids and dipeptide, which when tested showed mild to no antihypertensive properties [27].

Recently, we synthesized two alkaloids containing the quinazoline-2,4-dione ring skeleton – 1-methyl-3-(2'-phenylethyl)-1H,3H-quinazoline-2,4-dione (1ab) and 1-methyl-3-[2'-(4'-methoxyphenyl)ethyl]-1H,3H-quinazoline-2,4-dione (1ae) – which have been isolated from the seed husks of *Zanthoxylum arborescens* [28]. Alkylation reactions were performed with methyl iodide and TMG as a base, but the reagents are expensive and toxic and take about one hour at 55°C to complete the reaction [29]. Herein, we propose a novel methodology for the alkylation using inexpensive dimethyl and diethyl carbonates which are very stable liquids, non-reactive under normal conditions. The reactions were assisted and optimized by microwaves, taking only a few minutes to complete. This efficient process was applied to a quinazolinedione library to improve the methodology without toxic reagents.

![Figure 1. Examples of quinazoline-2,4-diones: Pelanserine (5f) a potent anti-hypertensive agent, and two natural products (5b,5e).](image)

Results and Discussion

Alkylation of NH-containing heteroaromatic compounds is an important transformation that regularly employs toxic and hazardous reagents such as methyl iodide [29] or dimethyl sulfate [30]. Diallyl carbonates are an attractive alternative as alkylation reagents for NH-containing heteroaromatic compounds. Quinazoline-2,4-diones 5(a,b,c,d,e,f) were thus prepared using our methodology [26]. Initially, we prepared the ortho-aminobenzamides from the reactions of isatoic anhydride with amines and the cyclization was carried out with bis(trichloride methyl)carbonate (BTC, triphosgene). Finally, the alkylation with dimethyl carbonate was optimized under microwave irradiation and the conditions were fixed at 200 W, 130 °C, for 15 minutes, using K₂CO₃ as base...
The reaction was filtered, to get a >94% yield. The alkylation with diethyl carbonate was similar, in this case it was necessary to increase the temperature to 160 °C to obtain the ethylquinazoline-2,4-diones in a >92% yield. Ethylation products had to be purified by column chromatography on silica gel to remove the excess of diethyl carbonate. By applying microwave irradiation further rate enhancements were accomplished.

**Scheme 1.** Steps to obtain to the N-methyl quinazoline-2,4-diones.

\[
\begin{align*}
&\text{(2)} & \text{N} & \text{H} \\
&+ R^1\text{NH}_2 & \text{(3)} & \text{com} \\
&\text{CO}_2 & \text{i)} & \text{(4)} \\
&\text{N} & \text{H} \\
&\text{O} & \text{N} \\
&\text{R}^1 & \text{NH}_2 \\
&\text{ii)} & \text{(5)} \\
&\text{O} & \text{N} \\
&\text{O} & \text{N} \\
&\text{R}^1 & \text{R}^2 \\
&\text{Microwave} & \text{Yield >92%} & \text{iii)} \\
&\text{R}^1: a) \text{PhCH}_2 & b) 2-\text{CH}_3\text{OPhCH}_2\text{CH}_2 & c) 3-\text{CH}_3\text{OPhCH}_2\text{CH}_2 \\
&d) 4-\text{CH}_3\text{OPhCH}_2\text{CH}_2 & e) \text{PhCH}_2\text{CH}_2 & f) \text{PhN(CH}_2\text{CH}_2\text{NCH}_2\text{CH}_2\text{CH}_2 \\
&\text{R}^2: a) \text{CH}_3 & b) \text{CH}_3\text{CH}_2 \\
&\text{i)} \text{DMF/ 60°C} & \text{ii)} \text{BTC/CH}_2\text{Cl}_2 & \text{iii)} (\text{R}_2\text{CO})_2\text{O/ K}_2\text{CO}_3
\end{align*}
\]

The new methodology has the advantages of rapid reaction times, ease of operation and purification and the use of readily available reagents, and the avoidance of toxic alkylating reagents. In this work methyl and ethyl quinazoline-2,4-dione libraries were prepared, which are detailed in Table 1. The yields obtained with the optimized method were excellent, with conversions of 92-98%. Therefore, this is a very efficient method, with easy purification of products, since no by-products were observed.
Table 1. Alkylated quinazoline-2,4-diones.

| Entries | R1          | R2          | % Yield |
|---------|-------------|-------------|---------|
| 1aa     | PhCH2       | CH3         | 94      |
| 1ab     | PhCH2CH2    | CH3         | 98      |
| 1ac     | 2-CH3OPhCH2CH3 | CH3     | 95      |
| 1ad     | 3-CH3OPhCH2CH3 | CH3     | 96      |
| 1ae     | 4-CH3OPhCH2CH3 | CH3     | 98      |
| 1af     | PhN(CH2)4NCH2CH2CH3 | CH3 | 93      |
| 1ba     | PhCH2       | CH3CH2     | 96      |
| 1bb     | PhCH2CH2    | CH3CH2     | 96      |
| 1bc     | 2-CH3OPhCH2CH3 | CH3CH2 | 95      |
| 1bd     | 3-CH3OPhCH2CH3 | CH3CH2 | 94      |
| 1be     | 4-CH3OPhCH2CH3 | CH3CH2 | 97      |
| 1bf     | PhN(CH2)4NCH2CH2CH3 | CH3CH2 | 92      |

Conclusions

We have developed a simple method to methyl or ethyl alkylation of amide-NH functions with dialkyl carbonates, which were assisted by microwave irradiation. We used several quinazoline-2,4-diones which were previously synthesized by our group for biological evaluation as potential antihypertensive agents. We have proven that this method is very fast, clean, with almost complete conversion, using stable reagents avoiding possible contamination. We are currently exploring this reaction without solvent, as a green chemistry process. The amounts of K2CO3 are important which were established at three equivalents, thus working in a more efficient way. After several experiments, optimum conditions were determined. The basic backbone provides a source for introduction of different heterocyclic extension on the amide –NH, in order to diversify the quinazoline-2,4-dione structural system.

Experimental

General

Melting points were measured on an Electrothermal 88629 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR 1600 spectrometer. 1H-NMR and 13C-NMR spectra were recorded at 200 MHz and 50.289 MHz, respectively, on a Varian Mercury 200 spectrometer in CDCl3 with TMS as internal standard. Mass spectra were obtained on an Agilent 1100 series LC/MSD Trap, SL Spectrometer by electrospray insertion. Microwave equipment was a self-tuning single mode CEM Discover™ Focused Synthesizer.

General Method for Methylation of Quinazoline-2,4-diones

1-Methyl-3-(2'-phenylethyl)-1H,3H-quinazoline-2,4-dione (1ab). Dimethyl carbonate (1.25 mL) was added to a solution of 3-phenylethyl-1H-quinazoline-2,4-dione (5b, 0.125g, 0.38 mmol) in DMF
Molecules 2009, 14 1864

(1.25 mL) and K$_2$CO$_3$ (3 equiv) as base. The mixture was placed in a microwave reactor vessel (10 mL) and heated at 130 °C for 15 minutes and cooled to RT, then diluted with CH$_2$Cl$_2$ and H$_2$O. The aqueous layer was removed, and the organic layer was washed with H$_2$O, twice with 2 M HCl or 10% aqueous citric acid, twice with saturated aqueous NaHCO$_3$, and twice with H$_2$O. The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under vacuum to afford 1ab as a white solid. Yield >98%; mp 99-101°C (Lit. [25], mp. 100-102°C); IR (KBr): 3042, 2929, 1701, 1654, 1610, 1481 cm$^{-1}$; $^1$H-NMR: $\delta$ 8.23 (dd, 1H, $J_1=1.7$, $J_2=7.8$ Hz, Ar-H), 7.65 (ddd, 1H, $J_1=1.7$, $J_2=7.3$, $J_3=8.4$ Hz, Ar-H), 7.34-7.16 (m, 7H, Ar-H), 4.29 (ddd, $J_1=5.6$, $J_2=J_3=7.8$ Hz, 2H, N-CH$_2$), 3.57 (s, 3H, N-CH$_3$), 2.96 (ddd, $J_1=5.2$, $J_2=J_3=8.0$ Hz, Ar-CH$_2$) ppm; $^{13}$C-NMR: $\delta$ 161.3, 150.5, 140.2, 138.3, 134.8, 129.9, 128.7, 128.6, 128.2, 126.2, 122.7, 120.9, 113.3, 43.3, 33.9, 30.6 ppm; ESI-MS (m/e): 280.1[M+ H]$^+$. The following compounds were prepared in similar fashion:

1-Methyl-3-[2'-(2'-methoxyphenyl)ethyl]-1H,3H-quinazoline-2,4-dione (1ac). White solid. Yield >95%; mp 155-163°C; IR (KBr): 2943, 1703, 1651, 1608, 1484, 1243, 1028 cm$^{-1}$; $^1$H-NMR: $\delta$ 8.21 (dd, 1H, $J_1=1.6$, $J_2=7.9$ Hz, Ar-H), 7.66 (ddd, 1H, $J_1=1.7$, $J_2=7.3$, $J_3=8.2$ Hz, Ar-H), 7.28-7.16 (m, 5H, Ar-H), 6.85 (ddd, 1H, $J_1=1.0$, $J_2=J_3=7.4$ Hz, Ar-H), 4.33 (ddd, 2H, $J_1=5.6$, $J_2=J_3=7.4$ Hz, Ar-CH$_2$), 3.81 (s, 3H, O-CH$_3$), 3.58 (s, 3H, N-CH$_3$), 3.02 (ddd, 2H, $J_1=5.8$, $J_2=J_3=7.4$ Hz, Ar-CH$_2$) ppm; $^{13}$C-NMR: $\delta$ 161.3, 157.8, 140.2, 134.9, 130.6, 128.6, 127.7, 127.1, 122.8, 120.4, 113.4, 110.2, 55.3, 41.8, 30.6, 28.7 ppm; ESI-MS (m/e): 310.9[M+ H]$^+$; 332 [M +Na]$^+$. 1-Methyl-3-[2'-(3'-methoxyphenyl)ethyl]-1H,3H-quinazoline-2,4-dione (1ad). White solid. Yield 96%; mp 131-133°C; IR (KBr): 2945, 2833, 1699, 1656, 1604 cm$^{-1}$; $^1$H-NMR: $\delta$ 8.23 (dd, 1H, $J_1=1.6$, $J_2=7.9$ Hz, Ar-H), 7.63 (ddd, 1H, $J_1=1.0$, $J_2=J_3=8.2$ Hz, Ar-H), 4.30 (ddd, 2H, $J_1=5.4$, $J_2=J_3=7.6$ Hz, N-CH$_2$), 3.79 (s, 3H, O-CH$_3$), 3.58 (s, 3H, N-CH$_3$), 2.98 (ddd, 2H, $J_1=5.1$, $J_2=J_3=7.6$ Hz, Ar-CH$_2$) ppm; $^{13}$C-NMR: $\delta$ 162.5, 159.9, 148.5, 140.5, 132.8, 132.4, 129.7, 127.0, 126.4, 122.7, 117.4, 116.8, 116.3, 112.1, 55.1, 40.7, 35.7 ppm; ESI-MS (m/e): 332.9 [M +Na]$^+$. 1-Methyl-3-[2'-(4'-methoxyphenyl)ethyl]-1H,3H-quinazoline-2,4-dione (1ae). White solid. Yield >98%; mp 134-136°C; IR (KBr): 3301, 2928, 1701, 1647, 1600, 1400, 1261 cm$^{-1}$; $^1$H-NMR: $\delta$ 8.22 (dd, 1H, $J_1=1.6$, $J_2=7.9$ Hz, Ar-H), 7.69 (ddd, 1H, $J_1=1.7$, $J_2=7.4$, $J_3=8.5$ Hz, Ar-H), 7.30-7.18 (m, 6H, Ar-H), 6.80 (ddd, 1H, $J_1=1.0$, $J_2=2.5$, $J_3=8.2$ Hz, Ar-H), 4.26 (ddd, 2H, $J_1=5.2$, $J_2=J_3=7.8$ Hz, N-CH$_2$), 3.80 (s, 3H, O-CH$_3$), 3.59 (s, 3H, N-CH$_3$), 2.95 (ddd, 2H, $J_1=5.2$, $J_2=J_3=7.8$ Hz, Ar-CH$_2$) ppm; $^{13}$C-NMR: $\delta$ 161.8, 158.2, 140.5, 130.1, 129.2, 124.2, 114.0, 113.6, 55.5, 43.7, 33.4, 31.0 ppm; ESI-MS (m/e): 332.9 [M +Na]$^+$. 1-Methyl-3-(benzyl)-1H,3H-quinazoline-2,4-dione (1aa). White solid. Yield 94%; mp 103-106°C; IR (KBr): 3416, 2918, 1700, 1652, 1604, 1480, 1266, cm$^{-1}$; $^1$H-NMR: $\delta$ 8.22 (dd, 1H, $J_1=1.6$, $J_2=7.9$ Hz, Ar-H), 7.64 (ddd, 1H, $J_1=1.6$, $J_2=7.3$, $J_3=8.5$ Hz, Ar-H), 7.52 (ddd, 2H, $J_1=1.7$, $J_2=J_3=7.8$ Hz, Ar-H), 7.34-
7.13 (m, 5H, Ar-H), 5.27 (s, 2H, N-CH₂), 3.57 (s, 3H, N-CH₃) ppm; ¹³C-NMR: δ 161.7, 150.9, 140.9, 137.0, 135.1, 129.7, 129.0, 128.3, 127.5, 122.9, 115.5, 113.5, 44.9, 30.7 ppm; ESI-MS (m/e) 288.9 [M+Na]⁺.

1-Methyl-3-(3-(4-phenylpiperazin-1-yl)propyl)-1H,3H-quinazoline-2,4-dione (1af). White solid. Yield >93%; IR (KBr): 3018, 2932, 2880, 2803, 1695, 1647, 1604, 1223, 1110 cm⁻¹. ¹H-NMR: δ 8.18 (dd, 1H, J₁=1.6, J₂= 7.9 Hz, Ar-H), 7.62 (ddd, 1H, J₁=1.6, J₂=7.4, J₃=8.4 Hz, Ar-H), 7.25-7.11 (m, 3H, Ar-H), 6.88-6.75 (m, 3H, Ar-H), 4.16 (m, 2H, N-CH₂), 3.58 (s, 1H, N-CH₃), 3.10 (m, 4H, N-CH₂), 2.55 (m, 6H, N-CH₂), 1.95 (dd, 3H, J₁=7.1, J₂=14.3 Hz, CH₂) ppm; ¹³C-NMR: δ 161.8, 151.3, 148.8, 140.5, 135.0, 129.1, 128.9, 128.8, 119.5, 115.9, 112.8, 56.1, 55.2, 53.0, 49.1, 40.5, 30.6, 24.8 ppm; ESI-MS (m/e): 392.2 [M+ H⁺].

General Method for Ethylation of 2,4 Quinazoline-2,4-diones

1-Ethyl-3-(2′-phenylethyl)-1H,3H-quinazoline-2,4-dione (1bb). Diethyl carbonate (1.25 mL), was added to a solution of 3-phenyl ethyl-1-H-quinazoline-2,4-dione (5b) (0.125g, 0.38 mmol) in DMF (1.25 mL) and K₂CO₃ (3 equiv) as base. The mixture was placed in a microwave reactor vessel (10 mL) and heated at 160 °C for 15 minutes and cooled to RT, then diluted with CH₂Cl₂ and washed with NaCl to remove DMF. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The crude was purified by silica gel column chromatography with silica gel first hexane (60 mL) and then EtOAc (60 mL) to give 1bc as a yellow viscous liquid. Yield >96%; IR (NaCl): 3033, 2929, 1705, 1657, 1605, 1483, 1402, 1229 cm⁻¹; ¹H-NMR: δ 8.25 (dd, 1H, J₁=1.7, J₂=7.8 Hz, Ar-H), 7.68 (ddd, 1H, J₁= 1.7, J₂=7.3, J₃=8.4 Hz, Ar-H), 7.34-7.20 (m, 7H, Ar-H), 4.31 (ddd, J₁= 5.6, J₂= J₃=7.8 Hz, 2H, N-CH₂), 4.20 (q, 2H, J=7.1 Hz, -CH₂), 2.98 (ddd, 2H, J₁= 5.2, J₂= J₃=8.0 Hz, Ar-CH₂), 1.34(t, 3H, J=7.1 Hz, -CH₃) ppm; ¹³C-NMR: δ 161.6, 150.4, 139.5, 138.6, 135.0, 129.1, 129.0, 128.4, 126.4, 122.7, 115.8, 113.3, 43.2, 38.7, 34.0, 12.5 ppm; ESI-MS (m/e): 294.1[M+ H⁺].

The following compounds were prepared in similar fashion:

1-Ethyl-3-(benzyl)-1H,3H-quinazoline-2,4-dione (1ba). White solid. Yield >96%; mp. 103-105 °C; IR (NaCl): 2974, 2922, 1701, 1657, 1605, 1483 cm⁻¹; ¹H-NMR: δ 8.26 (dd, 1H, J₁=1.7, J₂=7.8 Hz, Ar-H), 7.66 (ddd, 1H, J₁= 1.7, J₂=7.3, J₃=8.4 Hz, Ar-H), 7.52 (dd, 2H, J₁=1.8, J₂=7.9 Hz, Ar-H), 7.35-7.18 (m, 5H, Ar-H), 5.28 (s, 2H, N-CH₂), 4.20 (q, 2H, J=7.1 Hz, -CH₂), 1.34 (t, 3H, J=7.1 Hz, -CH₃) ppm; ¹³C-NMR: δ 161.4, 150.3, 139.6, 137.0, 135.1, 129.3, 129.0, 128.4, 127.5, 127.2, 120.2, 113.3, 44.9, 38.8, 12.5 ppm; ESI-MS (m/e): 280.1[M+ H⁺].

1-Ethyl-3-[2′-(2′-methoxyphenyl)ethyl]-1H,3H-quinazoline-2,4-dione (1be). White solid. Yield >95%; mp.128-130°C; IR (NaCl): 2915, 2848, 1701, 1657, 1605, 1483, 1240 cm⁻¹; ¹H-NMR: δ 8.24 (dd, 1H, J₁=1.7, J₂=7.8 Hz, Ar-H), 7.66 (ddd, 1H, J₁= 1.7, J₂=7.3, J₃=8.4 Hz, Ar-H), 7.28-7.16 (m, 5H, Ar-H), 6.85 (ddd, 1H, J₁=1.0, J₂=J₃=8.2 Hz, Ar-H), 4.34 (ddd, 2H, J₁= 5.6, J₂= J₃=7.8 Hz, N-CH₂), 4.16 (q,
2H, $J=7.1$ Hz, -CH$_2$), 3.79 (s, 3H, O-CH$_3$), 3.03 (ddd, 2H, $J_1=5.8$, $J_2=J_3=7.4$ Hz, Ar-CH$_2$), 1.30 (t, 3H, $J=7.2$ Hz, -CH$_3$) ppm; $^{13}$C-NMR: $\delta$ 161.6, 150.4, 157.5, 139.1, 134.5, 130.2, 128.8, 127.4, 122.2, 120.1, 112.9, 109.9, 55.1, 41.5, 38.5, 29.6, 12.5 ppm; ESI-MS (m/e): 324.1[M+ H]$^+$.  

1-Ethyl-3-[2’-(3’-methoxyphenyl)ethyl]-1H,3H-quinazoline-2,4-dione (1bd). White solid. Yield >94%; mp.112-114°C; IR (NaCl): 2966, 2841, 1701, 1653, 1605, 1483, 1258 cm$^{-1}$; $^1$H-NMR: $\delta$ 8.25 (dd, 1H, $J_1=1.6$, $J_2=J_3=7.8$ Hz, Ar-H), 7.68 (ddd, 1H, $J_1=1.7$, $J_2=7.3$, $J_3=8.5$ Hz, Ar-H), 7.29-7.18 (m, 4H, Ar-H), 6.91 (m, 1H, Ar-H), 6.77 (ddd, 1H, $J_1=0.9$, $J_2=2.6$, $J_3=8.2$ Hz, Ar-H), 4.31 (ddd, 2H, $J_1=5.6$, $J_2=J_3=7.4$ Hz, N-CH$_2$), 4.20 (q, 2H, $J=7.1$ Hz, -CH$_2$), 3.79 (s, 3H, O-CH$_3$), 2.97 (ddd, 2H, $J_1=5.6$, $J_2=J_3=8.4$ Hz, Ar-CH$_2$), 1.35 (t, 3H, $J=7.2$ Hz, -CH$_3$) ppm; $^{13}$C-NMR: $\delta$ 161.6, 150.4, 157.5, 139.1, 134.5, 130.2, 128.8, 127.4, 122.2, 120.1, 112.9, 109.9, 55.1, 41.5, 38.5, 29.6, 12.5 ppm; ESI-MS (m/e): 324.1[M+ H]$^+$.  

1-Ethyl-3-[2’-(4’-methoxyphenyl)ethyl]-1H,3H-quinazoline-2,4-dione (1be). White solid. Yield >97%; mp.110-112°C; IR (NaCl): 2974, 2833, 1701, 1657, 1609, 1509, 1483, 1244 cm$^{-1}$; $^1$H-NMR: $\delta$ 8.24 (dd, 1H, $J_1=1.7$, $J_2=7.8$ Hz, Ar-H), 7.66 (ddd, 1H, $J_1=1.4$, $J_2=7.3$, $J_3=8.4$ Hz, Ar-H), 7.28-7.18 (m, 4H, Ar-H), 6.84 (ddd, 2H, $J_1=2.2$, $J_2=J_3=6.6$ Hz, Ar-H), 4.31-4.12 (m, 4H, 2 N-CH$_2$), 3.77 (s, 3H, O-CH$_3$), 2.93 (ddd, 2H, $J_1=5.6$, $J_2=J_3=8.2$ Hz, Ar-CH$_2$), 1.34 (t, 3H, $J=7.1$ Hz, -CH$_3$) ppm; $^{13}$C-NMR: $\delta$ 161.6, 158., 150.3, 135.0, 130.7, 129.9, 129.1, 122.7, 115.4, 114.2, 113.3, 113.2, 55.1, 43.1, 38.7, 34.0, 12.5 ppm; ESI-MS (m/e): 324.1[M+ H]$^+$.  

1-Ethyl-3-(3-(4-phenylpiperazin-1-yl)propyl)-1H,3H-quinazoline-2,4-dione (1bf). White solid. Yield >92%; mp. 94-96°C; IR (KBr): 3010, 2937, 2880, 2803, 1695, 1647, 1604, 1223, 1110 cm$^{-1}$. $^1$H-NMR: $\delta$ 8.10 (dd, 1H, $J_1=1.6$, $J_2=7.8$ Hz, Ar-H), 7.73 (ddd, 1H, $J_1=1.8$, $J_2=7.4$, $J_3=8.8$ Hz, Ar-H), 7.45 (d, 1H, $J=8.4$ Hz, Ar-H), 7.31-7.14 (m, 3H, Ar-H), 6.89-6.72 (m, 3H, Ar-H), 4.22-4.04 (m, 4H, 2 N-CH$_2$), 3.77 (s, 1H), 3.19-2.99 (m, 4H, N-CH$_2$), 2.56-2.40 (m, 6H, N-CH$_2$), 1.86 (dd, 3H, $J_1=7.0$, $J_2=14.2$ Hz, CH$_2$), 1.25 (t, 3H, $J=7.1$ Hz, CH$_3$) ppm; $^{13}$C-NMR: $\delta$ 164.9, 154.7, 153.7, 143.1, 138.8, 132.5, 131.8, 126.2, 119.1, 118.9, 117.7, 59.4, 56.5, 52.1, 51.4, 43.32, 28.0, 16.0 ppm; ESI-MS (m/e): 392.2[M+ H]$^+$.  

Acknowledgements  

We are grateful to Consejo Nacional de Ciencia y Tecnología in México (CONACYT, grant No. SEP-2004-C01-47835) and Dirección General de Educación Superior Tecnológica (DGEST) for supporting this project. Leticia Guerrero thanks to CONACYT for a scholarship.

References  

1. Piers, E.; Grierson, R.J. Alkylation of 1,5-dimethoxy-1,4-cyclohexadiene. A convenient synthesis of 2-alkyl-and-2-alkenyl-1,3-cyclohexanediones. J. Org. Chem. 1977, 42, 3755-3756.  
2. Merz, A. Phase-transfer-catalyzed Alkylation of Alcohols by Dimethyl Sulfate in an Aqueous System. Angew. Chem. Int. 2003, 12, 846-847.  
3. Haniti, M.; Hamid, S.A.; Williams, J.M.J. Ruthenium catalyzed N-alkylation of amines with alcohols. Chem. Commun. 2007, 725-727.
4. MacPhee, J.A.; Dubois, J.E. Steric effects in synthesis-steric limits to the alkylation of nitriles and carboxylic acids. *Tetrahedron* 1980, 36, 775-777.

5. Goto, S.; Tsuboi, H.; Kanoda, M.; Mukai, K.; Kagara, K. The Process Development of a Novel Aldose Reductase Inhibitor, FK366. Part 1. Improvement of Discovery Process and New Synthesis of 1-Substituted Quinazolinenediones. *Org. Process Res. Dev.* 2003, 7, 700-706.

6. Larksarp, C.; Alper, H. Palladium-Catalyzed Cyclocarbonylation of O-Iodoanilines with Heterocumulenes: Regioselective Preparation of 4(3H)-Quinazoline Derivatives. *J. Org. Chem.* 2000, 65, 2773-2777.

7. Herneecz, I.; Kökosi, J.; Podanyi, B.; Szasz, G. Synthesis of Indolyl-4(3H)-Quinazolinones. *Heterocycles* 1994, 37, 903-914.

8. Katritzky, A.R.; Rees, C.W. *Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds, Part 2B*; Pergamon Press: New York, USA, 1984; Volume 3.

9. Pelletier, S.W. *Alkaloids: Chemical and Biological Perspectives*; John Wiley & Sons Ltd.: New York, USA, 1985; Volume 1.

10. Scovill, J.; Blank, E.; Konnick, M.; Renortas, E.; Shapiro, T. Antitrypanosomal Activities of Tryptanthrins. *Antimicrob. Agents Chemother.* 2002, 46, 882-883.

11. Penn, J.; Mantle, P.G.; Bilton, J.N.; Sheppard, R.N. Glycansynepine, a novel anthranilic acid-containing metabolite of Aspergillus clavatus. *J. Chem. Soc. Perkin Trans. 1*, 1992, 1495-1496.

12. Hong, S-M.; Musza, L.L.; Kydd, G.C.; Kullnig, R.; Gillum, A.M.; Cooper, R. Fiscalins: new substance P inhibitors produced by the fungus Neosartorya fischeri. *J. Antibiot.* 1993, 46, 545-553.

13. Fujimoto, H.; Negishi, E.; Yamaguchi, K.; Nishi, N.; Yamazaki, M. Isolation of new tremorgenic metabolites from an ascomycete, Corynascus setosus. *Chem. Pharm. Bull.* 1996, 44, 1843-1848.

14. Numata, A.; Takahashi, C.; Matsushita, T.; Miyamoto, T.; Kawai, K.; Usami, Y.; Masumura, E.; Inoue, M.; Ohishi, H.; Shingu, T. Fumiquinazolines, novel metabolites of a fungus isolated from a saltfish. *Tetrahedron Lett.* 1992, 33, 1621-1624.

15. Takahashi, C.; Matsushita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kameda, Y.; Numata, A. Fumiquinazolines A-G, novel metabolites of a fungus separated from a Pseudolabrus marine fish. *J. Chem. Soc. Perkin Trans 1* 1995, 2345-2353.

16. Karwowsk, J. P.; Jackson, M.; Rasmussen, R. R.; Humphrey, P. E.; Poddig, J. B.; Kohl, W. L.; Scherr, M.H.; Kadam, S.; McAlpine, J.B. 5-N-Acetylardeemin, a novel heterocyclic compound which reverses multiple drug resistance in tumor cells. *J. Antibiot.* 1993, 46, 374-379.

17. Hochlowski, J.E.; Mullally, M.M.; Spanton, S.G.; Whittern, D.N.; Hill, P.; McAlpine, J.B. 5-N-Acetylardeemin, a novel heterocyclic compound which reverses multiple drug resistance in tumor cells. *J. Antibiot.* 1993, 46, 380-386.

18. Larsen, T.O.; Frydenvang, K.; Frisvad, J.C.; Christopersen, C. UV-Guided Isolation of Alantrypinone, a Novel Penicillium Alkaloid. *J. Nat. Prod.* 1998, 61, 1154-1157.

19. Barrow, C. J.; Sun, H. H. Spiroquinazoline, a Novel Substance P Inhibitor with a New Carbon Skeleton, Isolated from Aspergillus flavipes. *J. Nat. Prod.* 1994, 57, 471-476.
20. Hernández, F.; Buenadicha, F.L.; Avendaño, C.; Söllhuber, M. 1-Alkyl-2,4-dihydro-1H-pyrazino[2,1-b]quinazoline-3,6-diones as glycine templates. Synthesis of Fiscalin B. *Tetrahedron Asymmetry* **2001**, *12*, 3387-3398.

21. Hayao, S.; Havera, H.J.; Strycker, W.G.; Hong, E. Hypotensive, antiadrenergic, and antihistaminic 3-substituted 2-methyl-(or 2-phenyl)-4(3H)-quinazolones. *J. Med. Chem.* **1969**, *12*(5), 936-938.

22. Shiau, C.Y.; Chern, J.W.; Tien, J.H.; Liu, K C. Reactions of 2-Aminothiobenzamide with Isocyanates: A New Synthesis of 2,3-Dihydroimidazo[1,2-c]quinazolin-5(6H)-one and 3,4-Dihydro-2H-pyrimido[1,2-c]quinazolin-6(7H)-one. *J. Heterocyclic Chem.* **1989**, *26*, 595-596.

23. Nishikawa, Y.; Shindo, T.; Ishii, K.; Nakamura, H.; Kon, T.; Uno, H. Acrylamide derivatives as antiallergic agents. 2. Synthesis and structure activity relationships of N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(3-pyridyl)acrylamides. *J. Med. Chem.* **1989**, *32*, 583-593.

24. Hayao, S.; Havera, H.J.; Strycker, W.G.; Leipzig, T.J.; Kulp, R.A.; Hartzler, H.E. New Sedative and Hypotensive 3-Substituted 2,4(1H,3H)-Quinazolinediones. *J. Med. Chem.* **1965**, *8*, 807-811.

25. Hayao, S. Quinazolinedione derivatives. *US Patent 3274194*, **1965**.

26. Cortez, R.; Rivero, I.A.; Somanathan R.; Aguirre G.; Ramirez , F.; Hong, E. Synthesis of Quinazolinedione Using Triphosgene. *Synth. Commun.* **1991**, *21*, 285-292.

27. Rivero, I.A.; Somanathan, R.; Hellberg, L.H. Synthesis of 3-Dipeptidyl-2,4(1H,3H)-Quinazolinediones as Potential Anti-hypertensive Agents. *Synth. Commun.* **1998**, *28*, 2077-2086.

28. Dreyer, D.L.; Brenner, R.C. Alkaloids of some Mexican Zanthoxylum species. *Phytochemistry* **1980**, *19*, 935-939.

29. Rivero, I.A.; Espinoza, K.; Somanathan, R. Synthesis of Quinazoline-2,4-dione Alkaloids and Analogues from Mexican Zanthoxylum Species. *Molecules* **2004**, *9*, 609-616.

30. Hunig, S.; Quast, H.; Brenninger, W.; Frankenfield, E. Tetramethyl-<i>p</i>-phenylenediamine. *Org. Synth.* **1973**, *5*, 1018-1021.

**Sample Availability:** Available from the authors.

© 2009 by the authors; licensee Molecular Diversity Preservation International, Basel, Switzerland. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).