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SYNTHESIS OF FLUORINE CONTAINING SOME NEW SCHIFF BASES AS POTENTIAL BIOACTIVE AGENTS.

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ABSTRACT

Fifteen new Fluorine substituted Schiff bases were prepared by condensation of different substituted benzaldehyde with 4-fluoroaniline. The structures of these Schiff bases have been confirmed by IR, ¹H NMR, mass and elemental analysis. All the new compounds synthesized have been evaluated for their action against bacteria and fungi.

Key words: Schiff bases, 4-fluoroaniline, substituted benzaldehyde, antimicrobial activity.

INTRODUCTION

The utility of Schiff bases lay in their usefulness as synthons in the synthesis of bioactive molecules such as 4-thiazolidinines, 2-azetidiones, benzoxazines, formazans, etc. Schiff bases are known to have useful biological activity like insecticidal¹, antibacterial², antituberculosis³, antimicrobial⁴, anticonvulsant⁵. Schiff bases belongs to a widely used group of organic intermediates important for production of specially chemicals, pharmaceutical or rubberadditives⁶, an amino protective groups in organic synthesis⁷⁻¹⁰. Numerous drugs containing fluorine including antipsychotics such as fluphenazine, HIV protease inhibitors, such as fipranavir, antibiotics such as oflaxacin and trovafloxacin and anasthetics such as halothae¹¹⁻¹². Recently More and Rama reported fluorinated propanediones as antiinflammatory¹³ compounds.

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Fluroquinolone¹⁴ are commonly used family of broad-spectrum antibiotics. Due to these observations in view and continuation of our work on biological heterocycles¹⁵⁻¹⁷, a new fluoro Schiff bases were synthesized and studied for antimicrobial activity.

MATERIALS AND METHODS

Melting points were determined in an open capillary tube and uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrometer. ¹H NMR spectra were recorded on a Gemini 300 MHz instrument in CDCl₃ / DMSO as solvent and TMS as an internal standard. The mass spectra were recorded on EI-SHIMADZU-GC-MS spectrometer. Elemental analysis was carried out on Carlo-Erba mass analyzer. The purity of products was checked by thin layer chromatography (TLC) on silica-gel.

General procedure for synthesis of Schiff bases (3a-o).

Equimolar mixture of 4-fluoroaniline (0.01mol) and substituted benzaldehyde (0.01mol) were dissolved in 15-20 ml ethanol, 3-4 drops of acetic acid added and refluxed for 30 min., reaction was monitored on TLC. On cooling to room temperature solid separated out which was filtered and re-crystallized from ethyl alcohol. Physical data of newly synthesized Schiff bases are given in (Table 1).

2-[(4-Fluoro-phenylimino)-methyl]-phenol (3a): IR (ν) cm⁻¹: 3250 (OH), 1620 (C=N), 1590, 1550, 1490 (C=C). ¹H NMR : δ 6.95-7.45 (m, 8H, Ar-H), δ 8.20 (s, 1H, =CH), δ 11.05 (s, 1H, Ar-OH). MS (m/z) 216 (M⁺). Anal.Calcd. for C₁₃H₁₀FNO: C, 72.15; H, 3.90. Found: C, 72.20; H, 3.92.

4-Chloro-2-[(4-fluoro-phenylimino)-methyl]-phenol (3b): IR (ν) cm⁻¹: 3412 (OH), 1620 (C=N), 1550, 1506, 1492 (C=C). ¹H NMR: δ 6.95-7.50 (m, 7H, Ar-H), δ 8.25 (s, 1H, =CH), δ 11.08 (s, Ar-OH). MS (m/z) 249 (M⁺). Anal.Calcd. for C₁₃H₉ClFNO: C, 62.65; H, 3.12. Found: C, 62.50; H, 3.10.

2,4-Dibromo-6-[(4-fluoro-phenylimino)-methyl]-phenol (3c): IR (ν) cm⁻¹: 3410 (OH), 1625 (C=N), 1550, 1500, 1460 (C=C). ¹H NMR: δ 6.80-7.45 (m, 6H, Ar-H), δ 8.20 (s, 1H, =CH), δ 13.0 (s, 1H, Ar-OH). MS (m/z) 373 (M⁺). Anal.Calcd. for C₁₃H₈Br₂FNO: C, 41.82; H, 2.14. Found: C, 41.70; H, 2.10.

4-[(4-Fluoro-phenylimino)-methyl]-benzene-1,3-diol (3e): IR (ν) cm⁻¹: 3210 (OH), 1620 (C=N), 1590, 1560, 1495 (C=C). ¹H NMR: δ 6.90-7.20 (m, 7H, Ar-H), δ 11.05 (s, 1H, 1 Ar-OH), δ 13.05 (s, 1H, 3 Ar-OH). MS (m/z) 231 (M⁺). Anal.Calad. for C₁₃H₁₀FNO₂: C, 67.53; H, 4.32. Found: C, 67.50; H, 4.30.

2-Bromo-6-ethoxy-4-[(4-fluoro-phenylimino)-methyl]-phenol (g): IR (v) cm^{-1} : 3308 (OH), 1620 (C=N), 1575, 1492, 1454 (C=C). ^1H NMR: δ 6.95-7.45 (m, 6H, Ar-H), δ 1.5 (t, 3H, CH_3), δ 4.1 (q, 2H, $-\text{CH}_2$), δ 8.30 (s, 1H, =CH), δ 11.10 (s, 1H, Ar-OH). MS (m/z) 339 (M^+). Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{BrNO}_2$: C, 53.25; H, 3.84. Found: C, 53.50; H, 3.60.

2-Chloro-4-[(4-fluoro-phenylimino)-methyl]-6-methoxy-phenol (j): IR (v) cm^{-1} : 3220 (OH), 1622 (C=N), 1595, 1585, 1492 (C=C). ^1H NMR: δ 6.85-7.50 (m, 6H, Ar-H), δ 3.8 (s, 3H, OCH_3), δ 8.35 (s, 1H, =CH), δ 11.25 (s, 1H, Ar-OH). MS (m/z) 280 (M^+). Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{ClFNO}_2$: C, 60.0 H, 3.92. Found: C, 60.15; H, 3.94.

(4-Fluoro-benzylidene)-(4-fluoro-phenyl)-amine (m): IR (v) cm^{-1} : 1620 (C=N), 1595, 1502, 1467 (C=C). ^1H NMR: δ 6.90-7.50 (m, 8H, Ar-H), δ 8.35 (s, 1H, =CH), MS (m/z) 217 (M^+). Anal. Calcd. For $\text{C}_{13}\text{H}_9\text{F}_2\text{N}$: C, 71.88; H, 4.14. Found: C, 71.90; H, 4.10.

(4-Chloro-benzylidene)-(4-fluoro-phenyl)-amine (n): IR (v) cm^{-1} : 1618 (C=N), 1590, 1500, 1460 (C=C). ^1H NMR: δ 6.90-7.50 (m, 8H, Ar-H), δ 8.25 (s, 1H, =CH), MS (m/z) 234 (M^+). Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{ClFN}$: C, 66.66; H, 3.84. Found: C, 66.50; H, 3.80.

(3,4-Dimethoxy-benzylidene)-(4-fluoro-phenyl)-amine (o): IR (v) cm^{-1} : 1620 (C=N), 1577, 1508, 1500 (C=C). ^1H NMR: δ 6.45-7.35 (m, 7H, Ar-H), δ 8.20 (s, 1H, =CH), δ 3.9 (s, 6H, 2 x OCH_3). MS (m/z): 259 (M^+). Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{FNO}_2$: C, 69.49; H, 5.40. Found: C, 69.50; H, 5.30.

Antimicrobial activity

The antimicrobial activities of the synthesized compounds were evaluated following the standard methods¹⁸ against two animal pathogens *Escherichia coli*, *Bacillus subtilis* and two fungal phytopathogens e.g. *Aspergillus flavus*, *Aspergillus niger*, respectively, using the cup plate agar diffusion method. The results were standardized against streptomycin as antibacterial and fluconazole as antifungal standard. The screening results are given (Table 1).

RESULTS AND DISCUSSION

The Schiff bases (3a-o) were prepared by condensing 4-fluoroaniline with different substituted benzaldehyde (Figure 1). The IR spectra of compounds (3a-o) showed peak near at 1620cm^{-1} due to C=N stretching vibration, a band near at 1586, 1495cm^{-1} due to aromatic stretching and a broad band near at 3350cm^{-1} due to hydroxy group.

The ^1H NMR spectra of compounds (3a-o) showed multiplet in the region δ 7.2-8.2 due to aromatic protons. A singlet of azomethine was observed near at δ 8.5-9 and phenolic hydroxyl group appears as a singlet near at δ 13. The synthesized Schiff bases (3a-o) showed mild to good

inhibitory activity against the microorganism. The compound (3c,3d,3g,3h) with Cl, Br and Iodo substituted along with –OH group at o/p position have shown to be more inhibitory than standard for comparison.

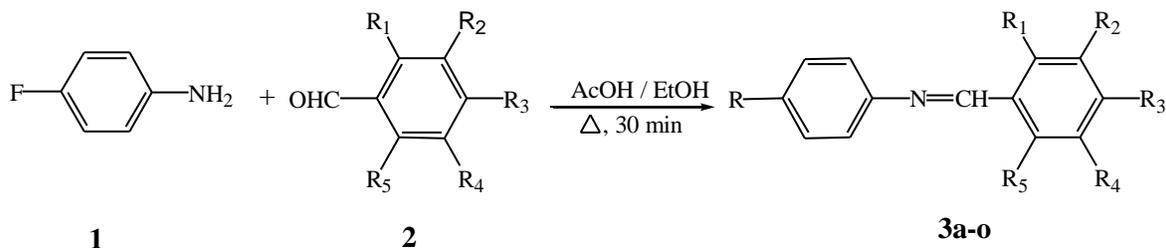


Figure 1 : Synthesis of Fluorine Containing Some New Schiff Bases.

Where **3a**: R₁= OH; R₂, R₃, R₄= H

3i: R₁= H; R₂= OCH₃; R₃= OH; R₄= Br

3b: R₁= OH; R₂, R₃= H; R₄= Cl

3j: R₁= H; R₂= OCH₃; R₃= OH; R₄= Cl

3c: R₁= OH; R₂, R₄= Br; R₃= H

3k: R₁= H; R₂= OCH₃; R₃= OH; R₄= I

3d: R₁= OH; R₂, R₄= I; R₃= H

3l: R₁, R₂, R₄= H; R₃= F

3e: R₁, R₃= OH; R₂, R₄= H

3m: R₁, R₂, R₄= H; R₃= Cl

3f: R₁, R₄= H; R₂= OC₂H₅; R₃= OH

3n: R₁, R₄= H; R₂, R₃= OCH₃

3g: R₁= H; R₂= OC₂H₅; R₃= OH; R₄= Br

3o: R₁, R₄= H; R₂, R₃= OCH₃

3h: R₁= H; R₂= OC₂H₅; R₃= OH; R₄= I

Table 1: Physical and bioactivity data of Fluorine Containing Some New Schiff Bases (3a-o)

Compound	Crystal appearance	M.P. (°C)	Zone of Inhibition (mm)			
			Antibacterial Activity		Antifungal Activity	
			<i>E.coli</i>	<i>B.subtilis</i>	<i>A.flavus</i>	<i>A.niger</i>
3a	Yellow	90	5	10	5	18
3b	Orange	125	5	7	5	19
3c	Faint yellow	115	26	27	26	25
3d	Orange	140	30	25	20	15
3e	Yellow	80	15	21	15	18
3f	Brown	125	10	10	10	15
3g	Faint brown	104	26	26	27	28
3h	Colourless	125	29	28	26	27

3i	White	110	5	10	5	15
3j	White	135	5	10	5	15
3k	Faint yellow	130	5	10	5	10
3l	Yellow	65	5	10	10	5
3m	Colourless	65	10	10	5	10
3n	White	100	10	10	10	10
3o	Colourless	125	10	10	10	10
Streptomycin			26	26	--	--
Fluconazole			--	--	26	26

CONCLUSION

The present study revealed that the Schiff bases containing –OH group at *o/p* along with iodo group in the moiety showed significant inhibition of growth of bacteria and fungi (**3a-3o**).

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