

# Condensation Reactions of 2-Aminobenzohydrazide with Various Carbonyl Compounds

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Technical iodine was found to catalyze the condensation between 2-aminobenzohydrazide (**1**) and some aldehydes and ketones in absolute ethanol under mild conditions to afford hydrazone and quinazoline derivatives, respectively. Condensation of **1** with terephthalaldehyde (**2**) in 1 : 1 molar ratios afforded the hydrazone **3**, while hydrazone **4** was formed on using a double molar ratio of **1**. On the other hand, compound **1** condensed with 4-formyl [2.2]paracyclophane (**5**) to give the hydrazone **6**. However, spiro-quinazolines **8**, **10**, **12**, and **14** were formed when compound **1** reacted with ketones such as *N*-benzylpiperidone (**7**), indane-1,2,3-trione (**9**), cyclohexane-1,2-dione (**11**), and dimedone (**13**), respectively. Treatment of **1** with tetrabromophthalic anhydride (TBPA, **18**) and pyromellitic dianhydride (PMDA, **20**) furnished phthalazino-quinazoline **19** and **21**, respectively. The products were fully characterized according to their spectral analyses. The mechanisms of formation of the products have been rationalized.

**Key words:** Quinazolines, Aminobenzohydrazide, Aldehydes, Ketones, Anhydrides, Hydrazones

## Introduction

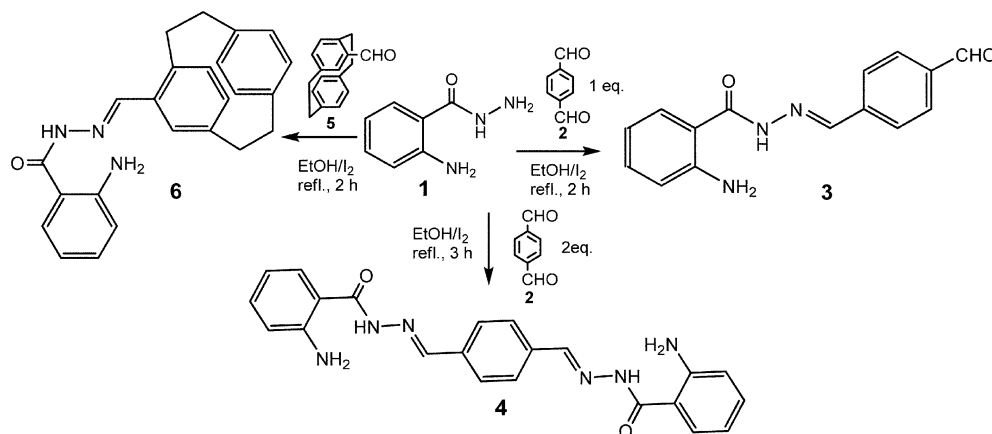
As a result of their antimicrobial, antifungal and antibacterial properties, carboxylic acid hydrazides are of great biological importance [1]. 2-Aminobenzohydrazide has been widely used as a starting material in the synthesis of various bioactive heterocyclic compounds [2]. Spiro-heterocyclic compounds are well known to possess various pharmacological activities [3–6], and hence their synthesis has always been a challenge and of attraction to organic chemists. As part of our ongoing research program on heterocyclic compounds which may serve as leads for designing novel antitumor agents, we were particularly interested in quinazoline derivatives [7–13].

Quinazolines occupy a prominent position among heterocyclic compounds and are in demand because of their potential biological and pharmaceutical activities. Quinazoline systems have been reported to act as potent antihypertensive agents [14] and anti-inflammatory activity inhibitors [15–17]. Quinazoline derivatives were also found to show bronchodilatory [18] and anti-allergic [19] properties. In ad-

dition, quinazoline derivatives also have a therapeutic benefit as an anti-invasive agent with potential for activity in early and advanced solid tumors, metastatic bone disease and leukemias [20]. We considered the well known activity of the quinazoline nucleus in chemotherapy, where many of its substituted derivatives are effective antitumor agents [21, 22]. Furthermore, more recent data have reported that a broad class of quinazolines also act as potent and highly selective inhibitors of epidermal growth factor receptor (EGFR) or epidermal growth factor receptor tyrosine kinase (EGFR-TK) [23–25]. Beside, their uses as precursors in the synthesis of fused ring compounds make them worthy to be synthesized and evaluated [26–29].

## Results and Discussion

Recently, we have reported that hydrazino compounds can be considered as key starting materials for the synthesis of diverse nitrogen bridgehead compounds [30]. This prompted us to reinvestigate the proclivity of compound **2** towards electrophilic reagents such as terephthalaldehyde (**2**), 4-formyl [2.2]paracy-



Scheme 1. Reaction of 2-aminobenzohydrazide (**1**) with aldehydes **2** and **5**.

clophane (**5**), *N*-benzylpiperidone (**7**), indane-1,2,3-trione (**9**), cyclohexane-1,2-dione (**11**), and dimedone (**13**) as well as tetrabromophthalic anhydride (TBPA, **18**) and pyromellitic dianhydride (PMDA, **20**).

Condensation of 2-aminobenzohydrazide (**1**) with terephthalaldehyde (**2**) in the presence of a catalytic amount of iodine in boiling ethanol afforded hydrazones **3** and **4** depending on the molar ratios of **1**. Condensation of 4-formyl [2.2]paracyclophane (**5**) with **1** under the same reaction conditions furnished hydrazone **6** as shown in Scheme 1.

The molecular structures of the products are supported by elemental and spectral analyses. For example, compound **3** exhibits in the IR spectrum four strong absorption bands at 3417, 3390, 3201, and 1678  $\text{cm}^{-1}$  characteristic for  $\text{NH}_2$ , NH and CO groups, respectively. The  $^1\text{H}$  NMR spectrum of **3** shows three characteristic singlets at  $\delta = 6.34$ , 8.81 and 9.88 ppm assignable to  $\text{NH}_2$ , NH and CHO protons, respectively. The mass spectrum exhibits the molecular ion peak at  $m/z = 267$ .

Compound **4** was formed when a double molar ratio of **1** was condensed with one mole of **2**. The structure assigned to **4** was fully supported by its elemental analysis and mass spectrum, which suggest the molecular formula  $\text{C}_{22}\text{H}_{20}\text{N}_6\text{O}_2$  ( $m/z = 399$ ).

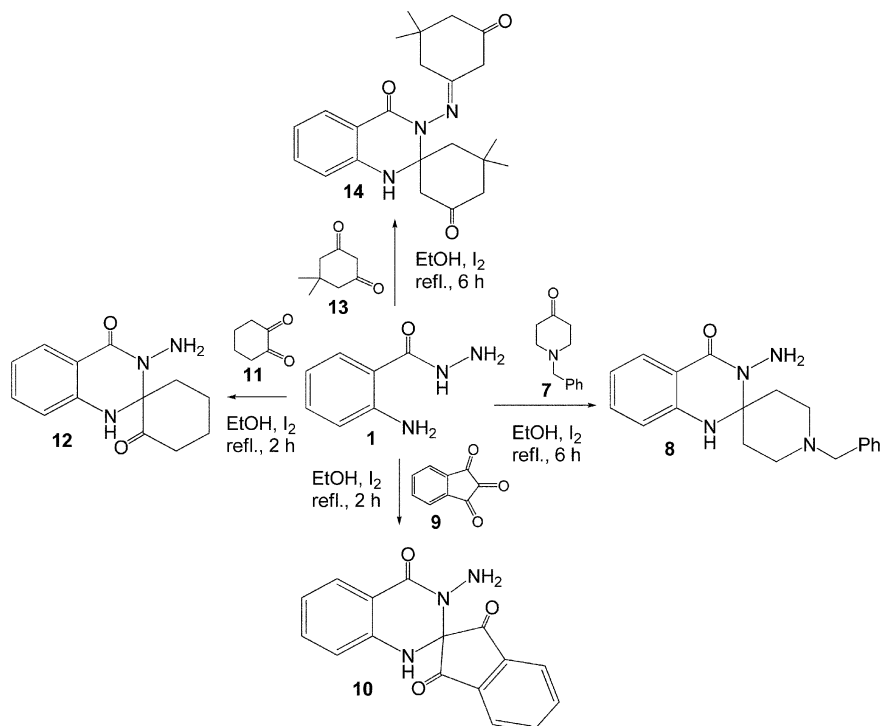
The reactivity of **1** towards ketones **7**, **9**, **11**, and **13** has also been studied and shown to give spiro-quinazolines **8**, **10**, **12**, and **14** (Scheme 2). The structural assignments of the products were made on the basis of the NMR data and were supported by their IR spectra. Of special interest are three strong absorption bands at

3313, 3201 and 1643  $\text{cm}^{-1}$  assigned to  $\text{NH}_2$ , NH and CO groups, respectively (see Experimental Section).

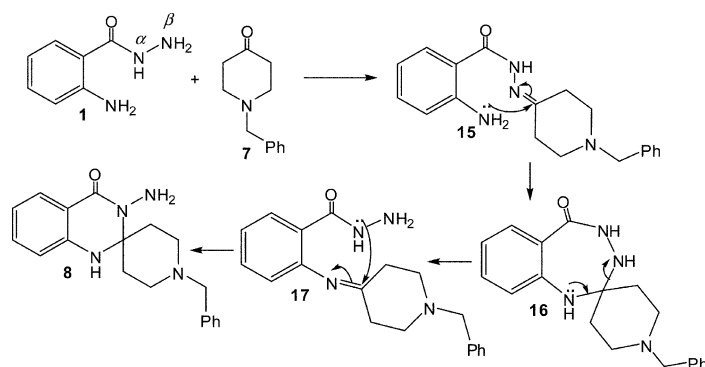
The  $^1\text{H}$  NMR spectrum of the quinazoline derivative **8** as an example revealed two characteristic broad singlets at  $\delta = 7.42$  and 9.60 ppm assigned to  $\text{NH}_2$  and NH groups, respectively. Furthermore, a multiplet was present in the region of  $\delta = 1.80\text{--}3.35$  ppm due to the methylene protons of the electrophile, in addition to a singlet signal at  $\delta = 4.75$  ppm for the benzyl- $\text{CH}_2$  protons and a multiplet at  $\delta = 6.70\text{--}7.65$  ppm for the aromatic protons. Moreover, the spiro-carbon atom of **8** resonated in the  $^{13}\text{C}$  NMR spectrum at  $\delta = 114.00$  ppm, and the carbonyl carbon atom resonated at 163.00 ppm. The molecular formula of compound **8** is supported by elemental analysis and a mass spectrum that gave the expected molecular ion peak and fragmentation patterns.

Scheme 3 outlines a rational pathway for the formation of product **8**. We suggest that initial nucleophilic attack occurs by the most nucleophilic site ( $\beta$ -nitrogen atom) of **1** on the carbonyl group of **7** leading to the loss of a molecule of water to produce the intermediate **15**. The aromatic amino nitrogen atom attacks on the imine-carbon atom to afford the spiro-triazepinone **16** with a 1,3- $\text{H}^+$  shift. The intermediate **17** is formed through the nucleophilic attack of the aromatic NH group on the spiro-carbon atom causing ring opening. The final product **8** is obtained after nucleophilic attack of the  $\alpha$ -nitrogen atom on the imine-carbon atom followed by 1,3- $\text{H}^+$  shift (Scheme 3).

Treatment of **1** with dimedone **13** in refluxing ethanol in the presence of iodine leads to the forma-



Scheme 2. Reaction of 2-aminobenzohydrazide (**1**) with ketones **7**, **9**, **11**, and **13**.

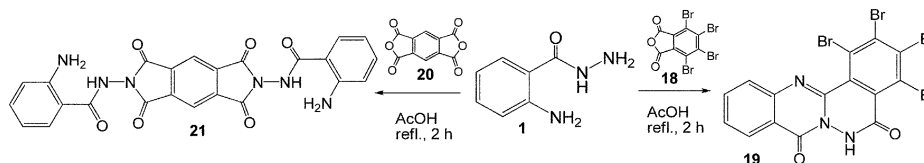
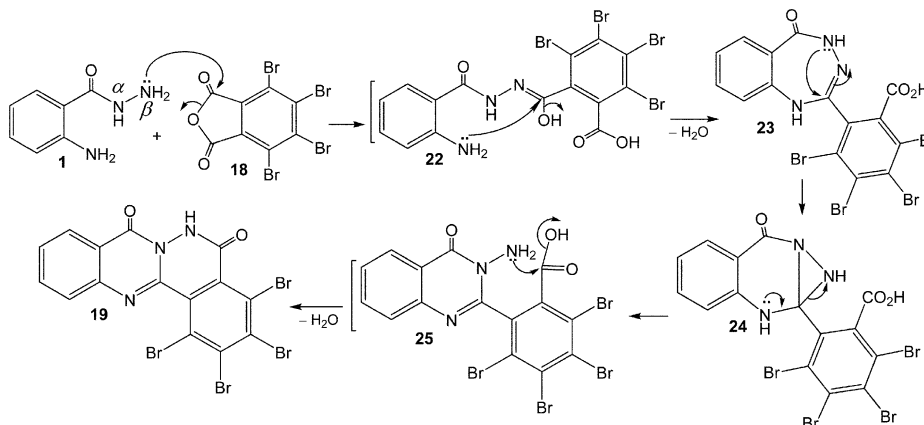


Scheme 3. Rational pathway for the formation of compound **8**.

tion of the quinazoline **14** (Scheme 2). The constitution of product **14** was confirmed by elemental analysis and spectral data. The IR spectrum of **14** displayed two strong absorption bands at 3228 (NH) and 1647  $\text{cm}^{-1}$  for the two different (CO) groups, in addition to the absence of the absorption bands of the  $\text{NH}_2$  group. The  $^1\text{H}$  NMR spectrum of **14** confirmed the disappearance of the  $\text{NH}_2$  group, while the NH proton resonated at 7.59 ppm. The spiro-carbon atom resonated in the  $^{13}\text{C}$  NMR spectrum at  $\delta = 100.00$  ppm. Furthermore, the

signals of the carbonyl carbon atoms and the  $\text{C}=\text{N}$  carbon atom appeared at 198.22, 167.55 and 169.55 ppm, respectively.

Scheme 4 outlines the synthesis of 1,2,3,4-tetrabromo-5*H*-phthalazino[1,2-*b*]quinazoline-5,8(6*H*)-dione (**19**) and *N,N'*-(1,3,5,7-tetraoxopyrrolo[3,4-*f*]isoindole-2,6-(1*H*,3*H*,5*H*,7*H*)-diyl)bis(2-aminobenzamide) (**21**) from the reaction of the target molecule **1** with tetrabromophthalic anhydride (TBPA, **18**) and pyromellitic dianhydride (PMDA, **20**), respectively.

Scheme 4. Reaction of **1** with anhydrides **18** and **20**.Scheme 5. Rational pathway for the formation of compound **19**.

The suggested mechanism for the formation of product **19** is as shown in Scheme 5. We propose that the  $\beta$ -amino group of **1** attacks the carbonyl group of the anhydride leading to opening of the anhydride ring of compound **18** and affording the intermediate **22**. This intermediate loses a molecule of water, as a result of nucleophilic attack of the aromatic amino group on the (C-OH) carbon atom, to give the triazepinone derivative **23**. The intermediate **24** is suggested to be formed by nucleophilic attack of the  $\alpha$ -nitrogen atom on the C=N carbon atom. Intermediate **24** undergoes rearrangement under the effect of the lone pair of electrons of the aromatic amino group to give the quinazoline derivative **25**. Product **19** is finally obtained by losing a molecule of water through nucleophilic attack of the amino group on the carbonyl group of the carboxylic acid group (Scheme 5).

## Conclusion

In this study, the proclivity of 2-aminobenzohydrazide (**1**) towards carbonyl compounds such as aldehydes, ketones and carboxylic anhydrides in boiling EtOH or AcOH was investigated. The simple workup procedures, in addition to the neutral reaction

conditions, are the main advantages of our approach to interesting heterocyclic products.

## Experimental Section

### General

All reagents were purchased from Alfa Aesar or Fluka and were used without further purification. Melting points were measured in capillary tubes using a Büchi 530 melting point apparatus and are uncorrected. IR spectra were measured using a Bruker Tensor 27 instrument.  $^1\text{H}$  NMR (300 or 400 MHz) and  $^{13}\text{C}$  NMR (75 or 101 MHz) spectra were recorded in  $[\text{D}_6]\text{DMSO}$  on Bruker Avance II-300 and Avance DRX-400 spectrometers with TMS (for  $^1\text{H}$ ) or the solvent (for  $^{13}\text{C}$ ,  $\delta_{\text{C}} = 77.01$  ppm) as the internal standards. Mass spectral measurements (EI, 70 eV) were performed using a Finnigan MAT 8430 spectrometer.

### Synthesis of (*E*)-2-amino-*N'*-(4-formylbenzylidene)benzohydrazide (**3**)

A mixture of compound **1** (151 mg, 1 mmol), compound **2** (134 mg, 1 mmol) and a catalytic amount of iodine in ethanol (20 mL) was refluxed, and a yellow precipitate was formed after 30 min. The reaction was continued for 2 h. After completion of the reaction (TLC analysis), the precipitate was filtered off, washed, dried and recrystallized from DMF/EtOH. Yellow powder (yield: 89%), m. p. 246–250 °C. – IR (film):

$\nu = 3417, 3390, 3201, 1678 \text{ cm}^{-1}$ . –  $^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ):  $\delta = 6.34$  (s, 2H,  $\text{NH}_2$ ), 6.45–6.76 (m, 4H, ArH), 7.23–7.85 (m, 5H), 8.81 (s, 1 H, NH), 9.88 (s, 1H, CHO) ppm. – MS (EI, 70 eV):  $m/z$  (%) = 269 (15)  $[\text{M}+2]^+$ , 267 (34)  $[\text{M}]^+$ , 251 (16), 244 (14), 232 (46), 223 (42), 211 (14), 192 (17), 182 (48), 179 (48), 157 (27), 154 (46), 149 (20), (52), 137 (52), 114 (36), 91 (41), 81 (76), 62 (56), 60 (43), 48 (100). –  $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_2$  (267.28): calcd. C 67.40, H 4.90, N 15.72; found C 67.21, H 4.83, N 15.57.

*Synthesis of  $N',N'''$ -(1,4-phenylenebis(methanylidene))-bis(2-aminobenzohydrazide) (4)*

A mixture of compound **2** (134 mg, 1 mmol), compound **1** (302 mg, 2 mmol) and a catalytic amount of iodine in ethanol (20 mL) was refluxed, and a yellow precipitate was formed after 30 min. The reaction was continued for 2 h. After completion of the reaction (monitoring by TLC), the precipitate was filtered off and washed with DMF. (The product is insoluble in the available deuterated solvents). Yellow powder (yield: 75%), m. p. 280–282 °C. – IR (film):  $\nu = 3435, 3275, 1655, 1614 \text{ cm}^{-1}$ . – MS (EI, 70 eV):  $m/z$  (%) = 399 (15)  $[\text{M}-1]^+$ , 337 (8), 308 (4), 306 (8), 288 (12), 260 (10), 231 (6), 198 (8), 182 (26), 169 (30), 153 (68), 145 (51), 131 (44), 111 (100), 107 (51), 81 (72), 70 (69), 76 (11). –  $\text{C}_{22}\text{H}_{20}\text{N}_6\text{O}_2$  (400.43): calcd. C 65.99, H 5.03, N 20.99; found C 65.80, H 4.95, N 20.79.

*Synthesis of (E)-2-amino- $N'$ -(4-paracyclophanylidene)-benzohydrazide (6)*

A solution of **1** in dry EtOH (151 mg, 1 mmol) was mixed with a solution of an equimolar amount of **5** (236 mg, 1 mmol) in dry EtOH (15 mL) in the presence of a catalytic amount of iodine. The mixture was refluxed for 2 h. An orange precipitate was formed. The precipitate was collected, washed and recrystallized from 1,4-dioxane. Orange powder (yield: 45%), m. p. 232–234 °C. – IR (film):  $\nu = 3417, 3390, 3201, 1678 \text{ cm}^{-1}$ . –  $^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ):  $\delta = 2.64$ – $2.65$  (m, 2H,  $\text{CH}_2$ ), 2.94–3.18 (m, 6H,  $3\text{CH}_2$ ), 6.35 (s, 2H,  $\text{NH}_2$ ), 6.47–6.74 (m, 4H, ArH), 7.07–7.09 (d, 1H, ArH,  $J = 2.0 \text{ Hz}$ ), 7.20–7.29 (t, 1H, ArH,  $J = 4.0 \text{ Hz}$ ), 7.45–7.47 (m, 1H, ArH), 7.59–7.66 (m, 4H, ArH), 8.22 (s, 1 H, CH), 8.59 (s, 1 H, NH) ppm. – MS (EI, 70 eV):  $m/z$  (%) = 369 (30)  $[\text{M}]^+$ , 290 (10), 274 (12), 260 (12), 249 (2), 248 (10), 222 (14), 160 (2), 143 (12), 127 (14), 115 (10), 104 (18), 103 (26), 91 (77), 77 (100). –  $\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}$  (369.46): calcd. C 78.02, H 6.27, N 11.37; found C 77.78, H 6.21, N 11.17.

*Synthesis of 3'-amino-1-benzyl-1'-H-spiro[piperidine-4,2'-quinazolin]-4'(3'H)-one (8)*

A mixture of **1** (151 mg, 1 mmol), compound **7** (189 mg, 1 mmol) and a catalytic amount of iodine in ethanol (20 mL)

was refluxed for 6 h. A colorless precipitate was formed. After completing the reaction (TLC follow), the precipitate was filtered off, washed and recrystallized from DMF/EtOH. Colorless powder (yield: 82%), m. p. 198–200 °C. – IR (film):  $\nu = 3313, 3201, 1643, 1612, \text{ cm}^{-1}$ . –  $^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ):  $\delta = 1.80$  (m, 2H,  $\text{CH}_2$ ), 2.20 (m, 2H,  $\text{CH}_2$ ), 2.55 (m, 2H,  $\text{CH}_2$ ), 3.35 (m, 2H,  $\text{CH}_2$ ), 4.75 (s, 2H,  $\text{NCH}_2\text{Ph}$ ), 7.42 (brs, 2H,  $\text{NH}_2$ ), 6.70–7.65 (m, 9H, ArH), 9.60 (brs, 1 H, NH) ppm. –  $^{13}\text{C}$  NMR (150 MHz,  $[\text{D}_6]\text{DMSO}$ ):  $\delta = 22.00$  ( $4\text{CH}_2$ ), 48.00 ( $\text{NCH}_2$ ), 114.00 (C-2), 115.00, 126.00, 127.00, 128.00, 129.00 (CH-Ar), 134.00, 138.00, 146.00 (C-Ar), 163.00 (C=O) ppm. – MS (EI, 70 eV):  $m/z$  (%) = 323 (4)  $[\text{M}+1]^+$ , 322 (9)  $[\text{M}]^+$ , 306 (20), 278 (14), 231 (11), 203 (15), 188 (16), 176 (10), 172 (17), 160 (6), 146 (22), 91 (100), 77 (5). –  $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}$  (322.40): calcd. C 70.78, H 6.88, N 17.38; found C 70.49, H 6.78, N 17.21.

*Synthesis of 3'-amino-1'-H-spiro[indene-2,2'-quinazoline]-1,3,4'(3'H)-trione (10)*

A mixture of **9** (178 mg, 1 mmol) and **1** (151 mg, 1 mmol) in the presence of a catalytic amount of iodine in ethanol (20 mL) was heated under reflux conditions. A brown precipitate was formed, and the reaction was continued for a further 2 h. The precipitate was filtered off and recrystallized from 1,4-dioxane. Brown powder (yield: 70%), m. p. 295–297 °C. – IR (film):  $\nu = 3448, 3336, 3247, 3058, 1678, 1617 \text{ cm}^{-1}$ . –  $^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ):  $\delta = 6.05$  (brs, 2H,  $\text{NH}_2$ ), 6.70–6.80 (m, 2H, ArH), 6.30–8.00 (m, 7H, ArH + NH) ppm. – MS (EI, 70 eV):  $m/z$  (%) = 292 (5)  $[\text{M}-1]^+$ , 263 (6), 262 (2), 248 (9), 239 (9), 235 (4), 22 (10), 219 (8), 146 (3), 136 (7), 121 (9), 120 (100), 119 (10), 92 (25), 91 (4), 65 (13). –  $\text{C}_{16}\text{H}_{11}\text{N}_3\text{O}_3$  (293.28): calcd. C 65.53, H 3.78, N 14.33; found C 65.34, H 3.71, N 14.20.

*Synthesis of 3'-amino-1'-H-spiro[cyclohexane-1,2'-quinazoline]-2,4'(3'H)-dione (12)*

The reactants **1** (151 mg, 1 mmol) and **11** (112 mg, 1 mmol) were dissolved in ethanol (20 mL), and a catalytic amount of iodine was added. The reaction mixture was boiled for 2 h and then poured onto cold water (25 mL). A yellow precipitate was formed, separated by filtration and recrystallized from chloroform/petroleum ether. Yellow powder (yield: 65%), m. p. 180–182 °C. – IR (film):  $\nu = 3410, 3335, 3210, 1670, 1545 \text{ cm}^{-1}$ . –  $^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ):  $\delta = 1.23$ – $2.15$  (m, 8H,  $4\text{CH}_2$ ), 6.63 (brs, 2H,  $\text{NH}_2$ ), 6.78–7.08 (m, 4H, ArH), 7.64 (s, 1H, NH) ppm. – MS (EI, 70 eV):  $m/z$  (%) = 246 (14)  $[\text{M}+1]^+$ , 245 (100)  $[\text{M}]^+$ , 228 (16), 217 (60), 200 (83), 172 (93), 156 (42), 149 (17), 128 (41), 104 (38), 77 (15). –  $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_2$  (245.28): calcd. C 63.66, H 6.16, N 17.13; found C 63.44, H 6.13, N 16.99.

*Synthesis of (E)-3'-((3,3-dimethyl-5-oxocyclohexyliden)-amino)-3,3-dimethyl-1'H-spiro[cyclo-hexane-1,2'-quinazoline]-4',5(3'H)-dione (14)*

A solution of 2-aminobenzohydrazide (**1**) in EtOH (151 mg, 1 mmol), dimedone (**13**) (280 mg, 2 mmol) and a catalytic amount of iodine were mixed in ethanol (10 mL). The reaction mixture was heated for 6 h under reflux conditions. After completion of the reaction (TLC analysis), the reaction mixture was left to cool to room temperature. After cooling a precipitate was formed, which was collected by filtration and recrystallized from EtOH. Yellow powder (yield: 68%), m. p. 240–242 °C. – IR (film):  $\nu = 3228, 3055, 1647, 1612 \text{ cm}^{-1}$ . –  $^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ):  $\delta = 0.82\text{--}1.07$  (m, 12H, 4CH<sub>3</sub>), 1.57 (s, 2H, CH<sub>2</sub>), 1.60 (s, 2H, CH<sub>2</sub>), 2.15 (s, 4H, CH<sub>2</sub>), 2.27 (s, 4H, 2CH<sub>2</sub>), 6.63–6.79 (m, 2H, ArH), 7.04–7.06 (m, 2H, ArH), 7.59 (s, 1H, NH) ppm. –  $^{13}\text{C}$  NMR (150 MHz,  $[\text{D}_6]\text{DMSO}$ ):  $\delta = 21.29$  (4CH<sub>3</sub>), 33.89 (C-(CH<sub>3</sub>)<sub>2</sub>), 34.56 (C-(CH<sub>3</sub>)<sub>2</sub>), 40.00 (CH<sub>2</sub>), 42.65 (CH<sub>2</sub>), 50.00 (CH<sub>2</sub>), 52.79 (CH<sub>2</sub>), 54.32 (CH<sub>2</sub>), 100.00 (C-2), 125.85, 128.81 (CH-Ar), 139.74, 142.16 (C-Ar), 167.55 (CO), 169.55 (C=N), 198.22 (2CO) ppm. – MS (EI, 70 eV):  $m/z(\%) = 397$  (24)  $[\text{M}+2]^+$ , 336 (10), 305 (8), 277 (9), 224 (12), 189 (100), 174 (42), 146 (5), 121 (23), 103 (38), 91 (25), 77 (30). – C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub> (395.49): calcd. C 69.85, H 7.39, N 10.62; found C 69.67, H 7.36, N 10.50.

*Synthesis of 1,2,3,4-tetrabromo-5H-phthalazino[1,2-b]-quinazoline-5,8(6H)-dione (19)*

A mixture of **1** (151 mg, 1 mmol) and tetrabromophthalic anhydride (TBPA, **18**) (463 mg, 1 mmol) in glacial acetic acid (15 mL) was heated for 2 h. After completion of the reaction a precipitate was formed. It was collected by filtration and recrystallized from 1,4-dioxane. Yellow powder (yield: 77%), m. p. 280–282 °C. – IR (film):  $\nu = 3204, 3066,$

1739, 1647, 1620  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR (400 MHz,  $[\text{D}_6]\text{DMSO}$ ):  $\delta = 6.57\text{--}6.61$  (m, 1H, ArH), 6.73–6.78 (m, 1H, ArH), 7.24–7.28 (m, 1H, ArH), 7.60–7.72 (m, 1H, ArH), 8.61 (s, 1H, NH) ppm. –  $^{13}\text{C}$  NMR (150 MHz,  $[\text{D}_6]\text{DMSO}$ ):  $\delta = 109.36, 114.66, 116.80, 121.41, 128.48, 128.93, 133.55, 137.62, 150.80, 160.80, 161.77, 167.30$  ppm. – MS (EI, 70 eV):  $m/z(\%) = 580/578/576$  (12/22/8)  $[\text{M}]^+$ , 397 (24), 336 (10), 305 (8), 277 (9), 224 (12), 189 (100), 174 (42), 146 (5), 121 (23), 103 (38), 91 (25), 77 (30). – C<sub>15</sub>H<sub>5</sub>Br<sub>4</sub>N<sub>3</sub>O<sub>2</sub> (578.84): calcd. C 31.12, H 0.87, N 7.26; found C 30.88, H 0.84, N 7.11.

*Synthesis of N,N'-(1,3,5,7-tetraoxopyrrolo[3,4-f]isoindole-2,6(1H,3H,5H,7H)-diyl)bis(2-amino-benzamide) (21)*

A mixture of 2-aminobenzohydrazide (**1**) (302 mg, 2 mmol) and pyromellitic dianhydride (PMDA, **20**) (218 mg, 1 mmol) in glacial acetic acid (10 mL) was heated under reflux conditions for 2 h. A pale-yellow precipitate was formed. After completion of the reaction (monitoring by TLC), the precipitate was collected by filtration and washed with DMF. (It is insoluble in the available deuterated solvents). Pale-yellow powder (yield: 80%), m. p. > 360 °C. – IR (film):  $\nu = 3409, 3332, 3124, 1670 \text{ cm}^{-1}$ . – MS (EI, 70 eV):  $m/z(\%) = 484$  (25)  $[\text{M}]^+$ , 483 (18), 470 (21), 469 (100), 453 (32), 426 (26), 395 (100), 363 (88), 337 (28), 309 (39), 299 (19), 283 (34), 267 (65), 186 (37), 171 (93), 126 (32), 113 (45), 97 (34), 85 (59), 77 (25). – C<sub>24</sub>H<sub>16</sub>N<sub>6</sub>O<sub>6</sub> (484.42): calcd. C 59.51, H 3.33, N 17.35; found C 59.31, H 3.29, N 17.16.

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- [1] S. K. Phadtare, S. K. Kamat, G. T. Panse, *Indian J. Chem.* **1983**, 22B, 496–498.
- [2] M. R. Mahmoud, E. A. A. El-Bordainy, M. E. Azab, E. A. Soliman, *Phosph. Sulfur Silicon* **2007**, 182, 1275–1289.
- [3] G. Periyasami, R. Raghunathan, G. Surendiran, N. Mathivanan, *Eur. J. Med. Chem.* **2009**, 44, 959–966.
- [4] K. M. Amin, M. M. Kamel, M. M. Anwar, M. Khedr, Y. M. Syamb, *Eur. J. Org. Chem.* **2010**, 45, 2117–2131.
- [5] R. R. Kumar, S. Perumal, S. C. Manju, P. Bhatt, P. Yogeeswari, D. Sriram, *Bioorg. Med. Chem. Lett.* **2009**, 19, 3461–3465.
- [6] R. M. Shaker, A. Hamoda, Y. R. Ibrahim, K. M. El-Shaieb, F. F. Abdel-Latif, *Z. Naturforsch.* **2011**, 66b, 487–492.
- [7] K. M. El-Shaieb, P. G. Jones, *Z. Naturforsch.* **2009**, 64b, 945–951.
- [8] K. M. El-Shaieb, H. Hopf, P. G. Jones, *Arkivoc* **2009**, x, 146–160.
- [9] K. M. El-Shaieb, H. Hopf, P. G. Jones, *Arkivoc* **2010**, x, 98–109.
- [10] K. M. El-Shaieb, H. Hopf, P. G. Jones, *Z. Naturforsch.* **2009**, 64b, 858–864.
- [11] F. F. Abdel-Latif, K. M. El-Shaieb, A. G. El-Deen, *Z. Naturforsch.* **2011**, 66b, 965–971.

- [12] F. F. Abdel-Latif, K. M. El-Shaieb, A. G. El-Deen, *J. Chem. Res.* **2010**, *34*, 699–701.
- [13] F. F. Abdel-Latif, K. M. El-Shaieb, A. G. El-Deen, *J. Chem. Res.* **2010**, *34*, 449–451.
- [14] R. E. Harris, G. A. Alshafie, H. Abou-Issa, K. Seibert, *Cancer Res.* **2000**, *60*, 2101–2103.
- [15] A. C. Tinker, H. G. Beaton, N. B. Smith, T. R. Cook, S. L. Cooper, L. F. Rae, K. Hallam, P. Hamley, T. McNally, D. J. Nicholls, A. D. Pimm, A. V. Wallace, *J. Med. Chem.* **2003**, *46*, 913–916.
- [16] G. M. Buckley, N. Davies, H. J. Dyke, P. J. Gilbert, D. R. Hannah, A. F. Yaughan, C. A. Hunt, W. R. Pitt, R. H. Profit, N. C. Ray, M. D. Richard, A. Sharpe, A. J. Taylor, J. M. Whitworth, S. C. Williams, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 751–754.
- [17] V. D. Piaz, M. P. Giovannoni, *Eur. J. Med. Chem.* **2000**, *35*, 463–480.
- [18] H. B. Cottam, H. Shih, L. R. Tehrani, B. Wasson, D. A. Carson, *J. Med. Chem.* **1996**, *39*, 2–9.
- [19] D. P. Jindal, R. S. Bhatti, S. Ahlawat, R. Gupta, *Eur. J. Med. Chem.* **2002**, *37*, 419–425.
- [20] J. C. Sircar, T. Capiris, S. J. Kesten, D. J. Herzig, *J. Med. Chem.* **1981**, *24*, 735–742.
- [21] M. Tobe, Y. Isobe, H. Tomizawa, T. Nagasaki, F. Obara, H. Hayashi, *Bioorg. Med. Chem.* **2003**, *11*, 609–616.
- [22] R. J. Griffin, S. Srinivasan, K. Bowman, A. H. Calvert, N. J. Curtin, D. R. Newell, L. C. Pemberton, B. T. Golding, *J. Med. Chem.* **1998**, *41*, 5247–5256.
- [23] J. B. Smaill, G. W. Rewcastle, J. A. Loo, K. D. Greis, O. H. Chan, E. L. Reyner, E. Lipka, H. D. H. Showalter, P. W. Vincent, W. L. Elliott, W. A. Denny, *J. Med. Chem.* **2000**, *43*, 1380–1397.
- [24] A. Wissner, D. M. Berger, D. H. Boschelli, M. B. J. Floyd, L. M. Greenberger, B. C. Gruber, B. D. Johnson, N. Mamuya, R. Nilakantan, M. F. Reich, R. Shen, H. R. Tsou, E. Upeslakis, Y. F. Wang, B. Wu, F. Ye, N. Zhang, *J. Med. Chem.* **2000**, *43*, 3244–3256.
- [25] A. J. Bridges, H. Zhou, D. R. Cody, G. W. Rewcastle, A. McMichael, H. D. H. Showalter, D. W. Fry, A. J. Kraker, W. A. Denny, *J. Med. Chem.* **1996**, *39*, 267–276.
- [26] D. J. Brown, *The chemistry of heterocyclic compounds: Quinazolines*. Suppl. 1, (Ed.: E. C. Taylor), Vol. 55, J. Wiley & Sons, Inc., New York **1996**.
- [27] S. Tamaoki, Y. Yamauchi, Y. Nakano, S. Sakano, A. Asagarsu, M. Sato, *J. Pharm. Exp. Ther.* **2007**, *322*, 1315–1323.
- [28] S. Madapa, Z. Tusi, A. Mishra, K. Srivastava, S. K. Pandey, R. Tripathi, S. K. Puri, S. Batra, *Bioorg. Med. Chem.* **2009**, *17*, 222–234.
- [29] G. M. Chinigo, M. Paige, S. Grindrod, E. Hamel, S. Dakshanamurthy, M. Chruszcz, W. Minor, M. L. Brown, *J. Med. Chem.* **2008**, *51*, 4620–4631.
- [30] K. M. El-Shaieb, M. A. Ameen, F. F. Abdel-Latif, A. H. Mohamed, *J. Chem. Res.* **2012**, *36*, 528–531.