

Synthesis of some new tricyclic 4(3H)-quinazolinone derivatives

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Abstract

Quinazolinones are interesting molecules with a wide range of biological activities. We prepared a number of quinazolinone derivatives by the condensation of 5-bromo- or 5-nitro-substituted anthranilic acids with chloro-acyl chlorides. Anthranilic acid derivatives were treated with either 3-chloro-propionyl chloride or 4-chloro-butyryl chloride to yield the corresponding *N*-acyl-anthranilic acids. The resultants were reacted with acetic anhydride to afford the benzoxazinone intermediates, which upon condensation with elected amines in either DMF or ethanol gave the corresponding tricyclic 4(3H)-quinazolinone derivatives. It was found that reactions in DMF produced higher yields.

Keywords: Anthranilic acid; Benzoxazinone; Tricyclic quinazolinone

INTRODUCTION

4(3H)-Quinazolinone ring backbone have been incorporated in several important heterocyclic compounds (1). Some of those have been prepared for their antibacterial, antifungal (2-4), anti inflammatory (5) and anticancer (6) properties. Literature surveys revealed that the syntheses of quinazolinones were achieved by the use of anthranilic acid (7-9), 2-aminobenzamide (7,10) and 2-aminobenzonitril or their derivatives (7). Quinazolinone based natural products demanding more structurally complex precursors have been constructed indirectly via thioamid formation, oxidation of dehydro-quinazolinone and aza-witting condensation (11,12). Most of these procedures have significant drawbacks such as long reaction times, harsh reaction condition, difficult work-up and use of environmentally toxic reagents or media (11). In contrast to the hitherto described methods, herein, in a simple and direct method, we report the reactions of substituted anthranilic acids with 3-chloro propionyl chloride or 4-chloro butyryl chloride for the preparation of the tricyclic quinazolinone target compounds.

MATERIALS AND METHODS

Instrumentation

Melting points were determined in open capillaries using electrothermal 9200 melting point apparatus and are uncorrected. IR (KBr discs) was recorded with a WQF -510 FT-IR-spectrophotometer.

¹H-NMR spectra were recorded on Bruker 400 or 80 MHz spectrometers using TMS as an internal standard and either DMSO-d₆ or CDCl₃ as solvents. Mass spectra were recorded on Shimadzu Mass spectrometer. All chemical were purchased from Merck Company.

Preparation of compounds

Various synthetic procedures, as described throughout the text where appropriate, were used to prepare target compounds. Synthetic routes for the preparation of the target compounds are shown in Schemes 1-4. The target compounds were then purified by column chromatography and/or preparative thin layer chromatography and their structures were confirmed by ¹HNMR, mass spectrometer and FT-IR spectrophotometer.

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RESULTS

Details of preparation procedures and chemistry of synthesized compounds**5-Bromo-2-(4-chlorobutanamido) benzoic acid (2)**

4-Chlorobutyl chloride (0.075 mol, 9 ml) was added drop wise to a solution of (0.069 mol, 15 g) 5-bromo anthranilic acid (**1**) in dimethyl formamide (35 ml) and stirred at room temperature for 3 h. The mixture was poured into water. The precipitate was collected by filtration, washed with water, and dried under reduced pressure to give **2** as a white solid (79% yield).

(Scheme 1), m.p.: 152.5-154.4°C. MS (m/z) 320.4 (M^+), 322 ($M+2$) for ($C_{11}H_{11}BrClNO_3$); M.W. 320.4. IR ν_{max} , 3323(N-H), 3060 (C-H Ar), 2966 (C-H), 1676, 1700 (C=O), 1600 (C=C Ar), 791 (C-Cl) cm^{-1} . 1H NMR δ_H (80 MHz; $CDCl_3$), 11.2 (1H, s, NH), 8.5 (1H, d, $J=8.8$ Hz, H-3 Ar), 8.1 (1H, s, H-6 Ar), 7.7 (1H, d, $J=8.8$ Hz, H-4 Ar), 3.7 (2H, t, $J=8.4$ Hz, NH-CO-CH₂-CH₂-CH₂-Cl), 2.6 (2H, t, $J=8.4$ Hz, NH-CO-CH₂-CH₂-CH₂-Cl), 2.1 (2H, qui, $J=8.4$ Hz, NH-CO-CH₂-CH₂-CH₂-Cl).

6-Bromo-2-(3-chloropropyl)-4H-benzo[d][1,3]oxazin-4-one (3)

Compound **2** (0.018 mol, 6 g) was dissolved in acetic anhydride (180 ml) and heated for 1 h with vigorous stirring. The solvent was removed by distillation under reduced pressure to give **3** as a light yellow solid (62% yield). (Scheme 1), m.p.: 114.7-115°C. 1H NMR δ_H (80MHz; $CDCl_3$), 8.2 (1H, s, H-5 Ar), 7.8 (1H, d, $J=6.9$ Hz, H-8 Ar), 7.4 (1H, d, $J=6.9$ Hz, H-7 Ar), 3.7 (2H, t, $J=5.2$ Hz, N=C-CH₂-CH₂-CH₂-Cl), 2.8 (2H, t, $J=5.2$ Hz, N=C-CH₂-CH₂-CH₂-Cl), 2.3 (2H, qui, $J=5.2$ Hz, N=C-CH₂-CH₂-CH₂-Cl).

N-(6-Bromo-2-(3-chloropropyl)-4-oxoquinazolin-3(4H)-yl)-4-chloro-butanamide (4) and 8-bromo-1,2,3,4-tetrahydropyridazino[6,1-b]quinazolin-10-one(5)

Benzoxazinone (**3**) (0.11 mol, 3.51 g) was treated with excess amounts of hydrazine hydrate in ethanol or DMF under reflux condition for 2 h. The obtained product by either procedure was purified by column chromatography on silica gel using $CHCl_3$ -MeOH (49:1) as eluent to afford **4** and **5** (Scheme 1).

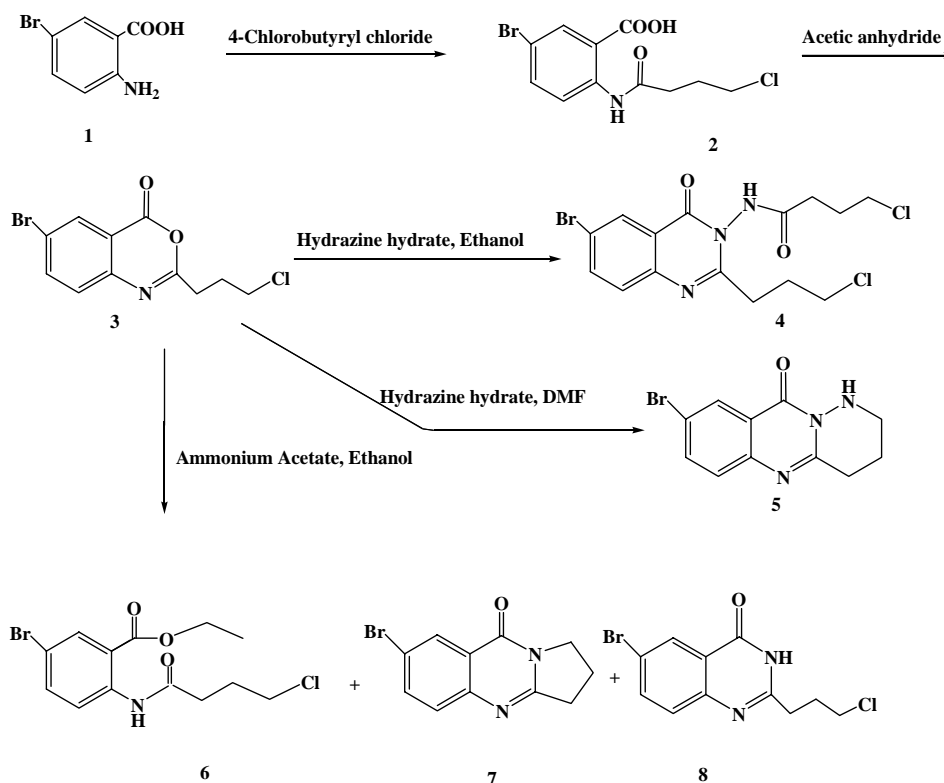


Fig. 1. Synthesis of the target compounds 4-8

(4): White middle crystals (25% yield), m.p.: 208.8-209.1°C, MS (m/z, %): 421 (M^+ , 16), 317 (100), 253 (10) for ($C_{15}H_{16}BrCl_2N_3O_2$); M.W. 421.12, IR ν_{max} , 3263 (N-H), 3122-3076 (C-H, Ar), 2926-2854 (C-H), 1691, 1680 (C=O), 1620 (C=N) cm^{-1} . 1H NMR δ_H (400MHz; $CDCl_3$), 10.9 (1H, s, NH), 8.7 (1H, d, $J=9.2$ Hz, H-8 Ar), 8.0 (1H, s, H-5 Ar), 7.6 (1H, d, $J=9.2$ Hz, H-7 Ar), 3.7 (2H, t, $J=6$ Hz, N=C-CH₂-CH₂-CH₂-Cl), 3.6 (2H, t, $J=6.4$ Hz, -N-NH-CO-CH₂-CH₂-CH₂-Cl), 3.1 (2H, t, $J=7.6$ Hz, N=C-CH₂-CH₂-CH₂-Cl), 2.7 (2H, t, $J=7.2$ Hz, -N-NH-CO-CH₂-CH₂-CH₂-Cl), 2.3 (2H, qui, $J=6.8$ Hz, N=C-CH₂-CH₂-CH₂-Cl), 2.2 (2H, qui, $J=6.4$ Hz, -N-NH-CO-CH₂-CH₂-CH₂-Cl). (5): White crystals (50% yield), m.p.: 203.7-204.8°C, MS (m/z, %): 280 (M^+ , 100), 251 (25), 224 (7.5) for ($C_{11}H_{10}BrN_3O$); M.W. 280. IR ν_{max} , 3251 (N-H), 2954 (C-H), 1664 (C=O), 1606 (C=C, Ar) cm^{-1} ; 1H NMR δ_H (400MHz; $CDCl_3$), 8.4 (1H, s, H-9 Ar), 7.8 (1H, d, $J=8$ Hz, H-7 Ar), 7.7 (1H, d, $J=8$ Hz, H-6 Ar), 7.1 (1H, s, N-H), 3.3 (2H, t, $J=7.2$ Hz, N=C-CH₂-CH₂-CH₂), 3.2 (2H, t, $J=7.2$ Hz, N=C-CH₂-CH₂-CH₂), 2.2 (2H, qui, $J=7.2$ Hz, N=C-CH₂-CH₂-CH₂).

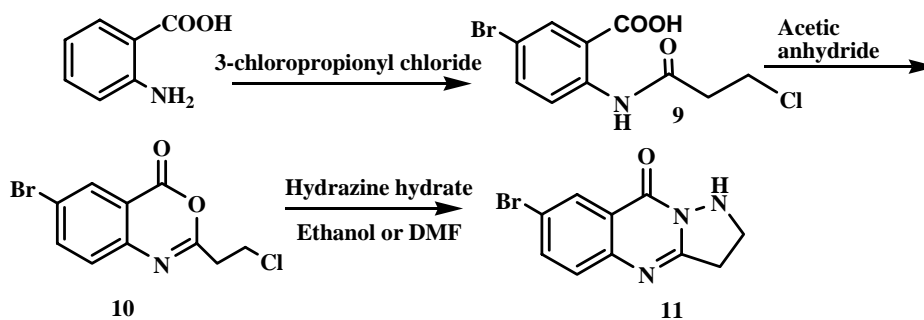
Ethyl -5- bromo -2- (4-chlorobutanamido) benzoate (6), 7-bromo-2, 3-dihydropyrrolo [2, 1-b] quinazolin-9(1H)-one (7) and 6-bromo-2-(3-chloropropyl) quinazolin-4(3H)-one (8)

Benzoxazinone (3) (0.11 mol, 3.51 g) was treated with excess amounts of ammonium acetate in ethanol or DMF and refluxed for 2 h. The residues from both reactions were purified by column chromatography on silica gel using an eluent of $CHCl_3$ -MeOH 19:1 to obtain 6, 7 and 8 from the ethanolic solution and 7, 8 from DMF (Scheme 1).

(6): White crystals (24% yield), m.p.: 79.5-80.8°C. MS (m/z, %): 348 (M^+ , 26), 243 (100), 215(10), 197 (40) for ($C_{13}H_{15}BrClNO_3$); M.W. 348. IR ν_{max} , 3321 (N-H), 2925-2852 (C-H), 1678, 1725 (C=O), 1597 (C=C, Ar) cm^{-1} . 1H NMR δ_H (400 MHz; $CDCl_3$), 11.2 (1H, s, NH), 8.6 (1H, d, $J=9.2$ Hz, H-3 Ar), 8.1 (1H, d, $J=2.4$ Hz, H-6 Ar), 7.6 (1H, dd, $J=8.8$ Hz, $J=2.4$ Hz, H-4 Ar), 4.4 (2H, qua, $J=7.2$ Hz, COO-CH₂-CH₃), 3.6 (2H, t, $J=6.4$ Hz, NH-CO-CH₂-CH₂-CH₂-Cl), 2.6 (2H, t, $J=6.8$ Hz, NH-CO-CH₂-CH₂-CH₂-Cl), 2.2 (2H, qui, $J=6.8$ Hz, NH-CO-CH₂-CH₂-CH₂-Cl), 1.4 (3H, t, $J=7.2$ Hz, COO-CH₂-CH₃).

(7): Light yellow (24% yield from ethanol, 31% yield from DMF), m.p.: 187.8-189.5°C. MS (m/z, %): 265 (M^+ , 100), 238 (6.6), 184 (25) for ($C_{11}H_9BrN_2O$); M.W. 265. IR ν_{max} , 2925-2852 (C-H), 1685 (C=O), 1616 (C=C Ar), 1259 (C-N) cm^{-1} . 1H NMR δ_H (400MHz; $CDCl_3$), 8.4 (1H, d, $J=3.8$ Hz, H-8 Ar), 7.8 (1H, dd, $J=8.8$ Hz, $J=4$ Hz, H-6 Ar), 7.5 (1H, d, $J=8.4$ Hz, H-5 Ar), 4.2 (2H, t, $J=7.2$, N=C-CH₂-CH₂-CH₂), 3.1 (2H, t, $J=8$ Hz, N=C-CH₂-CH₂-CH₂), 2.3 (2H, qui, $J=7.2$ Hz, N=C-CH₂-CH₂-CH₂).

(8): White crystals (50% yield from ethanol, 63% yield from DMF), m.p.: 251-252°C. MS (m/z, %): 265 (100), 236 (62), 210 (20) for ($C_{11}H_{10}BrClN_2 \cdot HCl$); M.W. 301.5. IR ν_{max} , 3076 (C-H Ar), 3026-2962 (C-H), 1645 (C=O), 1022-1074 (Br-Ar) cm^{-1} . 1H NMR δ_H (400MHz; DMSO), 8.1 (1H, d, $J=2$ Hz, H-5 Ar), 7.9 (1H, dd, $J=9$ Hz, $J=2$ Hz, H-7 Ar), 7.5 (1H, d, $J=8.5$ Hz, H-8 Ar), 4.2 (2H, t, $J=7.5$ Hz, N=C-CH₂-CH₂-CH₂-Cl), 3.0 (2H, t, $J=8$ Hz, N=C-CH₂-CH₂-CH₂-Cl), 2.2 (2H, qui, $J=7.5$ Hz, N=C-CH₂-CH₂-CH₂-Cl).



Scheme 2. Synthesis of the target compound 11

5-Bromo-2-(3-chloropropanamido)benzoic acid (9)

3-Chloropropionyl chloride (0.075 mol, 7.21 ml) and 5-bromoanthranilic acid (0.069 mol, 15 g) were reacted according to the procedure explained for **2** to give **9** as a light yellow solid (65% yield). (Scheme 2), m.p.: 184.7-185.9°C. MS (m/z) 306.5 (M⁺), 308.8 (M+2) for (C₁₀H₉BrCl NO₃), M.W. 306.5. IR ν_{\max} , 3319 (N-H), 3060 (C-H Ar), 2974 (C-H), 1678, 1700 (C=O), 1599 (C=C Ar), 789 (C-Cl) cm⁻¹. ¹HNMR δ_{H} (80 MHz; DMSO), 11.2 (1H, s, NH), 8.5 (1H, d, *J*=8.4 Hz, H-3 Ar), 8.1 (1H, d, *J*=4.2 Hz, H-6 Ar), 7.7 (1H, dd, *J*=8.5 Hz, *J*=4.2 Hz, H-4 Ar), 3.9 (2H, t, *J*=8 Hz, NH-CO-CH₂-CH₂-Cl), 2.9 (2H, t, *J*=8 Hz, NH-CO-CH₂-CH₂-Cl).

6-Bromo-2-(2-chloroethyl)-4H-benzo[d][1,3]oxazin-4-one (10)

Compound **9** (0.019 mol, 6 g) was dissolved in acetic anhydride (15 ml) and heated for 1 h with vigorous stirring. The solvent was re-moved by distillation under reduced pressure. The obtained unstable yellow residue was used for the next step without purification (Scheme 2).

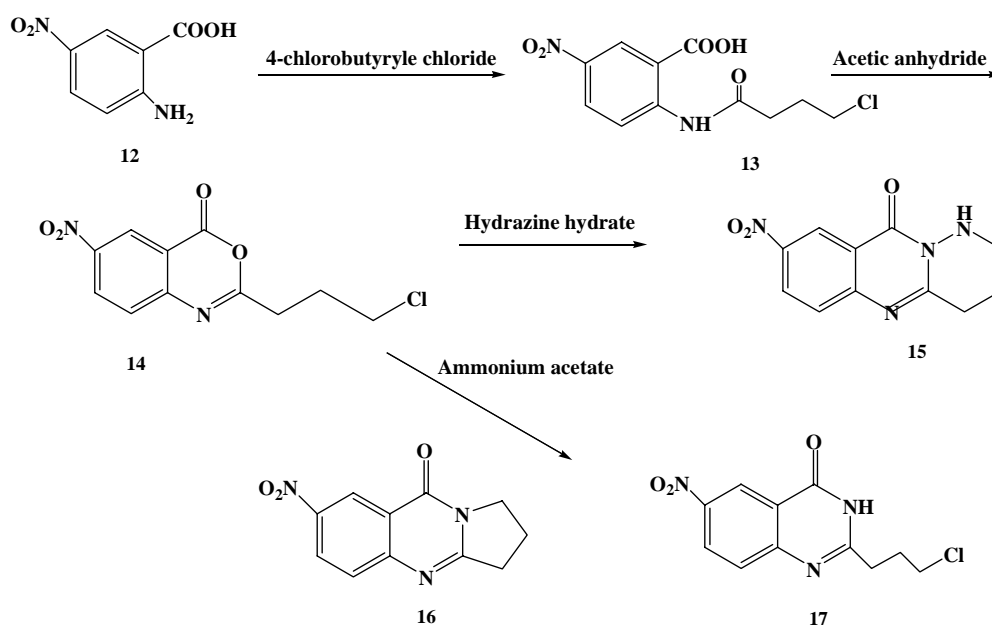
7-Bromo-2, 3-dihydropyrazolo [5, 1-b]quinazolin-9(1H)-one (11)

Compound **10** (0.012 mol, 3.5 g) and excess

of hydrazine hydrate were refluxed in DMF or Ethanol for 3 h. The reaction mixtures under both conditions were purified by column chromatography on silica gel using an eluent of CHCl₃-MeOH (49:1) to give **11** as light yellow crystals (68% yield from DMF, 37% yield from ethanol), (Scheme 2) m.p.: 212.5-213°C, MS (m/z, %): 266 (M⁺, 100), 253 (4), 238 (16.6), 210 (20), 197 (13) for (C₁₀H₈ Br N₃O); M.W. 266, IR ν_{\max} , 3228 (N-H), 2914 (C-H), 1658 (C=O), 1622 (C=C, Ar) cm⁻¹. ¹HNMR δ_{H} (400 MHz; CDCl₃), 8.4 (1H, s, H-8 Ar), 7.8 (1H, d, *J*=8 Hz, H-6 Ar), 7.5 (1H, d, *J*=8 Hz, H-5 Ar), 5.8 (1H, br s, NH), 3.7 (2H, t, *J*=7.6 Hz, N=C-CH₂-CH₂), 3.4 (2H, t, *J*=7.6 Hz, N=C-CH₂-CH₂).

2-(4-Chlorobutanamido)-5-nitrobenzoic acid (13)

4-Chlorobutyryl chloride (0.059 mol, 6.6 ml) was added dropwise to a solution of (0.054 mol, 10g) 5-nitroanthranilic acid (**12**) in DMF (27 ml). The mixture was poured into water and stirred for 1 h. The precipitated product was collected by filtration, washed with cold water, and dried under reduced pressure to give **13** as a light yellow solid (77% yield). (Scheme 3) m.p.: 150.5-151.2°C. MS (m/z) 286.5 (M⁺), 288 (M+2) for (C₁₁H₁₁ClN₂O₅); M.W. 286.5 IR: ν_{\max} , 3124 (N-H), 2970 (C-H), 1703, 1630 (C=O), 1576, 1352 (NO₂) cm⁻¹. ¹HNMR δ_{H} (400 MHz; DMSO): 13.0 (1H, bs,



Scheme 3. Synthesis of the target compounds **15-17**

2-(4-Chlorobutanamido)-5-nitrobenzoic acid (13)

4-Chlorobutylchloride (0.059 mol, 6.6 ml) was added dropwise to a solution of (0.054 mol, 10g) 5-nitroanthranilic acid (**12**) in DMF (27 ml). The mixture was poured into water and stirred for 1 h. The precipitated product was collected by filtration, washed with cold water, and dried under reduced pressure to give **13** as a light yellow solid (77% yield). (Scheme 3) m.p.: 150.5-151.2°C. MS (m/z) 286.5(M⁺), 288 (M+2) for (C₁₁H₁₁ClN₂O₅); M.W. 286.5 IR: ν_{\max} , 3124 (N-H), 2970 (C-H), 1703, 1630 (C=O), 1576, 1352 (NO₂) cm⁻¹. ¹HNMR δ_{H} (400 MHz; DMSO): 13.0 (1H, bs, COOH), 11.5 (1H, s, NH), 8.6 (2H, m, H-6, H-3 Ar), 8.4 (1H, d, *J*=6.4 Hz, H-4 Ar), 3.7 (2H, m, NH-CO-CH₂-CH₂-CH₂-Cl), 2.6(2H, m, NH-CO-CH₂-CH₂-CH₂-Cl), 2.0 (2H, m, NH-CO-CH₂-CH₂-CH₂-Cl).

2-(3-Chloropropyl)-6-nitro-4H-benzo[d][1,3]oxazin-4-one (14)

Compound **13** (0.013 mol, 4 g) was dissolved in acetic anhydride (12 ml) and heated for 1 h with vigorous stirring. The solvent was removed by distillation under reduced pressure. The obtained unstable residue was used for the next step without purification (Scheme 3).

8-Nitro-1,2,3,4-tetrahydropyridazino [6,1-b]quinazolin-10-one (15)

To a solution of **14** (0.012 mol, 3.48 g) in ethanol or DMF was added excess of hydrazine hydrate and heated at reflux temperature for 2 h. Colored suspensions, orange (in ethanol) and red (in DMF) were filtrated off and washed with *iso*-propanol to provide **15** as pure light brown solid (50% yield from DMF, 25% yield from ethanol). (Scheme 3), m.p.: 251-252°C. MS (m/z, %): 246 (M⁺, 100), 219 (16) for (C₁₁H₁₀N₄O₃); M.W. 246, IR ν_{\max} , 3251 (N-H), 3032-2879 (C-H), 1666 (C=O), 1608 (C=C Ar), (1595, 1342 NO₂) cm⁻¹. ¹HNMR δ_{H} (400MHz; CDCl₃), 9.1 (1H, d, *J*=2.8 Hz, H-9 Ar), 8.5 (1H, dd, *J*=9.2 Hz, *J*=2.8 Hz, H-7 Ar), 7.7 (1H, d, *J*=9.2 Hz, H-6 Ar), 7.1(1H, s, NH), 3.3 (2H, t, *J*=6.8 Hz, N=C-CH₂-CH₂-CH₂-Cl), 3.1 (2H, t, *J*=7.2 Hz, N=C-CH₂-CH₂-CH₂-Cl), 2.2 (2H, qui, *J*=7.2 Hz, N=C-CH₂-CH₂-CH₂-Cl).

7-Nitro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (16) and 6-nitro 2-(3-chloropropyl)-quinazolin-4(3H)-one (17)

The benzoxazinone (**14**) (0.012 mol, 3.48 g) was reacted with excess of ammonium acetate in ethanol or DMF to give yellow suspensions which was filtrated off and washed with *iso*-propanol. The yellowish precipitated products from both solvents were fractionated by column chromatography on silica gel using an eluent of CHCl₃-MeOH (49:1) to give **16** and **17** (Scheme 3).

(**16**): Light yellow, (35.7% yield from DMF, 30% yield from ethanol), m.p.: 190.8-191.3°C. MS (m/z, %): 231 (M⁺, 100), 201 (38), 185 (21), 173(16) for (C₁₁H₉N₃O₃); M.W. 231, IR ν_{\max} , 3105-3076 (C-H, Ar), 2970 (C-H), 1693 (C=O), 1606 (C=C, Ar), 1570, 1388 (NO₂) cm⁻¹. ¹HNMR δ_{H} (400MHz; CDCl₃), 9.0 (1H, d, *J*=2.4 Hz, H-8 Ar), 8.4 (1H, dd, *J*=8.8 Hz, *J*=2.4 Hz, H-6 Ar), 7.7 (1H, d, *J*=8.8 Hz, H-5 Ar), 4.2 (2H, t, *J*=7.6 Hz, N=C-CH₂-CH₂-CH₂-Cl), 3.2 (2H, t, *J*=8 Hz N=C-CH₂-CH₂-CH₂-Cl), 2.3 (2H, qui, *J*=7.6 Hz, N=C-CH₂-CH₂-CH₂-Cl).

(**17**): Light yellow, (33% yield from DMF, 24% yield from ethanol), m.p.: 228.9-229.5°C. MS (m/z, %): 267(M⁺, 31), 253(8), 222 (8), 231(100), 185 (23) for (C₁₁H₁₀ClN₃O₃); M.W. 267.5, IR ν_{\max} , 3093 (C-H, Ar), 3041 (C-H), 1645 (C=O), 1612 (C=C Ar), 1520, 1338 (NO₂) cm⁻¹. ¹HNMR δ_{H} (400MHz; DMSO), 8.7 (1H, s, H-5 Ar), 8.5 (1H, d, *J*=8.4 Hz, H-7 Ar), 7.7 (1H, d, *J*=8.8Hz, H-8 Ar), 4.3 (2H, t, *J*=7.6 Hz, N=C-CH₂-CH₂-CH₂-Cl), 3.0 (2H, t, *J*=8Hz, N=C-CH₂-CH₂-CH₂-Cl), 2.2 (2H, qui, *J*=7.6 Hz, N=C-CH₂-CH₂-CH₂-Cl).

2(3-chloropropanamido)-5-nitrobenzoic acid (18)

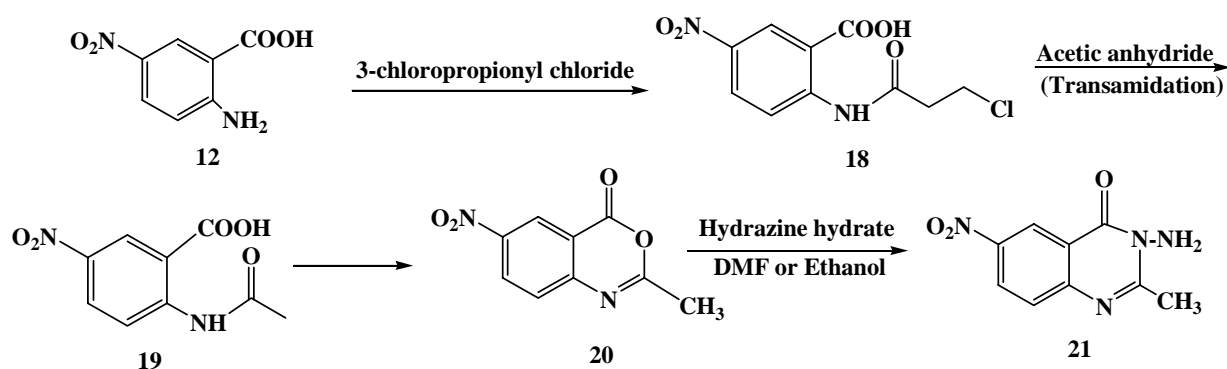
3-Chloropropionyl chloride (0.059 mol, 5.6 ml) was added dropwise to a solution of (0.054 mol, 10 g) 5-nitro anthranilic acid (**12**) in DMF (25 ml). The mixture was poured into water and stirred for 1 h. The precipitated product was collected by filtration, washed with cold water, and dried under reduced pressure to give **18** as a yellow solid (70% yield). Since the product was precipitated in reaction and was pure enough further recrystallization was not required (Scheme 4).

3-Amino-2-methyl-6-nitroquinazolin-4(3H)-one (21)

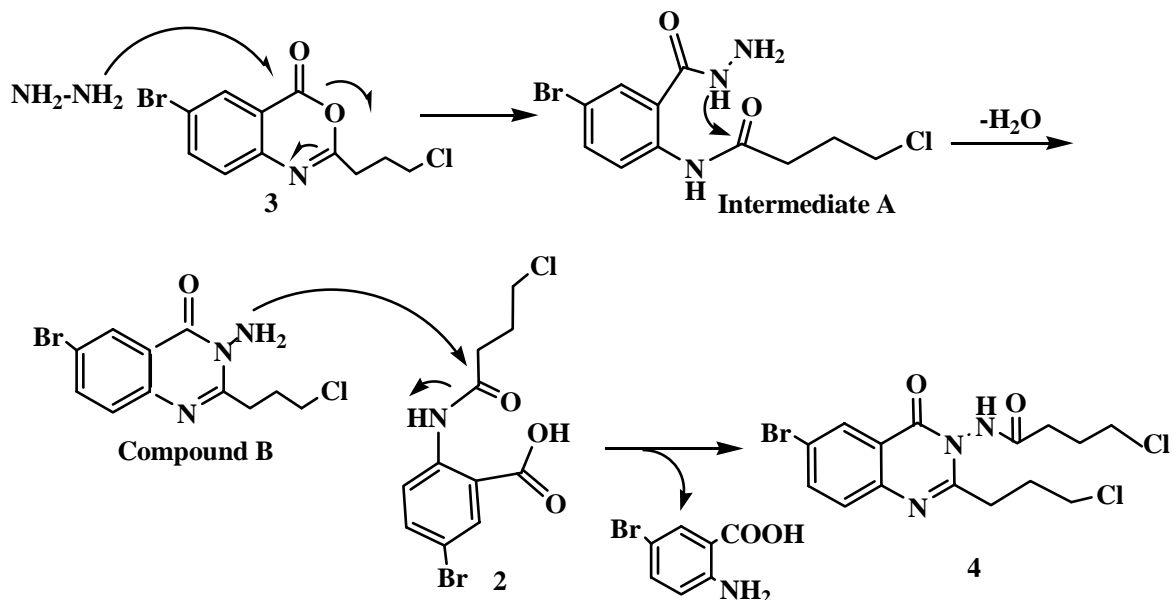
Compound **18** (0.02 mole, 6 g) was treated with acetic anhydride to give the corresponding benzoxazinone (**20**). The resulting benzoxazinone was refluxed in ethanol in the presence of excess hydrazine hydrate for 2 h. "This reaction was repeated in DMF with the same reaction condition". The red solution was cooled to give a precipitate, which was fractionated by column chromatography on silica gel using an eluent of CHCl₃-MeOH (49:1) to give **21** as orange solid (25% yield from DMF, 18% yield from ethanol), m.p.: 197.7-198.8°C. MS (m/z, %): 220 (M⁺, 100),

191 (37.5) for (C₉H₈N₄O₃); M.W. 220, IR ν_{\max} , 3419 (N-H), 2962-2856 (C-H), 1558, 1340 (NO₂) cm⁻¹. ¹HNMR δ_{H} (400MHz; CDCl₃), 9.1 (1H, d, *J*=5 Hz, H-5 Ar), 8.5 (1H, dd, *J*=8.8 Hz, *J*=5 Hz, H-7 Ar), 7.7 (1H, d, *J*=8.5 Hz, H-8 Ar), 4.9 (2H, s, NH₂), 2.7 (3H, s, CH₃).

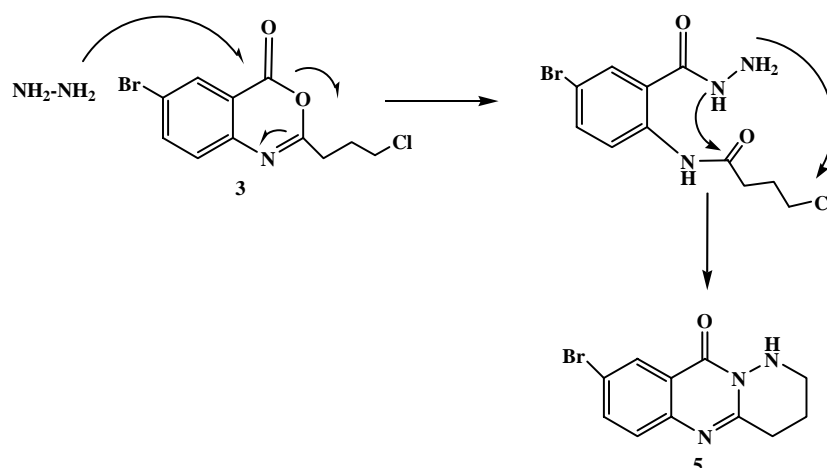
Formation of unexpected product as **21** could be explained by trans amidation of **18** to **19** (was not isolated) by means of direct effect of acetic anhydride. Further steps were carried out as the usual procedure for preparation of benzoxazinon (**20**) (was not isolated) and quinazolinon (**21**) (Scheme 4).



Scheme 4. Synthesis of compound **21**



Scheme 5. Proposed mechanism for the synthesis of compound **4**



Scheme 6. Proposed mechanism for the synthesis of compound **5**

DISCUSSION

In the first step to produce quinazolinone derivatives, 5-bromoanthranilic acid (**1**) was treated with 4-chloro-butyryl chloride to yield amide **2**. Treatment of **2** with acetic anhydride afforded the benzoxazinone (**3**) through dehydrative cyclization mechanism (8,13). The benzoxazinone (**3**) was then reacted with hydrazine hydrate in ethanol or DMF to give **4** and **5**, respectively. Interestingly, the products obtained from the third step of the reactions were found to be mainly depended on the nature of the solvent used. The reaction of **3** with excess of hydrazine hydrate in ethanol yielded **4**, while refluxing a mixture of **3** with excess of hydrazine hydrate in DMF gave rise to a cyclic quinazolinone product (Scheme 1, compound **5**).

In ethanol, hydrazine hydrate acted as a nucleophile and attacked the carbonyl group of the benzoxazinone molecule which resulted in the ring opening to afford the intermediate compound A. Subsequently the lone pair electron of nitrogen of the intermediate compound A attacked to the carbonyl group of the side chain to form an intermediate, which upon its dehydration produced compound B. Then, NH_2 functionality in compound B attacked to **2** to afford **4** and 5-bromoanthranilic acid as shown in scheme 5.

In DMF solvent hydrazine hydrate acted as a nucleophile and reacted with the carbonyl group of cyclic ester **3**. As shown in Scheme 6,

nucleophilic attacks of individual carbohydrazine nitrogens to the carbonyl group of the amide and methylene chloride functionality resulted in the production of **5**. In a similar manner, the benzoxazinone (**3**) was treated with excess amounts of ammonium acetate in ethanol or DMF. The residues from either reaction were purified by column chromatography to obtain **6**, **7** and **8** (from ethanol) and **7** and **8** (from DMF) (Scheme 1).

Similarly, we synthesized benzoxazinone (**10**) using 3-chloro propionyl chloride. The benzoxazinone (**10**) and excess hydrazine hydrate were refluxed in DMF or ethanol for 3 h. The reaction mixtures from both solvents were purified by column chromatography to obtain **11** (Scheme 2). Reaction in DMF was cleaner compared with the one in ethanol. Compound **11** which is a five-membered ring analogue of **5** was produced by a similar mechanism explained for the synthesis of **5**.

Next, as shown in Scheme 3, 5-nitroanthranilic acid (**12**) was used as the starting material. 4-Chlorobutyryl chloride was added to a solution of 5-nitroanthranilic acid in DMF to produce **13** which was subsequently cyclized to the benzoxazinone intermediate **14** by heating with acetic anhydride. Then, to a solution of **14** in ethanol or DMF excess hydrazine hydrate was added. Orange ethanolic and reddish DMF suspensions were filtrated off and washed with isopropanol to provide **15** as a pure product. In a similar reaction, the benzoxazinone (**14**) was reacted

with excess ammonium acetate in ethanol or DMF to give yellow suspensions which was filtrated off and washed with isopropanol. The yellowish precipitated products in both solvents were fractionated by column chromatography to give **16** and **17** (Scheme 3).

Finally, 5-nitroanthranilic acid (**12**) was reacted with 3-chloropropionyl chloride (Scheme 4) to obtain **18**, which treated with acetic anhydride to give the corresponding benzoxazinone (**20**) via intermediate (**19**).

Benzoxazinone (**20**) was then refluxed in ethanol or DMF with excess of hydrazine hydrate to give **21** (Scheme 4). Reaction of **18** with acetic anhydride did not follow the usual manner to give the corresponding benzoxazinone; instead, transamidation of (**18**) with the acetic anhydride gave **19** which upon its ring closure afforded intermediate (**20**).

CONCLUSION

In conclusion, application of chloro acyl chloride instead of acyl chloride in quinazolinone synthetic procedures resulted in a second ring closure. This second ring closure was achieved when an intramolecular nucleophilic attack to the end methylen chloride group was possible. Formation of highly stable five- or six-membered ring may be counted as a good reason for this ring closure. Generally, reaction in DMF resulted in more clean reactions with higher yields compared with that of ethanol. Initial screening of the target compounds indicated that some of them had considerable anti-bacterial, antifungal and cytotoxic activities.

ACKNOWLEDGMENT

This work was financially supported by research council of Isfahan University of Medical Sciences.

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