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Research Article

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SYNTHESIS AND EVALUATION OF SOME NEW QUINOLINE AND PYRIDO[2,3-b]INDOLE DERIVATIVES

Alok Singh Thakur[1*], A. K. Jha[1], Parmanand Verma[1], Ravitas Deshmukh[1], Dhansay Devangan[2] and Anish Chandy[3]

[1]Shri Shankaracharya Institute of Pharmaceutical Science, Bhilai, Chhattisgarh, India.
[2]Rungta College of Pharmaceutical Sciences and Research, Bhilai, Chhattisgarh, India.
[3]School of Pharmacy, CEC, Bilaspur, Chhattisgarh, India.

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ABSTRACT

Reaction of aryl compounds containing primary amine with acetic anhydride gave the compound **1(a-f)** and **4(a-f)**. Which on further treatment with Vilsmeier–Haack reagent (DMF+ $POCl_3$) gave the fused pyridine ring by cyclization, which gave compound *2-chloroquinoline-3-carbaldehyde* ***2a-f*** and *2-chloro-9H-pyrido [2,3-b]indole-3-carbaldehyde* **5a-f** respectively. These compounds were containing the free aldehyde group in their structure which form schiff base on treatment with the different substituted aniline this was because off the presence of primary amine group. These compounds were containing quinoline **(3a-f)** and pyrido indole **(6a-f)** with schiff base (substituted *–N-((2-chloroquinolin-3-yl) methylene)benzenamine* **3a-f** and *substituted –N-((2-chloro-9H-pyrido[2,3-b]indol-3-yl) methylene)benzenamine* **6a-f**) which showed antimicrobial activity due to the presence of these potent groups in their structure.

Keywords: Schiff base, quinoline, pyridoindole, antibacterial activity.

INTRODUCTION

Many derivatives of quinoline have been studied for the different biological activity such as Antimicrobial[1], anti-inflammatory[2], antileishmanial[3], antituberculosis[4], antimalarial[5], cytotoxicity[6] and HIV-1 Integrase Inhibitors[7]. In such sequence of study it has seen that the activity of such nucleus may be due to the presence of fused pyridine because other literature also shown such derivatives which give such activities in the presence of pyridine in their structure. In literature review the indole also been reported as potent antimicrobial activity. After these thorough studies of literature, it has been postulated that the fusion of pyridine nucleus with the indole may also give some potent antimicrobial derivatives.

The different substituted schiff bases were prepared to enhance the antimicrobial[8] activity of quinoline and fused indole derivatives. In the present study the schiff base was used because schiff bases are more frequently used for the preparation of such derivatives which produce various biological activities due to its versatile nature.

Therefore in the present study we have prepared some fused derivatives by combining these potent organic fragments which have reported for their antimicrobial activity to produce more potent derivatives.

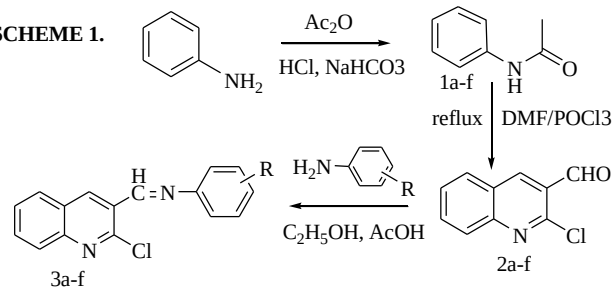
CHEMISTRY

The quinoline nucleus was prepared by the method reported in the literature.[9,10] In which the primary aryl amine was taken as starting compound and its acetylation occurs by the treatment with the acetic anhydride.

***Corresponding Author:**
Alok Singh Thakur,
Assistant Professor,
SSIPS, Bhilai, chhattisgarh, India.
Contact no: +91-900143023; E-mail: alokthakur1985@yahoo.com

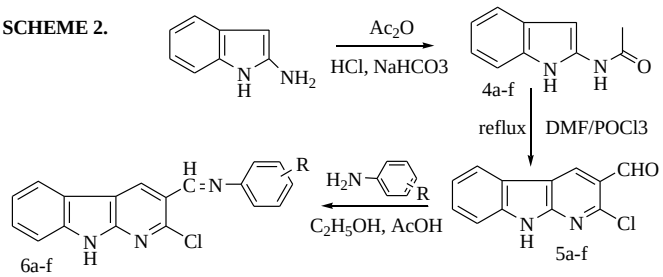
The resulting aryl acetamide is further cyclized by the treatment with the Vilsmeier–Haack reagent (DMF+ $POCl_3$) which results the quinoline nucleus with primary aldehyde. This aldehyde group is turned to schiff base after the treatment with substituted anilines and gives the various derivatives **(scheme 1)**.

SCHEME 1.



By the use of same method of preparation of fused pyridine, pyrido indole was prepared the only difference is the use of indole amine instead of aryl amine **(scheme 2)** to prepare various derivatives.

SCHEME 2.



In-vitro ANTIBACTERIAL SCREENING

The synthesized compounds **3a-f** to **6a-f** were tested for their antibacterial activity in vitro in comparison with ofloxacin as a reference drug using the standard agar disc

diffusion method[11] against four bacterial species: *S. aureus*, *B. subtilis*, *E. coli* and *P. aeuriginosa* (Gram-positive and Gram-negative strains). Nutrient Agar (Beef extract 10 gm, Peptone 10 gm, Sodium Chloride 5 gm, Agar 20 gm, purfied water 1000ml) was employed as culture media for antibacterial studies. The ingredients were dissolved in water, and adjust the PH to 7.2 to 7.4 by using dilute alkali/dilute acid and autoclave at 120 °C for 20 min. 30-35 ml of nutrient agar was transferred to the Petri dish. 1000µg/disc, 500µg/disc, 250µg/dish concentration of the test compounds are prepared & Dimethyl Foramide (DMF) was used as vehicle and ofloxacin (1000µg/disc) was used as standard. Nutrient agar plates were prepared aseptically to get a thickness of 5-6 mm. The plates were allowed to solidify and inverted to prevent condensate falling on the agar surface. The plates were dried at 37°C just before inoculation. The standard inoculums is inoculated in the plates prepared earlier aseptically by dipping a sterile swab in the inoculums, removing the excess of inoculums by pressing and rotating the swab firmly against the sides of the culture tube above the level of the liquid and finally streaking the swab all over the surface after each application. Finally press the swab round the edge of the agar surface. The sterilized discs for the test drugs were placed in the Petri dishes aseptically. Incubate the Petri dish at 37°C ± 0.2°C for about 18-24 hrs, after placing them in the refrigerator for one hour to facilitate uniform diffusion. The average zone diameter of the plates were measured and recorded. All compounds synthesized were tested for antibacterial activity against five gram (+) ve & five gram (–) ve bacteria.

RESULTS AND DISCUSSION

The spectral data of synthesized compounds are evident and showed that all the proposed compounds are synthesized properly and the common mechanism of synthesis of pyridine nucleus can be used to produce pyrido indole **(6a-f)** and quinoline **(3a-f)**. After the same substitution of schiff base in both the heterocyclic nucleus give easier way to compare the antimicrobial activity. The antimicrobial activity of all the synthesized compounds showed that the quinoline compounds are moderately active against all used bacterial strain as compared to the pyrido indole compounds except compound **3d** which containing para sulphonamide group in schiff base. The **6a**, **6c** and **6d** are revealed good antimicrobial activity. All the compounds synthesized still not significant against microbes under investigation but the further purification and modification in the synthesized derivatives give scope for further development in the same heterocyclic nucleus.

Table 1: Characterization of substituted –N-((2-chloroquinolin-3-yl)methylene)benzenamine (3a-f) and substituted -N-((2-chloro-9H-pyrido[2,3-b]indol-3-yl) methylene)benzenamine (6a-f):

Compound	R	Molecular formula	Yield value	Elemental analysis Found/calculated (%)		
				C	H	N
3a	4-Cl	$C_{16}H_{10}Cl_2N_2$	81	67.05	3.71	9.52
3b	4-OH	$C_{16}H_{11}ClN_2O$	73	67.80	3.56	9.80
3c	4-COOH	$C_{17}H_{11}ClN_2O_2$	68	65.22	3.39	9.04
3d	4-SO_2NH_2	$C_{16}H_{12}ClN_3O_2S$	74	56.02	3.51	12.76
3e	4-OCH_3	$C_{17}H_{13}ClN_2O$	78	68.45	3.98	10.01
3f	4-NO_2	$C_{16}H_{10}ClN_3O_2$	74	60.91	3.09	12.90
6a	4-Cl	$C_{18}H_{11}Cl_2N_3$	83	63.36	3.32	12.24
6b	4-OH	$C_{18}H_{12}ClN_3O$	68	67.11	3.63	12.97
6c	4-COOH	$C_{19}H_{12}ClN_3O_2$	66	66.09	3.11	11.89
6d	4-SO_2NH_2	$C_{18}H_{13}ClN_4O_2S$	71	58.13	3.25	13.90
6e	4-OCH_3	$C_{19}H_{14}ClN_30$	74	66.76	4.08	11.89
6f	4-NO_2	$C_{18}H_{11}ClN_40_2$	75	32.20	3.56	14.98

Table 2: In vitro Anti-bacterial substituted –N-((2-chloroquinolin-3-yl)methylene)benzenamine (3a-f) and substituted –N-((2-chloro-9H-pyrido[2,3-b]indol-3-yl) methylene)benzenamine (6a-f)

Compound	Zone of Inhibition(mm)			
	E. coli	*P. aeuriginosa*	*S. aureus*	*B. subtilis*
3a	21	20	20	22
3b	19	17	18	16
3c	20	22	21	21
3d	22	23	23	21
3f	17	16	14	18
6a	22	21	22	23
6b	20	19	21	23
6c	23	22	20	21
6d	24	24	23	24
6e	23	19	21	22
6f	22	21	23	22
Ofloxacin	30	24	30	19

CONCLUSION

In the current research some substituted –N-((2-chloroquinolin-3-yl) methylene) benzenamines and substituted –N-((2-chloro-9H-pyrido[2,3-b]indol-3-yl) methylene) benzenamines have been synthesized and tested for their *in-vtro* antibacterial some Gram +ve & Gram –ve bacterial species using standard agar disk diffusion method. From the above results, it can be conclude that quinoline compounds are moderately active

against all used bacterial strain as compared to the pyrido indole compounds.

Although the compounds synthesized are not much significant against microbes under investigation but the further purification and modification of synthesized derivatives give scope for further development in the same heterocyclic nucleus.

EXPERIMENTAL

Melting points were determined with open capillary and are uncorrected. Proton NMR spectra were taken in $CDCl_3$ and recorded at 300 MHz in Bruker DRX-300. Chemical shifts (δ) were measured in ppm with respect to TMS. FTIR spectra recorded on instrument simadzu 2100 S and Perkin Elmer BX. MS were obtained on a JEO JMC-300 instrument. Elemental analysis performed on Elementar Vario EL III.

General procedure for synthesis of acetanilide 1a-f: Aniline (10 mmol) was added into the water (50 ml) to produce heterogenous suspension which becomes homogenous after addition of 6N HCl (5 ml) with continuous stirring. The resulting homogenous solution was cooled in an ice bath. In the above solution acetic anhydride (10 mmol) was added followed by the addition of solid sodium bicarbonate until there was no effervescence. The precipitated product filtered and dried and finally dried in a vacuum desicator.

General procedure for synthesis of N-(1H-indole-2yl) acetamide 4a-f*:* Indole-2 amine (10 mmol) was added into the water (50 ml) to produce heterogenous suspension which becomes homogenous after addition of 6N HCl (5 ml) with continuous stirring. The resulting homogenous solution was cooled in an ice bath. In the above solution acetic anhydride (10 mmol) was added followed by the addition of solid sodium bicarbonate until there was no effervescence. The precipitated product filtered and dried and finally dried in a vacuum desicator.

General procedure for the cyclization to prepare fused pyridine ring (*2-chloroquinoline-3-carbaldehyde 2a*-f and *2-chloro-9H-pyrido [2,3-b]indole-3-carbaldehyde* 5a-f): The $POCl_3$ (7 ml) was added drop wise to a stirring solution of the acetamide solution **(2a-f/ 4a-f)** in ice cooled DMF (2 ml) and the resulting mixture was heated at 130˚C for 2 hrs, the solution was cooled and poured on to ice-water (150 ml) to precipitate synthesized fused pyridine compound.

General procedure for the synthesis of final compounds (substituted –N-((2-chloroquinolin-3-yl)methylene)benzenamine 3a-f and substituted–N-((2-chloro-9H-pyrido[2,3-b]indol-3-yl) methylene) benzenamine 6a-f): Cyclized pyridine compound was dissolved in 30 ml of ethanol containing few drops of glacial acetic acid. The substituted aniline (10 mmol) was added into the above mixture. The reaction mixture was refluxed for 5 hrs at 70^{0}C. The reaction mixture was cooled and poured in crushed ice. The solution was filtered and purified by recrystallization from ethanol.

4-chloro- N- ((2-chloroquinolin- 3-yl) methylene) benzeneamine 3a: mp 138-140˚C, FTIR (KBr) cm^{-1}**:** 3025.45 (Ar-C-H), 1500.31 (Ar C-C), 40.31(Ar C=C), 1540.21(C=N), 931.65(C-N), 762.54(C-Cl), ^{1}H NMR ($CDCl_3$) **:** 7.37-8.74 (9H, Ar-H), 10.23(1H, -NCH-), MS (*m/z*): 301.

4-((2-chloroquinolin-3-yl) methyleneamino) phenol 3b: mp 105-108˚C, FTIR (KBr) cm^{-1}: 3135.45(Ar-C-H), 750.31(C-Cl), 1631.40 (C=C), 965.47(Ar C-C), 1545.64(C=N), 926.86(C-N), 3303.27(O-H), ^{1}H NMR ($CDCl_3$) **:** 7.27-7.74 (9H, Ar-H), 10.23(1H, -NCH-), 3.2(1H, -OH), MS (*m/z*): 283.

4-((2-chloroquinolin-3-yl) methyleneamino) benzoic acid 3c: mp 128-130˚C, FTIR (KBr) cm^{-1}: 3135.45(Ar-C-H), 820.31(C-Cl), 1730.31(C=C), 1003.73(Ar C-C), 1710.21(C=N), 971.64(C-N), 1720.31(C=O) , ^{1}H NMR ($CDCl_3$) : 6.8-7.3(9H, Ar-H), 11.3(1H, -NCH-), 11.54(1H, COOH), MS (*m/z*): 311.

4-((2-chloroquinolin-3-yl) methyleneamino) benzene sulfonamide 3d: mp 140-142˚C, FTIR (KBr) cm^{-1}: 3267.86(Ar-C-H), 1576.45(C=C), 332.43(Ar C-C), 1528.21(C=N), 1085.64(C-N), 3445.64(-NH). 1178.53(S=O), 1H NMR ($CDCl_3$): 6.5-7.8(9H, Ar-H), 10.75(1H, -NCH-), 4.3-4.7(2H,-NH_2), MS (*m/z*): 346.

N-((2-chloroquinolin-3-yl) methylene) -4-methoxy benzenamine 3e: mp 100-104˚C, FTIR (KBr) cm^{-1}: 3235.45(Ar-C-H), 650.31(C-Cl), 1631.40(C=C), 965.47(Ar C-C), 1545.64(C=N), 926.86(C-N), 1229.66(C-O, OCH3), ^{1}H NMR ($CDCl_3$) **:** 7.3-7.8(9H, Ar-H), 10.48(1H, -NCH-), 3.11-4(3H, -OCH_3), MS (*m/z*): 297.

N-((2-chloroquinolin-3-yl) methylene) -4-nitro benzenamine 3f: mp 112-114˚C, FTIR (KBr) cm^{-1}: 3154.67(Ar-C-H), 699.75(C-Cl), 1567.75(C=C), 1132.43 (Ar C-C), 1540.21(C=N), 985.64(C-N), 1564.34(N=O, NO_2), ^{1}H NMR ($CDCl_3$) **:** 6.8-7.9(9H, Ar-H), 11.76(1H, -NCH-), MS (*m/z*): 312.

4-chloro-N-((2-chloro -9H-pyrido [2,3-b] indol-3-yl) methylene)benzenamine 6a: mp 154-158˚C, FTIR (KBr) cm^{-1}: 3345.06(Ar-C-H), 728.53(C-Cl), 1654.64(C=C), 1533.43 (Ar C-C), 1654.21(C=Ns), 1001.64(C-N), ^{1}H NMR ($CDCl_3$) **:** 7.1-7.8(9H, Ar-H), 10.04 (1H, -NCH-), MS (*m/z*): 340.

4-((2-chloro-9H-pyrido [2,3-b] indol-3-yl) methylene amino)phenol 6b: mp 108-110˚C, FTIR (KBr) cm^{-1}: 3045.06(Ar-C-H), 763.28(C-Cl), 1451.45(C=C), 1345.43 (Ar C-C), 1623.21(C=N), 1109.64(C-N), 3403.27(O-H), ^{1}H NMR ($CDCl_3$) : 7.1-7.7(10H, Ar-H), 10.84(1H, -NCH-), 3.6-4.5(1H,-OH), MS (*m/z*): 322.

4-((2-chloro-9H-pyrido [2,3-b] indol-3-yl) methylene amino)benzoic acid 6c: mp 132-138˚C, FTIR (KBr) cm^{-1}**:** 3154.67(Ar-C-H), 699.75(C-Cl), 1567.75(C=C), 1132.43 (Ar C-C), 1540.21(C=N), 985.64(C-N), 1685.64(C=O), ^{1}H NMR ($CDCl_3$) **:** 7.3-7.8(9H, Ar-H), 10.48(1H, -NCH-), 11.54(1H, COOH), MS (*m/z*): 350.

4-((2-chloro-9H-pyrido [2,3-b] indol-3-yl) methylene amino)benzenesulfonamide 6d: mp 148-152˚C, FTIR (KBr) cm^{-1}**:** 3334.67(Ar-C-H), 709.75(C-Cl), 1677.75(C=C), 1012.43 (Ar C-C), 1540.21(C=N), 1085.64(C-N), 1128.53(S=O), ^{1}H NMR ($CDCl_3$) **:** 6.8-7.9(9H, Ar-H), 11.76(1H, -NCH-),4.3-4.7(2H,-NH_2), MS (*m/z*): 353.

N-((2-chloro-9H-pyrido [2,3-b] indol-3-yl) methylene)-4-methoxybenzenamine 6e: mp 118-120˚C, FTIR (KBr) cm^{-1}: 3334.67(Ar-C-H), 709.75(C-Cl), 1677.75(C=C), 1012.43(Ar C-C), 1540.21(C=N), 1085.64(C-N), 1229.66(C-O, OCH3), ^{1}H NMR ($CDCl_3$) : 7.1-7.7(9H, Ar-H), 10.84(1H, -NCH-),3.6-4.5(1H, -(OCH_3), MS (*m/z*): 336.

N-((2-chloro-9H-pyrido [2,3-b] indol-3-yl) methylene)-4-nitrobenzenamine 6f: mp 122-124˚C, FTIR (KBr) cm^{-1}: 3135.45(Ar-C-H), 820.31(C-C), 1730.31(C=C str), 1003.73(Ar C-Cstr), 1710.21(C=N), 971.64(C-N), 1444.34(N=O, NO_2), ^{1}H NMR ($CDCl_3$) : 7.37-8.74 (9H, Ar-H), 10.23(1H, -NCH-), MS (*m/z*): 351.

REFERENCES

1. Mohammed I A, Subrahmanyam E V S; Synthesis, characterization and antimicrobial activity of some substituted N'-arylidene-2-(quinolin-8-yloxy) aceto hydrazides, *Acta Pharmaceutica Sciencia* 2009; 51:163-168.
2. Pellerano C, Savini L, Massarelli P, Bruni G, Fiaschi A I; New quinoline derivatives: synthesis and evaluation for antiinflammatory and analgesic properties, *Farmacol* 1990; 45(3):269-84.
3. Fournet A, Barrios A A, Munoz V, Hocquemiller R, Cave A, Bruneton J; 2-Substituted Quinoline Alkaloids as Potential Antileishmanial Drugs, *American Society for Microbiology* 1993; 31(4):859-863.
4. Upadhayaya R S, Vandavasi J K, Vasireddy N R, Sharma V, Dixit S S, Chattopadhyaya J; Design, synthesis, biological evaluation and molecular modelling studies of novel quinoline derivatives against Mycobacterium tuberculosis, *Bioorganic & Medicinal Chemistry* 2009; 17:2830–2841.
5. Vlahov R, Parushev St, Vlahov J; Synthesis of some new quinoline derivatives potential antimalarial drugs, *Pure & Appl. Cbem* 1990; 62(7):1303-1 306.
6. Lamazzi C, Leonce S, Pfeiffer B, Renard P, Guillaumet G, Reese C W, Besson T; Expeditious synthesis and cytotoxic activity of new cyanoindolo[3,2-c]quinolines and benzimidazo [1,2-c]quinazolines, *Bioorganic & Medicinal Chemistry letters* 2000; 10(19):2183-2185.
7. Luo Z, Zeng C, Wang F, He H, Wang C, Du H, Hu L; Synthesis and Biological Activities of Quinoline Derivatives as HIV-1 Integrase Inhibitors, *chem. res. chinese universities* 2009; 25(6): 841-845.
8. Kumar S, Niranjan M S, Chaluvaraju K C, Jamakhandi C M, Kadadevar D; Synthesis and Antimicrobial Study of Some Schiff Bases of Sulfonamides, *Journal of Current Pharmaceutical Research* 2010; 01: 39-42.
9. Taddei D, Poriel C, Moody*a* C J; An expedient approach to the 2,3,5,6-tetrasubstituted pyridine core of nosiheptide using oxidative cleavage of 2,3,5,8-tetrasubstituted quinolines, *ARKIVOC* 2007; 11:56-63.
10. Kalita P K, Baruah B, Bhuyan P; Synthesis of novel pyrano[2,3-b]quinolines from simple acetanilides via intramolecular 1,3-dipolar cycloaddition, *Tetrahedron Letters* 2006; 47:7779–7782.
11. Hewitt W; An Introduction to Quantitative Principles and Evaluation, in Microbiological Assay, Academic Press, New York 1977.