

**INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN  
CHEMISTRY AND PHARMACEUTICAL SCIENCES**

(p-ISSN: 2348-5213; e-ISSN: 2348-5221)

[www.ijcrpcs.com](http://www.ijcrpcs.com)

DOI:10.22192/ijcrpcs

Coden: IJCROO(USA)

Volume 3, Issue 11 - 2016

Research Article

DOI: <http://dx.doi.org/10.22192/ijcrpcs.2016.03.11.010>

## Synthesis, Characterization and Biological studies of some (E)-N-(4-Fluoro-3-Phenoxybenzylidene)-substituted benzenamines

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### Abstract

In the present study, six numbers of Schiff bases (1-6) have been synthesized by the condensation of substituted aromatic amines and 4-Fluoro-3-phenoxybenzaldehyde. The purities of these Schiff bases have been checked by their physical constants, IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR spectral data. The biological activities of these Schiff bases have been evaluated using Bauer-Kirby method.

**Keywords:** 4-Fluoro-3-phenoxybenzaldehyde, IR spectra, NMR spectra, biological activities.

### 1. Introduction

The chemistry of Schiff base compounds has been studied extensively. Strictly speaking Schiff bases are compounds having a formula RR'C=NR'' where R is an aryl group, R' is a hydrogen atom and R'' is either an alkyl or aryl group. However, usually compounds where R'' is an alkyl or aryl group and R' is an alkyl or aromatic group are also counted as Schiff bases [1].

Schiff base compounds (–RC=N–) are usually formed by the condensation of a primary amine with an active carbonyl. These Schiff bases are biologically [2] as well as synthetically [3] important nitrogen containing compounds having azomethine group.

Schiff bases have wide applications in food industry, dye industry, analytical chemistry, catalysis, fungicidal, agrochemical and biological activities with the increasing incidence of deep mycosis, there has been increasing emphasis on the screening of new and more effective antimicrobial drugs with low toxicity [4].

Schiff bases have gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like anti-inflammatory [5–7], analgesic [8], antimicrobial [9, 10], anticonvulsant [11], antitubercular [12], anticancer [13, 14], antioxidant [15], anthelmintic [16], Schiff's base complexes play an important role in designing metal complexes related to synthetic and natural oxygen carriers [17].

Schiff bases are important intermediates for the synthesis of some bioactive compounds such as β-lactams [18-20], and employed as ligands for the Complexation of metal ions [21]. Scientists in many different disciplines become more interested in new compounds, either synthesized or obtained from natural sources that could provide active components to prevent or reduce the impact of oxidative stress on cell [22,23].

In the present investigation the synthesis of some new Schiff bases from substituted aromatic amines and 4-Fluoro-3-phenoxybenzaldehyde. The synthesised Schiff bases were characterized by IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR.

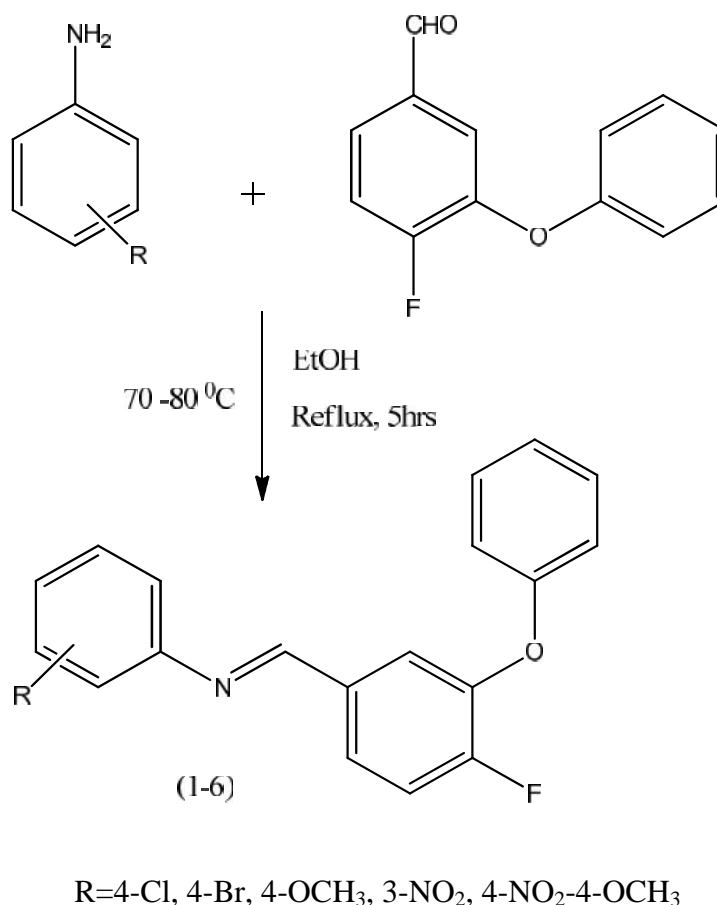
The Schiff bases were also screened for their antimicrobial activities. The prepared compounds were assessed against Gram-positive bacteria, Gram – negative bacteria and fungi.

## 2. Materials and Method

All the chemicals involved in the present investigation, have been procured from Sigma-Aldrich and E-Merck chemical companies. Melting points of all imines have been determined in open glass capillaries on SUNTEX melting point apparatus and are uncorrected. Infrared spectra (KBr, 4000–400  $\text{cm}^{-1}$ ) have been recorded on Avatar-330 FT-IR spectrophotometer. The NMR spectra of all synthesized compounds have been recorded on Bruker 400 MHz spectrometer operating at 400 MHz for recording  $^1\text{H}$  spectra and 100 MHz for  $^{13}\text{C}$  spectra in  $\text{CDCl}_3$  solvent using TMS as internal standard.

## 3. General Procedure for Preparation of (E)-N-(4-Fluoro-3-Phenoxybenzylidene)-Substituted benzenamines

The Schiff bases were obtained by refluxing equimolar quantities of the substituted aromatic amine, 4-Fluoro-3-phenoxybenzaldehyde and few drops of glacial acetic acid, (0.01 mole of each in 25 mL ethanol) on a water bath for 5-6 hrs as shown in Scheme - 1. After the completion of the reaction, as monitored by TLC, the resulting solution was cooled to room temperature, and then poured in crushed ice with constant stirring. The precipitate was filtered and washed with cold water. Then this was recrystallized using ethanol to obtain pale yellow solid. The analytical and spectral data of synthesized Schiff bases are given below.



Scheme-1: Synthesis of (E)-N-(4-Fluoro-3-Phenoxybenzylidene)-substituted benzenamines

### 3.1 Spectral data of (E)-N-(4-fluoro-3-phenoxybenzylidene)-4-chlorobenzeneamine (1)

IR(  $\text{cm}^{-1}$ ) = 1589.34 (C=N);  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ )  $^1\text{H-NMR}$  (ppm) = 8.296(1H, s, CH=N); 7.160-7.820(12H, m, Ar-H);  $^{13}\text{C-NMR}$  (100

MHz,  $\text{DMSO-d}_6$ )  $^{13}\text{C-NMR}$  (ppm) = 159.21(C=N), 155.09(C<sub>1</sub>) 123.72(C<sub>2</sub> & C<sub>6</sub>), 130.11(C<sub>3</sub> & C<sub>5</sub>), 133.20(C<sub>4</sub>), 129.94(C<sub>10</sub>), 118.38(C<sub>11</sub>), 144.63(C<sub>12</sub>), 157.62(C<sub>13</sub>), 116.73(C<sub>14</sub>), 124.33(C<sub>15</sub>), 156.87(C<sub>17</sub>), 116.62(C<sub>18</sub> & C<sub>22</sub>), 126.79(C<sub>19</sub> & C<sub>21</sub>), 122.60(C<sub>20</sub>). M.F. C<sub>19</sub>H<sub>13</sub>ClFNO; M.W. 325.8; m.p. 60 - 61 °C.

### 3.2 Spectral data of (E)-N-(4-fluoro-3-phenoxybenzylidene)-4-bromobenzenamine (2)

IR(  $\text{cm}^{-1}$ ) = 1589.34 (C=N);  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{d}_6$ )  $^1\text{H-NMR}$ ( ppm) = 8.353(1H, s,CH=N); 7.160-7.820(12H, m, Ar-H);  $^{13}\text{C-NMR}$  (100 MHz,DMSO- $\text{d}_6$ )  $^{13}\text{C-NMR}$ ( ppm) = 159.22(C=N), 155.08 (C<sub>1</sub>), 125.61(C<sub>2</sub>& C<sub>6</sub>),133.54 (C<sub>3</sub> & C<sub>5</sub>), 121.91(C<sub>4</sub>), 126.96(C<sub>10</sub>),118.38(C<sub>11</sub>), 144.63(C<sub>12</sub>), 157.62 (C<sub>13</sub>),116.25(C<sub>14</sub>),124.33(C<sub>15</sub>),156.90(C<sub>17</sub>),117.62(C<sub>18</sub>& C<sub>22</sub>),129.14.(C<sub>19</sub>&C<sub>21</sub>). M.F. C<sub>19</sub>H<sub>13</sub>BrFNO; M.W.370.2; m.p. 63 - 64 °C.

### 3.3 Spectral data of (E)-N-(4-fluoro-3-phenoxybenzylidene)-4-Methoxy benzenamines (3)

IR(  $\text{cm}^{-1}$ ) = 1589.34 (C=N);  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{d}_6$ )  $^1\text{H-NMR}$ ( ppm) = 8.398(1H, s,CH=N); 3.850(3H,s,OCH<sub>3</sub>), 7.082-7.703 (12H, m, Ar-H);  $^{13}\text{C-NMR}$  (100 MHz,DMSO- $\text{d}_6$ )  $^{13}\text{C-NMR}$ ( ppm) = 158.51(C=N);144.52 (C<sub>1</sub>) 123.59(C<sub>2</sub>& C<sub>6</sub>),117.51 (C<sub>3</sub> & C<sub>5</sub>), 157.29 (C<sub>4</sub>), 129.92(C<sub>9</sub>), 118.38(C<sub>10</sub>), 144.40 (C<sub>11</sub>)157.05(C<sub>12</sub>),117.32(C<sub>13</sub>),125.30(C<sub>14</sub>),156.13(C<sub>16</sub>), 117.67(C<sub>17</sub>&C<sub>21</sub>), 55.49(OCH<sub>3</sub>). M.F. C<sub>20</sub>H<sub>16</sub>FNO<sub>2</sub>; M.W.321.3; m.p. 66 - 68 °C.

### 3.4 Spectral data of (E)-N-(4-fluoro-3-phenoxybenzylidene)- 2-Nitro -4- Methoxy benzenamines (4)

IR(  $\text{cm}^{-1}$ ) = 1598 (C=N);  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{d}_6$ )  $^1\text{H-NMR}$ ( ppm) = 9.887(1H, s,CH=N);3.798(3H,s,OCH<sub>3</sub>),7.036 -7.656(11H, m, Ar-H);  $^{13}\text{C-NMR}$  (100 MHz,DMSO- $\text{d}_6$ )  $^{13}\text{C-NMR}$ ( ppm) = 160.1(C=N), 140.10 (C<sub>1</sub>), 126.82(C<sub>2</sub>),124.31(C<sub>3</sub>), 160.1 (C<sub>4</sub>), 106.10(C<sub>5</sub>),145.54(C<sub>6</sub>),131.37(C<sub>9</sub>),118.35(C<sub>10</sub>),156.23(C<sub>12</sub>),117.67(C<sub>13</sub>),120.78(C<sub>14</sub>),156.09(C<sub>16</sub>),117.86(C<sub>17</sub>& C<sub>21</sub>),130.08(C<sub>18</sub>& C<sub>20</sub>), 55.83 (OCH<sub>3</sub>). M.F. C<sub>20</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>4</sub>; M.W.366.1; m.p. 92-93 °C.

### 3.5 Spectral data of (E)-N-(4-fluoro-3-phenoxybenzylidene)-3-Nitro benzenamines (5)

IR(  $\text{cm}^{-1}$ ) = 1591.27 (C=N);  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{d}_6$ )  $^1\text{H-NMR}$ ( ppm) = 8.395(1H, s,CH=N); (8.082 -7.063) (12 H, m, Ar-H);  $^{13}\text{C-NMR}$  (100 MHz,DMSO- $\text{d}_6$ )  $^{13}\text{C-NMR}$ ( ppm) = 157.86(C=N), 152.60(C<sub>1</sub>),124.31(C<sub>2</sub>),130.10(C<sub>3</sub>),120.65(C<sub>4</sub>),148.87 (C<sub>5</sub>),117.53(C<sub>6</sub>),130.00(C<sub>9</sub>),144.93(C<sub>11</sub>),156.69(C<sub>12</sub>),11 5.43(C<sub>13</sub>),123.89(C<sub>14</sub>),118.33(C<sub>16</sub>),117.72(C<sub>17</sub>),126.01(C<sub>18</sub>),121.20(C<sub>19</sub>),126.08(C<sub>20</sub>),117.90(C<sub>21</sub>),M.F.C<sub>19</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>3</sub>; M.W.336.3;m.p. 81 - 82 °C.

### 3.6 Spectral data of (E)-N-(4-fluoro-3-phenoxybenzylidene)-4-Nitro benzenamine (6)

IR(  $\text{cm}^{-1}$ ) = 1589.34 (C=N);  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{d}_6$ )  $^1\text{H-NMR}$ ( ppm) = 9.892(1H, s,CH=N); 6.621-8.892 (12H, m, Ar-H);  $^{13}\text{C-NMR}$  (100 MHz,DMSO- $\text{d}_6$ )  $^{13}\text{C-NMR}$ ( ppm) = 163.3 (C=N), 159.20 (C<sub>1</sub>), 126.76(C<sub>2</sub>& C<sub>6</sub>),126.38 (C<sub>3</sub> & C<sub>5</sub>), 133.47 (C<sub>9</sub>),118.36(C<sub>10</sub>), 156.61(C<sub>12</sub>), 113.35 (C<sub>13</sub>), 156.10(C<sub>16</sub>),117.67(C<sub>17</sub>&C<sub>21</sub>), 120.81(C<sub>19</sub>),126.84(C<sub>20</sub>). M.F. C<sub>19</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>3</sub>; M.W.336.3;m.p. 96 - 97 °C.

## 4. Biological activity studies

### 4.1 Antibacterial activity

(E)-N-(4-Fluoro-3-Phenoxybenzylidene)-substituted benzenamines (1-6) were tested for their antibacterial activity against two gram positive pathogenic strains *Bacillus subtilis*, *Staphylococcus aureus* and two gram negative strains *Escherichia coli* and *P.aerogenosa*. The disc diffusion technique was followed using the Kirby–Bauer [24] method, at a concentration of 250 mg/mL with ciprofloxacin taken as the standard drug. The antibacterial screening effect of (E)-N-(4-Fluoro-3-Phenoxybenzylidene)-substituted benzenamines is shown in Fig-1 (Plates1–8). The measured zone of inhibitions is shown in Table-1 and the clustered column chart in Fig-2.

**Table-1** Zone of Inhibition (mm) values of antibacterial activities of (E)-N-(4-Fluoro-3-Phenoxybenzylidene)-substituted benzenamines

S.No.	Substituents	Zone of Inhibition (mm)			
		Gram positive Bacteria		Gram negative Bacteria	
		<i>B.subtilis</i>	<i>S.aureus</i>	<i>E.coli</i>	<i>Pseudomonas</i>
1	4-Cl	21	-	-	25
2	4-Br	12	25	26	25
3	4-OCH <sub>3</sub>	18	25	21	21
4	3-NO <sub>2</sub>	18	23	12	21
5	4-NO <sub>2</sub>	14	12	16	23
6	2-NO <sub>2</sub> -4-OCH <sub>3</sub>	30	21	25	23
Standard	Ciprofloxacin	26	28	26	19
Control	DMSO	-	-	-	-

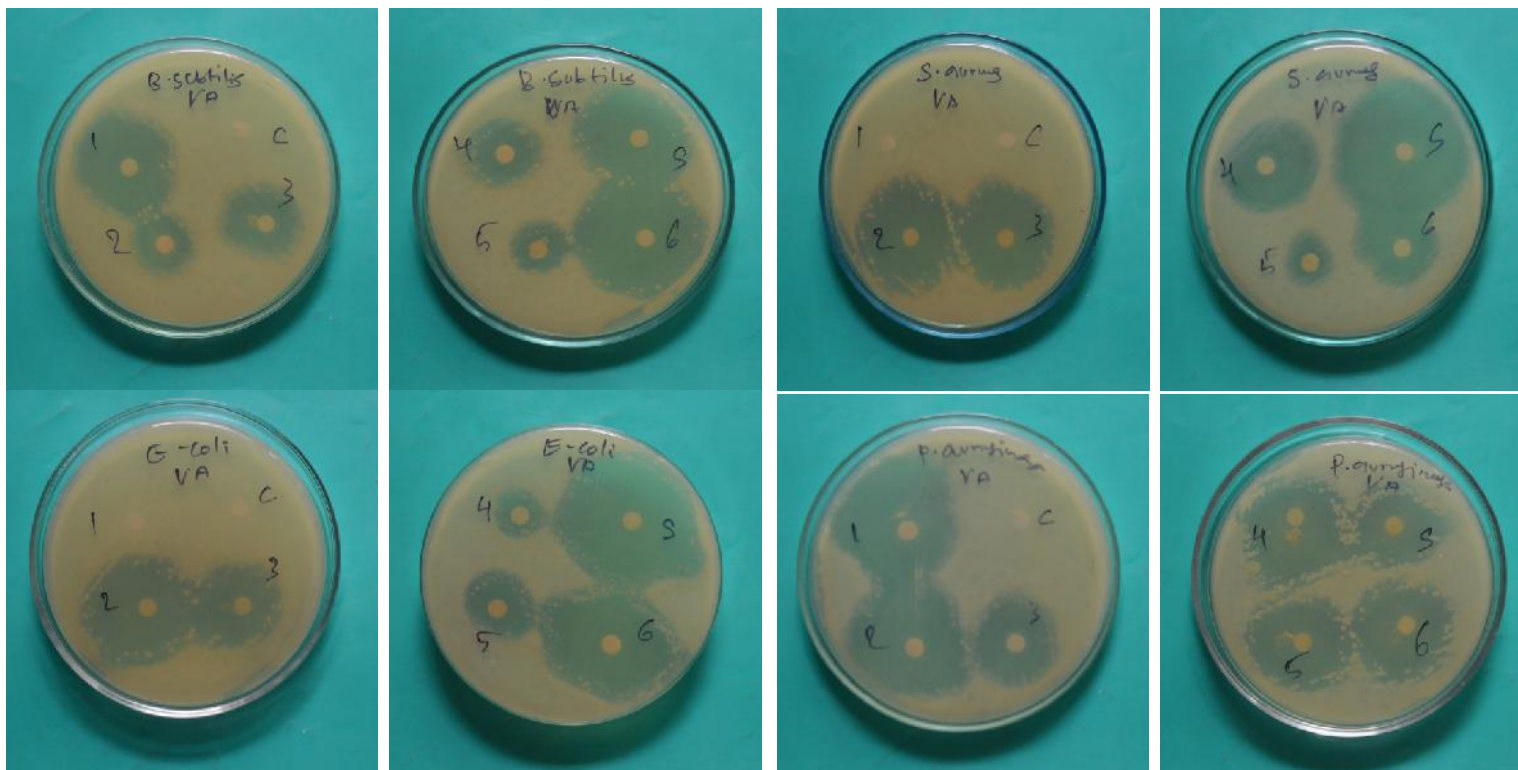


Fig-1 Petri-plates for antibacterial activities of (E)-N-(4-Fluoro-3-Phenoxybenzylidene)-substituted benzenamines

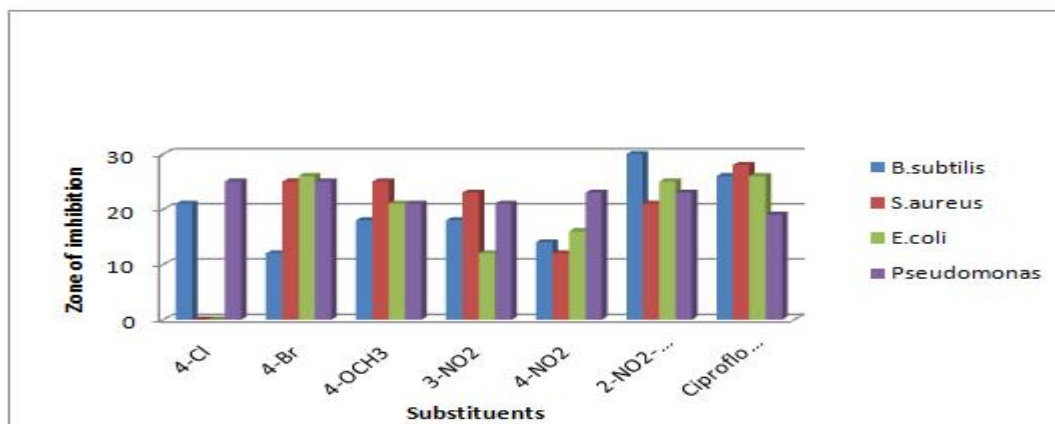


Fig-2 Cluster Column for Antibacterial activity of (E)-N-(4-Fluoro-3-Phenoxybenzylidene)-substituted benzenamines

Thus, compound containing NO<sub>2</sub> group in position 2 and OCH<sub>3</sub> group in position 4 in the phenyl ring were showing better activity (30mm) than the standard ciprofloxacin (26mm) when treated against gram positive bacteria *B.subtilis*. Another gram positive and Gram-negative bacteria *S.aureus* and *E.coli* were employed to check the activity of the series of compounds synthesized and. Compound containing electron withdrawing group bromo(25mm against *S.aureus* and 26mm against *E.coli*) exhibited best inhibition value compared with standard drug ciprofloxacin (26mm).

All the compounds have shown good activity against Gram-negative bacteria *P. aeruginosa* and far better than the standard drug. Overall, amongst the targeted molecules, only compound containing chloro substituent in para-position in the phenyl ring did not respond to any against *S.aureus* and *E.coli*, whereas compounds 4-Br, 4-OCH<sub>3</sub>, 3-NO<sub>2</sub>, 4-NO<sub>2</sub> and 2-NO<sub>2</sub>-4-OCH<sub>3</sub> have exhibited excellent activity against all the bacterial strain.

#### 4.2 Antifungal activity

The antifungal activities of all the synthesized compounds have been studied against *Tricoderma viridi*, *Aspergillus niger*, *Mucor* species and *Candida albicans*. The disc diffusion technique was followed using the Kirby-Bauer [24] method, at a concentration of 250 mg/mL with Miconazole taken as the standard drug. The antifungal activities of (E)-N-(4-Fluoro-3-Phenoxybenzylidene)-substituted benzenamines have been studied and are shown in Fig-3. Plates (9-16)

All the compounds except 2-NO<sub>2</sub>-4-OCH<sub>3</sub> substituent have shown moderate activity against *Tricoderma viridi*. All the compounds except 4-OCH<sub>3</sub> substituent have shown moderate activity against *Mucor* species and *Candida albicans*. The compounds with 4-OCH<sub>3</sub> and 3-NO<sub>2</sub> substituents have shown excellent activity against *Aspergillus niger* It is of interest that compound 3 containing electron donating methoxyl group was found to exhibit the most potent in vitro antifungal activity with 27mm against *Aspergillus niger* which is even so much more potent than standard drug miconazole with 24mm against *Aspergillus niger*. Also, the remaining substituents have shown moderate activity against *Aspergillus niger*. The title compounds showed no significant difference in their inhibition values; however the compounds containing substituted phenyl groups exhibited more activity than the un-substituted phenyl group. The compounds having the phenyl group substituted with electron withdrawing groups like chloro, bromo or nitro displayed more activity than the compounds containing phenyl group substituted with electron releasing groups like methoxyl.

**Table-2** Zone of Inhibition (mm) values of antifungal activities of (E)-N-(4-Fluoro-3-Phenoxybenzylidene)-substituted benzenamines

S.No.	Substituents	Zone of Inhibition (mm)			
		<i>Tricoderma viridi</i>	<i>Aspergillus niger</i>	<i>Mucor</i> species	<i>Candida albicans</i>
1	4-Cl	21	21	18	12
2	4-Br	12	-	23	17
3	4-OCH <sub>3</sub>	17	27	-	-
4	3-NO <sub>2</sub>	10	24	12	13
5	4-NO <sub>2</sub>	8	15	19	14
6	2-NO <sub>2</sub> -OCH <sub>3</sub>	-	20	12	14
Standard	Miconazole	26	24	21	21
Control	DMSO	-	-	-	-

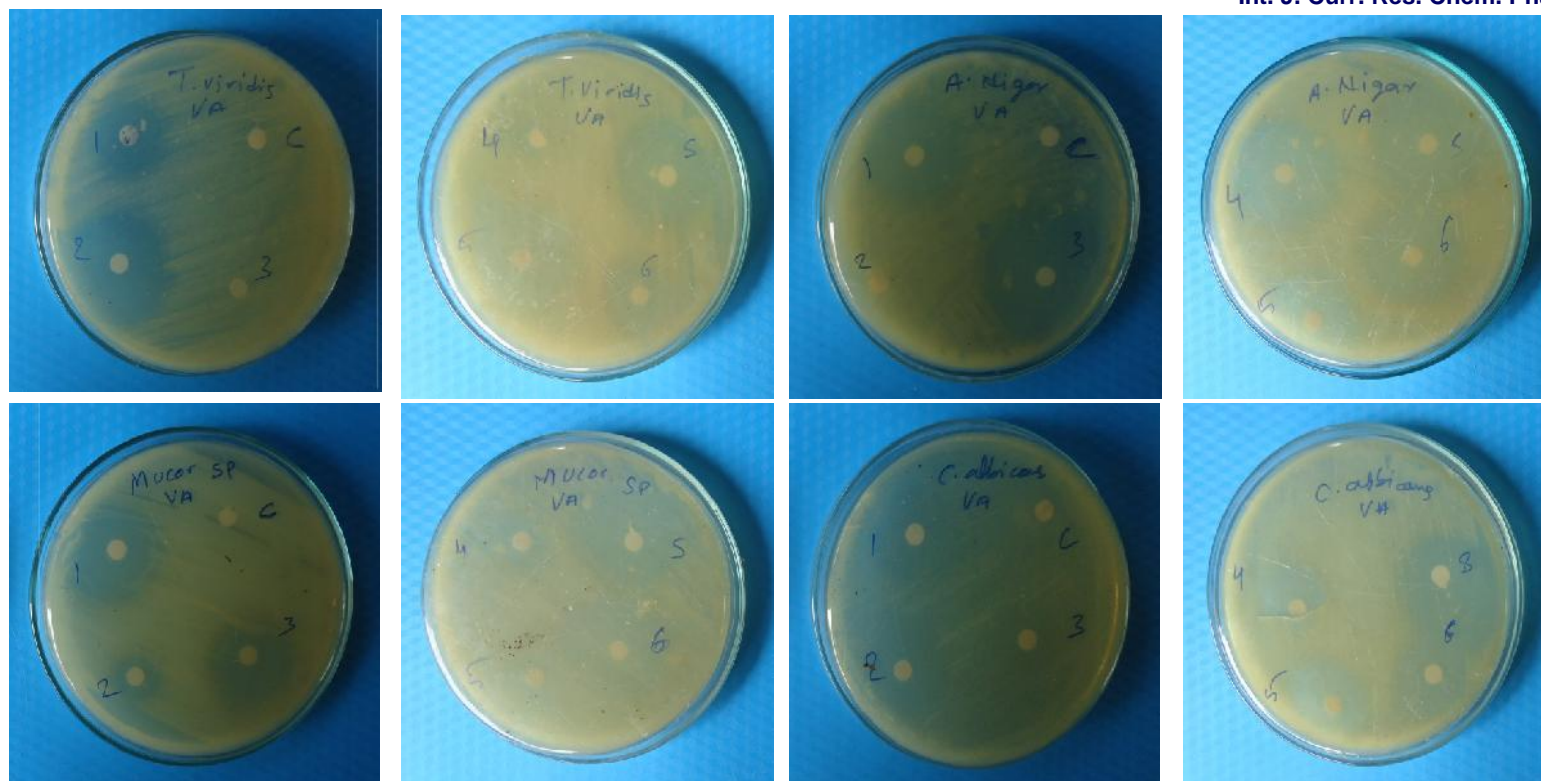


Fig-3 Petri-plates for antifungal activities of (E)-N-(4-Fluoro-3-Phenoxybenzylidene)-substituted benzenamines

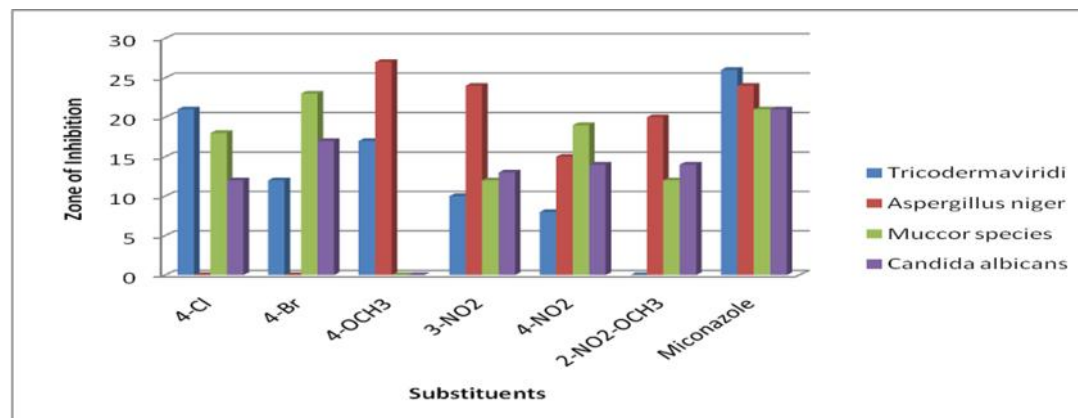


Fig-4 Cluster Column for fungal activity of (E)-N-(4-Fluoro-3-Phenoxybenzylidene)-substituted benzenamines

## 5. Conclusion


Some schiff bases have been synthesized by condensation method. These schiff bases have been characterized by their physical constants, IR, <sup>1</sup>HNMR & <sup>13</sup>CNMR spectral data. The biological activities of all synthesized schiff bases have been studied using Bauer-Kirby method. Most of the synthesized schiff bases have shown better activity against Gram positive, Gram negative bacterial and Fungal Species compared to standard drugs Ciprofloxacin and Miconazole.

## Acknowledgments

The authors thank DST NMR facility, Department of Chemistry, Annamalai University, Annamalainagar-608 002, for recording NMR spectra of all compounds.

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### How to cite this article:

G. Jesu Retna Raj, P. Jayanthi, M. Sekar, and V. Thanikachalam. (2016). Synthesis, Characterization and Biological studies of some (E)-N-(4-Fluoro-3-Phenoxybenzylidene)-substituted benzenamines. *Int. J. Curr. Res. Chem. Pharm. Sci.* 3(11): 67-73. DOI: <http://dx.doi.org/10.22192/ijrcrps.2016.03.11.010>