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Efficient synthesis of fused benzo[*b*] indazolo[6,7-*h*] [1,6] naphthyridines

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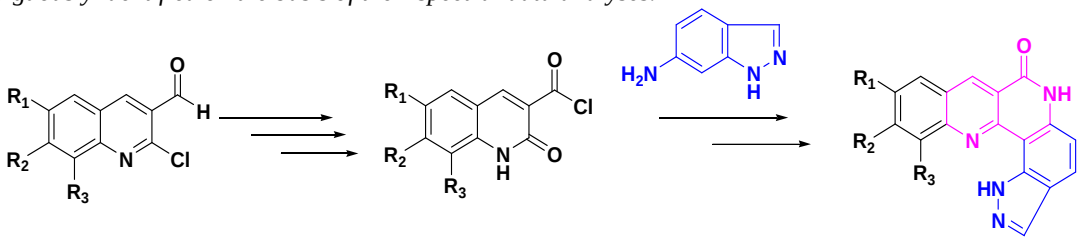
ABSTRACT

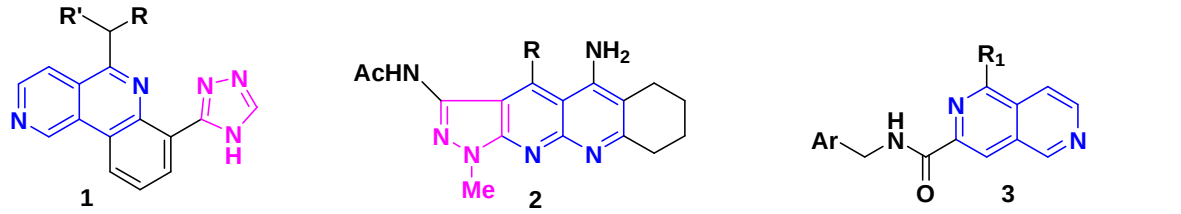
This paper describes the synthetic route to benzo[b]-1H-Indazolo[6,7-h][1,6]naphthyridine-7[6H]-ones, from 2-chloroquinoline-3-carbaldehydes. 2-chloroquinoline-3-carbaldehydes prove to be excellent starting material for the synthetic sequence.2- chloroquinoline-3-carbaldehydes were converted into 2-oxo quinoline-3- carbonyl chlorides from reported literature method. The carbonyl chloride condensed with 1H-Indazole-6-amine led to the formation of 3-(6'-amido-1'H-Indazolo)quinoline-2-[1H]-one. The cyclisation of 3-(6'-amido-1'H-Indazolo) quinoline-2-[1H]-one with PPA resulted the cyclised benzo[b]-1H-Indazolo[6,7-h][1,6]naphthyridine-7[6H]-ones. The reaction sequence was generalized and was extended to synthetic derivatives. All the synthesized compounds were unambiguously identified on the basis of their spectral data analyses.



Keywords: 3-(6'-amido-1'*H*-Indazolo)quinoline-2-[*1H*]-ones; benzo[*b*]-1*H*-Indazolo[6,7-*h*][1,6] naphthyridine-7-[*6H*]-ones; 1*H*-Indazole-6-amine; 2-chloroquinoline-3-carbaldehydes.

INTRODUCTION

The interest in the study of naphthyridine derivatives is due to the exceptionally broad spectrum of their biological activities [1-5]. Such naphthyridine systems namely 7-(4*H*-1,2,4-Triazol-3-yl) benzo[*c*][2,6]naphthyridines [6],benzo[b]pyrazolo[4,3-*g*][1,8]naphthyridine [7],1,6Naphthyridine -7-carboximate [8] also display enhanced activity towards cancer cell lines,possess anti bacterial properties and pim kinase inhibitors with potent cell antiproliferative activity (**Figure 1-3**). A number of fused (1,6) naphthyridines that have been prepared in our laboratory were screened against several bacterial species, and they display moderate cytotoxic activity [9]. In present phase research, we report an efficient synthesis of benzo [*b*] Indazolo[6,7-*h*][1,6]naphthyridine 7-[*6H*]-ones **7a-e** using 2- chloroquinoline-3-carbaldehydes **4a-e** as starting material.

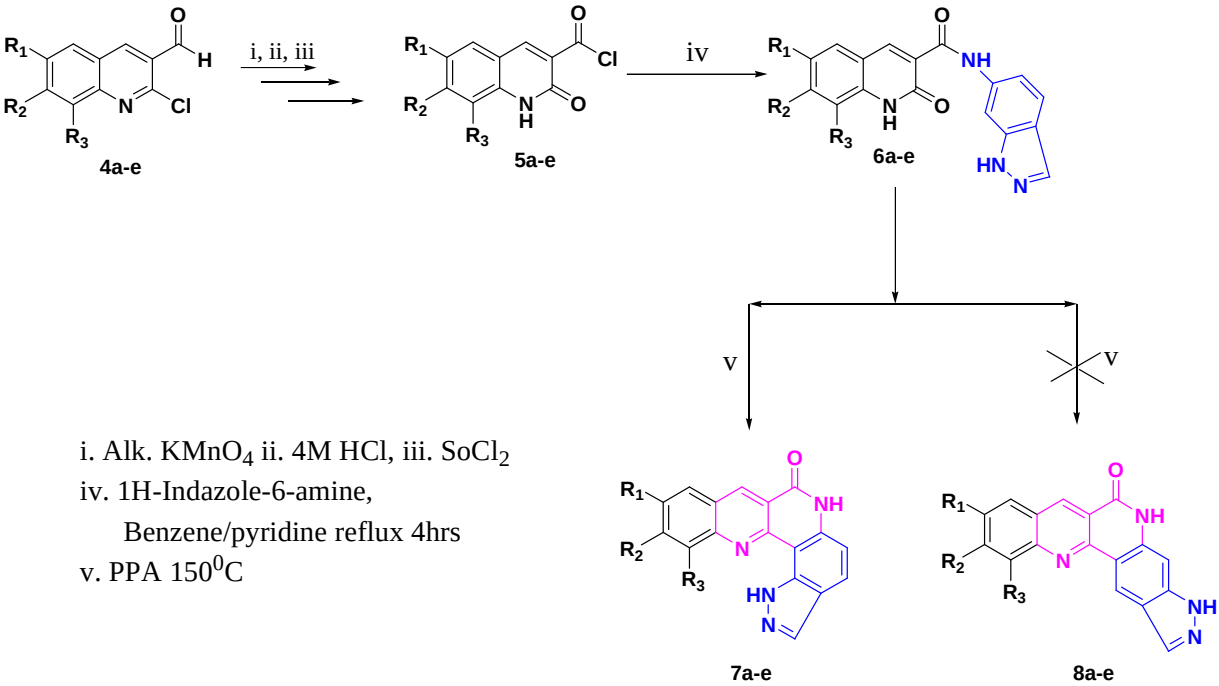


7-(4H-1,2,4-Triazol-3-yl)benzo[c] [2,6]naphthyridines [6]

benzo [b]pyrazolo [4,3-g] [1,8]naphthyridine [7]

1,6-Naphthyridine-7-carboximate [8]

General structure and naphthyridine ring systems for new analogues. (**Figure 1-3**)



i. Alk. $KMnO_4$ ii. 4M HCl, iii. $SoCl_2$

iv. 1H-Indazole-6-amine,

Benzene/pyridine reflux 4hrs

v. PPA 150^0C

Scheme 1. Synthesis of benzo [*b*] Indazolo [6,7-*h*][1,6] naphthyridine 7-[*6H*]-ones 7a-e

MATERIALS AND METHODS

Commercial solvents and reagents were used as received. IR spectra were recorded on a Shimadzu FT IR 8201PC(S) spectrometer in KBr pellets and reported in cm-1. ^{1}H NMR were measured on a Bruker AV- 400MHz spectrometer using TMS as an internal standard and dimethyl sulfoxide (DMSO)-d_6 and chloroform-D ($CDCl_3$) as solvent. *J* values are in hertz (Hz) chemical shift are expressed in parts per million down field from internal standard trimethylsilane. The ESI-MS were recorded in Thermo Scientific mass spectrometer detector and electrospray ionization. Melting points were determined using a Raga melting point apparatus and were not corrected. The reactions were monitored by TLC performed using glass plates coated with silica gel-G containing 13% calcium sulphate as binder. 2-Chloroquinoline-3- carbaldehydes were prepared according to Otto-Meth Cohn *et al.*procedure. [10,11]

General procedure for synthesis of 3-(6'-amido Indazolo quinoline-2-[1*H*]-ones (6a-e)

To a solution of the corresponding acid chlorides **6a–e** (0.5g, 2 mmol) in dry benzene (10 mL) 1*H*-Indazole-6-amine (0.3g, 2 mmol) and a few drops of pyridine were added and refluxed for 5 hour on water bath. The reaction mixture was poured into crushed ice, and neutralized with 1:1 HCl filtered, dried, and purified on silica gel column using

petroleum ether – methanol 95:5, as eluent yielded brown yellow colored compound. The obtained products **6a–e** were recrystallised from absolute Methanol.

3-(6'-amido Indazolo) quinoline-2-[1*H*]-one (6a).
Yield 51%; yellow brown solid; m.p 280-288^{0}C; IR (KBr) ν_{max}/cm^{-1}: 3353,3200, 3196 (NH),1691, 1639(C=O); ^{1}H NMR (DMSO-*d6*) δ, ppm 11.00(1H, s, NH), 10.43(1H, s, NH), 8.27 (1H, s, C7-H), 7.76-7.95 (5H, m, C4,C5,C6,C,7 &C8-H), 8.14(1H, d, C4'-H ,*J*=8.00 Hz,), 9.01 (1H, d, C5'-H *J*=8.00 Hz, ArH), 9.21(1H, s, C3-H); ESI-MS [Found: m/z 304.14 (M+ H)$^+$; calcd for $C_{17}H_{12}N_4O_2$: M+H, 304.30]. Found: 409.0862; Anal. Calcd for $C_{17}H_{12}N_4O_2$: C, 67.10; H, 3.97; N, 18.41. Found: C, 67.44; H, 4.03; N, 18.54.

6-Methyl-3-(6'-amido Indazolo) quinoline-2-[1*H*]-one (6b).
Yield 62%; brown yellow solid; m.p 275-282^{0}C; IR (KBr) ν_{max}/cm^{-1}: 3353,3210, 2919 (NH),1691, 1664(C=O); ^{1}H NMR (DMSO-d_6); δ, ppm 1.80(3H,s, CH_3),14.40(1H, s,NH), 11.86(1H, s,NH), 9.85(1H, s, C4-H), 8.80 (1H, d,C5'-H,*J*=8.00 Hz), 8.29(1H, s,C7'-H), 8.22(1H, d, C4'-H *J*=8.8 Hz), 7.63(1H, s,1H,C3'-H), 7.61(1H, d, C7-H, *J*=7.2 Hz), 7.43 (1H, d,C8-H, *J*=8.00 Hz), 7.34(1H, s,C6-H); ESI-MS [Found: m/z 318.01 (M+ H)$^+$, calcd for $C_{18}H_{14}N_4O_2$: M+H, 318.33]; Anal. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60. Found: C, 68.04; H, 4.53; N, 17.35.

6-Methoxy-3-(6'-amido Indazolo) quinoline-2-[1*H*]-one (6c).
Yield 57%; light yellow brown solid; m.p >315^{0}C; IR (KBr) ν_{max}/cm^{-1}: 3344, 3237, 3053 (NH),1691, 1639(C=O); ^{1}H NMR(DMSO-d_6) δ, ppm 3.94(3H, s, OCH_3),10.90(1H,s,NH), 11.22(1H,s, 3H, NH), 6.72-8.38(8H, m,C4,C5,C6,C8,C3',C4',C5',C7'-H); ESI-MS [Found: m/z 334.98 (M+ H)$^+$, calcd for $C_{18}H_{14}N_4O_3$:M+H, 334.33]; Anal. Calcd for $C_{18}H_{14}N_4O_3$: C, 64.66; H, 4.22; N, 16.76. Found: C, 64.95; H,4.33; N, 16.98

7- Methyl -3-(6'-amido Indazolo) quinoline-2-[1*H*]-one (6d).
Yield 60%; yellow solid; m.p 292-310^{0}C; IR (KBr) ν_{max}/cm^{-1}: 3353,3200, (NH),1691, 1639(C=O); ^{1}H NMR (DMSO-d_6) δ, ppm 2.5(3H, s, CH_3),13.00(1H, s, NH), 11.43(1H, s, NH), 7.76-8.95 (5H,m, C4,C5,C6,C8 and Indazolo NH), 8.14(1H, d, C4-H, *J*=8.00 Hz), 9.01 (1H, d, C5-H, *J*=8.00 Hz), 9.21(1H,s,C7'H); ESI-MS [Found: m/z 318.01 (M+ H)$^+$, calcd for $C_{18}H_{14}N_4O_2$: M+H, 318.33]; Anal. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60. Found: C, 68.10; H, 4.38; N, 17.52.

8-Methyl -3-(6'-amido Indazolo) quinoline-2-[1*H*]-one (6e).
Yield 65%; yellow solid; m.p 293-308^{0}C; IR (KBr) ν_{max}/cm^{-1}: 3353, 3200, 3057 (NH), 1691, 1661(C=O); ^{1}H NMR (DMSO-d_6) δ,ppm 2.71(3H, s, CH_3), 12.00(s, 1H, NH), 10.43(s, 1H, NH), 6.92-8.38(8H, m, C3',C4',C5',C7',and C4,C5,C6,C7-H), 9.31(1H,s, Indazolo NH); ESI-MS [Found: m/z 318.38 (M+ H)$^+$, calcd for $C_{18}H_{14}N_4O_2$: M+H, 318.33]; Anal. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.91; H,4.43;N, 17.60. Found: C, 68.04; H, 4.53; N, 17.35.

General procedure for synthesis of benzo [*b*]-1*H*- indazolo[6,7-*h*][1,6]naphthyridin-7-[6*H*]-ones (7a-e)
3-(6'-amido indazolo quinoline-2[1*H*]-ones **6a–e** (0.5g, 1 mmol) was heated in polyphosphoric acid (prepared by mixing P_2O_5 6 g and H_3PO_4 3 mL) at 150°C for 5 hours. After the completion of the reaction, the reaction mixture was poured into crushed ice, filtered, and purified on silica gel column using ethyl acetate: methanol (85:15) as eluent. The products **7a–e** were recrystallised from absolute ethanol.

Benzo [*b*]-1*H*- indazolo[6,7-*h*][1,6]naphthyridin-7-[6*H*]-one (7a).
Yield 63%; light brown solid; m.p 195-203^{0}C; IR (KBr) ν_{max}/cm^{-1}: 3174, 3200 (NH), 1736 (C=O); ^{1}H NMR (DMSO-d_6) δ, ppm 12.47(s, 1H, NH), 7.55-7.70(6H,m, C8,C9,C10,C11,C12-H and Indazolo NH), 7.50 (1H, d, C5-H, *J*=8.8 Hz), 7.43(1H, d, C4-H, *J*=7.6 Hz), 7.02 (1H, s, C3-H); ESI-MS [Found: m/z 286.03 (M+ H)$^+$, calcd for $C_{17}H_{10}N_4O$:M+H, 286.29]; Anal. Calcd for $C_{17}H_{10}N_4O$: C, 71.32; H, 3.52; N, 19.57. Found: C, 71.65; H, 3.78; N, 17.89.

10-Methyl benzo[*b*]-1*H*- indazolo[6,7-*h*][1,6]naphthyridin-7-[6*H*]-one (7b).
Yield 78%; brown solid; m.p 225-231^{0}C; IR (KBr) ν_{max}/cm^{-1}: 3178,3210 (NH),1724(C=O); ^{1}H NMR ($CDCl_3$) δ, ppm 2.67(3H, s, CH_3), 10.8(1H,s, 1H), 9.17(1H,s,C8-H), 9.06(1H, s,C9-H), 8.31(1H, d, C12-H, *J*=9.00 Hz), 8.00(1H, d, C5-H, *J*=8.5 Hz), 7.94(1H, s, C3-H), 7.84 (1H, dd,C11-H, *J*=8.5 Hz), 7.67(1H, dd, C4-H, *J*=8.5 Hz); ESI-MS [Found: m/z 299.95(M+ H)$^+$, calcd for $C_{18}H_{12}N_4O$: M+H, 300.31]; Anal. Calcd for $C_{18}H_{12}N_4O$: C, 71.99; H, 4.03; N, 18.66. Found: C, 71.90; H, 3.95; N, 18.59.

10-Methoxy benzo[*b*]-1*H*- indazolo[6,7-*h*][1,6]naphthyridin-7-[6*H*]-one (7c).
Yield 59%; dark brown solid; mp252-261^{0}C. IR (KBr) ν_{max}/cm^{-1}: 3179,3200 (NH),1724(C=O); ^{1}H NMR (DMSO-d_6) δ, ppm 3.97(3H, s, OCH_3), 11.96(1H, s, NH), 8.32(1H, s,C8-H), 7.91(1H, dd, C11-H, *J*=9.2 Hz), 7.71(1H, d, C12-H, *J*=8.8 Hz), 7.67(1H, s, C3-H), 7.25-7.33 (2H, m, C4,C5-H), 6.56(1H, s,C9-H); ESI-MS [Found: m/z 316.04 (M+ H)$^+$, calcd for $C_{18}H_{12}N_4O_2$: M+H, 316.31]; Anal. Calcd for $C_{18}H_{12}N_4O_2$: C, 72.72; H, 4.07; N, 7.07. Found: C, 73.00; H, 4.33; N, 7.35. C, 68.35; H, 3.82; N, 17.71; O, 10.12

11-Methyl benzo[*b*]-1*H*- indazolo[6,7-*h*][1,6]naphthyridin-7-[6*H*]-one (7d).
Yield 72%; brown solid; mp230-231^{0}C. IR (KBr) ν_{max}/cm^{-1}: 3167,3215 (NH),1723(C=O); ^{1}H NMR ($CDCl_3$) δ, ppm 2.62(3H, s, CH_3), 10.03(1H, s, NH), 9.99(1H, s, NH), 9.26(1H, s,C8-H), 8.76 (1H, s, C12-H), 8.20(1H,d, C5-H, *J*=8.5 Hz), 7.83(1H,s, C3-H), 7.76 (1H, d, C4-H, *J*=8.5 Hz,), 7.40(1H, d, C9-H, *J*=8.0 Hz), 7.23 (1H, t,C10-H, *J*=8.00 Hz); ESI-MS [Found: m/z 300.06 (M+ H)$^+$, calcd for $C_{18}H_{12}N_4O$: M+H, 300.31]; Anal. Calcd for $C_{18}H_{12}N_4O$: C, 72.72; H, 4.07; N, 7.07. Found: C, 73.00; H, 4.33; N, 7.35.

12-Methyl benzo[*b*]-1*H*- indazolo[6,7-*h*][1,6]naphthyridin-7-[6*H*]-one (7e).
Yield 76%; brown solid; mp220-225^{0}C. IR (KBr) ν_{max}/cm^{-1}: 3174,3200 (NH),1736(C=O); ^{1}H NMR ($CDCl_3$) δ, ppm 2.7(3H,s, CH_3), 10.03(1H, s, NH), 9.99(1H, s, NH), 9.26(1H, s,C8-H), 8.76 (1H, s, C4-H), 8.20(1H, d, C5-H, *J*=8.5 Hz), 7.83(1H, s, C4-H), 7.76 (1H,d, C9-H, *J*=8.5 Hz,), 7.40(1H, t, C10-H, *J*=8.0 Hz), 7.23 (1H, d,C11-H, *J*=8.00 Hz); ESI-MS [Found: m/z 300.71 (M+ H)$^+$ calcd for $C_{18}H_{12}N_4O$: M+H, 300.31]; Anal. Calcd for $C_{18}H_{12}N_4O$: C,72.72; H,4.07; N, 7.07. Found: C, 73.00; H, 4.33; N, 7.35.

RESULTS AND DISCUSSION

Synthesis of benzo [*b*] Indazolo[6,7-*h*][1,6] naphthyridine 7-[*6H*]-ones (9a-e)
The 2-oxoquinoline-3-carbonyl chlorides **5a–e** which was synthesized from 2-chloroquinoline-3-carbaldehydes **4a-e** was reported previously [10-13]. The acid chlorides **5a** were reacted with1*H*- Indazole-6-amine in dry benzene containing a catalytic amount of pyridine under refluxed for 5 hours. After the completion of reaction as indicated by TLC spot change, the reaction mixture was poured into crushed ice, and neutralized with 1:1 HCl then filtered, dried and chromatographed over silica gel using ethyl acetate-methanol (95:5) (v/v) as eluent which yielded yellow brown colored compound. In this reaction 3-(6'-amido-1'*H*-indazolo) quinoline -

2-[*1H*]-one **6a** were obtained in good yield 51%. The structure of compounds **6a** was assigned using spectroscopy and analytical methods. For instance IR spectrum of compound **6a** showed two pairs of amide carbonyl group (NH–C=O) stretching at 1691 and 1639 cm–1 and amino group at 3353 and 3196 cm–1. The ^{1}H NMR spectrum showed the peculiar C7-H appeared as a singlet at δ 8.27. All the other 8 aromatic protons appeared at δ 7.76–9.21 while two broad singlets integrated at δ 10.43 and δ 11.00 and were assigned quinoline NH and another one out of NH proton. And its mass spectrum showed the molecular ion peak at m/z 304.14. From these details, the structure of the compound was confirmed as 3-(6'-amido -1'*H*-Indazolo) quinoline-2[*1H*]-one **6a**. The reaction sequence was extended to other intermediate derivatives **6a-e** To obtain the targeted hetero fused benzo[1,6]naphthyridines **7a** 3-(6'-amido -1'*H*-Indazolo) quinoline-2[*1H*]-one **6a** were heated in polyphosphoric acid at 150°C for 5 hours on heating mantle. After purification on column chromatography over silica gel using petroleum ether: ethyl acetate (85:15) (v/v) as eluent which yielded light brown colored compound. benzo[*b*]-1*H* indazolo[6,7-*h*][1,6]naphthyridine-7[*6H*]-one **7a** were obtained in good yield (63%). The structure of benzo[*b*]-1*H*-indazolo[6,7-*h*][1,6] naphthyridine-7[*6H*]-one **7a** were assigend using specrtoscopic and analytical methods. For instance IR spectrum of compound **7a** showed just one pair of amide carbonyl and amide group (NH-C=O) stretching at 1720 and 3170 cm–1, respectively. The 1H NMR spectrum of compound **7a** still contains a resonance signal of the integral intensity of aromatic signal is reduced to eight, and only one NH group proton signal is present. The disappearance of singlet at δ 8.27 ppm, which correspondence to C7 proton of **6a**, confirm that the cyclisation had occurred, obtained to the expected product **7a**.Therefore, another possible product **8a** was ruled out. Hence, based on the above spectral data, it was confirmed that **7a** was formed by benzo [*b*] Indazolo [6,7-*h*][1,6] naphthyridine 7-[*6H*]-one **7a** yield 43%, mp 195-2030C. Its mass spectrum showed the molecular ion peak at m/z 286.03. The above reaction procedure was extended to the other derivatives of **6a-e & 7a-e Scheme 1.**

CONCLUSION

In summary, we have new reported an efficient synthesis of benzo[*b*]-1*H*-indazolo [6,7-*h*][1,6] naphthyridine-7[*6H*]-ones through the condensation reaction of 2-oxo quinoline 3-carbonyl chlorides and 1*H*- Indazole-6-amine with dry benzene in the presence of pyridine as a catalyst followed by cyclisation and dehydration. The starting materials were prepared from 2-chloro- 3-formylquinolines using Otto-Meth Cohn *et al* procedure. This Efficient method affords the desired products with good yields.

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