

## A CONVENIENT SYNTHESIS OF QUINAZOLINES DIMERS DERIVATIVES

S. Hichri and R. Abderrahim\*

*Laboratory of Physics of Lamellaires Materials and Hybrids Nanomaterials, University of Carthage, Faculty of Sciences of Bizerte, Zarzouna 7021, Bizerte, Tunisia*

\*Email: [abderrahim.raoudha@gmail.com](mailto:abderrahim.raoudha@gmail.com)

**Abstract:** In this work, we will describe, two new methods for the synthesis of some quinazoline dimer derivatives **1**. The first, we will show how this series of **1** were synthesized by the sequential one-pot reaction via the condensation reaction of anthranilonitrile with ethylene diamine and orthoester under reflux condition. Then we will see how, the synthesis of **1** and **1'**, consists to isolate the imidate **2**, which reacts easily with ethylene diamine to obtain the quinazoline dimer derivatives **1** and **1'** in good yield. The structures of the products have been established with the help of spectral and analytical data.

**Key words:** anthranilonitrile, ethylene diamine, orthoester, quinazoline dimer.

### Introduction

To introduce let us state that, the quinazoline nucleus is of great importance to chemists as well as biologists<sup>I</sup> as it is available in a large variety of naturally occurring compounds. It is also found in clinically useful molecules having diverse biological activities<sup>II</sup> such as antimalarial, antiviral, antibacterial, anticonvulsant, anti-inflammatory<sup>III, IV</sup>; anticancer<sup>IV</sup>]; antioxidant activities<sup>V</sup>; antineoplastic agents<sup>VI</sup>;  $\alpha_1$ -adrenoceptor antagonist<sup>VII, IX</sup>; as antiplasmodial activity<sup>VIII</sup>; antihypertensive<sup>IX</sup>; antiviral<sup>X, XII</sup>. These literature reports prompted us to develop a new synthetic route to novel quinazoline fused heterocyclics.

In addition, it is important to say that quinazolines constitute a large family of compounds with pharmacological properties as well as industrial uses<sup>[XIII-XV]</sup>. In fact many methods for the synthesis of quinazolines have been reported in the literature<sup>[XVI-XVII]</sup>.

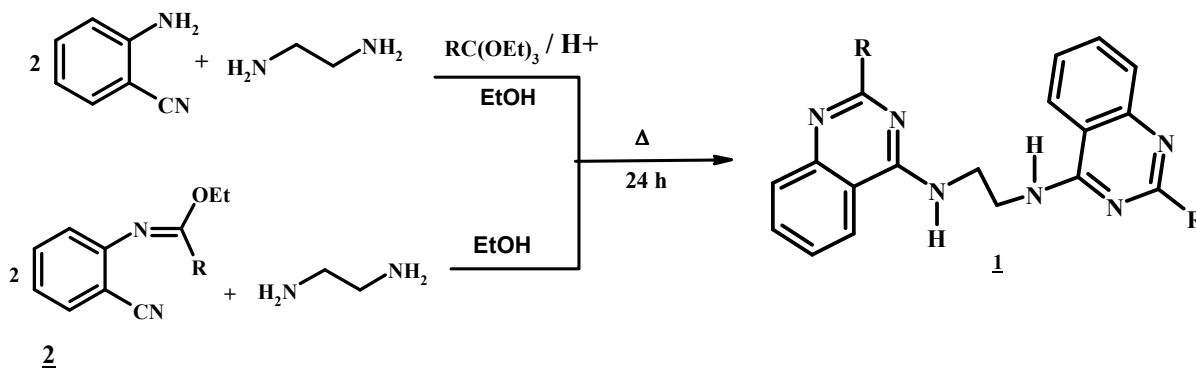
Dimeres constitute a family of compounds which have aroused the interest of the chemists because of their biological and pharmacological properties<sup>XVIII-XX</sup>. Since, they are very known for their cytotoxic, anticancer, antimicrobial, antibacterial and antitumoral activities<sup>XXI-XXIV</sup>. Actually these types of dimers can also have complexes of transition metals and lanthanides<sup>XXV</sup>.

Diverses methods were reported in the literature may be dependent on the nature of the monomer implied in the reaction of dimerisation<sup>XXVI-XXXIII</sup>. In fact, the quinazoline dimer showed moderate inhibition against EGFR in vitro and its further bioactivity<sup>XXXIV</sup> evaluation is in progress.

A facile method was developed for the construction of quinazoline dimers and which hoped to be useful in the synthesis of other dimers, but to our knowledge, there are only a limited number on studies on the synthesis of quinazoline dimers derivatives which have been reported. We report in this work, two novel methods of synthesis of some dimeric quinazoline derivatives.

## Results and discussion

In this paper, we describe here an efficient and operationally two simple methods for the synthesis of quinazolines dimers derivatives. The reaction of two equivalents of 2-aminobenzonitrile and one equivalent of ethylene diamine and one equivalent of orthoesters in the presence of a catalytic quantity of acetic acid, under reflux of ethanol gives a series of bis quinazoline dimers **1** (Scheme 1). On the other hand compounds **1** were also independently synthesized through another pathway via the condensation of imidate **2** with ethylene diamine. And that when we condense two different iminoethers with ethylene diamine, we obtained the dimers **1'**(Scheme 2).



Scheme 1. Reagents and reaction conditions in synthesis of **1**

<b>1</b>	<b>1a</b>	<b>1b</b>	<b>1c</b>
<b>R</b>	<b>Et</b>	<b>Me</b>	<b>Ph</b>

Hence, the reaction of orthoesters with anthranilonitrile under reflux of orthoester<sup>XXXV</sup> leads to the iminoethers derivatives **2a**. So, a tentative mechanism is given in Scheme 3.

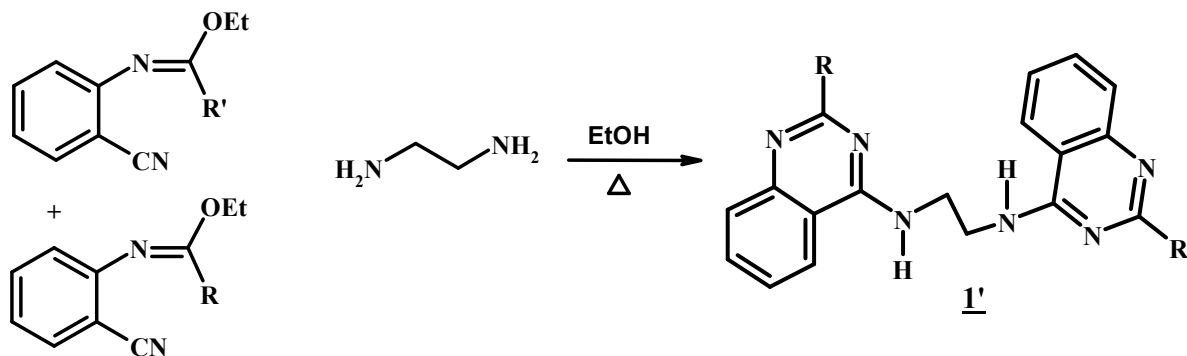
The structure of compounds **1** and **1'** was established by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, DEPT, COESY and MS spectral data. The IR spectrum of compounds **1** and **1'** exhibited absorption bands for NH at 3240-3315 cm<sup>-1</sup>, for C=N at 1627-1650 cm<sup>-1</sup>, and for C=C at 1600 cm<sup>-1</sup>.

The <sup>1</sup>H NMR spectrum of compounds **1a** for example revealed the presence of multiplet to CH<sub>2</sub>-CH<sub>2</sub>-NH- as the magnetically and chemically non-equivalent respectively and showed the presence of new signals assigned to NH. The chemical shifts of different carbons and the assignments of the carbons are made using the <sup>13</sup>C NMR spectra of **1** and **1'**.

The <sup>13</sup>C NMR spectra of **1a** displayed the characteristic signals of all carbons and revealed two signals attributable to the carbons of CH<sub>2</sub>-CH<sub>2</sub>-NH at  $\delta_c = 46$  and 53 ppm corresponding to the two CH<sub>2</sub> non equivalent of ethylene diamine and the absence of two signals corresponding to the ethoxy group.

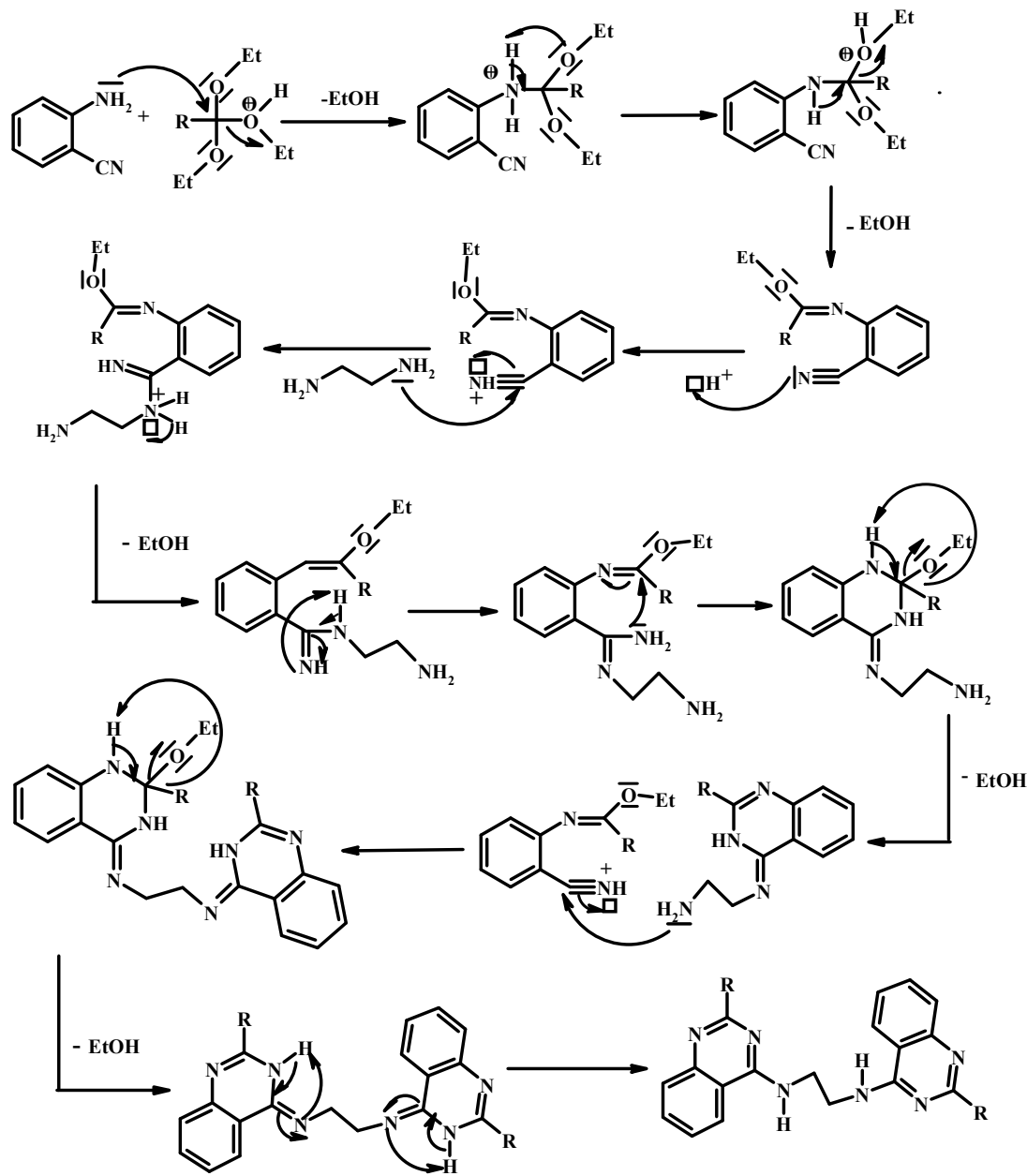
Distortionless enhancement of NMR signals by polarization transfer (DEPT) is used to better distinguish the different types of carbons present in **1** and **1'**.

The DEPT spectrum of **1a** gives the CH<sub>2</sub> peaks at 28.18, 46.53, 53.21 ppm and CH peak at 115.10, 117.74, 125.14, 125.83, 126.44, 132.29, 132.97, 133.96 ppm. It can be seen that there is one CH<sub>3</sub> at 10.56 ppm. The other peaks of <sup>13</sup>C NMR except for the peaks in DEPT spectrum are quaternary carbons. Assignments of the protons and carbons are also made by two-dimensional homonuclear and heteronuclear correlated experiments. showed <sup>1</sup>H-<sup>1</sup>H NMR COSY and XHCOR spectra in CDCl<sub>3</sub>. The COSY spectrum shows the presence of the correlation between the CH<sub>2</sub>-CH<sub>2</sub>- of ethylene diamine where as the magnetically and chemically non-equivalent, and these assignments were confirmed by the spectra of correlation <sup>1</sup>H-<sup>13</sup>C (XHCOR).



	<b>1'a</b>	<b>1'b</b>	<b>1'c</b>
<b>R</b>	Et	ph	Me
<b>R'</b>	Me	Et	Ph

**Scheme-2 Reagents and reaction conditions in synthesis of **1'****



**Scheme 3: Proposed mechanism**

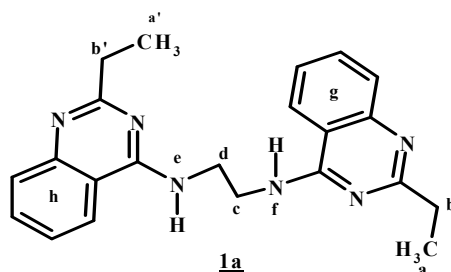
## EXPERIMENTAL

IR spectra were recorded on Nicolet TR 200 FT-IR spectrometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded with  $\text{CDCl}_3$  solvent containing TMS (tetramethylsilane) on a Brüker 300 spectrometer ( $^1\text{H}$ : 300 MHz,  $^{13}\text{C}$ : 75.47 MHz). The chemical shifts ( $\delta$ ) are reported in ppm relative to TMS (internal reference). For the  $^1\text{H}$  NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, and m: multiplet. Melting points were obtained using a Büchi melting point apparatus and are uncorrected. Elemental microanalysis

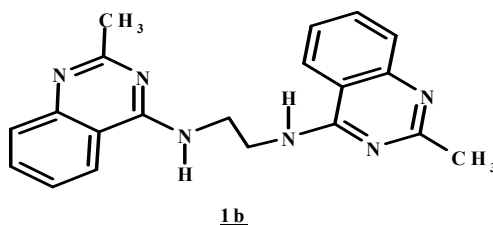
was performed on a Perkin-Elmer CHN-2400 analyzer apparatus. Mass spectra were recorded on a HP-5890 A using the impact mode (70 eV).

**Synthesis of dimeric *N,N'*-bisquinazolinyl 1a-c. General procedure.**

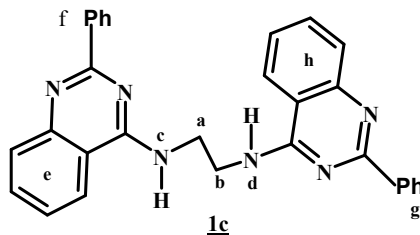
To anthranilonitrile (0.01mole) dissolved in ethanol, we added orthoester (0.015mol) and ethylene diamine (0.01mole), using CH<sub>3</sub>COOH (0,5mL) as a catalyst. Then the reaction mixture was refluxed for 24 h. the formed product filtered under reduced pressure and recrystallised out of alcohol. The products were characterized on the basis of m.p, IR, NMR, mass of one of compounds and elemental analysis spectra.



**1a: *N,N'*-bis(2-ethylquinazolin-4-yl) ethyl-1,2-diamine:** Yield (90%). It was obtained as white solid. Mp: 268-265°C IR ( $\nu$  (cm<sup>-1</sup>))  $\nu$ (NH) = 3248,  $\nu$ (C=N) = 1648. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.25 (t, <sup>3</sup>J<sub>HH</sub> = 6.0 Hz, 6 H, 2 CH<sub>3</sub>), 2.46 (q, <sup>3</sup>J<sub>HH</sub> = 6.0 Hz, 4 H, 2CH<sub>2</sub>), 3.99 (m, 2H, CH<sub>2</sub>), 4.07 (m, 2H, CH<sub>2</sub>), 3.04 (broad s, H, NH), 4.54 (broad s, H, NH), 6.84-7.72 (m, 8H, H<sub>arom</sub>). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 10.51; 28.16; 46.11; 53.28; 115.10; 117.53; 117.58; 117.81; 125.31; 125.80; 126.47; 132.29; 132.90; 133.93; 146.83; 149.75; 155.38; 156.09; 160.20; 160.28. MS: 143(60%); 157(75 %); 170(90 %); 199(85%) Calcd.for C<sub>22</sub>H<sub>24</sub>N<sub>6</sub>: %C = 70.96 % H = 6.45 % N = 22.58; Found: %C = 70.90 % H = 6.44 % N = 22.55.



**1b: *N,N'*-bis(2-methylquinazolin-4-yl) ethyl-1,2-diamine:** white solid. Mp: 262-264 °C; Yield (86%). IR ( $\nu$  (cm<sup>-1</sup>)):  $\nu$  (NH) = 3245,  $\nu$  (C=N) = 1652. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.15 (s, 3H, CH<sub>3</sub>), 3.95 (m, 2H, CH<sub>2</sub>), 4.05 (m, 2H, CH<sub>2</sub>), 3.50 (broad s, H, NH), 4.47 (broad s, H, NH), 6.84-7.92 (m, 8H, H<sub>arom</sub>). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 21.87; 47.03; 53.17; 115.12; 117.41; 117.66; 117.75; 125.16; 125.84; 126.15; 132.26; 133.00; 133.96; 146.68 ; 149.94; 152.39; 155.00; 162.20. Calcd.for C<sub>20</sub>H<sub>20</sub>N<sub>6</sub>: %C = 69.76 % H = 5.81 % N = 24.41; Found: %C = 69.75 % H = 5.80 % N = 24.40.



**1c:** *N,N'*-bis (2-phenylquinazolin-4-yl) ethyl-1,2-diamine: Yield (63%). It was obtained as yellow solid. Mp: 274-276 °C; IR ( $\nu$  (cm<sup>-1</sup>))  $\nu$  (NH) = 3315,  $\nu$  (C=N) = 1652. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 3.75 (m, 2 H, CH<sub>2</sub>), 3.90 (m, 2 H, CH<sub>2</sub>), 6.50 (broad s, 1H, NH), 8.47 (broad s, 1H, NH), 7.33-8.9 (m, 18 H, H<sub>arom</sub>). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 43.25 (N-CH<sub>2</sub>); 53.97; 111.20; 115.14; 117.26; 117.45; 125.26; 125.32; 126.51; 127.19; 127.34; 128.25; 128.32; 128.91; 129.83; 131.29; 132.26; 133.00; 133.96; 134.53; 165.53; 165.62; 166.10; 166.28; 168.50; 168.72. Calcd. for C<sub>30</sub>H<sub>24</sub>N<sub>6</sub>: %C = 76.92 % H = 5.12 % N = 17.94; Found: %C = 76.90 % H = 5.12 % N = 17.92.

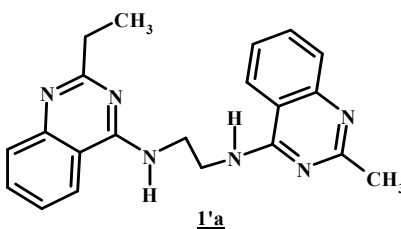
### Reactivity of imidates N-cyanophenyl **2** with ethylene diamine.

The reaction anthranilonitrile with orthoesters is a convenient synthetic approach to prepare imidates **2**. These imidates were obtained by refluxing the anthranilonitrile in a large excess of orthoester. The synthesis of imidates is usually followed by their combination with nucleophiles, in particular with primary amine to generate amidines, important units in biologically active compounds <sup>XXXV-XXXVI</sup>. Nevertheless, the formation of quinazolines dimers from the reaction of imidates with ethylene diamine has not been reported. We have obtained the quinazoline dimers **1** and **1'** starting from the anthranilonitrile in two steps. First the formation of iminoesters **2** by the reaction of anthranilonitrile with orthoesters, and in a second step, the reaction of ethylene diamine with two equivalents of imidates, realized under reflux of absolute ethanol, this allows us a series of non symmetric *N,N'*- bisquinazolinyl dimers **1**. When two types of imidate **2** react with ethylene diamine, dimers **1'** with R and R' were different were obtained.

### Synthesis of quinazolines dimers **1'**.

A mixture of imidates **2** (0.02 mole + 0.02 mole (R ≠ R')) and ethylene diamine (0.02 mole) dissolved in absolute ethanol (15mL) was heated under reflux for 24 h. After evaporating off the solvent in vacuum, the resulting solid product was recrystallized with ethanol/ ether (30/70).

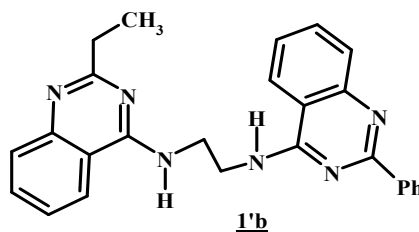
### **1'a:** *N*<sup>1</sup>-(2-ethylquinazolin-4-yl)-*N*<sup>2</sup>-(2-methylquinazolin-4-yl) ethyl-1,2-diamine



Yield (89%). White solid. Mp: 262-264 °C; IR ( $\nu$  (cm<sup>-1</sup>)):  $\nu$  (NH) = 3235,  $\nu$  (C=N) = 1651. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.18 (t, <sup>3</sup>J<sub>HH</sub> = 9.0 Hz, 3H, CH<sub>3</sub>), 2.08 (s, 3H, CH<sub>3</sub>), 2.40 (q, <sup>3</sup>J<sub>HH</sub> = 9.0 Hz, 2 H, CH<sub>2</sub>), 3.94 (m, 2H, CH<sub>2</sub>), 4.02 (m, 2H, CH<sub>2</sub>), 4.72 (broad s, 2H, NH), 6.74-7.80 (m, 8H, H<sub>arom</sub>). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 17.87; 21.29; 30.46; 46.48; 52.53; 115.44; 116.18; 116.86; 117.37; 124.24; 124.70; 125.51; 132.26; 132.53; 133.56; 146.14; 146.34; 150.82;

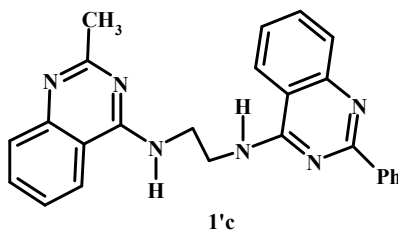
152.60; 154.17; 159.15. MS: 117(70%), 143(75%), 157(65%); 198(99%). Calcd. for  $C_{21}H_{22}N_6$ : %C = 70.39 % H = 6.14 % N = 23.46; Found: %C = 70.30 % H = 6.13 % N = 23.45.

**1'b: N<sup>1</sup>-(2-ethylquinazolin-4-yl)-N<sup>2</sup>-(2-phenylquinazolin-4-yl) ethyl-1,2-diamine**



Yield (91%). Yellow solid. Mp: 274-276 °C; IR ( $\nu$  (cm<sup>-1</sup>))  $\nu$  (NH) = 3322,  $\nu$  (C=N) = 1652. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.28 (t, <sup>3</sup>J<sub>HH</sub> = 6.0 Hz, 3H, CH<sub>3</sub>), 2.50 (q, <sup>3</sup>J<sub>HH</sub> = 6.0 Hz, 2 H, CH<sub>2</sub>), 3.85 (m, 2 H, CH<sub>2</sub>), 4.05 (m, 2 H, CH<sub>2</sub>), 5.35 (broad s, 2H, NH), 6.63-8.9 (m, 13H, H<sub>arom</sub>). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 14.80; 27.56; 46.00; 52.65; 111.60; 114.84; 116.36; 116.93; 124.61; 125.22; 125.52; 125.87; 131.29; 132.26; 132.54; 133.96; 143.53; 146.28; 147.20 ; 150.42 ; 154.10; 154.28; 159.72. Calcd. for  $C_{26}H_{24}N_6$ : %C = 74.28 % H = 5.71 % N = 20.00; Found: %C = 74.25 % H = 5.69 % N = 19.98.

**1'c :N<sup>1</sup>-(2-methylquinazolin-4-yl)-N<sup>2</sup>-(2-phenylquinazolin-4-yl) ethyl-1,2-diamine**



Yield (80%). Yellow solid. Mp: 274-276 °C; IR ( $\nu$  (cm<sup>-1</sup>))  $\nu$  (NH) = 3326,  $\nu$  (C=N) = 1654. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.30 (s, 3H, CH<sub>3</sub>), 3.82 (m, 2 H, CH<sub>2</sub>), 4.02 (m, 2 H, CH<sub>2</sub>), 5.54 (broad s, 2H, NH), 6.61-7.90 (m, 13H, H<sub>arom</sub>). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 21.22; 46.42; 52.46; 111.30; 114.94; 116.72; 116.85; 124.71; 125.24; 125.27; 125.47; 132.29; 132.26; 132.54; 133.96; 143.65; 149.28; 156.15 ; 150.42; 154.18; 154.42; 159.90. Calcd. for  $C_{25}H_{22}N_6$ : %C = 73.80 % H = 5.46 % N = 20.68; Found: %C = 72.10 % H = 5.42 % N = 19.12.

**References**

- I. S. Jantova, S. Stankovsky and K. Spirkova. *Biologia Bratislava* 59, 741(2004)
- II. P.C.S. Reddy, CH.K. Reddy, K. Kondal Reddy, V.M. Reddy. *Ind. J. Hetero. Chem* 5, 129(1995).
- III. A.A.Abu-Hashem, M.A. Gouda, F.A.Badria. *Eur. J. Med. Chem* 45, 1976(2010).

- IV. P. Mani Chandrika, T. Yakaiah, A. Raghu Ram Rao, B. Narsaiah, N. Chakra Reddy, J.V. Rao. *Eur. J. Med. Chem.* 43, 846 (2009).
- V. A.B.A. El Gazzar, M.M. Youssef, A.M.S. Abu-Hashem, F.A. Badria. *Eur. J. Med. Chem.* 44, 609 (2009).
- VI. V. Murugan, M. Kulkarni, R.M. Anand, E.P. Kumar, B. Suresh. *Asian. J. Chem.* 18, 900(2006)
- VII. F. Hao, Y. Min, L. Xia. *Chin. Chem. Lett.* 18, 41(2007).
- VIII. N. Primas, P. Verhaeghe, A. Cohen, C. Kieffer, A. Dumètre, S. Hutter, S. Rault, P. Rathelot, N. Azas and P. Vanelle. *Molecules* 17, 8105 (2012).
- IX. V.A. Alabaster, S.F. Campbell, J.C Danilewicz, C.W. Greengrass, R. M. Plews. *J. Med. Chem.* 30, 999(1987)
- X. A. Foster, H.A. Coffrey, M.J. Morin, F. Rastinejad. *Science* 286, 2507(1999).
- XI. T.-C. Chien, C.-S. Chen, F.-H. Yu, J.-W. Chem. *Pharm. Bull.* 52, 1422 (2004).
- XII. T. Herget, M. Freitag, M. Morbitzer, R. Kupfer, T. Stamminger, M. Marschall, *Antimicrob. Agents Chemother.* 48, 4154 (2004).
- XIII. R. Rohini, M. Reddy, K. Shanker, A. Hu, V. Ravinder. *Eur. J. Med. Chem.* 45, 1200(2010).
- XIV. V. Murugan, N.P.Padmavathy, G.V.S. Ramasarma, B. Suresh. *Ind. J. Heterocycl. Chem.* 13, 143(2003).
- XV. C.M. Marson. *Chem. Rev.* 111, 7121 (2011).
- XVI. R. Chioua, F. Benabdelouahab, M. Chioua, R. Martínez-Alvarez, A.H. Fernández, *Molecules.* 7, 507(2002).
- XVII. Y. Ohta, Y. Tokimizu, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* 12, 3963 (2010),
- XVIII. D. Passarella, D. Comi, G. Cappelletti, D. Cartelli, J. Gertsch, A. Quesada, J. Borlak and K. Altmann, *Bioorg. Med. Chem.* 17, 7435 (2009).
- XIX. C. Demetzos, K. S. Dimas, *Stud. Nat. Prod. Chem.* 25, 235 (2001).
- XX. M. W. Pertino, C. Theoduloz, J. A. Palenzuela, M. M. Afonso, E. Yesilada, F. Monsalve, P. González, D. Droguett and G. S. Hirschmann, *Molecules.* 16, 8614 (2011).
- XXI. B. K. Ponou, R. B. Teponno, M. Ricciutelli, L. Quassinti, M. Bramucci, G. Lupidi, L. Barboni and L. A. Taponjoui, *A. Chev. Phytochemistry.* 71, 2108 (2010).
- XXII. M. K. Hadden, B. S. Blagg, *J. Med. Chem.* 8, 807 (2008).
- XXIII. D. Slade, A. M. Galal, W. Gul, M. M. Radwan, S. A. Ahmed, S. I. Khan, B. L. Tekwani, M. R. Jacob, S. A. Ross and M. A. ElSohly, *Bioorg. Med. Chem.* 17, 7949 (2009).
- XXIV. J. P. Jeyadevan, P. G. Bray, J. Chadwick, A. E. Mercer, A. Byrne, S. A. Ward, B. K. Park, D. P. Williams, R. Cosstick and J. Davies, *J. Med. Chem.* 47, 1290 (2004).
- XXV. G. Muller, J.-C. G. Bunzli, K. J. Schenk, C. Piguet and G. Hopfgartner, *Inorg. Chem.* 40, 2642(2001).
- XXVI. M. W. Pertino, C. Theoduloz, M. Bastías and G. S. Hirschmann, *Molecules.* 18, 5936 (2013).
- XXVII. S. F. Alshahateet, N. M. Algezawi and R. Bishop, *J. J. Chem.* 6, 139 (2011).
- XXVIII. S. P. Chen, Y. Sun, S. B. Wan and T. Jiang, *Chin. Chem. Lett.* 22, 1033 (2011).
- XXIX. E. Marinho, R. Araújo and F. Proença, *Tetrahedron. Lett.* 66, 8681 (2010).
- XXX. M. Saha, E. Karim, J. N. Vishwakarma, *J. Chem. Scien. CSJ-43*(2012).



- XXXI. E. Bouthenet, K. B. Oh, S. Park, N. K. Nagi, H. S. Lee and S. E. Matthews, *Bioorg. Med. Chem. Lett.* 21, 7142 (2011).
- XXXII. M. Saha, E. Karim, R. L. Nongkhlaw and J. N. Vishwakarma, *Ind. Chem. Soc.* 89, 117 (2012).
- XXXIII. M. F. Pereira, V. Thiéry and T. Besson, *Tetrahedron. Lett.* 63, 847 (2007).
- XXXIV. S. P. Chen, Y. Sun, S. B. Wan and T. Jiang, *Chin. Chem. Lett.* 22, 1033 (2011).
- XXXV. G. V. Boyd, In *The Chemistry of Functional Groups: The Chemistry of Amidines and Imidates*, S. Patai, Z. Rappoport, Eds.; John Wiley & Sons: New York, NY, 2, 8.3(1991).
- XXXVI (a) J. V. Greenhill, P. Lue, *Prog. Med. Chem.* 30, 203 (1993); (b) M. Y. Lee, M. H. Kim, J. Kim, S. H. Kim, B. T. Kim, I. H. Jeong, S. Chang, S. H. Kim and S. Y. Chang, *Bioorg. Med. Chem. Lett.* 20, 541 (2010).

Received on June 21, 2014.