Synthesis, Characterization and Antimicrobial Efficacy of Quinoline derivative

Pratibha J Vora, A G Mehta

[1]Assistan professor,[2]Professor

[1]Department of Chemistry,

[1]Shree Ramkrishna Institute of Computer Education and Applied Sciences, Surat, India

Abstract - In the reported work we synthesized some quinoline based compounds from aryl amine and ethylacetoacetate via benzaldehyde(6-chloro-2-methylquinolin-4-yl) hydrazone (IIA) and substitued diazotized sulfonamides to 4-[(4'-benzylidine) hydrazino-N2-6-cholro,2-methyl quinolinyl] azosulfonamides. The resulting newly synthesized compounds are characterized by IR, H^1NMR and ^{13}C-NMR. All the newly synthesized compounds have been evaluated for their antibacterial activity towards Gram positive and Gram negative bacteria and antifungal activity towards Aspergillus niger and C.albicans. Some selected synthesizes compounds have also been evaluated for their antitubercular activity with mycobacterium tuberculosis bacilli. The results obtained from antimicrobial activity are found that some compounds have higher antibacterial activity and antifungal activity, where as the rest of the compounds show varying activity. Some of the selected compounds show higher antitubercular activity.

Index Terms - Quinoline derivatives, Sulfonamide, Azosulfonamide, Anti bacterial activity, Anti fungal activity, Anti tubercular activity.

1. INTRODUCTION

Some sulfonamidequinoline derivatives[**1]** and azobenzenesulfonamide derivatives[**2]** have been found to be biologically active. One such area in which azo dyes are well known for dyeing to textile materials, while their pharmaceutical activity[**3,4]** is also known; some are useful as chemotherapeutic agent[**5]** and some of organic dyes have been used extensively as antibacterial agents[**6]**.Few compounds of N1[substituted benzylidine hydrazino] -N2-(substituted quinolinyl)azobenzenes have been found to show antitubercular activity**[7,8]**.Hence, it was thought interesting to evaluate the antitubercular activity of some selected compounds.Realizing the medicinal importance of azo compounds[**9-13]**, quinoline derivatives and sulfonamides, it was considered worthwhile to incorporate these two moieties. It was therefore thought interesting to synthesize the title compounds with an object of ascertaining whether such compounds could augment their antibacterial and antifungal activity.

2. EXPERIMENTAL

2.1 Preparation of 2-methyl-6-chloro-4-hydroxyquinoline:

2.1.1 Ethyl-β-4-chloroanilinocrotonate

A mixture of p-chloro-aniline (6.375g, 0.05 mol) and acetoacetic ester (6.5g, 0.05 mol) with a trace of concentrated hydrochloric acid was kept in a desiccator for 24hr. The residue was cyclized by PPA.

2.1.2 Polyphosphoric acid (PPA)

Polyphosphoric acid was prepared by dissolving phosphorus pentoxide (40.0 g) into orthophosphoric acid (24 ml; $\delta = 1.75$). The mixture was heated at 95–100°C for half an hour; the scum was removed and clear solution thus obtained was used for the cyclization step.

2.1.3 2-methyl-6-chloro-4-hydroxyquinoline(I)

The crude crotonate was mixed with freshly prepared PPA at room temperature, stirred well for some time and then the temperature was raised to 100°C effervescences and was kept in desiccators for 24 hr. Next day,

the temperature was slowly raised and lowered by 10°C until it reached 140°C over 1 hr. This treatment helps in getting clean product in high yield. The reaction mass was cooled and decomposed with crushed ice and neutralized with liquor ammonia on the acidic side. The product was filtered washed with water dried and crystallized from alcohol. Yield 69%; mp: 321°C; Anal. Calcd for $C_{10}H_8ONCl$ (193.5): C, 62.0; H, 4.13; N, 7.23. Found: C, 61.89; H, 4.00; N, 7.21.

2.1.4 2-methyl-4,6-dichloroquinoline(II)

2-methyl-6-chloro-4-hydroxyquinoline (3.0 g) was refluxed with phosphorus oxychloride (25.0 ml) for one hour. After cooling to room temperature, it was poured in ice and neutralized with liquor ammonia on the acidic side, when a voluminous mass of chloro compound separated. The product was washed with water and crystallized from ethanol. Yield 72%, mp 104 °C. Anal. Calcd for $C_{10}H_7NCl_2$ (202.0): C, 56.60; H, 3.30; N, 6.60. Found: C, 56.51; H, 3.24; N, 6.30.

2.2 Preparation of 2-methyl-6-chloro-4-quinolinylhydrazine(III)

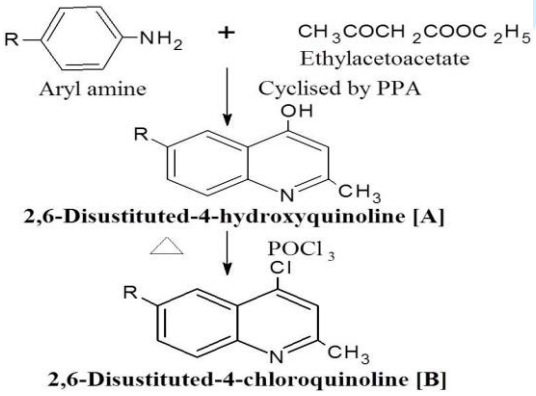
A mixture of 2-methy-4,6-dichloroquinoline (4.24gm, 0.02M) and hydrazine hydrate (5.0ml, 0.02M) was refluxed for 5 hours in absolute alcohol in a water bath. The reaction mixture was transferred in an evaporating dish and allowed to solidify. It was then treated with water and filtered. The resulting product was crystallized from alcohol. Yield 77%; mp: 296°C. Anal. Calcd for $C_{10}H_{10}N_3Cl$ (207.5): C, 57.83; H, 4.82; N, 20.24. Found: C, 57.74; H, 4.76; N, 20.10.

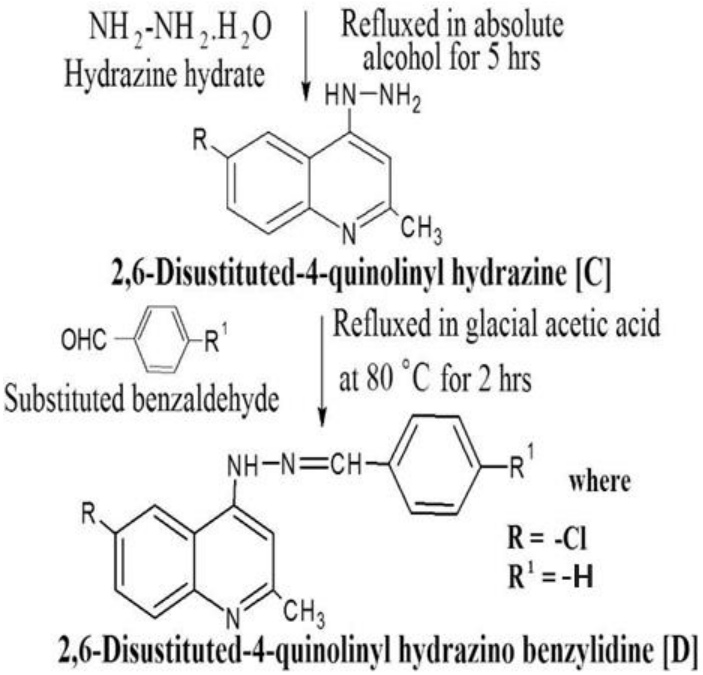
2.3 Preparation of benzaldehyde(6-chloro-2-methylequinolin-4-yl) hydrazone(IV)

A mixture of 4-hydrazino-6-chloro-2-methylquinoline (1.0gm, 0.005M) and benzaldehyde (0.5ml, 0.005M) was refluxed for 2 hours in glacial acetic acid at 80°C in water bath. The reaction mixture was cooled, poured in ice water and neutralized with liquor ammonia in slightly acidic side. The resulting product was crystallized from alcohol.

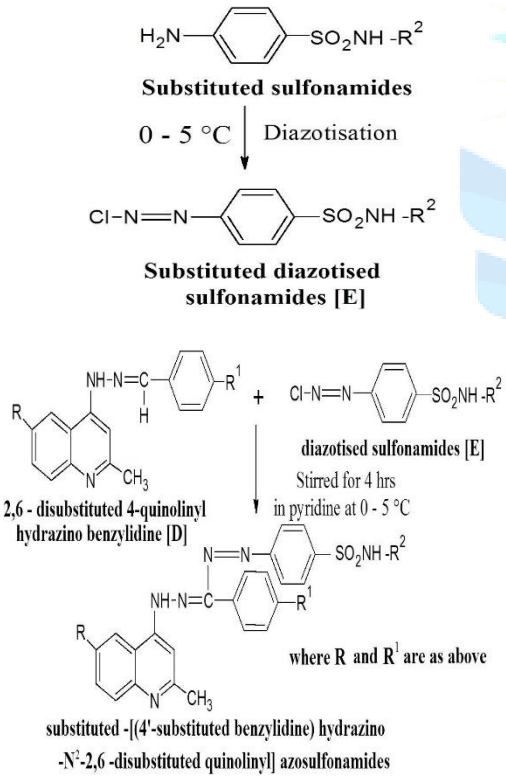
Yield 77%; mp: 271°C; FT-IR [m, cm-1, KBr]: 3325 (N–H), 1367 (C–N), 761 (C–Cl), 2910(C-H, aromatic), 1525(C=C), 1319(Ar-CH_3). 1H NMR [400 MHz, δ, ppm, DMSO-d6]: 7.9 (1H, –NH), 2.12 (3H, –CH_3), 6.7–7.8 (8H, Ar-H), 8.47(1H, -CH=N). 13C NMR [400 MHz, δ, ppm, DMSO-d6]: 21(–CH_3), 129(Benzene), 151(Quinoline), 159(imine)). Anal. Calcd for $C_{17}H_{14}ClN_3$ (295.5): Required N, 14.21. Found: N, 14.10

Scheme-1

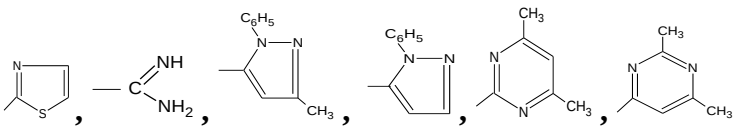




Scheme-2



where R^2 = -H,



2.4 General procedure for the preparation of 4-({(6-chloro-2-methylquinolin-4-yl)(phenyl)carbonohydrazonoyl}diazenyl)substituted benzenesulfonamide (IVa-g)

IVa:4-({(6-chloro-2-methylquinolin-4-yl)(phenyl)carbonohydrazonoyl}diazenyl)benzenesulfonamide

Diazotisation of sulfanilamide:

Sulfanilamide (0.774gm, 0.0045M) was dissolved in hydrochloric acid (10ml, 50%) and the solution was cooled to 0-5ºC. A solution of sodium nitrite (0.5gm, 0.0045M) in water (2ml) previously cooled to 0ºC was then added over a period of five minutes with constant stirring and maintaining the temperature of the mixture at 0-5ºC; stirring was continued for half an hour, maintaining the same temperature with positive test for nitrous acid on starch iodide paper. Excess of nitrous acid was destroyed by adding the required quantity of sulfamic acid. The resulting solution was used for coupling reaction.

Following the above procedure, other sulfonamides were diazotized and used for coupling reaction.

Coupling of diazotized solution with IVa:

A clear solution of **IV** (1.33gm; 0.0045M) in pyridine (5ml) was cooled below 5ºC. To this well stirred solution, diazotized solution was added dropwise over a period of 10-15 minutes, maintaining the pH 7 to 7.5. The stirring was continued for 4 hours at 0-5ºC. The product was filtered, washed with water and crystallized from glacial acetic acid.

Yield 69%; mp: 301°C; FT-IR [m, cm-1, KBr]: 3351 (N–H), 1311 (Ar-CH_3), 761 (C–Cl). 1589(N=N), 1174(S=O, RSO_2NH_2), 740(C-S), ^{1}H NMR [400 MHz, δ, ppm, DMSO-d6]: 6.62-7.99 (14H, Ar-H), 7.31 (1H, –SO_2NH), 3.05(6H, –CH_3). Anal. Calcd for $C_{23}H_{29}N_6O_2SCl$ (488.5): Required N, 17.55 Found N, 17.36

IVb:4-({(6-chloro-2-methylquinolin-4-yl)(phenyl) carbonohydrazonoyl}diazenyl)-N-1,3-thiazol-5-yl benzenesulfonamide

Yield 77%; mp: 314°C; FT-IR [m, cm-1, KBr]: 3326 (N–H), 1317 (Ar-CH_3), 779 (C–Cl). 1595(N=N), 1172(S=O, RSO_2NH_2), 692(C-S), ^{1}H NMR [400 MHz, δ, ppm, DMSO-d6]: 2.59(3H,-CH_3),8.73(1H,-NH),6.62-7.99 (14H, Ar-H), 7.33 (1H, –SO_2NH). ^{13}C NMR [400 MHz, δ, ppm, $CDCl_3$]: 43(N-CH_3), 112(thiazole), 126(aromatic carbons), 151(quinoline), 21(C–CH_3), 156(N=N) Anal. Calcd for $C_{26}H_{20}N7O_2S_2Cl$ (561.5), Required N, 17.44 Found N, 17.32

IVc:N-[amino(imino)methyl]-4-({(6-chloro-2-methylquinolin-4-yl)(phenyl)carbonohydrazonoyl}diazenyl)benzenesulfonamide

Yield 72%; mp: 306°C; FT-IR [m, cm-1, KBr]: 3342 (N–H), 3020 (Ar-CH_3), 771 (C–Cl), 1590(N=N), 1186(S=O, RSO_2NH_2), ^{1}H NMR [400 MHz, δ, ppm, DMSO-d6]: 2.59 (3H, –CH_3), 8.73 (1H,–NH), 6.60-7.95 (12H, Ar-H). Anal. Calcd for $C_{24}H_{21}N_8O_2SCl$ (520.5): Required N, 21.51 Found N, 21.36

IVd:4-({(6-chloro-2-methylquinolin-4-yl)(phenyl)carbonohydrazonoyl}diazenyl)-N-(3-methyl-1-phenyl-1H-pyrazol-5-yl)benzenesulfonamide

Yield 75%; mp: 234°C; FT-IR [m, cm-1, KBr]: 3346 (N–H), 1322 (Ar-CH_3), 760 (C–Cl), 1578(N=N), 1179(S=O, RSO_2NH_2), ^{1}H NMR [400 MHz, δ, ppm, DMSO-d6]: 2.58 (3H, –CH_3), 8.70 (1H,–NH), 6.64-7.85 (18H, Ar-H). Anal. Calcd for $C_{33}H_{27}N_8O_2SCl$ (634.5): Required N, 17.64 Found N, 17.55

IVe:4-({(6-chloro-2-methylquinolin-4-yl)(phenyl) carbonohydrazonoyl}diazenyl)-N-(1-phenyl-1H-pyrazol-5-yl) benzenesulfonamide

Yield 80%; mp: 238°C; FT-IR [m, cm-1, KBr]: 1321(Ar-CH_3), 1592(N=N), 3345 (N-N), 690 (C–S), 1342(S=O, RSO_2NH_2). ^{1}H NMR [400 MHz, δ, ppm, DMSO-d6]: 2.7(3H,–CH_3), 8.65(1H, –NH), 6.62–7.99 (14H, Ar-H), 7.40(1H,-SO_2NH). ^{13}C NMR [400 MHz, δ, ppm, $CDCl_3$]: 153(N=N), 128(aromatic carbons), 154(quinoline), 48(-CH_3). Anal. Calcd for $C_{32}H_{25}N_8O_2SCl$ (620.5): Required N, 18.04 Found N, 17.89

IVf:4-({(6-chloro-2-methylquinolin-4-yl)(phenyl) carbonohydrazonoyl}diazenyl)-N-(4,6-dimethylpyrimidin-2-yl) benzenesulfonamide

Yield 72%; mp: 275°C; FT-IR [m, cm-1, KBr]: 3340 (N–H), 1325 (Ar-CH_3), 779 (C–Cl), 1585(N=N), 1175(S=O, RSO_2NH_2). Anal. Calcd for $C_{29}H_{25}N_8O_2SCl$ (584.5): Required N, 19.15 Found N, 19.00

IVg:4-({(6-chloro-2-methylquinolin-4-yl)(phenyl) carbonohydrazonoyl}diazenyl)-N-(2,6-dimethylpyrimidin-4-yl) benzenesulfonamide

Yield 53%; mp: 298°C; FT-IR [m, cm-1, KBr]: 3348 (N–H), 1330 (Ar-CH_3), 750 (C–Cl), 1583(N=N), 1180(S=O, RSO_2NH_2). Anal. Calcd for $C_{29}H_{25}N_8O_2SCl$ (584.5): Required N, 19.15 Found N, 19.00

3. Result & Discussion

3.1 Chemistry

The final Structures of compounds **IVa-g** were confirmed on the basis of Infrared spectroscopy and NMR spectroscopy. The IR spectra of compounds shows characteristic bands at 1618-1480cm-1 (Substituted quinolines), 1330 cm-1 (C-H stretching), 1350-1280 cm-1 (C-N stretching-secondary amine), 1630-1575 cm-1(N=N stretching), 1370-1330 cm-1 and 1180-1160 cm-1(RSO_2NH_2), 779-651 cm-1(C-Cl stretching). ^{1}HNMR signal at δ2.58(-CH_3), δ7.9(-NH), δ6.9-7.9(Ar-H), δ8.57(-CH=N), δ7.41(-SO_2NH).^{13}C NMR signal at δ151-156(quinoline), δ43(-N(CH_3)$_2$), δ119(thaizole).

3.2 Biological Activity

3.2.1 Anti Bacterial Activity

Antibacterial activities of all the compounds were studied against Gram-positive bacteria [Staphylococcus aureus and Bacillus subtilis] and Gram-negative bacteria [Escherichia coli and Pseudomonas aeruginosa] at a concentration of 100 µg/ml by agar cup plate method. The area of inhibition of zone measured in millimeter. An examination of the data reveals that all compounds showed antibacterial activity. Results are presented in Table 1.

3.2.2 Anti Fungal Activity

The synthesized compounds were also screened for their antifungal activity against Candida albicans and aspergillus niger using the agar cup plate diffusion method by dissolving in DMF at a concentration of 100 µg/mL. The zone of inhibition was measured after 3 days at 20°C. Results are presented in Table 1.

3.2.3 Anti Tubercular Activity

In the present work some selected compounds were also tested for their antitubercular activity against INH sensitive strain of $H_{37}R_v$ at 12.5µg/ml with the help of BacT/ALERT 3D Detection System. Result is presented in Table 1.

Table1 Anti microbial activity of 4-({(6-chloro-2-methylquinolin-4-yl)(phenyl) carbonohydrazonoyl}diazenyl)substitutedbenzenesulfonamide (IVa-g)

Compound	Zone of inhibition (mm)						Anti Tubercular Activity µg/ml
	Anti Bacterial Activity				Anti Fungal Activity		
	E.coli	Ps. Aeruginosa	B. subtilis	S. aureus	A. niger	C. albicans	INH 12.5µg/ml
IVa	08	09	10	08	09	09	-
IVb	07	09	08	10	8.5	09	-
IVc	08	08	07	09	10	09	-
IVd	09	10	16	13	06	07	-
IVe	13	12	11	10	07	08	-
IVf	08	09	10	08	09	08	Sensitive
IVg	13	12	16	13	08	09	-
IV	08	08	11	10	11	11	-

4. CONCLUSIONS

From table-1 the highest antibacterial activity is exhibited by the compounds **IVe** and **IVg** against gram negative bacteria while **IVd** and **IVg** towards gram positive organisms. Comparing the antibacterial activity of these compounds with the parent compound **IV**, it appears that most of the compounds shows either the antibacterial activity is decreased of retained against. It also appears that all the compounds do not show any appreciable antifungal activity against both the fungi. Compound **IVf** shows sensitive response at 12.5µg/ml against INH sensitive strain of $H_{37}R_v$.

5. REFERENCES

[1] A. R. Shah, C. M. Desai and B. M. Desai, *J. South Guj. Uni.*, Surat, **7**, 85 (1978); J. Inst. Chemists (India), **59**, 257 (1987).

[2] A. R. Shah, C. M. Desai and B. M. Desai, *J. Inst. Chemists (India)*, **60**, 15 (1988), Turkey.

[3] K. N. Gaind and J. M. Khanna, *Ind. J. Pharm.*, **26**, 34 (1964).

[4] K. N. Gaind and S. K. Gulati, *Ind. J. Pharm.*, **28**, 272 (1966).

[5] L. S. Goodman and A. Gilman, *"The Pharmacological basis of Therapeutics"*, 4th Ed., Mac Millan, New York, P.III (1970).

[6] Anjani Solankee, *Ph. D. Thesis*, South Guj. Uni., Surat, 234 (1984).

[7] D. C. Tandel, *Ph.D. Thesis*, South Gujarat Uni., Surat, 196(1993).

[8] Jigna K. Machhi, *Ph.D. Thesis*, South Gujarat Uni., Surat, 205(2000).

[9] Burger, *"A Medicinal Chemistry"*, Vol. 1, p.668, John Willey, New York (1970).

[10] A. Goerner and H. L. Haley, J. Tab. Clin. Med., **16**, 957 (1931).

[11] C. O. Wilson Ole Gisvold, Robert F. Doerge and B. Lippincott, *"A Text Book of Organic Medicinal Pharmaceutical Chemistry"*, 6th Ed., 193 (1971).

[12] L. S. Goodman and A. Gilman, *"The Pharmacological basis of Therapeutics"*, p. 1009, 5th Ed., Mac Millan Publishing Company, Inc., New York, (1975).

[13] J. Bhagwan, Y. C. Joshi, R. P. Tyagi, B. C. Joshi and H. N. Mangal, *J. Inst. Chemists (India)*, **55**, 58 (1983).