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Anton V. Dolzhenko, Anna V. Dolzhenko and Wai-Keung Chui

Reaction of 2-guanidino-4-quinazolinone with arylaldehydes

Department of Pharmacy, Faculty of Science, National University of Singapore, 18 Science Drive 4, Singapore 117543, Singapore.
E-mails: phada@nus.edu.sg, phacwk@nus.edu.sg

Abstract

The reaction of 2-guanidino-4-quinazolinone with arylaldehydes was found to afford 2-amino-4-aryl-4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-ones. The structures of the compounds obtained were established using NMR spectroscopy, including 2D NOESY experiments.

Key words: triazines, quinazolines, guanidines, cyclization.

Introduction

Naturally occurring and synthetic quinazolinone derivatives, including fused systems, are known to possess a wide range of biological activities [1-4]. In continuation of our investigations [5-7] of the reactions of heterylguanidines with aldehydes, we describe herein the reaction of 2-guanidino-4-quinazolinone (**1**) with arylaldehydes.

Results and Discussion

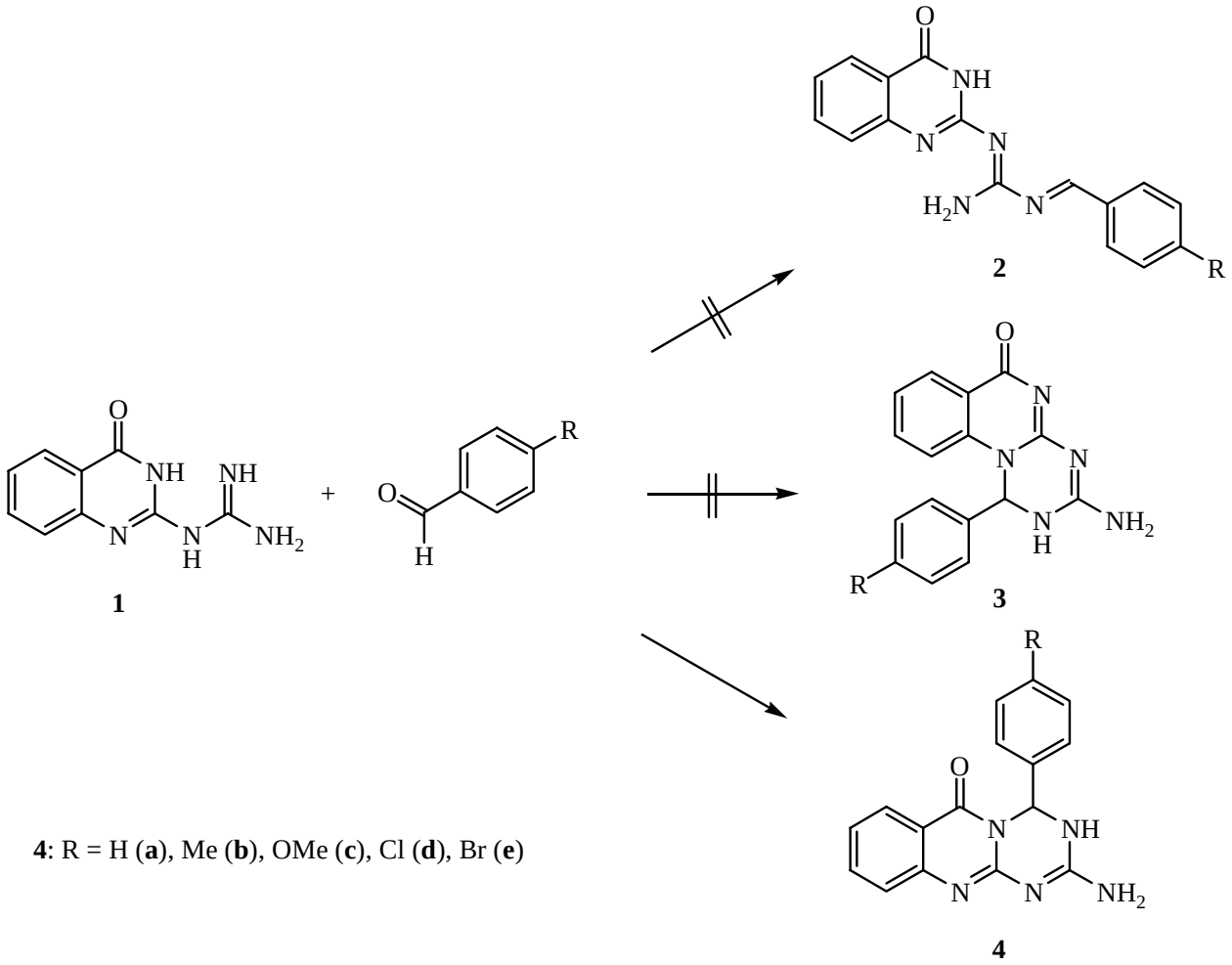
The reported method [8] was used for the preparation of 2-guanidino-4-quinazolinone (**1**).

The reaction of 2-guanidino-4-quinazolinone (**1**) with benzaldehyde in refluxing DMF proceeded *via* (5+1) heterocyclization and afforded the formation of hitherto unknown 2-amino-4-phenyl-4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-one (**4a**) (Scheme 1). Similarly, a number of substituted benzaldehydes were used successfully for the preparation of corresponding 2-amino-4-aryl-4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-ones (**4b-e**).

The NMR spectroscopic studies were used for confirmation of the product structure. The formation of the dihydro-*s*-triazine ring in the reaction was suggested by the singlet of H-4 observed at 6.90-7.04 ppm in the ^{1}H NMR spectra of **4**, together with the signal of C-4 at 60.4-61.0 ppm in the ^{13}C NMR spectra. This strong evidence of the sp^{3} hybridization of C-4 ruled out the possible formation of the azomethine carbon of Schiff base-like compound **2**. The alternative structure of the 1,3,5-triazino[1,2-*a*]quinazolines (**3**) for the prepared compounds would gave cross-peaks between the H-4 singlet and one of the doublet of the phenylene part of the molecule

in 2D NOESY experiments. Inasmuch as no cross-peaks were found for these signals the structure of 1,3,5-triazino[2,1-*b*]quinazolines (**4**) was assigned for the prepared compounds.

Scheme 1

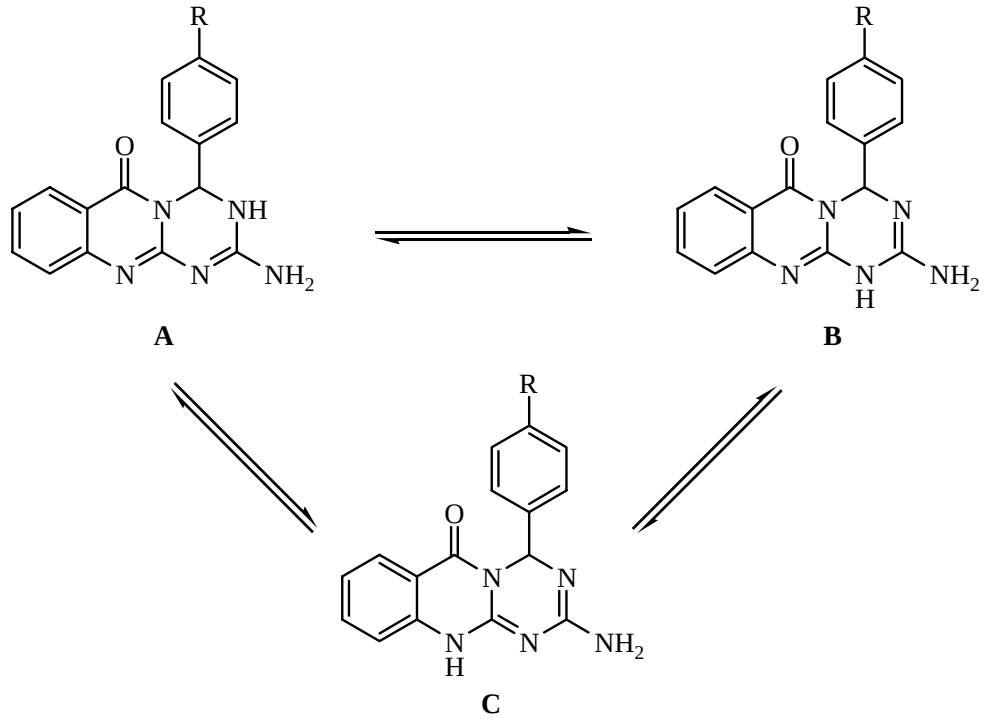


4: R = H (**a**), Me (**b**), OMe (**c**), Cl (**d**), Br (**e**)

Annular prototropic tautomerism was observed in DMSO solution for compounds **4** (*viz.* 1*H*-, 3*H*- and 11*H*- tautomeric forms) (Scheme 2). The prototropic interconversion between these tautomeric forms was postulated based on the broadening of the several signals of 4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-one heterocyclic system in the ^{13}C NMR spectra of compounds **4**. It should be noted that broadening of C-10 and C-10a is not only an indication of the tautomerization but also a confirmation of structure **4**, because in the alternative structure **3** these phenylene carbons are not in close proximity with the nitrogen atoms involved in the tautomerization.

In summary, the present work demonstrated the use of a simple cyclocondensation method for the synthesis of 2-amino-4-aryl-4,6-dihydro-1(3)(11)*H*-[1,3,5]triazino[2,1-*b*]quinazolin-6-ones; their biological activity investigation is in progress.

Scheme 2



Experimental procedures

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. NMR spectra were recorded on a Bruker DPX-300 spectrometer, using DMSO-d_6 as a solvent and TMS as an internal reference.

Reaction of heterylguanidines with arylaldehydes.

A solution of 0.51 g (2.5 mmol) of 2-guanidino-4-quinazolinone (**1**) and appropriate arylaldehyde (5.0 mmol) in DMF (5 ml) was heated under reflux for 2-10 h and concentrated under vacuum. After cooling, the product was filtered, washed with ethanol and recrystallized from DMF.

*2-Amino-4-phenyl-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazolin-6-one (**4a**).*

Yield 61%, mp 302-303ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ 6.98 (2H, br s, NH_2), 7.00 (1H, s, H-4), 7.17 (1H, t, *J* = 7.5 Hz, H-8), 7.24-7.40 (6H, m, H-10 and Ph), 7.62 (1H, td, *J* = 7.7, 1.5 Hz, H-9), 7.94 (1H, dd, *J* = 7.9, 1.5 Hz, H-7), 8.32 (1H, s, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 60.9, 117.7, 122.4, 125.3, 125.5 (2C), 126.2, 128.4 (2C), 128.6, 127.9, 140.2, 149.9, 150.5, 156.8, 160.4.

*2-Amino-4-(4-methylphenyl)-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazolin-6-one (**4b**).*

Yield 52%, mp 248-251ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (3H, s, Me), 6.97 (1H, s, H-4), 7.03 (2H, br s, NH_2), 7.10-7.23 (5H, m, H-8, H-2', H-3', H-5' and H-6'), 7.32 (1H, d, *J* = 7.9 Hz, H-10), 7.62 (1H, t, *J* = 7.5 Hz, H-9), 7.94 (1H, d, *J* = 7.9 Hz, H-7), 8.42 (1H, br s, NH).
^{13}C NMR (75 MHz, DMSO-d_6): δ 20.5, 61.0, 117.7, 122.4, 125.2 (3C), 126.2, 129.1 (2C), 134.2, 137.3, 137.8, 149.8, 150.2, 156.6, 160.3.

*2-Amino-4-(4-methoxylphenyl)-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazolin-6-one (**4c**).*
Yield 55%, mp 246-248ºC.
^{1}H NMR (300 MHz, DMSO-d_6): δ 3.70 (3H, s, OMe), 6.90 (2H, d, *J* = 8.7 Hz, H-2' and H-6'), 6.95 (1H, s, H-4), 6.97 (2H, br s, NH_2), 7.16 (1H, t, *J* = 7.5 Hz, H-8), 7.21 (2H, d, *J* = 8.7 Hz, H-3' and H-5'), 7.31 (1H, d, *J* = 8.3 Hz, H-10), 7.61 (1H, t, *J* = 7.5 Hz, H-9), 7.93 (1H, d, *J* = 7.9 Hz, H-7), 8.26 (1H, br s, NH).
^{13}C NMR (75 MHz, DMSO-d_6): δ 55.0, 60.6, 113.9 (2C), 117.7, 122.3, 125.4, 126.2, 126.7 (2C), 132.4, 134.2, 149.8, 150.4, 156.9, 159.2, 160.3.

*2-Amino-4-(4-chlorophenyl)-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazolin-6-one (**4d**).*
Yield 63%, mp 263-264ºC.
^{1}H NMR (300 MHz, DMSO-d_6): δ 7.01 (1H, s, H-4), 7.02 (2H, br s, NH_2), 7.18 (1H, t, *J* = 7.5 Hz, H-8), 7.29 (2H, d, *J* = 8.3 Hz, H-2' and H-6'), 7.32 (1H, d, *J* = 7.9 Hz, H-10), 7.44 (2H, d, *J* = 8.3 Hz, H-3' and H-5'), 7.63 (1H, t, *J* = 7.5 Hz, H-9), 7.94 (1H, d, *J* = 7.9 Hz, H-7), 8.32 (1H, br s, NH).
^{13}C NMR (75 MHz, DMSO-d_6): δ 60.4, 117.7, 122.5, 125.5, 126.2, 127.3 (2C), 128.7 (3C), 133.1, 134.3, 149.6, 150.4, 156.8, 160.4.

*2-Amino-4-(4-bromophenyl)-4,6-dihydro-1(3)(11)H-[1,3,5]triazino[2,1-b]quinazolin-6-one (**4e**).*
Yield 74%, mp 267-269ºC.
^{1}H NMR (300 MHz, DMSO-d_6): δ 6.99 (1H, s, H-4), 7.04 (2H, br s, NH_2), 7.18 (1H, t, *J* = 7.7 Hz, H-8), 7.22 (2H, d, *J* = 8.3 Hz, H-2' and H-6'), 7.33 (1H, d, *J* = 7.9 Hz, H-10), 7.58 (2H, d, *J* = 8.3 Hz, H-3' and H-5'), 7.63 (1H, t, *J* = 7.9 Hz, H-9), 7.94 (1H, d, *J* = 7.9 Hz, H-7), 8.31 (1H, br s, NH).
^{13}C NMR (75 MHz, DMSO-d_6): δ 60.5, 117.6, 121.6, 122.4, 125.5, 126.2, 127.6 (2C), 131.6 (2C), 134.3, 139.6, 149.6, 150.4, 156.7, 160.4.

References

[1] S.B. Mhaske and N.P. Argade, *Tetrahedron*, 2006, **62**(42), 9787-9826.
[2] G.A. El-Hiti and M.F. Abdel-Megeed, *Heterocycles*, 2005, **65**(12), 3007-3041.
[3] D.J. Connolly, D. Cusack, T.P. O'Sullivan and P.J. Guiry, *Tetrahedron*, 2005, **61**(43), 10153-10202.
[4] P.S. Reddy, P.P. Reddy and T. Vasantha, *Heterocycles*, 2003, **60**(1), 183-226.
[5] A.V. Dolzhenko and W.K. Chui, *J. Heterocyclic Chem.*, 2006, **43**(1), 95-100.

[6] A.V. Dolzhenko, W.K. Chui and A.V. Dolzhenko, *ECSOC-9*, Nov. 1-30, 2005 C012/1-C012/6.
[7] A.V. Dolzhenko, W.K. Chui, A.V. Dolzhenko and L.W. Chan, *J. Fluorine Chem.*, 2005, **126**(5), 759-763.
[8] B. Skowronska-Serafinowa and T. Urbanski, *Rocz. Chem.*, 1952, **26**, 51-57.