

Clean and Efficient Microwave Synthesis of 6, 6'-dimethyl-6, 7-dihydro-1, 8, 9, 14-tetraaza-pentaphene and 3, 3a, 4, 5-tetrahydro-4, 4-dimethyl-3-phenylindolo [5, 4-b] [1, 8] naphthyridin-2-one and derivatives

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ABSTRACT

Reaction of 2-aminopyridine-3-carbaldehyde with 5,5'-Dimethyl-Cyclohexane-1,3-dione afforded 8,8'-dimethyl-8,9-dihydro-7H-benzo[b][1,8]naphthyridin-6-one (1). Friedlander condensation of (1) with 2-aminopyridine-3-carbaldehyde yielded 6,6-dimethyl-6,7-dihydro-1,8,9,14-tetraaza-pentaphene (2), in good yield. Bromination of (1) with one equivalent of N-Bromosuccinamide gave 7-bromo-8, 9-dihydro-8,8-dimethylbenzo[b][1,8]naphthyridin-6(7H)-one(3). The compound (3) on reaction with one equivalent of [(ethoxycarbonyl)-methylene] triphenylphosphorane (aza-Wittig reaction) gave ethyl 2-(7-bromo-8,9-dihydro-8,8-dimethylbenzo[b][1,8]naphthyridin-6(7H)-ylidene)acetate (4). Further the compound (4) on cyclisation with anilines to provide the cyclised compounds, 3,3a,4,5-tetrahydro-4,4-dimethyl-3-phenylindolo[5,4-b][1,8]naphthyridin-2-one (5a-e).

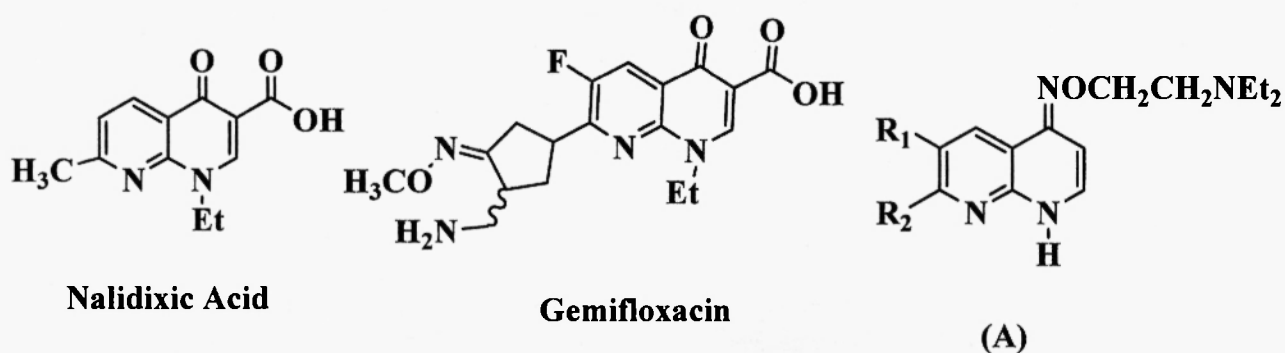
Keywords: 2-aminopyridine-3-carbaldehyde, Ethyl 2-(7-bromo-8,9-dihydro-8,8-dimethylbenzo[b][1,8]naphthyridin-6(7H)-ylidene)acetate, and amide ring cyclisation.

INTRODUCTION

Naphthyridine or Naphthyridone systems are of great importance due to their broad spectrum of Biological activities and pharmaceutical applications, The derivatives of 1,8-naphthyridines, Nalidixic acid became available for use in the United Kingdom for urinary tract infections². In addition, Gemifloxacin is antibacterial³, (E) and (Z)-O-(diethyl amino)ethyl oximes of 1,8-naphthyridine series (A) are potential drugs for local anesthesia⁴, and 1-(2-fluorobenzyl)-3-(2-tolyl)-1,8-naphthyridin- 2(1H)-one is used for the treatment of memory disorders, in particular, Alzheimer's disease⁵. 2-Amino-N-hydroxy-1,8-naphthyridine-3-carboxamide possesses herbicidal properties and used for the selective control of weeds in barley, wheat, maize, sorghum and rice crops⁶, some 3-phenyl-1,8-naphthyridines which carry piperidyl, piperazinyl or morpholinyl groups or an N-diethanolamine side-chain in the 2,7- and 2,7- positions have

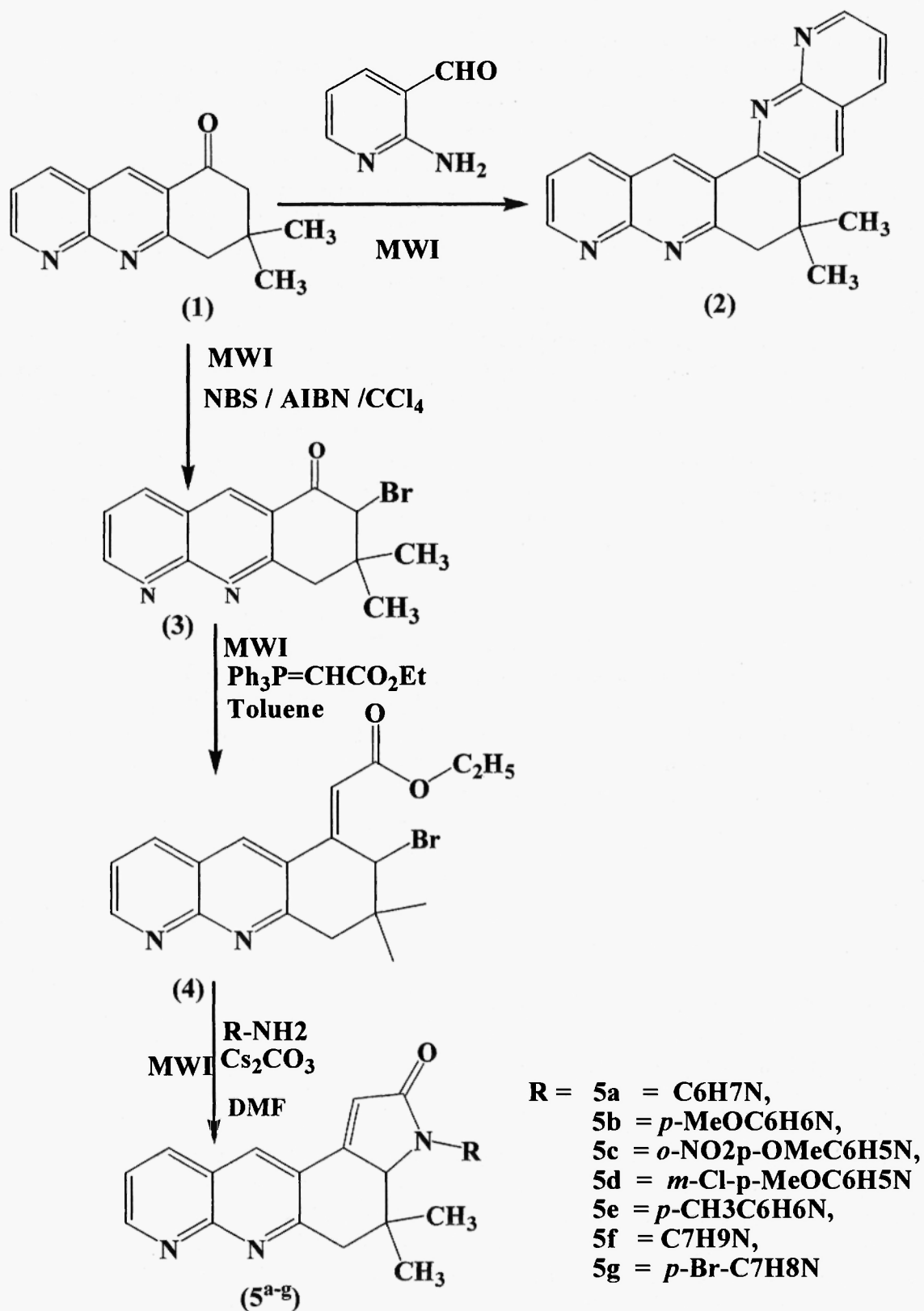
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been reported to show significant activity as inhibitors of human platelets aggregation induced by arachidonate and collagen⁷. In addition, 4-(*N*-methylenecycloalkylamino)-1,8-naphthyridine derivatives substituted in positions 2 and 7 are effective as antihypertensive agents⁸. 7-Amino-2-(4-carbethoxypiperazin-1-yl)-4-phenyl-1,8-naphthyridine has recently been synthesized and reported to have marked activity against *Mycobacterium tuberculosis*⁹. These important biological activities stimulated us to synthesize new derivatives of 1,8-naphthyridines. A survey of the literature shows that the major synthetic approaches that are used to prepare various a types of 1,8-naphthyridine system involves condensation of 2-aminopyridine derivatives with carbonyl compounds containing an activated methylene group¹⁰⁻¹⁶ or with β -ketoesters¹⁷. Another general procedure for the Preparation of 1,8-naphthyridine condensed ethanolic 2-amino-3-formylpyridines, in the presence piperidine base, with active methylene compounds, aldehydes, acyclic and cyclic ketones or diketones¹⁸⁻²⁴. In addition, we report several new heterocyclic compounds.



EXPERIMENTAL SECTION

Our initial strategy targeted compound (3) and its conversion to the corresponding 3,3a,4,5-tetrahydro-4,4-dimethyl-3-phenylindolo[5,4-b][1,8]naphthyridin-2-ones (5a-g). The preparation of the compound (3) was done *via* Aza-Wittig reaction by using one equivalent of [(ethoxycarbonyl)-methylene] triphenylphosphorane²⁴. The compound (2) was accomplished *via* friedlander condensation^{25, 26} by using 2-aminopyridine-3-carbaldehyde and piperidine as a base. Melting points were determined in open capillaries and are uncorrected. IR (KBr) spectra were recorded using a Perkin-Elmer 1600 FTIR spectrophotometer and all values are expressed as ν_{\max} cm⁻¹. ¹H NMR spectra on a Varian 500 MHz and 200 MHz instrument with TMS as internal Standard and chemical shifts are expressed δ ppm, solvent used id DMSO d₆, CDCl₃ and Mass spectrum on a Hewlett Packard mass spectrometer operating at 70eV. Compounds (5a-g) were recrystallised from ethanol.



SCHEME-I

8,9-dihydro-8,8-dimethylbenzo[b][1,8]naphthyridin-6(7H)-one (1) :

To a mixture of 2-amino pyridines-3-carboxaldehyde (1.0g, 8.19 mmole) and 5,5-dimethyl-cyclohexane-1,3-dione (1.37g, 9.83 mmol), was taken in 25 mL erlenmeyer flask, was added piperidine (0.34g, 4.09 mmole) the resulting suspension was subjected to microwave irradiation at 800 W intermittently at 30 secintervals for 5.5 min. The reaction completion was monitored by TLC. The resulting solids were taken in ethyl acetate (20mL) and washed with water (2x10mL), dried over anhydrous Na₂SO₄, evaporated the solvent under reduced pressure, recrystallised in ethanol. to yield cream colour solid (1) (1.6g, 86 %). ¹H NMR (DMSO-d₆, 500MHz) 1.19 (s, 6H), 2.65 (s, 2H), 3.32 (s, 2H), 7.52-7.58 (m, 1H), 8.31-8.36 (d, 1H), 8.82 (s, 1H), 9.21 (s, 1H). ¹³C NMR (500 MHz, DMSO-d₆): 193.57, 162.66, 144.2, 131.77, 131.14, 124.36, 128.64, 53.27, 48.17, 25.24, 23.56; IR(KBr): 1695 cm⁻¹ (CO); MS: m/z (ES), 227 [(M+1)].

6, 6'-Dimethyl-6,7-dihydro-1,8,9,14-tetraazapentaphene (2) :

A solution of 8,8'-Dimethyl-8,9-dihydro-7H-benzo[b][1,8]-naphthyridin-6-one (1) (0.5g, 2.21 mmole) in ethanol (2 mL) was taken in 25 mL erlenmeyer flask, was added 2-Amino pyridines-3-carboxaldehyde (0.26g, 2.21 mmole) and piperidine (0.09g, 1.10 mmole), the resulting suspension was subjected to microwave irradiation at 800 W intermittently at 30 secintervals for 6 min. The completion of reaction was monitored by TLC. after completion of starting material, poured in ice-cold water, the resulting solids were filtered and dried, recrystallised in ethanol. which yield brown colour solid (2) (0.64g, 93 %); ¹H NMR (DMSO-d₆, 500MHz) 1.34 (s, 6H), 3.65 (s, 2H), 7.32-7.36 (m, 2H), 8.32-8.48 (m, 3H), 8.71 (m, 1H), 8.92 (s, 1H), 9.14 (s, 1H). ¹³C NMR (500 MHz, DMSO-d₆): 173.27, 163.36, 154.22, 148.77, 146.14, 141.36, 139.64, 138.53, 48.26, 38.28, 26.29. MS: m/z (ES), 313 [(M+1)].

7-bromo-8,9-dihydro-8,8'-dimethylbenzo[b][1,8]-naphthyridin-6(7H)-one (3) :

To a solution of 8,8'-Dimethyl-8,9-dihydro-7H-benzo[b][1,8] naphthyridin-6-one (1) (0.5g, 2.21 mmole) in CCl₄ (2 ml) was taken in 25 mL Erlenmeyer flask. was added N-Bromosuccinamide (0.58g, 3.31 mmole) and catalytic amount of Aza-Bis isobutyronitrile (AIBN), the resulting solution was subjected to microwave irradiation at 600 W intermittently at 30 secintervals for 4.5 min. reaction completion was monitored by TLC, after completion of starting material, evaporated the carbon tetra chloride completely under reduced pressure, then dissolved in ethyl acetate (10 mL) washed with water twice (2x10 mL), brine (10 mL), dried over anhydrous Na₂SO₄, filtered and evaporated the solvent under reduced pressure. the resulting solids were recrystallised in ethanol. to yield light yellow colored solid (3) (0.61g, 90 %). ¹H NMR (DMSO-d₆, 500MHz) 1.36 (s, 6H), 2.75 (bs, 2H), 4.75 (s, 1H), 7.42-7.48 (m, 1H), 8.32-8.48 (d, 1H), 8.71 (m, 1H), 9.21 (s, 1H). ¹³C NMR (500 MHz, DMSO-d₆): 192.27, 173.36, 144.22, 138.77, 136.14, 133.36, 129.64, 128.53, 49.26, 48.28, 24.29; IR(KBr): 1645 cm⁻¹ (CO); MS: m/z (ES), 307 [(M+2)].

Ethyl 2-(7-bromo-8,9-dihydro-8,8'-dimethylbenzo[b][1,8]-naphthyridin-6(7H)-ylidene) acetate (4):

A solution of 7-bromo-8,9-dihydro-8,8'-dimethylbenzo[b][1,8]naphthyridin-6(7H)-one (3) (0.5g, 1.63 mmole) in Toluene (5 ml) was taken in erlenmeyer flask (25 mL), was added [(ethoxycarbonyl)-methylene]triphenylphosphorane (0.68g, 1.96 mmole), the resulting solution was subjected to microwave irradiation at 900 W intermittently at 30 secintervals for 6.8 min. reaction completion was monitored by TLC, after completion of starting material, evaporated the toluene completely under reduced pressure, then dissolved in ethyl acetate (10 mL) washed with water (2x10 mL), brine (10 mL), dried over anhydrous Na₂SO₄, filtered and evaporated the solvent under reduced pressure. the resulting solids were purified by column chromatography by using 100-200 mesh silica gel, eluted with 2-5% methanol in dichloromethane to yield off-white solid (4) (0.47g, 76 %). ¹H NMR (DMSO-d₆, 500MHz) 1.28 (s, 6H), 1.65 (t, 3H), 2.65 (bs, 2H), 4.25 (s, 1H), 4.65 (q, 2H), 6.45 (s, 1H), 7.32-7.38 (m, 1H), 8.22-8.28 (d, 1H), 8.61 (s, 1H), 9.11 (s, 1H). ¹³C NMR (500 MHz, DMSO-d₆): 183.21, 172.36, 164.22, 162.14, 160.61, 158.77, 146.14, 141.36, 139.64, 138.53, 48.26, 39.28, 26.69; IR(KBr): 1845 cm⁻¹ (CO); MS: m/z (ES), 377 [(M+2)].

3,3a,4,5-tetrahydro-4,4-dimethyl-3-phenylindolo[5,4-b][1,8]-naphthyridin-2-one (5a):

A solution of ethyl 2-(7-bromo-8,9-dihydro-8,8-dimethylbenzo[b][1,8]naphthyridin-6(7H)-ylidene)acetate (**4**) (0.5g, 1.33 mmole) in dimethyl formamide (2 ml) was taken in 25 mL erlenmeyer flask. was added aniline (0.13g, 1.46 mmole), and Cs_2CO_3 (1.3g, 4.05mmol), the resulting suspension was subjected to microwave irradiation at 1000 W intermittently at 30 sec intervals for 15 min. The reaction completion was monitored by TLC, poured in ice-cold water (10 mL), extracted with ethyl acetate, dried over anhydrous Na_2SO_4 , filtered and evaporated the solvent under reduced pressure. the resulting crude compound was purified by column chromatography by using 100-200 mesh silica gel, eluted with 2-5% methanol in dichloromethane to yield off-white solid (**2^a**) (0.32g, 70 %). ^1H NMR (DMSO- d_6 , 500MHz) 1.35 (s, 6H), 2.65 (bs, 2H), 4.33 (s, 1H), 6.25 (s, 1H), 6.65-6.69 (m, 1H) 7.32-7.38 (m, 2H), 7.42-7.48 (m, 1H), 7.52-7.56 (m, 2H), 8.36-8.39 (m, 2H), 9.24 (s, 1H). ^{13}C NMR (500 MHz, DMSO- d_6): 171.17, 168.36, 164.36, 163.16, 152.22, 149.77, 148.14, 147.36, 145.64, 139.53, 108.36, 78.26, 49.26, 39.28, 23.29; IR(KBr): 1885 cm^{-1} (CO); MS: m/z (ES), 342 [(M+1)].

Using a similar methodology the following derivatives were prepared:

3,3a,4,5-Tetrahydro-3-(4-methoxyphenyl)-4,4-dimethylindolo[5,4-b][1,8]-naphthyridin-2-one (5b):

Off-White solid, yield: 66 %. ^1H NMR (DMSO- d_6 , 500MHz) 1.28 (s, 6H), 2.65 (bs, 2H), 4.32 (s, 1H), 6.55-6.59 (m, 3H) 7.32-7.38 (m, 3H), 7.82-7.88 (m, 2H), 9.28 (s, 1H). ^{13}C NMR (500 MHz, DMSO- d_6): 171.17, 168.36, 164.36, 163.16, 152.22, 149.77, 148.14, 147.36, 145.64, 139.53, 108.36, 78.26, 49.26, 39.28, 23.29; IR (KBr): 1885 cm^{-1} (CO); MS: m/z (ES), 372 [(M+1)].

3,3a,4,5-Tetrahydro-3-(4-methoxy-2-nitrophenyl)-4,4-dimethylindolo[5,4-b][1,8]-naphthyridin-2-one (5c):

Off-White solid, yield: 72 %. ^1H NMR (DMSO- d_6 , 500MHz) 1.35 (s, 6H), 2.62 (bs, 2H), 4.13 (s, 1H), 4.33 (s, 3H), 6.25 (s, 1H), 6.65-6.69 (m, 1H) 7.32-7.38 (m, 2H), 7.42-7.48 (m, 1H), 7.52-7.56 (m, 2H), 8.36-8.39 (m, 2H), 9.24 (s, 1H). ^{13}C NMR (500 MHz, DMSO- d_6): 178.47, 174.36, 164.86, 163.96, 155.22, 148.77, 147.14, 146.36, 144.64, 138.53, 109.36, 79.26, 50.26, 49.28, 22.29; IR (KBr): 1895 cm^{-1} (CO); MS: m/z (ES), 342 [(M+1)].

3-(3-Chloro-4-methoxyphenyl)-3,3a,4,5-tetrahydro-4,4-dimethylindolo[5,4-b][1,8]-naphthyridin-2-one (5d):

Off-White solid, (**5^d**), yield: 75 %. ^1H NMR (DMSO- d_6 , 500MHz) 1.25 (s, 6H), 2.45 (bs, 2H), 4.13 (s, 1H), 4.33 (s, 3H), 6.35 (s, 1H), 6.62-6.64 (m, 1H) 7.38-7.42 (m, 2H), 7.52-7.58 (m, 1H), 7.62-7.66 (m, 2H), 8.36-8.39 (m, 2H), 9.34 (s, 1H). ^{13}C NMR (500 MHz, DMSO- d_6): 179.17, 178.36, 174.36, 163.16, 152.22, 149.77, 148.14, 147.36, 144.64, 141.53, 109.36, 88.26, 49.26, 38.28, 26.29; IR(KBr): 1865 cm^{-1} (CO); MS: m/z (ES), 406 [(M+1)].

3,3a,4,5-Tetrahydro-4,4-dimethyl-3-p-tolyindolo[5,4-b][1,8]-naphthyridin-2-one(5e):

Off-White solid, yield: 85 %. ^1H NMR (DMSO- d_6 , 500MHz) 1.28 (s, 6H), 2.48 (bs, 2H), 4.13 (s, 1H), 4.33 (s, 3H), 6.35 (s, 1H), 6.62-6.64 (m, 1H) 7.38-7.42 (m, 2H), 7.52-7.58 (m, 1H), 7.62-7.66 (m, 2H), 8.36-8.39 (m, 2H), 9.34 (s, 1H). ^{13}C NMR (500 MHz, DMSO- d_6): 179.17, 178.36, 174.36, 163.16, 152.22, 149.77, 148.14, 147.36, 144.64, 141.53, 109.36, 88.26, 49.26, 38.28, 26.29; IR(KBr): 1895 cm^{-1} (CO); MS: m/z (ES), 356 [(M+1)].


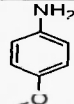
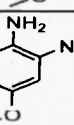
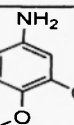
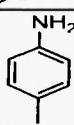
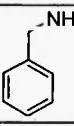
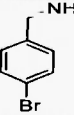
3-Benzyl-3,3a,4,5-tetrahydro-4,4-dimethylindolo[5,4-b][1,8]-naphthyridin-2-one(5f):

Off-White solid, yield: 81 %. ^1H NMR (DMSO- d_6 , 500MHz) 1.28 (s, 6H), 2.48 (bs, 2H), 4.13 (s, 1H), 4.63 (bs, 2H), 6.55 (s, 1H), 6.65-6.68 (m, 1H) 7.34-7.39 (m, 2H), 7.52-7.58 (m, 1H), 7.62-7.66 (m, 2H), 8.36-8.39 (m, 2H), 9.34 (s, 1H). ^{13}C NMR (500 MHz, DMSO- d_6): 179.17, 178.36, 174.36, 163.16, 152.22, 149.77, 148.14, 147.36, 144.64, 141.53, 109.36, 88.26, 49.26, 38.28, 26.29; IR(KBr): 1845 cm^{-1} (CO); MS: m/z (ES), 356 [(M+1)].

3-(4-Bromobenzyl)-3,3a,4,5-tetrahydro-4,4-dimethylindolo[5,4-b][1,8]- naphthyridin-2-one (5g):

Off-White solid, yield: 68 %. ¹H NMR (DMSO-d₆, 500MHz) 1.28 (s, 6H), 2.48 (bs, 2H), 4.23 (s, 1H), 4.73 (bs, 2H), 6.55 (s, 1H), 6.65-6.68 (m, 1H) 7.34-7.39 (m, 2H), 7.52-7.58 (m, 1H), 7.42-7.46 (m, 2H), 8.26-8.29 (m, 2H), 9.14 (s, 1H). ¹³C NMR (500 MHz, DMSO-d₆): 179.17, 178.36, 174.36, 163.16, 152.22, 149.77, 148.14, 147.36, 144.64, 141.53, 109.36, 88.26, 49.26, 38.28, 26.29; IR(KBr): 1845 cm⁻¹ (CO); MS: m/z (ES), 334 [(M+1)].

Characterization Table

S. No.	Compd	R	R1	Micro wave heating (Min)	M.Formula	Yield (%)	Melting Points	Found (%) (Calcd)		
								C	H	N
1	1	----	----	5.5	C ₁₄ H ₁₄ N ₂ O	86	244-246	74.31 74.12	6.24 6.01	12.38 12.18
2	2	----	----	6	C ₁₁ H ₁₀ N ₂ O ₂	93	262-264	65.34 64.14	4.98 3.98	13.85 12.35
3	3	----	----	4.5	C ₁₄ H ₁₃ BrN ₂ O	90	225-227	55.10 54.80	4.29 4.19	9.18 9.01
4	4	----	----	10	C ₁₈ H ₁₉ BrN ₂ O ₂	76	232-234	57.61 57.21	5.10 4.80	7.47 7.12
5	5a		----	10	C ₂₂ H ₁₉ N ₃ O	70	246-248	77.40 76.40	5.61 5.11	12.31 12.21
6	5b		----	06	C ₂₃ H ₂₁ N ₃ O ₂	62	272-274	74.37 73.13	5.70 5.24	11.31 10.13
7	5c		----	05	C ₂₃ H ₂₀ N ₄ O ₄	72	262-264	66.34 65.24	4.84 4.34	13.45 13.25
8	5d		----	10	C ₂₃ H ₂₀ ClN ₃ O ₂	75	225-227	68.06 67.36	4.97 3.97	10.35 10.12
9	5e		----	08	C ₂₃ H ₂₁ N ₃ O	85	232-234	77.72 77.22	5.96 5.36	11.82 10.89
10	5f		----	05	C ₂₃ H ₂₁ N ₃ O	81	246-248	77.72 76.62	5.96 5.76	11.82 11.22
11	5g		----	04	C ₂₃ H ₂₀ BrN ₃ O	68	272-274	63.60 63.20	4.64 4.24	9.67 9.37

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