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Some Multiring Fused Quinazolines#

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Summary. A number of condensed quinazolines have been synthesized by the reaction of 5-phenyl-3-hydrazino-1,2,4-triazolo[4,3-*c*]quinazoline with appropriate phenyl isothiocyanates, arylcarbaldehydes, ethyl orthoformate, acetic anhydride, and nitrous acid. The IR and ^{1}H NMR spectra of the products are presented.

Keywords. N-Phenylbenzimidoyl isothiocyanate; Quinazoline; 1,2,4-Triazolo[4,3-*c*]quinazoline.

Polycyclische kondensierte Chinazoline

Zusammenfassung. Durch Reaktion von 5-Phenyl-3-hydrazino-1,2,4-triazolo[4,3-*c*]chinazolinen mit geeigneten Phenylisothiocyanaten, aromatischen Aldehyden, Ethylorthoformiat, Essigsäureanhydrid und salpetriger Säure wurde eine Anzahl kondensierter Chinazoline hergestellt. Die Produkte wurden mittels IR- und ^{1}H-NMR-Spektroskopie charakterisiert.

Introduction

A wide spectrum of biological activities is associated with quinazolines and their condensed derivatives. A great number of papers has described their preparation as well as their biocidal and phytoeffectorial properties [1]. Some derivatives show antiviral, CNS-depressant, anticonvulsant, antimalaric, and other activities [2–5]. Such properties together with fact that incorporation of various pharmacophores such as tetrazole [6], pyrazole [7], and others into the molecule enhances its biological potency, led us to the synthesis of some condensed quinazoline derivatives containing two new rings.

Results and Discussion

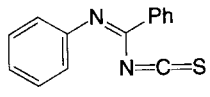
For the preparation of condensed quinazoline derivatives, 5-phenyl-2*H*-1,2,4-triazolo[4,3-*c*]quinazoline-3-thione (**2**) was used. This compound was prepared from the easily available *N*-phenylbenzimidoyl isothiocyanate (**1**) according to the procedures described in Refs. [8, 9]. Easy enolization of the thioamide group in the thione **2** facilitated direct substitution of the thiol group by hydrazine, affording 5-phenyl-3-hydrazino-1,2,4-triazolo[4,3-*c*]quinazoline (**3**). Reaction of **3** with phenyl

Dedicated to Professor Dr. *Fritz Sauter* in honour of his 65 birthday

isothiocyanate afforded the corresponding thiosemicarbazide **4**, which, if treated according to the procedure of *Marckwald* [10] (heating without solvent), lost aniline and gave 7-phenyl-4*H*-1,2,4-triazolo[3′,4′:5,1]-1,2,4-triazolo[4,3-*c*]quinazoline-3-thione (**5**). Heating of **4** with mercury(II) oxide resulted in a product identified as 3-anilino-7-phenyl-1,2,4-triazolo[3′,4′:5,1]-1,2,4-triazolo[4,3-*c*]quinazoline (**6**).

Reaction of **3** with 5-nitro-furaldehyde and 4-nitrobenzaldehyde, respectively, yielded the corresponding arylhydrazones **7a** and **7b**. Their oxidative cyclization with bromine in acetic acid furnished 7-phenyl-3-x-1,2,4-triazolo[3′,4′:5,1]-1,2,4-triazolo[4,3-*c*]quinozolines **8a** and **8b**.

Heating of the hydrazino derivative (**3**) with ethyl orthoformate yielded 7-phenyl-1,2,4-triazolo[3′,4′:5,1]-1,2,4-triazolo[4,3-*c*]quinazoline (**9**). On the other hand, heating of **3** with acetic anhydride afforded 7-phenyl-3-methyl-1,2,4-triazolo



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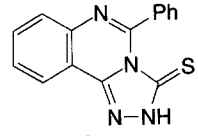

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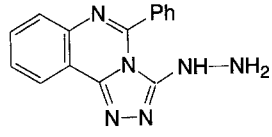

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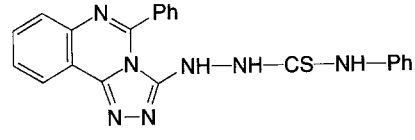

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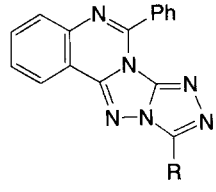
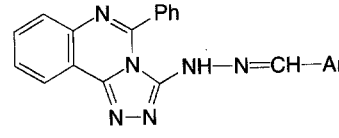


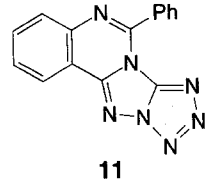
5, 6, 8a, 8b, 9, 10



7a, 7b

5 R = SH
6 R = NH—Ph
8a R = 5-nitro-2-furyl
8b R = 4-nitrophenyl
9 R = H
10 R = CH_3

7a Ar = 5-nitro-2-furyl
7b Ar = 4-nitrophenyl



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[3′,4′:5,1]-1,2,4-triazolo[4,3-*c*]quinazoline (**10**). The reaction of **3** with nitrous acid furnished 7-phenyl-1,2,3,4-tetrazolo[5′,1′:5,1]-1,2,4-triazolo[4,3-*c*]quinazoline (**11**) in almost quantitative yield.

For all new compounds, satisfactory microanalytical, IR, and ^{1}H NMR data were obtained.

Experimental

Infrared spectra (KBr disks) were measured with a Philips PU-9800 FTIR spectrometer. ^{1}H NMR spectra (*DMSO*-d_6, *TMS* as internal reference) were recorded with a BS 587 A Tesla spectrometer at 80 MHz.

5-Phenyl-3-hydrazino-1,2,4-triazolo[4,3-c]quinazoline (**3**)

5-Phenyl-2*H*-1,2,4-triazolo[4,3-*c*]quinazoline-3-thione (**2**, 5.56 g, 0.002 mol) and hydrazine hydrate (80%, 1.6 ml) in ethanol (25 ml) were refluxed till the evolution of hydrogen sulfide ceased (5–10 h). The solution was then cooled, the crude product was filtered off and crystallized from ethanol. Yield, 4.9 g (89%); m.p., 201–204 °C; $C_{15}H_{12}N_6$ (276.32); calcd.: 65.20% C, 4.38% H, 30.41% N; found: 65.03% C, 4.35% H, 30.18% N; IR (cm^{-1}): 3213, 3113 (ν_{NH}), 1633 ($\nu_{C=N}$), 1381 (ν_{C-N}); ^{1}H NMR (δ, ppm): 9.80 (bs, 1 H, NH), 8.40–6.70 (m, 9 H_{arom}), 4.0–2.6 (bs, $H_2O + NH_2$).

1-(5′-Phenyl-3′-(1,2,4-triazolo[4′,3′-c]quinazolyl)-4-phenylthiosemicarbazide (**4**)

5-Phenyl-3-hydrazino-1,2,4-triazolo[4,3-*c*]quinazoline (**3**, 2.76 g, 0.001 mol) was suspended in 100 ml boiling ethanol and a solution of phenyl isothiocyanate (1.4 g, 0.001 mol) in 20 ml ethanol was added through the condenser. After 1 h of refluxing, the solution was cooled, and the precipitate crystalline solid was collected by filtration and recrystallized from ethanol. Yield 2.67 g (65%); m.p., 258–260 °C; $C_{22}H_{17}N_7S$ (411.48); calcd.: 64.21% C, 4.16% H, 23.83% N; found: 64.13% C, 4.13% H, 23.69% N; IR cm^{-1}): 3229, 3186, 3127 (ν_{NH}), 1622 ($\nu_{C=N}$), 1383 (ν_{C-N}); ^{1}H NMR (δ, ppm): 11.2 (s, 3 H, NH), 8.28 (d, 1 H, C-10), 7.94–7.24 (m, 13 H_{arom}).

7-Phenyl-4H-1,2,4-triazolo[3′,4′:5,1]-1,2,4-triazolo[4,3-c]quinazoline-3-thione (**5**)

The substituted 4-phenylthiosemicarbazide (**4**, 4.11 g, 0.01 mol) was heated to its melting temperature without solvent on an oil bath. The obtained melt was dissolved in dioxane, boiled with charcoal, filtered and left to crystallize. The crude product was purified by recrystallization from hexane. Yield 1.65 g (52%); m.p., 141–144 °C; $C_{16}H_{10}N_6S$ (318.37); calcd.: 60.36% C, 3.18% H, 26.39% N, 10.05% S; found: 60.19% C, 3.10% H, 26.27% N, 9.78% S; IR (cm^{-1}): 1622 ($\nu_{C=N}$), 1361 (ν_{CN}); ^{1}H NMR (δ, ppm): 8.43 (d, 1 H, C-12), 7.51–7.47 (m, 8 H_{arom}).

3-Anilino-7-phenyl-1,2,4-triazolo[3′,4′:5,1]-1,2,4-triazolo[4,3-c]quinazoline (**6**)

A mixture of substituted 4-phenylthiosemicarbazide (**4** 4.11 g, 0.01 mol), 4.4 g yellow HgO, and 20 ml dry dichloroethane was stirred at boiling temperature for 1 h. Then another portion of 2.2 g HgO was added and the stirring was continued for further 5 h. The colloidal HgS precipitated on cooling was separated by filtration, the filtrate was boiled with charcoal, filtered, and evaporated in vacuum until dry. The residue was recrystallized from ethylacetate. Yield 1.69 g (45%); m.p., 298–300 °C; $C_{22}H_{15}N_7$ (377.39); calcd.: 70.01% C, 4.00% H, 25.98% N; found: 69.92% C, 3.99% H, 25.79% N; IR (cm^{-1}): 3250 (ν_{NH}), 1620($\nu_{C=N}$), 1361 ($\nu_{C=N}$); ^{1}H NMR (δ, ppm): 9.08 (bs, 1 H, NH), 8.28 (m, 1 H, C-12), 7.90–7.17 (m, 13 H_{arom}).

Arylcarbaldehyde-3-(5-phenyl-1,2,4-triazolo[4,3-c]quinazolyl)hydrazones (**7a**, **7b**)

Hydrazinoderivative (**3**, 2.76 g, 0.01 mol) and arylaldehyde (0.01 mol) in 20 ml ethanol were refluxed for 1 h. The solution was then cooled, and after addition of 20 ml cold water the separated precipitate was filtered off and crystallized from dimethylformamide.

5'-Nitro-2'-furancarbaldehyde-3-(5-phenyl-1,2,4-triazolo[4,3-c]quinazolyl) hydrazone (**7a**)

Yield, 3.59 g (90%); m.p., 181–183 °C; $C_{20}H_{13}N_7O_3$ (399.36); calcd.: 60.14% C, 3.28% H, 24.55% N; found: 59.92% C, 3.18% H, 24.29% N; IR (cm^{-1}): 3128 (ν_{NH}), 1616 ($\nu_{C=N}$), 1358 ($\nu_{C=N}$), 1516(ν_{asNO2}), 1314(ν_{sNO2}); ^{1}H NMR (δ, ppm): 8.91 (s, 1 H, CH=N), 8.12 (d, 1 H, H-4 of furan), 7.69 (d, 1 H, H-3 of furan, $J_{3,4} = 4{,}3$ Hz), 9.00–7.50 (m, 9 H_{arom}).

4'-Nitrobenzenecarbaldehyde-3-(5-phenyl-1,2,4-triazolo[4,3-c]quinazolyl) hydrazone (**7b**)

Yield, 3.19 g (78%); m.p., 209–212 °C; $C_{22}H_{15}N_7O_2$ (409.43); calcd.: 64.54% C, 3.69% H, 23.95% N; found 64.43% C, 3.60% H, 23.79% N; IR (cm^{-1}): 3227 (ν_{NH}), 1610 ($\nu_{C=N}$), 1363 (ν_{C-N}), 1545(ν_{asNO2}), 1342 (ν_{sNO2}); ^{1}H NMR (δ, ppm): 8.14 (s, 1H, CH=N), 7.65–6.75 (m, 13 H_{arom}).

7-Phenyl-3-X-1,2,4-triazolo[3',4':5,1]-1,2,4-triazolo[4,3-c]quinazolines (**8a**, **8b**)

0.5 g Sodium acetate was added to the stirred solution of the substituted hydrazone (**7**, 0.002 mol) in 20 ml acetic acid at room temperature. Bromine (0.32 g, 0.004 mol) in 10 ml acetic acid was introduced dropwise during 1 h; the mixture was then poured on crushed ice; the separated precipitate was filtered off and crystallized from dimethylformamide.

7-Phenyl-3-(5'-nitro-2'-furyl)-1,2,4-triazolo[3',4':5,1]-1,2,4-triazolo[4,3-c] quinazoline (**8a**)

Yield, 0.66 g (84%); m.p., 175–177 °C; $C_{20}H_{11}N_7O_3$ (397.34); calcd.: 60.45% C, 2.79% H, 24.68% N; found: 60.28% C, 2.75% H, 24.49% N; IR (cm^{-1}): 1624 ($\nu_{C=N}$), 1354 (ν_{C-N}), 1516 (ν_{asNO2}), 1335 (ν_{sNO2}); ^{1}H NMR (δ, ppm): 8.14 (d, 1H, H-4 of furan), 7.64 (d, 1H, H-3 of furan, $J_{3,4} = 4.3$ Hz), 8.90–7.20 (m, 9 H_{arom}).

7-Phenyl-3-(4'-nitrophenyl)-1,2,4-triazolo[3',4':5,1]-1,2,4-triazolo[4,3-c]quinazoline (**8b**)

Yield, 0.65 g (80%); m.p., 228–230 °C; $C_{22}H_{13}N_7O_2$ (407.26); calcd.: 64.88% C, 3.22% H, 24.07% N; found: 64.69% C, 3.17% H, 23.92% N; IR (cm^{-1}): 1601 ($\nu_{C=N}$), 1363 (ν_{C-N}), 1537 (ν_{asNO2}), 1340 (ν_{sNO2}); ^{1}H NMR (δ, ppm): 7.54–6.68 (m, 13 H_{arom}).

7-Phenyl-1,2,4-triazolo[3',4':5,1]-1,2,4-triazolo[4,3-c]quinazoline (**9**)

Hydrazinoderivate (**3**, 0.55 g, 0.002 mol), 10 ml ethyl orthoformate, and 0.5 g anhydrous potassium carbonate were refluxed for 3.5 h. The excess of potassium carbonate was filtered off, the residue was evaporated and crystallized from ethanol. Yield 0.33 g (58%); m.p., 79–83 °C; $C_{16}H_{10}N_6$ (286.31); calcd.: 67.12% C, 3.52% H, 29.35% N; found: 67.10% C, 3.48% H, 29.23% N; IR (cm^{-1}): 1620 ($\nu_{C=N}$), 1361 (ν_{C-N}); ^{1}H NMR (δ, ppm): 8.72 (s, 1H, C-3), 8.30–7.30 (m, 9 H_{arom}).

7-Phenyl-3-methyl-1,2,4-triazolo[3',4':5,1]-1,2,4-triazolo[4,3-c]quinazoline (**10**)

Hydrazinoderivative (**3**, 2.76 g, 0.01 mol) and acetic anhydride (2.0 g, 0.02 mol) were refluxed for 2 h. The separated precipitate was filtered off, washed repeatedly with 5% sodium bicarbonate solution

and water. Crystallization from ethanol-dimethylformamide afforded the pure product. Yield, 2.76 g (92%); m.p., 157–159 °C; $C_{17}H_{12}N_6$ (300.32); calcd.: 67.99% C, 3.99% H, 27.98% N; found: 67.81% C, 3.86% H, 27.80% N; IR (cm^{-1}): 1622 ($\nu_{C=N}$), 1386 (ν_{C-N}); ^1H NMR (δ, ppm): 8.70–7.10 (m, 9 H_{arom}), 2.15 (s, 3H, CH_3).

7-Phenyl-1,2,3,4-tetrazolo[5',1':5,1]-1,2,4-triazolo[4,3-c]quinazoline (**11**)

To a suspension of the hydrazinoderivative (**3**, 2.76 g, 0.01 mol) in 15 ml water and 3 ml 2 *N* hydrochloric acid, a solution of sodium nitrite (0.7 g, 0.01 mol) in 5 ml water was added dropwise under stirring at room temperature. After stirring for another hour, the solid part filtered off and recrystallized from ethanol. Yield, 2.67 g (93%); m.p., 257–258 °C; $C_{15}H_9N_7$ (288.28); calcd.: 62.49% C, 3.49% H, 34.01% N; found: 62.30% C, 3.44% H, 33.97% N; IR (cm^{-1}): 1628 ($\nu_{C=N}$), 1363 (ν_{C-N}); ^1H NMR (δ, ppm): 8.26 (m, 1H, C-12), 7.93–7.15 (m, 8 H_{arom}).

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