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Journal of Chemical and Pharmaceutical Research, 2012, 4(7):3562-3567

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of spiro-pyrimido [4,5-b]quinoline and study of their antimicrobial activities

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ABSTRACT

Spiro-pyrimido [4,5-b]quinoline was synthesized by condensation of 2-aminoquinoline-3-carboxamide with cyclic ketone in presence of zinc chloride and studied for their biological activity.

Keywords: spiro-pyrimido [4,5-b]quinoline, Lewis acid, antibacterial activity and antifungal activity, MIC

INTRODUCTION

Quinoline derivatives represent the major class of heterocycles and a number of preparations have been known since the late 1800s. The quinoline ring system occurs in various natural products, especially in alkaloids. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties. In 1820, quinine was isolated as the active ingredient from the bark of cinchona tree and successively replaced the crude bark for the treatment of malaria. In addition to the pyrimidine containing molecules are paramount importance in nucleic acid chemistry. Their derivatives including uracil, cytosine, adenine, and guanine are fundamental building blocks for DNA and RNA. The fused quinoline with pyrimidine ring would exhibit some interesting pharmacological activities. The especially the pyrimido [4,5-b]quinoline derivatives describe for potential use pharmacological activities such as anticancer [1-2], anti-inflammatories [3], antiallergics [4] and antimicrobials [5-8].

Spiro cyclic systems containing one carbon atom common to two rings are structurally interesting [9]. The asymmetric characteristic of the molecules due to the chiral spiro carbon is one of the important criteria of the biological activities. The presence of a sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds [10]. Spiro compounds represent an important class of naturally occurring substances and their characteristic is the highly pronounced biological properties [11-12]. Especially spiroquinazolinones have been reported to possess pharmaceutical activities such as potent inhibitor of inosine 5'-monophosphate dehydrogenase type II [13], nitric oxide synthase inhibitor [14], antiamebic activity [15], the plant-growth regulator agent [16].

In literature spiro-heterocyclic quinazolin-4-(1H)-one derivatives have been synthesized by condensation of 2-aminobenzamide with aromatic aldehyde or ketones using catalyst NH_4Cl, $AlCl_3$, $ZnCl_2$, PTSA, HCl, iodine and asymmetric Bronsted acid. [17-21]. These literature reports and our interest in spiro compounds encouraged us to synthesis of spiro pyrimido quinoline

EXPERIMENTAL SECTION

General

Melting points were determined on a Barnstead Electro Thermal melting point apparatus, Mod. No. IA-9200 inopen capillary tubes. The 1H NMR (400 MHz) and 13C NMR (100 MHz) spectra were recorded on Varian XL-300spectrometer. Chemical shifts were reported in ppm from internal tetramethylsilane standard and are given δ-units. The solvent for NMR spectra was deutero-chloroform otherwise stated. Infrared spectra were taken on Shimadzu IR-408, instrument in potassium bromide pellets unless otherwise stated. Elemental analyses were performed on a Hosli CH-Analyzer and are within ±0.3 of the theoretical percentage. High-resolution mass spectra were obtained with a Mat 112 Varian Mat Bremen (70 eV) mass spectrometer. Column chromatography was carried out on silica gel (S.D. Fine Chemicals, 60–80 mesh). Solutions were concentrated in a rotary evaporator under reduced pressure.

General procedure for the synthesis of spiro-pyrimido [4,5-b]quinoline(3a-3i)

To a solution of DMF (10 mL) and $ZnCl_2$ (100 mmol) were added substituted 2-aminocarboxamide (100 mol) and cyclic ketone (150 m mol). The mixture was heated at reflux for 3–4 h. After completion of the reaction as indicated by the TLC (eluent: ethyl acetate: n-hexane 9:1), the cooled reaction mixture was quenched in to water (50 mL) and the precipitate was separated by filtration. After filtration the crude product was purified by recrystallization from ethanol.

1'H-spiro[cyclohexane-1,2'-pyrimido[4,5-b]quinolin]-4'(3'H)-one (3a): Yield: 2.08 g (66%) mp 234-236°C pale yellow solid, IR(KBr): 3265 m, 3196 m, 2933 s,1649 s,1608 s, 1502 m, 1438 m, 804 m, 759 m cm-$^{1.}$ ^{1}H NMR (400 MHz): δ 1.42 (m, 2H), 1.55 (m, 4H), 1.82 (m, 4H), 5.95 (s, 1H), 7.26 (m, 1H), 7.62 (m, 3H), 7.78 (s, 1H), 8.75 (s, 1H); ^{13}C NMR (100 MHz): δ 21.46, 24.40, 39.58, 68.55, 122.0, 124.40, 125.85, 128.68, 132.08, 138.95, 149.50, 154.60, 163.80. mass m/z: 267.14 (100.0%), 268.14 (17.5%), *Anal*. Calcd. for $C_{16}H_{17}N_3O$ C, 71.89; H, 6.41; N, 15.72; Found: C,71.68, H, 6.59, N, 15.51.

4-methyl-1'H-spiro[cyclohexane-1,2'-pyrimido[4,5-b]quinolin]-4'(3'H)-one (3b): Yield: 2.11 g (64%) mp 244-246°C; pale yellow solid; IR(KBr): 3224m , 2923m , 2846m , 1705s , 1649s ,1504m ,1454m , 815m ,680m cm-$^{1.}$ ^{1}H NMR (400 MHz): δ 0.96 (d, 3H, CH_3), 1.52 (m, 4H), 1.61(m, 1H), 1.70 (m, 4H), 5.28 (s, 1H, N-H), 7.37 (m, 1H), 7.69 (m, 1H), 7.75 (d, 1H), 7.94 (d, 1H), 8.01(s, 1H, N-H), 8.75 (s, 1H). ^{13}C NMR (100 MHz): δ 20.22, 25.91 (2C), 31.32 (2C), 32.98, 85.21, 120.28, 125.40, 122.68, 123.42, 128.12, 131.34, 137.56, 146.64, 154.48, 164.58; MS (EI): m/z= 281.15 (100 %), 283.1 (1.8 %), *Anal*. Calcd. for $C_{17}H_{19}N_3O$ C, 72.57; H, 6.81; N, 14.94; Found: C,72.40,H ,6.68,N,14.72.

3-methyl-1'H-spiro[cyclohexane-1,2'-pyrimido[4,5-b]quinolin]-4'(3'H)-one (3c):Yield: 2.25 g (68 %); Yellow solid; mp 222-226°C ; IR(KBr) : 3259 m , 3219 m , 2943 m , 1645 s , 1610s , 1500 m , 1429 m , 800m , 761 m cm -$^{1.}$ ^{1}H NMR (400 MHz): δ 0.98 (d, 3H, CH_3), 1.22 (q, 1H), 1.60-1.98 (m, 6H), 2.22 (m, 2H), 2.98 (br s- 1H), 6.78 (s, 1H), 7.55 (m, 1H), 7.68 (t, 1H), 7.78 (t, 1H), 8.80 (s, 1H); ^{13}C NMR (100 MHz): δ 20.72, 22.71, 29.45, 34.89, 37.15, 43.12, 120.24, 122.95, 123.45, 125.32, 131.67, 128.21, 131.34, 137.62, 146.65, 155.42, and 164.8 *Anal*. Calcd. for $C_{17}H_{19}N_3O$ C, 72.57; H, 6.81; N, 14.94; Found: C, 72.28, H, 6.68, N, 14.72 .

2-methyl-1'H-spiro[cyclohexane-1,2'-pyrimido[4,5-b]quinolin]-4'(3'H)-one (3d): Yield: 2.05 g, mp 232-236°C; Pale yellow solid ; IR(KBr) : 3240 m , 3213 m , 2922 m, 1701 s , 1647 s , 1512 m , 1454 m , 771 m , 684 m cm-$^{1.}$ ^{1}H NMR (400 MHz): δ 0.96 (d, 3H, CH_3), 1.60-1.90 (m, 8H), 2.20 (m, 1H), 2.98 (s, 1H), 6.33 (s, 1H, NH), 7.60 (m, 1H), 7.80 (m, 2H), 8.68 (s, 1H); ^{13}C NMR (100 MHz): 20.27, 22.07, 26.87, 33.30, 37.88, 47.16, 68.22, 112.59, 122.41, 123.13, 125.15, 129.37, 131.41, 137.00, 149.84, 155.34, 161.81. *Anal*. Calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.94; Found : C, 72.79; H, 6.99; N, 15.12 .

***3,3,5-trimethyl-1'H-spiro[cyclohexane-1,2'-pyrimido[4,5-b]quinolin]-4'(3'H)-one (3e)*:** Yield: 2.58 g (71%); 242-244°C; Pale yellow solid ; IR (KBr) : 3254 m , 3208 m , 2927 m , 1632 s , 1608 s ,1492 m , 1450 m , 768 m , 680 m cm-^{1} . ^{1}H NMR (400 MHz): δ 0.87 (m, 1H), 0.72 (s, 2H), 1.80 (m, 2H), 2.20 (m, 1H), 7.24 (m, 1H), 7.27 (m, 1H), 7.52-7.63 (m, 2H), 7.84 (d, 1H), 8.48 (s, 1H), 8.01(s, 1H) ; ^{13}C NMR (100 MHz): 22.18, 23.17, 26.06, 31.25, 33.69, 44.52, 46.81, 51.54, 68.0, 112.99, 122.48, 123.24, 125.22, 129.36, 131.40, 136.99, 149.67, 155.94, 161.66. mass m/z: 309.41, (100.0%), 310.19 (20.9%), *Anal*. Calcd. for: $C_{19}H_{23}N_3O$: C, 73.76; H, 7.49; N, 13.58; Found : C, 73.52, H, 7.68; N, 13.36.

1'H-spiro[cyclopentane-1,2'-pyrimido[4,5-b]quinolin]-4'(3'H)-one (3f): Yield: 2.17g (73%); mp 228-232 °C; Pale yellow solid ; IR (KBr) : 3258 m , 3212 m , 2932 m , 1634 s , 1604 s , 1490 m , 1454 m , 772 m , 686 m cm-^{1} . ^{1}H NMR (400 MHz): δ 1.68 (q, 4H), 1.8 (q, 4H), 7.22 (m, 1H), 7.53 (m, 1H, *J* = 8.4Hz), 7.53 (m, 1H, J = 8.4 Hz), 7.83

(d, 1H, *J* = 8.4 Hz, 7.95 (s, 1H, N-H), 8.51 (s, 1H), 8.67 (s, 1H); ^{13}C NMR (100 MHz): δ 22.59, 76.95, 112.83, 123.20, 123.50, 125.61, 125.87, 132.28, 137.76, 149.56, 155.70, 158.20, 162.59; mass m/z 254.3 (m^{+1}), 276.2(m^{+Na}). *Anal*. Calcd. for: $C_{15}H_{15}N_3O$ C, 71.13; H, 5.97; N, 16.59; Found :C, 71.38; H, 5.72; N, 16.31.

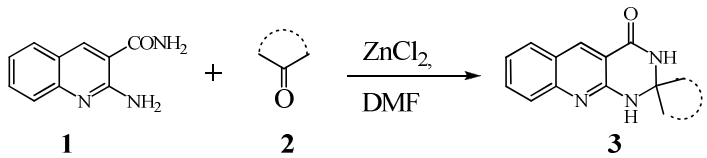
2,3-dihydro-1'H-spiro[indene-1,2'-pyrimido[4,5-b]quinolin]-4'(3'H)-one (3g):Yield: 2.41 g (64%); mp 230-234°C; Pale yellow solid ; IR (KBr) : 3192 m , 3055 m , 2935 m , 1674 s , 1616 s , 1504 m , 1437 m , 798 m , 758 m cm-^{1} . ^{1}H NMR (400 MHz): 2.45 (m, 2H), 3.1 (m, 2H), 6.24 (s, 1H, N-H), 7.24 (m, 2H), 7.4 (m, 2H), 7.6 (m, 2H), 7.62 (m, 2H), 7.81 (s, 1H), 8.80 (s, 1H); ^{13}C NMR (100 MHz): δ 23.00, 38.52, 90.00, 120.32, 121.89, 122.98, 125.25, 126.17 (2C), 128.14, 128.29 (2C), 131.23, 137.54, 138.64, 143.67, 146.73, 154.34, 164.82. *Anal*. Calcd. for: $C_{20}H_{17}N_3O_2$ C, 75.73; H, 5.02; N, 13.94; Found :$C_{20}H_{17}N_3O_2$ C, 75.96; H, 5.30; N, 14.08.

7-methoxy-3,4-dihydro-1'H,2H-spiro[naphthalene-1,2'-pyrimido[4,5-b]quinolin]-4'(3'H)-one (3h): Yield: 2.5 g (64%); mp 265-267°C; Pale yellow solid ; IR (KBr) : 3188 m , 3048 m , 2934 m , 1668s , 1608 s , 1528 m , 1432 m , 778 m , 748 m cm-^{1} . ^{1}H NMR (400 MHz): δ 1.82 (m, 2H, 2.14 (m, 2H), 2.62 (m, 2H), 3.68 (s, 3H, OCH_3), 6.80 (m, 1H), 7.12 (m, 2H), 7.31 (m,1H), 7.61 (m, 1H), 7.71(m, 1H), 7.80 (s, 1H, N-H), 8.12 (m, 1H), 8.78 (s, 1H), 9.12 (s, 1H, CO-NH), ^{13}C NMR (100 MHz): δ 12.82, 29.53, 45.89, 55.87, 82.78, 111.29, 112.22, 120.24, 122.75, 122.95, 124.98, 127.84, 128.11, 129.00, 131.30, 131.32, 137.56, 140.22, 146.45, 157.56, 158.22, 164.45. mass m/z=346.3 (m^{+1}). *Anal*. Calcd. for: $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17; Found; C, 73.28; H, 5.27; N, 12.32.

5-methoxy-3,4-dihydro-1'H,2H-spiro[naphthalene-1,2'-pyrimido[4,5-b]quinolin]-4'(3'H)-one (3i): Yield: 2.4 g (62%) mp 260-262°C; Pale yellow solid ; IR (KBr) : 3198 m , 3068 m , 2938 m ,1672s, 1614 s , 1532 m , 1442 m , 782 m , 752 m cm-^{1} . ^{1}H NMR (400 MHz): δ 1.92 (t, *J* = 7.6, 7.2 Hz, 2H), 2.19 (d, 8.4 Hz, 2H), 2.69 (t, *J* = 7.6, 7.2 Hz), 3.69 (s, 3H),.89 (m, 1H), 7.10 (m, 2H), 7.37 (m, 1H), 7.63 (m, 2H), 7.89 (s, 1H), 8.01 (d, *J* = 10 Hz 1H), 8.81 (s, 1H), 9.08 (s, 1H). ^{13}C NMR (100 MHz): 18.10, 27.78, 55.21, 69.74, 112.22, 112.50, 115.21, 122.13, 124.05, 129.26, 130.01, 130.12, 131.26, 133.20, 138.89, 139.93, 145.23, 157.70, 167.23. *Anal*. Calcd. for: $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17; Found; C, 73.28; H, 5.28; N, 12.28.

RESULTS AND DISCUSSION

Only a few reports describe the Spiro cyclization of anthranilamides with cycloalkanones [22-26]**.** As part of our program synthesis of spiro-oxazino-quinoline derivatives [27]. On continuation of work we herein report the synthesis and biological activity of spiro pyrimido-[4,5-b]quinoline derivatives which were prepared by condensation of 2-aminoquinoline-3-carboxamide with cyclic ketones in presence of zinc chloride scheme 1. The key intermediate in this study 2-aminoquinoline-3-carboxamide **1** was prepared by alkaline hydrolysis of 2-aminoquinoline-3-carbonitrile with hydrogen peroxide [28].



1 **2** **3**

Scheme 1 Synthesis of spiro pyrimido-[4,5-b]quinoline

In study of optimization reaction condensaion of 2-aminoquinoline-3-carboxamide, and cyclohexanone used as model substrate to screen suitable reaction conditions. Several solvents, catalysts also examined, the results of study are summarized in Table 1.

Table 1 Optimization of reaction conditions

entry	reagent	solvent	time hrs	yield % [a]
1	$AlCl_3$	DMF	6	35
2	$BF_3.OEt_3$	DMF	8	30
3	PTSA[b]	DMF	7	25
4	Alumina	DMF	8	0
5	silica	DMF	8	0
6	alum	DMF	8	0
7	$ZnCl_2$	DMF	4	73
8	$ZnCl_2$	1,4-dioxane	6	37
9	$ZnCl_2$	EDC	6	40
10	$ZnCl_2$	diphenylether	6	0

a) Yield is based on o-aminocarboxamide (b) PTSA-p-toluenesulphonic acid

As reported from Table 1 when $ZnCl_2$ was used in solvent DMF, as expected, the reaction was accelerated and proceded to completion within 4 hrs with an equimolar ratio of $ZnCl_2$ to give 73% yield (Table 1 entry 7). In the studies of solvents DMF was found to be the best solvent, reaction was incomplete and slow in 1,4-dioxane, EDC (entries 8, 9). No progress of reaction was observed in diphenylether. We also examined other catalysts such as $AlCl_3$, $BF_3.OEt_3$, PTSA Alumina, silica and alum (entries 1-6) and observed that reaction was incomplete with low yields.

To establish the generality of the reaction, various types of cyclic ketones subjected to condensation reaction under optimized conditions; the results are summarized in Table 2.

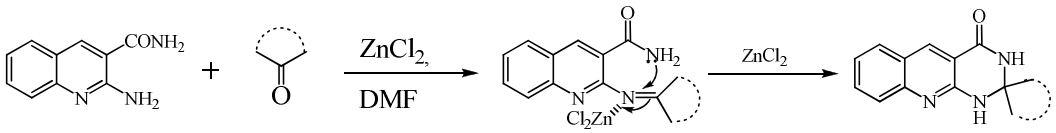
Table 2 Synthesis of spiro pyrimido [4,5-b]quinoline derivatives

entry	cyclic ketones 2	time hrs	products	yields
1	cyclohexanone	4	3a	66
2	4-Me-cyclohexanone	3.5	3b	64
3	3-Me-cyclohexanone	3.5	3c	68
4	2-Me-cyclohexanone	3.5	3d	62
5	3,3,5-trimethyl cyclohexanone	4	3e	71
6	cyclopentanone	3	3f	73
7	indanone	4	3g	64
8	7-methoxytetralone	4	3h	64
9	5-methoxytetralone	4	3i	68

As reported in Table 2, a variety of cyclic ketones five membered, six membered and sterically hindered indanone and tetralone undergo condensation reaction to give spiro pyrimido [4,5-b]quinoline derivatives in good to excellent yields. The structures of compounds were confirmed by spectroscopic and elemental analysis. For example ^{1}H NMR spectrum of compound **3a** show multiplet at δ 1.42-1.82 for ten protons of methylene groups of cyclohexane moiety. The multiplet between δ 7.26 -7.62 for aromatic four proton of benzene ring. Singlet appeared at 8.75 for aromatic proton of pyridine ring. The both N-H and O=C=NH proton appeared singlet at δ 5.95 and 7.78. The mass spectrum 3a displayed molecular ion peak at m/z 267.14 which is constitute molecular weight of compound 3a. The structure of compounds **3b-3i** confirmed similarly details are shown in experimental section. Compounds **3a-3i** was studied for their biological activities.

Possible reaction mechanism for formation of product 3

The proposed mechanism for the formation of pyrimido[4,5-b]quinolin-4'(3'H)-one derivatives described in Scheme 2. The first step is formation of imine and coordination bond with ZnCl2 enhanced the nucleophilic addition of nitrogen to intermediate to afford 3.



1 **2** **intermidiate** **3**

Scheme 2

In *vitro* antibacterial and antifungal activity assay (Table 3) indicated that all the synthesized compounds shows moderate to good against all the tested gram positive as well as gram negative bacteria and fungal pathogens determined at concentrations (100 and 200 μg/mL). From the antibacterial activity data, it was observed that compounds 3b **and 3g** are the moderate activity among all the tested compounds against Gram positive bacteria and Gram negative bacteria while all other compounds shows less antibacterial activity comparable to ciprofloxacin. The compound remaing compound shows less active against tested bacteria. The data indicated that indanone ring played crucial role in determining the antimicrobial activity. The in vitro antifungal activity of all the synthesized compounds shows moderate to excellent activity against tested species. From the antibacterial activity data, it was observed that compounds **3a** and **3b** are the more potent among all the tested compounds while compound **3f** shows comparable antifungal activity. The other remaing compound found less active **3f-3e & 3h-3i** compare Ketoconazole.

Table 3 Antimicrobial activity of synthesized compounds

comp	Conc. (mg/disc)	Zone of inhibition (mm)						
		A	B	C	D	E	F	G
3a	100	18	17	16	19	40	39	36
	200	22	21	19	21	43	42	40
3b	100	28	31	22	21	39	37	34
	200	32	35	26	22	44	41	39
3c	100	20	17	19	16	20	19	16
	200	22	18	22	18	23	21	19
3d	100	25	26	24	21	18	21	16
	200	28	29	27	26	20	23	19
3e	100	10	11	11	9	28	25	20
	200	11	11	11	10	31	27	23
3f	100	24	25	20	21	32	34	35
	200	28	27	24	23	37	39	38
3g	100	32	34	35	31	24	26	27
	200	36	38	39	37	27	29	30
3h	100	12	14	15	11	24	23	17
	200	14	15	17	12	27	25	20
3i	100	11	13	12	11	17	18	16
	200	16	16	15	14	20	22	17
Ciprofloxacin	100	34	36	40	37	-	-	-
	200	38	42	45	42			
Ketoconazole	100	-	-	-	-	38	38	38
	200	-	-	-	-	42	42	42

(A) S. aureus; (B) B. subtilis; (C) E. coli; (D) K. pneumoniae; (E) F. solaniI; C. lunata (G) A. niger

CONCLUSION

We synthesized novel spiro-pyrimido [4,5-b] quinoline derivatives via condensation of 2-aminocarboxamide with cyclic ketones in presence of zinc chloride. The result from biological activity study proved that **3g** showed good antibacterial activity when compared with standard. In antifungal activity the compound 3a **and 3b** possess excellent activity with standard.

Acknowledgements
The author thanks UGC, New Delhi, India, for financial support, Professor D. D. Dhavale, for providing spectroscopic and analytical data a nd Dr. V. B. Gaikwad, Principal, KTHM College for the facilities.

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