SYNTHESIS OF TETRAAZA-CHRYSEN-5-ONE AND CYCLOPENTA[*a*] PHENANTHREN-7-ONE DERIVATIVES FROM 4-AMINOQUINOLINE

Balasaheb P. Pagar[1*], Amol H. Kategaonkar[2], Arun M. Bhagare[3], Ravindra R. Zoman[4]

[1]*Dept of Chemistry, K.S.K.W Arts. Commerce and Science College, Cidco, Nashik (MS), India*
[2]*Dept of Chemistry, G.M.D. Arts, B.W. Com. and Sci. College, Sinnar, Nashik, (MS), India*
[3]*Dept of Chemistry, Arts, Commerce and Science College, Ozar (MIG), Nashik, (MS), India*
[4]*Dept of Chemistry, Arts, Commerce and Science College, Dindori, Nashik, (MS), India*
**Email: pagar_bp@rediffmail.com*

Abstract

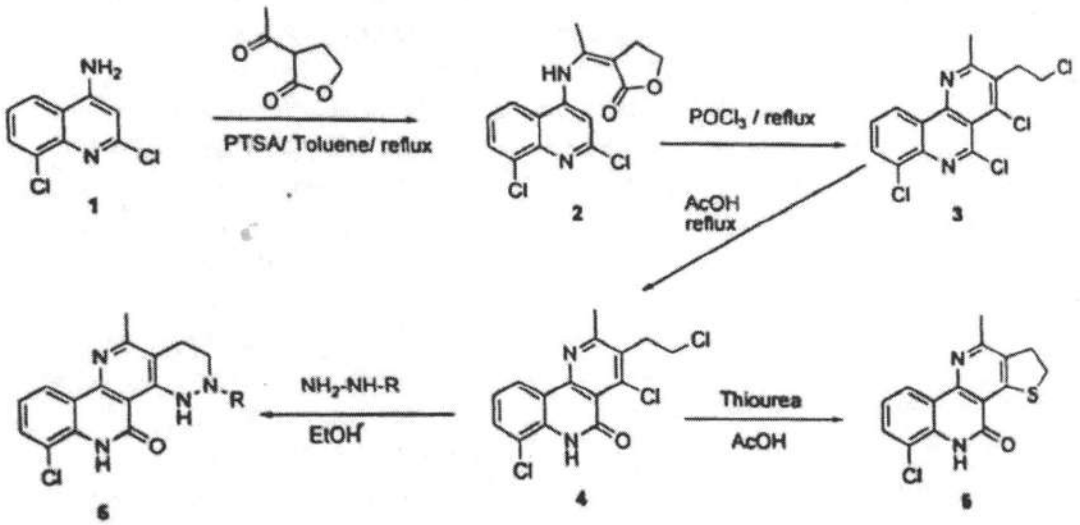
A convenient route was successfully developed for the synthesis of benzo[h][1,6]naphthyridine derivatives 3 from α-acetyl-γ-butyrolactone and 2,8-dichloroquinolin-4-amine 1. This paper describes the synthesis and novel reactions of 4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6] naphthyridine 3 having replaceable chloride atoms. Tetrahydropyrido 5 and dihdrothieno 6 benzo[h][1,6]naphthyridine derivatives were synthesized from benzo[h][1,6] naphthyridine 4. The title compound was characterized by analytical and spectral (IR, ^{1}HNMR, ^{13}CNMR and LC-MS) methods.

Keywords: *4-aminoquinoline, benzo[h][1,6]naphathyridine*

Introduction: The benzo[*h*][1,6]naphthyridine derivatives are class of heterocyclic compounds that exhibit broad spectrum of biological activities such as antimalarial[1], inhibitor of HIV-1 integrase[2-5], HCMV[6-7], FGF receptor-1 tyrosine kinase[8] and the enzyme acetyl cholinesterase[9]. As noted previously[10-11] several heterocycles having 2-chloroethyl side chain exhibited good in vitro activity against several cell lines of clinically isolated human tumor. For further information, the reported SAR studies[12] of these types of compounds and replacement by quinoline nucleus as carrier of reported substituents were of particular interest because of these structures in several cytotoxic agents[13]. Several antimalarial candidates possess usable functional group at C_4-position in tricyclic heteroaromatic nucleus[14] were synthesized by substituting chloride in benzo[*h*][1,6]naphthyridines with various *N*-alkyl-4-piperidinyl methanolates[15-19].

Results and Discussion: The required starting compound 2,8-dichloroqunolin-4-amine **1** was synthesized from commercially available substituted aniline by literature know procedures[20-21]. 2,8-Dichloroquinolin-4-amine **1** on reaction with α-acetyl γ-butyrolactone in toluene and catalytic amount of PTSA at 120 °C, furnished thermodynamically stable intermediate (*Z*)-2-aminoethylidene heterodihydrofuranone **2** in 77% yield. The structure of compound **2** was assigned using spectroscopic and analytical methods. For instance IR of **2** showed lactone carbonyl (C=O) stretching at 1689 cm,$^{-1}$ NH at 3122 cm^{-1} and (C=C) at 1575 cm.$^{-1}$ The lowering of lactone carbonyl was due to intramolecular H-bonding between CO and NH, also support the Z-configuration of furanone intermediate. The ^{1}H NMR spectrum of **2** in $CDCl_3$ showed the resonance at δ 2.32 ppm for methyl protons, two triplets were observed at δ 3.00

and δ 4.43 ppm with J = 7.5 Hz were assignable for CH_2CH_2O. The down field NH resonance showed sharp singlet at δ 11.03 (D_2O exchangeable), and the remaining aromatic protons resonance at expected chemical shifts and splitting pattern. The ^{13}C NMR spectrum in $CDCl_3$ showed the peak at δ 168 indicating the presence of lactone carbonyl. The EI-MS of 77 showed M+, M+2 and M+4 at 322, 324 and 326 m/z respectively indicating the presence of two chlorines.



Intermediate dihydrofuranone **2** was refluxed in $POCl_3$ furnished compound **3** in 40% yields. The compound **3** was separated by column chromatography eluting with toluene and structures were established by spectral and analytical data. The ^1H NMR spectra of compound **3** in $CDCl_3$ showed resonance singlet at δ 2.93 ppm for methyl protons, two triplets at δ 3.53 and δ 3.81 ppm, J = 7.2 Hz were assignable to CH_2CH_2Cl. The resonance of aromatic protons in compound **3** was observed between δ 7.53 and δ 8.95 ppm. The ^{13}C NMR spectrum in $CDCl_3$ showed the peaks at δ 25.13, 33.85, 41.08 indicating the presence of three aliphatic carbon atoms and the peaks in between δ 123.38-163.11 was assignable for aromatic carbon atoms. The EI-MS of **3** showed M+, M+2, M+4, M+6 and M+8 at 360, 362, 364, 366 and 368 m/z respectively due to the presence of four chlorines.

The iminechloride (-N=C-Cl) moiety in compound **3** was converted to lactum carbonyl[22] by refluxing in aqueous acetic acid containing small amount of water furnished amide derivative **4** in 93% yield. The structure of compound **4** was assigned by spectroscopic and analytical methods. For instance IR of compound **4** showed lactum carbonyl (C=O) stretching at 1676 cm^{-1} and NH at 3339 $cm.^{-1}$ The ^1H NMR spectrum of **4** in $CDCl_3$ showed the resonance singlet at δ 2.91 for CH_3 group, two triplets at δ 3.57 and 3.83 (J = 7.1 Hz) was assignable for 2-

chloroethyl side chain and singlet at δ 8.1 was assignable for NH proton. The remaining aromatic protons were resonance at expected chemical shifts and splitting pattern. The ^{13}C NMR spectrum showed the presence of carbonyl frequency corresponding to lactum carbonyl at δ 170.61. The compound **4**, substituted hydrazine and five drops of acetic acid in ethanol was refluxed for 5 h furnished 7-chloro-12-methyl-3-substituted-1,3,4,6-tetrahydro-*2H*-3,4,6,11-tetraazachrysen-5-one **5** in 80-82% yield. The structure of compound **5** was assigned using spectroscopic and analytical methods. For instance IR of compound **5b** showed lactum carbonyl (C=O) stretching at 1675 cm^{-1} and NH at 3330 $cm.^{-1}$ The ^1H NMR spectrum of **5b** in $CDCl_3$ showed the resonance singlet at δ 2.47 for CH_3 group, two triplets at δ 3.67 and 3.80 (J = 6.4 Hz) was assignable for CH_2CH_2N group. The aromatic protons showed peaks in between δ 6.94-8.66 ppm and two singlets at 8.85 and 10.58 were assignable for two NH protons. The ^{13}C NMR spectrum of **5b** in $CDCl_3$ showed the peak at δ 163.78 for the presence of lactum carbonyl carbon. The EI-MS of of **5b** showed M+ at 376 and M+2 at 378 m/z, indicating the presence of one chlorine atom.

Further, the compound **4** on reaction with tiourea in acetic acid furnished 4-chloro-12-methyl-16,17-dihydro-*6H*-15-thia-6,11-diazacyclopenta [*a*]phenanthren-7-one **6** in 77% yield. The structure of compound **6** was assigned using spectroscopic and analytical methods. For instance IR of compound **6** showed lactum carbonyl (C=O) stretching at 1653 cm^{-1} and NH at 3400 $cm.^{-1}$ The ^1H NMR spectrum of **6** in $CDCl_3$ showed the resonance singlet at δ 2.57 for CH_3 group, the two triplets were observed at δ 3.20 and at δ 4.75 (J = 8.5 Hz) assignable for SCH_2CH_2 group. The aromatic protons showed triplet at δ 7.18 for C_2H, the doublet at δ 7.52 for C_3H and δ 8.67 for C_1H protons. The singlet at δ 8.45 was due to SH proton. The ^{13}C NMR spectrum of **6** in $CDCl_3$ showed the peak at δ 159.26 was assignable for lactum carbonyl carbon. The EI-MS of of **6** showed M+ at 303 and M+2 at 305 m/z, indicating the presence of one chlorine atom.

Experimental: General: Common reagents grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures. The melting points were measured on Barnstead Electro Thermal melting point apparatus Mod. No. IA-9200 in open capillary tubes and are uncorrected. Elemental analyses were determined using Thermo Quest Model No. flash EA 1112-Elemental Analyzer. The IR spectra of compounds were recorded on Shimadzu IR-408, instrument in potassium bromide pellets. All mass spectra were recorded on Mat 112 Varian Mat Bremen mass spectrometer. Routine ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on VARIAN XL-300 instrument at 25 °C. The measurements were done using protiated solvents-$CDCl_3$ and DMSO-d_6, with TMS as an internal standard reference. Coupling constants (J) are quoted to the nearest 0.1 Hz and chemical shift (δ-scale) are quoted in parts per million (ppm) and following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad.

was collected by suction filtration, dried and recrystallized from ethanol/DMF (9:1) to yield title compound **4** (3.17 g, 93%) as pink colored prisms. Yield: 93% (3.17 g); M.p. 254 °C. *Rf* (toluene/ethyl acetate 9:1) 0.51. IR (KBr): *v* 3339 (NH), 3186, 3143, 1676 ($C=O_{lactum}$), 1249, 734 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$): δ 2.91 (s, 3H, CH_3), 3.57 (t, J = 7.1 Hz, 2H, CH_2CH_2Cl), 3.83 (t, J = 7.1 Hz, 2H, CH_2CH_2Cl), 7.59 (t, J = 7.5 Hz, 1H, C_9H), 7.77 (d, J = 7.5 Hz, 1H, C_8H), 8.1 (s, 1H, NH, D_2O exchangeable), 8.97 (d, J = 7.5 Hz, 1H, $C_{10}H$). ^{13}C NMR ($CDCl_3$): δ 23.26, 30.95, 42.65, 119.40, 121.72, 122.14, 126.75, 128.00, 128.20, 128.63, 128.74, 136.66, 142.23, 161.54, 170.61. MS: *m/z* (%): 347 (M+6, 10), 345 (M+4, 30), 343 (M+2, 50), 341 (M, 100), 274 (20), 198 (20), 99 (10).

7-Chloro-12-methyl-3-substituted-1,3,4,6-tetrahydro-2H-3,4,6,11-tetraaza-chrysen-5-one, 5(a-b): A mixture of 4,7-dichloro-3-(2-chloroethyl)-2-methylbenzo[*h*][1,6] naphthyridine-5(6*H*)-one **4** (1.023 g, 0.03 mmol), substituted hydrazine (0.06 mmol) and five drops of glacial acetic acid in ethanol (25 mL) was heated to reflux for 5 h. Reaction completion was monitored through TLC, the reaction mixture was cooled down to room temperature, then the methanol was added into the reaction mixture. The solid product precipitate was collected by suction filtration, washed with water, then methanol, dried and recrystallized from DMF / ethanol to yield compound **5a**. Yellow colored prisms; yield (0.738 g, 82%); mp 281 °C. IR (KBr): *v* 3390 (NH), 2926, 1683 (C=O), 1589, 1300, 812 cm.$^{-1}$ ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 2.70 (t, J = 6.5 Hz, 2H, CH_2), 3.50 (t, J = 6.5 Hz, 2H, CH_2N), 5.11 (s, 1H, NH), 7.24 (t, J = 7.5 Hz, 1H, C_9H), 7.66 (d, J = 7.5 Hz, 1H, C_8H), 8.55 (d, J = 7.5 Hz, 1H, $C_{10}H$), 9.99 (s, 1H, NH, D_2O exchangeable), 10.66 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 20.32, 22.43, 47.53, 111.10, 118.76, 121.89, 122.91, 124.32, 129.19, 132.63, 149.33, 150.24, 150.29, 159.43, 163.02. MS: *m/z* (%): 302 (M+2, 40), 300 (M+, 100), 284 (10), 272 (95), 245 (20), 150 (60), 136 (30), 42 (40).

7-Chloro-12-methyl-3-phenyl-1,3,4,6-tetrahydro-2H-3,4,6,11-tetraaza-chrysen-5-one, 5b: Yellow colored prisms; yield (0.902 g, 80%); mp 285 °C. IR (KBr): *v* 3330 (NH), 3026, 1675 (C=O), 1609, 1312, 850 cm.$^{-1}$ ^{1}H NMR (DMSO-d_6): δ 2.47 (s, 3H, CH_3), 2.67 (t, J = 6.4 Hz, 2H, CH_2), 3.80 (t, J = 6.4 Hz, 2H, CH_2N), 6.94 (t, J = 7.1 Hz, 1H, ArH), 7.07 (t, J = 7.1 Hz, 2H, ArH), 7.22 (m, 2H,, ArH), 7.24 (t, J = 7.2 Hz, C_9H), 7.55 (d, J = 7.2 Hz, 1H, C_8H), 8.66 (d, J = 7.2 Hz, $C_{10}H$), 8.85 (s, 1N, NH, D_2O exchangeable), 10.58 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 20.92, 22.74, 46.50, 102.79, 110.02, 116.59, 118.97, 121.62, 121.87, 122.80, 124.07, 129.32, 130.07, 132.81, 149.83, 150.09, 150.17, 159.86, 163.78. MS: *m/z* (%): 378 (M+2, 30), 376 (M+, 100), 299 (60), 272 (95), 285 (20), 270 (30), 150 (40), 136 (20), 42 (40).

4-Chloro-12-methyl-16,17-dihydro-*6H*-15-thia-6,11-diaza-cyclopenta[*a*]phenanthren-7-one, 6: A mixture of 4,7-dichloro-3-(2-chloroethyl)-2-methylbenzo[*h*][1,6]naphthyridin-5(6*H*)-one **4** (1.023 g, 0.03 mmol) and thiourea (0.304 g, 0.04 mmol) in glacial acetic acid (10

mL) was refluxed for 20 min. Reaction was monitored by TLC. The reaction mixture after cooling to room temperature, methanol (50 mL) was added. The crude product separated was collected by suction filtration, dried and recrystallized from ethanol/DMF (9:1) to give title compound **6** (0.697 g, 77%) as pink colored prisms. mp 309 °C. IR (KBr): ν 3400 (NH), 3173, 3046, 1653 (CO), 1605, 1553, 1409, 1133, 842 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$): δ 2.57 (s, 3H, CH_3), 3.20 (t, J = 8.5 Hz, 2H, CH_2), 4.22 (t, J = 8.5 Hz, 2H, CH_2), 7.18 (t, J = 8.7 Hz, 1H, C_2H), 7.52 (d, J = 8.7 Hz, 1H, C_3H), 8.45 (s, 1H, NH, D_2O exchangeable), 8.67 (d, J = 8.7 Hz, 1H, C_1H). ^{13}C NMR ($CDCl_3$): δ 22.43, 25.91, 57.61, 118.83, 122.51, 124.45, 126.22, 129.32, 130.10, 133.48, 145.79, 151.85, 154.39, 156.94, 159.26. MS: *m/z* (%): 305 (M+2, 40), 303 (M+, 100), 297 (15), 201 (10), 197 (40), 162 (60), 136 (90).

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