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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NOVEL SCHIFF BASES ANALOGUE OF 3-(4-AMINO) PHENYLIMINO) 5- FLUOROINDOLIN-2-ONE.

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ABSTRACT

The synthesis and the in vitro evaluation of antibacterial activity of new schiff bases analogues of 3-(4-Amino) Phenylimino) 5- substituted indolin-2-One are reported. The newly synthesized compounds were characterized by IR, ^{1}H NMR and Mass spectral studies. Representative compounds were screened for antibacterial (*Staphylococcus aureus* ATCC-9144, *Staphylococcus epidermidis* ATCC-155, *Micrococcus luteus* ATCC-4698, *Bacillus cereus* ATCC-11778, *Escherichia coli* ATCC-25922, *Pseudomonas aeruginosa* ATCC-2853, and *Klebsiella pneumoniae* ATCC-11298) and antifungal (*Aspergillus niger* ATCC-9029 and *Aspergillus fumigatus* ATCC-46645) activities by paper disc diffusion technique. The minimum inhibitory concentrations (MICs) of the compounds were also determined by agar streak dilution method.

INTRODUCTION

Schiff bases form an important class of organic compounds with a wide variety of biological properties[1–5]. Development of a new chemotherapeutic Schiff bases is now attracting the attention of medicinal Chemist[6]. Many studies have reported regarding the biological activities of Schiff bases, including their anticancer[7], antibacterial[8], antifungal, and herbicidal activities[9,10]. Schiff bases, derived from various heterocycles, were reported to possess cytotoxic[11], anticonvulsant[12], antiproliferative[13], anticancer, and antifungal activities[14]. A number of Schiff bases[15–18] have been tested for antibacterial[19–22], antifungal[21–23], anticancer[24, 25], and herbicidal[26] activities. Isatin and its analogs are versatile substrates, which can be used for the synthesis of numerous heterocyclic compounds. Isatins also have important pharmacological and biological activities[27]. A variety of biological activities are associated with Schiff bases of isatin including CNS activities as potentiation of pentobarbitone induce nercosis[28], analgesic[29], anticonvulsant [30], antidepressant [31], anti-inflammatory [32], antimicrobial, and effects on the central nervous system[33]. Isatins are capable of crossing the blood–brain-barrier[34]. The aim of the present study is therefore to prepare the desired Schiff bases which are based on the condensation of a suitable aliphatic / aromatic ketone precursor with amino group of 5- fluoroindolin 2-one and their chemical structures were confirmed by IR,

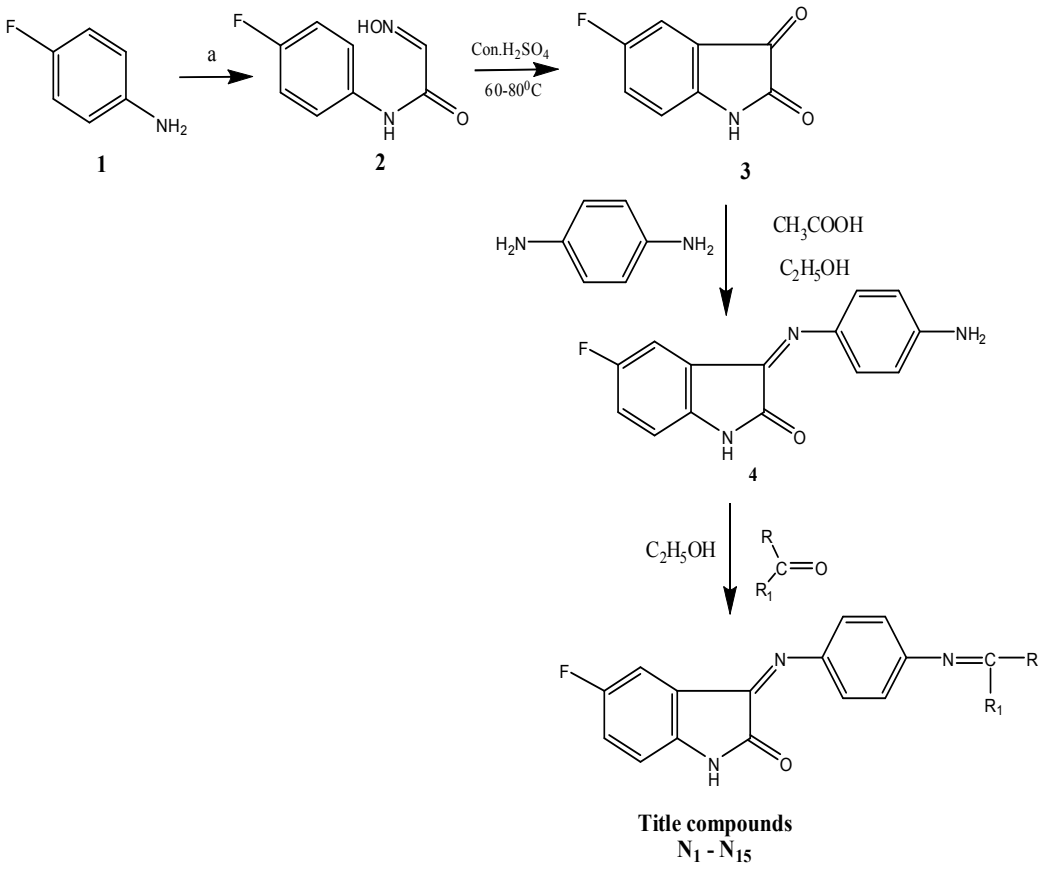
^{1}H NMR, Mass spectral and Elemental analysis. These compounds were investigate their effect on pathogenic strains of four Gram-positive and three Gram-negative bacteria.

MATERIALS AND METHODS

Chemistry

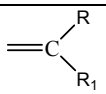
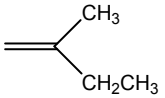
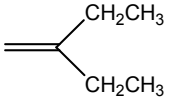
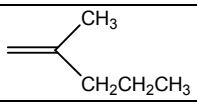
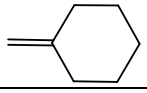
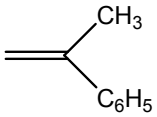
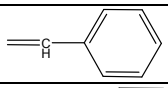
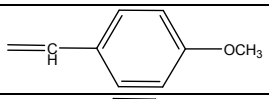
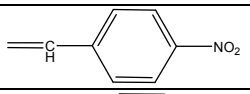
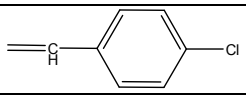
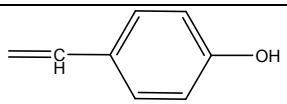
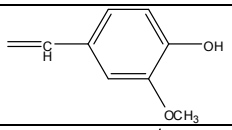
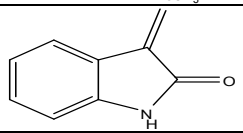
The key intermediate 5- fluoro imesatins (4) was prepared by reacting 4- Fluoro aniline (1) with hydroxylamine hydrochloride and Chloral hydrate in water to afford the 4- fluoro isonitrosoacetanilide (2). Compound 2 on reflux with Conc. H_2SO_4 to give 5- fluoro isatin (3) with 4 – amino aniline in ethanol yielded the desired 5- fluoro imesatins (4) in good yield (83%). The IR spectra of 4 show intense peaks at 3220 cm $^{-1}$ for cyclic (NH), 1675 cm^{-1} for carbonyl (C=O) stretching. ^{1}H NMR spectra of 4 showed multiplet at δ 7.15 – 8.10 for aromatic (7H) protons and a singlet at δ 9.20 indicating the presence of NH.

The novel Schiff Bases analogue of 3- (4 Amino) Phenylimino) 5- indolin-2-One (**N_1 – N_{12}**) were obtained by the condensation of amino group of 3-(4- amino) phenyl imino) -5-fluoroindolin-2-one (**4**) with a variety of alkyl and aryl ketones. The synthetic sequence leading to formation of targeted compounds (**N_1-N_{12}**) is depicted in Scheme 1. The IR and ^{1}H NMR spectrum of these compounds showed the presence of peaks due to (N =CRR_1) carbonyl (C=O), NH and aryl groups. The compounds reported (Table 1) in this study have been thoroughly characterized by spectral data and elemental analysis.



Scheme - 1 Synthesis of Schiff bases of 3(4-amino) Phenylimino)5- substituted Indolin-2-One (N_1-N_{12}).

Table 1
Physiochemical properties of synthesized compounds

Compounds		Molecular formula	Molecular weight[a]	Yield (%)	M.p [° C]
N_1		$C_{18}H_{16}FN_3O$	309	65	224 -226
N_2		$C_{19}H_{18}FN_3O$	323	82	243 -245
N_3		$C_{19}H_{18}FN_3O$	323	78	262 -264
N_4		$C_{21}H_{18}FN_3O$	347	87	247 -249
N_5		$C_{22}H_{16}FN_3O$	357	65	232 -234
N_6		$C_{21}H_{14}FN_3O$	343	78	253 -255
N_7		$C_{22}H_{16}FN_3O_2$	373	75	255 -257
N_8		$C_{21}H_{13}FN_4O_3$	388	69	234 -236
N_9		$C_{21}H_{13}ClFN_3O$	377	82	242 -244
N_{10}		$C_{21}H_{14}FN_3O_2$	359	74	260 -262
N_{11}		$C_{22}H_{16}FN_3O_3$	389	58	255 -257
N_{12}		$C_{22}H_{13}FN_4O_2$	384	55	255 -257

Biological Investigation

Anti-microbial activity

All the synthesized compounds were screened for antimicrobial activities by paper disc diffusion technique. The tested micro-organism strains were: *S. aureus* (ATCC-9144), *S. epidermidis* (ATCC-155), *M. luteus* (ATCC-4698), *B. cereus* (ATCC-11778), *E. coli* (ATCC-25922), *P. aeruginosa* (ATCC-2853), *K. pneumoniae* (ATCC-11298), *A. niger* (ATCC-9029) and *A. fumigatus* (ATCC-46645). The observed data on the anti-microbial activity of the synthesized compounds and standard drugs are given in Table 2.

Table 2
Anti-microbial activity of the synthesized compounds (100 µg/ml)

Comp	Invitro activity - zone of inhibition (MIC)								
	S.aureus	S.epidermidis	M.luteus	B.cereus	E.coli	P.aeuroinosa	K.pneumoniae	A.niger	A.fumigatus
N_1	15(25.2)	19(20.4)	13(27.8)	16(19.2)	18(21.9)	17(19.8)	14(23.6)	13(29.1)	11(30.6)
N_2	19(19.3)	18(21.2)	20(16.3)	17(15.3)	18(19.2)	18(18.6)	15(21.8)	19(17.9)	16(19.9)
N_3	21(10.4)	25(9.8)	23(11.2)	19(12.1)	21(14.8)	20(10.8)	22(13.9)	20(13.3)	19(13.6)
N_4	20(13.2)	20(17.6)	17(20.6)	18(16.7)	17(19.0)	17(19.7)	17(19.6)	18(21.3)	17(18.8)
N_5	19(13.6)	23(14.8)	20(12.4)	17(17.1)	20(14.4)	20(12.6)	24(11.8)	23(13.8)	18(14.2)
N_6	22(11.8)	18(20.2)	17(19.6)	16(21.2)	19(18.6)	16(18.6)	20(17.6)	19(20.2)	18(17.9)
N_7	24(9.2)	27(10.2)	24(11.6)	21(9.6)	23(12.1)	21(11.8)	25(10.6)	24(13.1)	19(14.5)
N_8	20(12.8)	18(18.6)	20(17.6)	16(20.2)	22(14.1)	16(21.4)	22(15.7)	24(12.8)	17(18.6)
N_9	22(10.6)	24(10.4)	21(12.1)	18(13.7)	22(13.2)	19(13.4)	22(14.3)	22(14.1)	15(20.8)
N_{10}	19(18.2)	22(13.8)	19(18.7)	17(18.6)	20(19.1)	16(20.8)	17(18.6)	18(17.7)	18(16.1)
N_{11}	21(12.5)	25(10.3)	22(14.1)	18(10.6)	21(13.4)	21(11.8)	23(12.8)	22(12.2)	20(12.9)
N_{12}	17(22.8)	14(24.0)	18(19.7)	15(20.7)	19(20.2)	14(21.6)	16(18.9)	15(21.8)	13(24.8)
	25	29	27	23	29	25	27	-	-
	-	-	-	-	-	-	-	29	26
	-	-	-	-	-	-	-	-	-

RESULTS AND DISCUSSION

In this present work a novel Schiff bases analogue of 5-fluoroindolin-2-one compounds were synthesized. Synthetic scheme illustrates the way used for the synthesis of target compounds. The structures of the compounds were characterized by IR, ^{1}H NMR, Mass spectral data and Elemental analysis. All the synthesized compounds were active against all tested micro-organisms with the range of MIC values for *S. aureus* (17.3-35.4 mg/ml), *S. epidermidis* (19.1- 33.6 mg/ml), *M. luteus* (17.2-34.2 mg/ml), *B. cereus* (19.3 - 36.1 mg/ml), *E.coli* (18.2-33.4 mg/ml), *P. aeruginosa* (19.3-37.2 mg/ml), *K. pneumoniae* (16.7- 35.7 mg/ml), *A. niger* (8.6 -15.2 mg/ml) and *A. fumigatus* (10.1-15.9 mg/ml).

3-(3,4,5-Trimethoy benzylideneamino)- 6,8-dibromo-2-phenylquinazolin-4(3H)-one 10 was found to exhibit the most potent in vitro anti-microbial activity with the MICs of 8.6, 10.1, 16.7, 18.2, 18.8, 18.9,19.1, 19.3 and 21.7 mg/ml against *A. niger, A. fumigatus, K. pneumoniae, E. coli, M. luteus, S. aureus, S. epidermidis, P. aeruginosa and B. cereus*, respectively.

Compound 7 exhibited significant anti-microbial activity when compared to standard drugs Ciprofloxin and Ketoconazole. Other compounds 1- 6, 8 - 9, 11 - 12 showed mild to moderate anti-bacterial and antifungal activity. The results revealed that most of the synthesized compounds exhibited significant anti-fungal activity. The most potent anti-bacterial and anti-fungal activity exhibited by compound 10 might be due to the presence of electron donating substituent three methoxy groups on the benzylidene amino moiety of the 2-phenyl substituted quinazolin-4(3H)-one. Similarly 3-(4-hydroxybenzylideneamino)-6,8-dibromo-2-phenylquinazolin- 4(3H)-one 7 also exhibited significant antimicrobial activity due to the presence of phenolic -OH group on the benzylideneamino group of the quinazoline-4(3H)-one moiety. While other compounds, though they contain both electron withdrawing groups like nitro, chloro and electron donating group like methoxy group do not exhibit significant in vitro anti-microbial activity (Scheme 1).

CONCLUSION

The anti-microbial activity of the synthesized compounds may be due the presence of the versatile pharmacophores and fluoro group which might increase the lipophilic character of the molecule, which facilitate the crossing through the biological membrane of the micro-organism and thereby inhibit their growth.

Experimental protocol

Chemistry

Melting points (mp) were taken in open capillaries on Thomas Hoover melting point apparatus and are uncorrected. The IR spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 398 spectrometer. The ^{1}H spectra were recorded on a DPX-300 MHz Bruker FT-NMR spectrometer. The chemical shifts were reported as parts per million (δ ppm) tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). Elemental analysis was performed on a Perkin-Elmer 2400 C, H, N analyzer and values were within the acceptable limits of the calculated values. The progress of the reaction was monitored on readymade silica gel plates (Merck) using chloroform/methanol (9:1) visualised by iodine vapors. Spectral data (IR, ^{1}H NMR and mass spectra) confirmed the structures of the synthesized compounds and the purity of these compounds was ascertained by microanalysis. Elemental (C, H, and N) analysis indicated that the calculated and observed values were within the acceptable limits (± 0.4%). All chemicals and reagents were obtained from Aldrich (USA), Lancaster (UK) or Spectrochem Pvt. Ltd (India) and were used without further purification.

*Synthesis of 5- Fluoroimesatins (**4**)*

Chloral hydrate (0.054 moles) in water (120 ml) was prepared. To this 4- Fluoro aniline (**1**) (0.158 mole) and sodium sulphate (0.05mol) was added dropwise for 30 min with stirring and finally aqueous hydroxylamine hydrochloride (50ml) was added gradually keeping the reaction mixture was heated in about 45 min. During the heating period some crystals of 4- fluoro isonitrosoacetanilide (**2**) separates out. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol. Concentrated sulphuric acid was added gradually to the resulting compound (**2**) and boil for 10 min. The reaction mixture was then poured into ice water and the 5- fluoro isatin (**3**) filtered and purified. 4 – amino aniline (0.01 mol) and the above prepared 5- fluoro isatin (**3**) were dissolved in warm ethanol and refluxed for 30 min. After standing for approximately 24h at room temperature, the 5- fluoro imesatins (**4**) were separated by filtration and recrystallised from warm ethanol. Yield = 83%, mp 260- 262 °C. IR (KBr) cm $^{-1}$: 3220 (NH), 1675 (C = O); ^{1}H NMR ($CDCl_3$): d 7.15-8.74 (m, 8H, Ar-H), 10.71 (s, 1H, NH); MS (m/z) 237 (M^+). Anal. Calcd for

$C_{14}H_{11}N_3O$: C, 70.87, H, 4.67; N, 17.71. Found: C, 70.83, H, 4.66, N, 17.72.

*General synthetic procedure for compounds (**N_1-N_{12}**).*

A mixture of 5- fluoroimesatin (**4**) (0.01mol) and 0.01 mol of appropriate ketone/ aldehyde were dissolved in 30 ml of ethanol. Then refluxed for 8h and kept aside. The solid obtained was filtered, washed with water, dried under high vacuum and recrystallized from chloroform/benzene (25:75) mixture.

3-(4-(butan-2-ylideneamino)phenylimino)-5-fluoroindolin-2-one [N_1]

Pale yellow crystal; IR (KBr, cm^{-1}): 3018 (Ar-CH), 2920 (CH in CH_3), 1720 (C=O), 1510 (C=N), 1460 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.05 (s, 1H; -N=C<u>H</u>-), 7.19-7.88 (m, 9H; Ar-H), 0.86 (s, 3H; C_2, -C<u>H</u>$_3$). EI-MS m/z (M+):309.45 (Calcd for $C_{21}H_{14}FN_3O$; 309.11). Anal. Calcd for $C_{21}H_{14}FN_3O$; C, 73.46; H, 4.11; F, 5.53; N, 12.24; O, 4.66.

5-fluoro-3-(4-(pentan-3-ylideneamino) phenylimino) indolin-2-one. [N_2]

Cream solid; IR (KBr, cm^{-1}): 3046 (Ar-CH), 2912 (CH in CH_3), 1724 (C=O), 1514 (C=N), 1462 (C=C), 1124 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 8.07 (s, 1H; -N=C<u>H</u>-), 6.81-7.92 (m, 8H; Ar-H), 3.70 (s, 3H; -OC<u>H</u>$_3$), 0.79 (s, 3H; -C<u>H</u>$_3$). EI-MS m/z (M+): 323.15 (Calcd for $C_{19}H_{18}FN_3O$; 323.31). Anal. Calcd for $C_{19}H_{18}FN_3O$; C, 70.57; H: 5.61; F: 5.88, N: 12.99; O: 4.95.

5-fluoro-3-(4-(pentan-2-ylideneamino) phenylimino)indolin-2-one. [N_3]

Pale yellow solid; IR (KBr, cm^{-1}): 3040 (Ar-CH), 2915 (CH in CH_3), 1722 (C=O), 1514 (C=N), 1457 (C=C) 1350,1205 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 7.99 (s, 1H; -N=C<u>H</u>-), 6.78-7.88 (m, 8H;Ar-H), 5.41 (s, 1H; Ar-O<u>H</u>), 0.82 (s, 3H; -C<u>H</u>$_3$). EI-MS m/z (M+): 323.67 (Calcd for $C_{19}H_{18}N_3O$; 323.29). Anal. Calcd for $C_{19}H_{18}N_3O$; C: 70.81; H, 5.98; N:12.05, F: 5.88: O: 4.94

3-(4-(cyclohexylidenemethyleneamino)phenyl imino) -5- fluoroindolin-2-one. [N_4]

Bright yellow crystal; IR (KBr, cm^{-1}): 3032 (Ar-CH), 2920 (CH in CH_3), 1720 (C=O), 1518 (C=N), 1453 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.02 (s, 1H; -N=C<u>H</u>-), 6.75-7.89 (m, 8H; Ar-H), 2.86 (s, 6H; -N-(C<u>H</u>$_3$)$_2$), 0.82 (s, 3H; -C<u>H</u>$_3$). EI-MS m/z (M+): 347.06 (Calcd for $C_{21}H_{18}FN_3O$; 347.36). Anal. Calcd for $C_{21}H_{18}FN_3O$; C: 72.61; H: 5.22; F: 5.47; N: 12.10; O: 4.61.

3-(4-(cyclohexylidenemethyleneamino)phenyl imino)-5-fluoroindolin-2-one [N_5]

Cream solid; IR (KBr, cm^{-1}): 3017 (Ar-CH), 2922 (CH in CH_3), 1715 (C=O), 1524 (C=N), 1522 and 1335 (N=O), 1450 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.09 (s, 1H; -N=C<u>H</u>-), 7.41-7.92(m, 7H;Ar-H), 0.92 (s, 3H; -C<u>H</u>$_3$). EI-MS m/z (M+): 347 (Calcd for $C_{21}H_{18}FN_3O$; 347.29). Anal. Calcd for $C_{21}H_{18}FN_3O$; C, 73.94; H, 4.51; F, 5.32; N, 11.76; O, 4.48

5-fluoro-3-(4-(1-phenylethylideneamino) phenylimino)indolin-2-one. [N_6]

Cream crystal; Yield: 76%; m.p. 164-166 °C; IR (KBr, cm^{-1}): 3041 (Ar-CH), 2926 (CH in CH_3) 1718 (C=O), 1522 (C=N), 1448 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.12 (s, 1H; -N=C<u>H</u>-), 7.09-7.81 (m, 8H,Ar-H), 2.36 (s, 3H; -C<u>H</u>$_3$), 0.92 (s, 3H; -C<u>H</u>$_3$). EI-MS m/z (M+): 347 (Calcd for $C_{22}H_{16}N_3O$; 347.29). Anal. Calcd for $C_{22}H_{16}N_3O$; C, 73.94; H, 4.51; F, 5.32; N, 11.76; O, 4.48

3-(4-(4-methoxybenzylideneamino)phenyl imino)-5-fluoroindolin-2-one. [N_7]

Pale yellow crystal; IR (KBr, cm^{-1}): 3024 (Ar-CH), 2924 (CH in CH_3), 1722 (C=O), 1514 (C=N), 1454 (C=C), 1355 and 1208 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 7.99 (s, 1H; -N=C<u>H</u>-), 6.82-7.88 (m, 8H; Ar-H), 5.44 (s, 1H; Ar-O<u>H</u>), 0.88 (s, 3H; -C<u>H</u>$_3$). EI-MS m/z (M+): 373 (Calcd for $C_{22}H_{16}FN_3O_2$; 373.29). Anal. Calcd for $C_{22}H_{16}FN_3O_2$: C: 68.79; H: 4.64; F: 5.09; N: 15.07.

3-(4-(4-nitrobenzylideneamino)phenylimino)-5-fluoroindolin-2-one. [N_8]

Pale yellow powder; IR (KBr, cm^{-1}): 3036 (Ar-CH), 2932 (CH in CH_3), 1726 (C=O), 1520 (C=N), 1446 (C=C), 729 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 8.12 (s, 1H; -N=C<u>H</u>-), 6.91-7.82 (m, 8H; Ar-H), 0.92 (s, 3H; -C<u>H</u>$_3$). EI-MS m/z (M+): 388 (Calcd

for $C_{21}H_{13}N_4O_3$; 388.73). Anal. Calcd for $C_{21}H_{13}N_4O_3$; C: 64.95; H: 3.37; F: 4.89; N: 14.43; O: 12.36.

3-(4-(4-chlorobenzylideneamino)phenyl imino)-5-fluoroindolin-2-one. [N_9]

Yellow crystal; IR (KBr, cm^{-1}): 3048 (Ar-CH), 2926 (CH in CH_3), 1715 (C=O), 1524 (C=N), 1518 and 1342 (N=O), 1452(C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.12 (s, 1H; -N=C<u>H</u>-), 7.35-7.99 (m, 8H; Ar-H), 0.82 (s, 3H; -C<u>H</u>$_3$). EI-MS m/z (M+): 308 (Calcd for $C_{21}H_{13}ClFN_3O$; 308.29). Anal. Calcd for $C_{21}H_{13}ClFN_3O$; C, 66.76; H, 3.47; Cl, 9.38; F, 5.03; N, 11.12; O, 4.23

3-(4-(4-hydroxybenzylideneamino)phenyl imino)-5-fluoroindolin-2-one. [N_{10}]

Bright yellow powder; IR (KBr, cm^{-1}): 3024 (Ar-CH), 2922 (CH in CH_3), 1724 (C=O), 1514 (C=N), 1463 (C=C), 1132 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 8.10 (s, 1H; -N=C<u>H</u>-), 7.38-7.92 (m, 4H; C_5,C_6,C_7,C_8,Ar-H), 6.61 (s, 1H; $C_{2'}$,Ar-H), 6.64 (s, 1H; $C_{6'}$,Ar-H), 3.82 (s, 9H; [O<u>CH</u>$_3$]$_3$), 0.91 (s, 3H; -C<u>H</u>$_3$). EI-MS m/z (M+): 359 (Calcd for $C_{21}H_{14}FN_3O_2$; 353.37). C, 70.19; H, 3.93; F, 5.29; N, 11.69; O, 8.905.

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