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# Synthesis of 4-[(2' substituited) phenyl]-1', 2'-di substituted anilino ethyl coumarin as anti bacterial and antifungal agents

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**ABSTRACT**

4 methyl coumarin (1) was prepared by the reaction of phenol and ethylacetoacetate in the presence of conc. $H_2SO_4$, (1) on react with substituted benzoldehyde in presence of 2% NaOH to gave 4[substituted styryl] coumarin (2a - 2d), further on bromination it converted into 4[2' substituted phenyl -1' 2' di bromo-ethyl] coumarin [3a - 3d], The solution of the compounds (3a - 3d) in methanol were refluxed with substituted aniline to form 4[2' (substituted phenyl) -1', 2' disubstituted anilinoethyl] coumarin (4a - 4t). Structure of all these newly synthesized compounds are confirmed by their analytical and spectral data. The compounds were evaluated for their antibacterial and antifungal activities. Most active compounds 4n and 4O were found to posses potent antibacterial and antifungal activities against Staph. aureus 209p and Candida albicans ATCC 10231 respectively.

**Key words:** 4 methyl coumarin, antibacterial and antifungal agents.

## INTRODUCTION

Coumarin is a simple oxygen containing heterocyclic compound, present in Melilot and Tonca been. It is the odoriferous principle Woodruffs which led to its wide spread used as perfumery in chemical industry. Coumarin derivatives have been found application as CNS represent antibiotics[1-2],antiinflammatory[3-7],antibecterial[8-9] and antifungal[10-12] activities. It is patent to mention that several antibacterial drugs are modulate on coumarin structure such as Novobiocion coumeromycin and Chartusein. In spite of synthesis of long numbers of derivatives of this heterocyclic nucleus, there is still need to prepare coumarins possessing different pharmacophores. In the present study, we have synthesized a substituted coumarin, incorporating different pharmacophoric groups with the hope getting compounds with better antibacterial as well as antifungal activities. The structure of all compound were delineated by analytical and spectral data and were also screening for their antimicrobial (antibacterial as well as antifungal) activities.

## EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. Analytical data of C, H, N were within ±0.04% of the theoretical values. IR spectra ($cm^{-1}$) were recorded on Beckman-Acculab-10 spectrophotometer. $^1$HNMR spectra were determined in $CDCl_3$ on Brucker 300-FT instrument.

### 4-Methyl coumarin (1)

To the solution of phenol (0.09 mole) and ethylacetoacetate (0.01 mole) was added in cone. $H_2SO_4$ (0.05 mole). The reaction mixture was stirred for 4 h at 0-10°C and kept at room temp, for 18 h

and then it was poured onto crushed ice (50g) with vigorous stirring, filtered and washed 5% NaOH (100mL). The product thus obtained was recrystallized from ethanol to give compound 1.
Compound 1 : m.p., 85ºC; yield, 60%, molecular formula, $C_{10}H_8O_2$.

**Spectral analysis**

*IR* (KBr) $V_{max}$ in $cm^{-1}$ : 1130 (C-O-C), 1525 (C-O of aromatic ring) , 1722 (C=O).

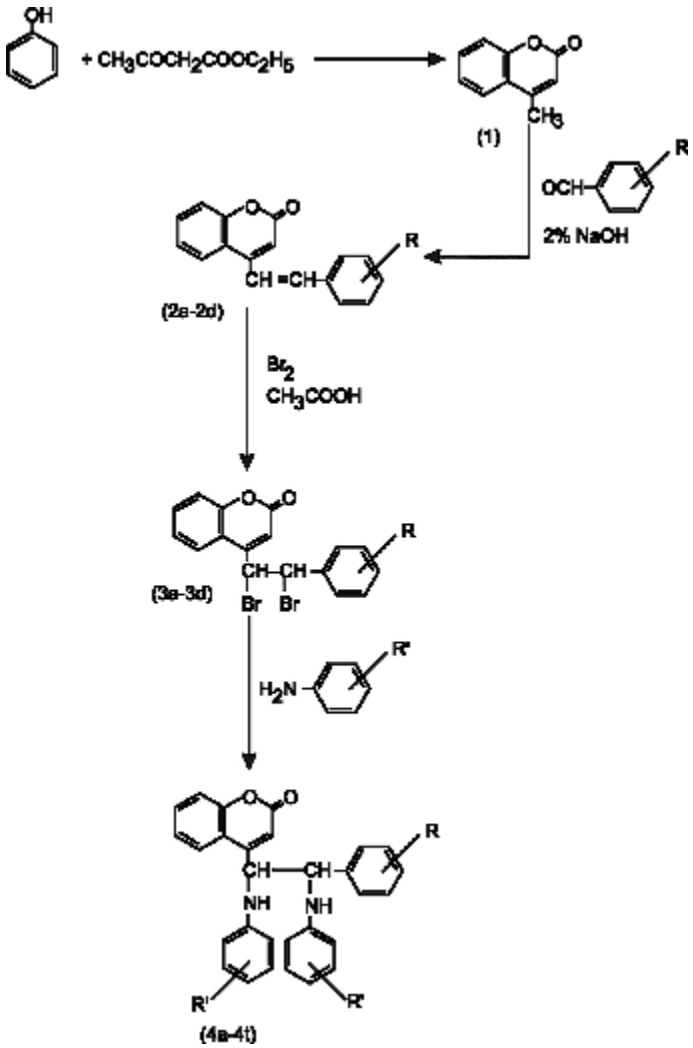
$^1H$ *NMR* ($CDCl_3$) $\delta$ in ppm: 2.15 (s, 3H, C<u>H</u>$_3$), 6.35 (s, 1H, $C_3$<u>H</u> of coumarin ring), 7.35-7.80 (m, 4H, Ar-<u>H</u>).

**4-(substitutedstyryl)-coumarin (2a - 2d)**

The methanolic solution of compound 1 (0.01 mole) and substituted benzaldehyde (0.01 mole), in the presence of 2% NaOH was refluxed for 12 h and the completion of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was concentrated, cooled and poured into ice water the separated solid was filtered off. The m.p. recrystallization solvents and elemental analysis of the compounds are given in table 1.

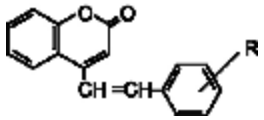
**Spectral analysis**

*IR* (KBr) $V_{max}$ in $cm^{-1}$:1140 (C-O-C), 1510 (C-C of aromatic ring), 1609 (C=C exocyclic styryl group), 1718 (C=O), 3402 (O-H).



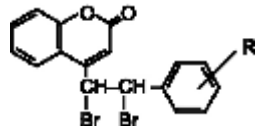

**Scheme 1**

**Table 1: Physical and analytical data of 4-[substitutedstryl] coumarins (2a-2d)**



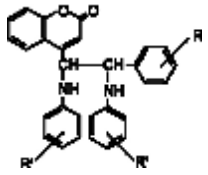

| Compd. No. | R | m.p. | Yield | Recrysta- (°C) | Molecular (%) | solvent | formula | Elemental analysis %C | | %H | | %N | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Calcd. | Found | Calcd. | | Found | | Calcd. | Found |
| 2a | p-$OCH_3$, m-OH | 178 | 50 | Methanol-water | $C_{18}H_{14}O_4$ | 73.47 | 73.56 | 4.76 | | 5.09 | | - | - |
| 2b | H | 189 | 50 | Acetic acid-water | $C_{17}H_{12}O_2$ | 82.26 | 82.64 | 4.84 | | 4.42 | | - | - |
| 2c | m-$N(CH_3)_2$ | 190 | 45 | DMF | $C_{19}H_{17}NO_2$ | 78.35 | 78.67 | 5.84 | | 5.56 | | 4.81 | 4.51 |
| 2d | o-$OCH_3$ | 180 | 55 | Ethanol-water | $C_{18}H_{14}O_3$ | 77.70 | 77.79 | 5.04 | | 5.45 | | - | - |

**Table 2: Physical and analytical data of 4-[2'-substitutedphenyl-1'2'-dibromoethyl] coumarins (3a-3d).**




| Compd. No. | R | m.p. (°C) | Yield (%) | Recrysta- solvent | Molecular formula | Elemental analysis %C | | %H | | %N | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| 3a | p-$OCH_3$, m-OH | 210 | 45 | Hexane-petroleum ether | $C_{18}H_{14}O_4Br_2$ | 47.58 | 47.65 | 3.08 | 3.25 | - | - |
| 3b | H | 208 | 48 | Methanol-water | $C_{17}H_{12}O_2Br_2$ | 50.00 | 50.35 | 2.94 | 2.65 | - | - |
| 3c | m-$N(CH_3)_2$ | 204 | 52 | Ethanol-water | $C_{19}H_{17}NO_2Br_2$ | 50.55 | 50.24 | 3.77 | 3.36 | 3.10 | 3.40 |
| 3d | o-$OCH_3$ | 210 | 45 | Ethanol-water | $C_{18}H_{14}O_4Br_2$ | 49.32 | 4 9.01 | 3.20 | 3.58 | - | |

**Table 3: Physical and analytical data of 4-[2'-substitutedphenyl-l',2'-substitutedanilinoethyl]-coumarins (4a-4t)**



| Compd. | R | $R^1$ | m.p. | Yield (°C) | Recrystalization (%) | Molecular solvent | formula | Elemental analysis %C | | %H | | No. %N | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| 4a | p-$OCH_3$, m-OH | p-Cl | 235 | 45 | Methanol-water | $C_{30}H_{24}N_2O_2Cl_2$ | 65.81 | 66.08 | 4.39 | 4.60 | 5.12 | 5.35 |
| 4b | p-$OCH_3$, m-OH | p-Cl | 240 | 50 | Ethanol-water | $C_{30}H_{24}N_2O_4C1_2$ | 65.81 | 65.49 | 4.39 | 4.70 | 5.12 | 4.78 |
| 4c | p-$OCH_3$, m-OH | p-$OCH_3$ | 220 | 55 | Ethanol-water | $C_{32}H_{30}N_2O_4$ | 71.38 | 71.50 | 5.58 | 5.84 | 5.20 | 5.64 |
| 4d | p-$OCH_3$,m-OH | p-$CH_3$ | 210 | 50 | DMF | $C_{32}H_{30}N_2O_4$ | 75.89 | 75.50 | 5.93 | 6.32 | 5.53 | 5.63 |
| 4e | p-$OCH_3$, m-OH | H | 240 | 48 | Ethanol-water | $C_{30}H_{26}N_2O_4$ | 75.31 | 75.38 | 5.44 | 5.84 | 5.86 | 5.60 |
| 4f | H | p-Cl | 210 | 52 | Ethanol-water | $C_{29}H_{22}N_2O_2Cl_2$ | 69.46 | 69.74 | 4.39 | 4.14 | 5.59 | 5.70 |
| 4g | H | p-Cl | 214 | 45 | DMF | $C_{29}H_{22}N_2O_2C1_2$ | 69.46 | 69.24 | 4.39 | 4.42 | 5.59 | 5.38 |
| 4h | H | o-$OCH_3$ | 240 | 45 | Ethanol-water | $C_{31}H_{28}N_2O_4$ | 75.61 | 75.91 | 5.69 | 5.93 | 5.69 | 5.45 |
| 4i | H | o-$CH_3$ | 210 | 40 | Methanol-water | $C_{31}H_{28}N_2O_2$ | 80.87 | 80.61 | 6.09 | 6.39 | 6.09 | 5.88 |
| 4j | H | H | 202 | 48 | Ethanol-water | $C_{29}H_{24}N_2O_2$ | 80.56 | 80.79 | 5.56 | 5.30 | 6.48 | 6.76 |
| 4k | m-$N(CH_3)_2$ | o-Cl | 201 | 50 | Methanol-water | $C_{31}H_{27}N_3O_2Cl_2$ | 68.36 | 68.68 | 4.96 | 5.23 | 7.72 | 8.01 |
| 41 | m-$N(CH_3)_2$ | m-Cl | 211 | 45 | Methanol-water | $C_{31}H_{27}N_3O_2Cl_2$ | 68.36 | 68.15 | 4.96 | 5.22 | 7.72 | 7.46 |
| 4m | m-$N(CH_3)_2$ | o-$OCH_3$ | 220 | 65 | DMF | $C_{33}H_{33}N_3O_4$ | 74.02 | 74.32 | 6.17 | 5.89 | 7.85 | 8.10 |
| 4n | m-$N(CH_3)_2$ | o-$CH_3$ | 265 | 55 | Acetic acid-water | $C_{33}H_{33}N_3O_2$ | 78.73 | 79.01 | 6.56 | 6.80 | 8.35 | 8.12 |
| 4o | m-$N(CH_3)_2$ | H | 215 | 50 | Ethanol-water | $C_{31}H_{29}N_3O_2$ | 78.32 | 78.05 | 6.11 | 6.41 | 8.84 | 9.05 |
| 4p | o-$OCH_3$ | o-Cl | 210 | 44 | DMF | $C_{30}H_{24}N_2O_3Cl_2$ | 67.80 | 68.10 | 4.52 | 4.28 | 5.27 | 5.06 |
| 4q | o-$OCH_3$ | m-Cl | 205 | 60 | acetone | $C_{30}H_{24}N_2O_3C1_2$ | 67.80 | 67.54 | 4.52 | 4.81 | 5.27 | 5.57 |
| 4r | o-$OCH_3$ | o-$OCH_3$ | 222 | 48 | Methanol-water | $C_{32}H_{30}N_2O_5$ | 73.56 | 73.82 | 5.75 | 5.99 | 5.36 | 5.06 |
| 4s | o-$OCH_3$ | o-$CH_3$ | 225 | 55 | Ethanol-water | $C_{32}H_{30}N_2O_3$ | 78.37 | 78.59 | 6.12 | 5.84 | 5.71 | 6.05 |
| 4t | o-$OCH_3$ | H | 232 | 48 | Methanol-water | $C_{30}H_{26}N_2O_3$ | 77.92 | 78.16 | 5.63 | 5.39 | 6.06 | 6.37 |

$^1$H *NMR* ($CDC1_3$) 5 in ppm: 3.39 (s, 3H, $OC\underline{H}_3$), 6.32 (s, 1H, $C_3\underline{H}$ of coumarin ring), 6.25 (d, 1H, C=CH-Coum), 6.95 (d, 1H, $\underline{H}C$=C-Ar), 7.25-8.20 (m, 7H, Ar-$\underline{H}$), 11.32 (ss, 1H, O$\underline{H}$ exchangeable).

**4-[2'-(substituted)phenyl-1'-2'-dibromoethyl]-coumarin (3a - 3d)**

A solution of bromine (0.02 mole) in acetic acid (l0mL) was added dropwise with constant stirring to the solution of compound 2a - 2d. (0.01 mole) in glacial acetic acid (10mL) at 0-2°C. The

**Table 4: Antimicrobial (antibacterial and antifungal) activity of compounds 2a-2d, 2a-3d, 4a-4t**

| Compd. No. | Antibacterial | | Antifungal | | | | |
|---|---|---|---|---|---|---|---|
| | *Staph. aureus* 209p | *E.coli ESS* 2231 | *Aspergillus fumigatus* | *Candida albicans* | *Candida albicans* ATCC 10231 | *Candida* krusei $GO_3$ | *Candida* glabrata $HO_5$ |
| 2a | 5 | 2 | 0 | 0 | 7 | 6 | 2 |
| 2b | 7 | 3 | 3 | 2 | 6 | 5 | 3 |
| 2c | 7 | 6 | 5 | 7 | 7 | 5 | 5 |
| 2d | 0 | 3 | 2 | 4 | 0 | 0 | 2 |
| 3a | 5 | 6 | 6 | 7 | 7 | 8 | 8 |
| 3b | 12 | 5 | 5 | 5 | 8 | 4 | 4 |
| 3c | 15 | 4 | 7 | 5 | 5 | 9 | 6 |
| 3d | 6 | 5 | 5 | 6 | 6 | 8 | 6 |
| 4a | 6 | 5 | 5 | 6 | 6 | 5 | 5 |
| 4b | 5 | 5 | 6 | 6 | 4 | 4 | 3 |
| 4c | 19 | 6 | 6 | 5 | 3 | 6 | 5 |
| 4d | 12 | 5 | 5 | 4 | 4 | 3 | 8 |
| 4e | 11 | 4 | 6 | 6 | 6 | 6 | 7 |
| 4f | 16 | 3 | 2 | 4 | 5 | 6 | 6 |
| 4g | 2 | 14 | 5 | 6 | 6 | 6 | 5 |
| 4h | 0 | 0 | 1 | 2 | 4 | 5 | 0 |
| 4i | 15 | 19 | 5 | 12 | 6 | 10 | 6 |
| 4j | 4 | 4 | 16 | 3 | 3 | 4 | 5 |
| 4k | 6 | 6 | 0 | 0 | 3 | 4 | 4 |
| 4l | 5 | 5 | 3 | 3 | 2 | 4 | 4 |
| 4m | 5 | 5 | 3 | 3 | 2 | 4 | 4 |
| 4n | 24 | 5 | 6 | 6 | 0 | 4 | 4 |
| 4o | 11 | 6 | 11 | 12 | 13 | 12 | 6 |
| 4p | 0 | 2 | 0 | 4 | 0 | 6 | 6 |
| 4q | 0 | 4 | 5 | 6 | 2 | 4 | 4 |
| 4r | 15 | 3 | 3 | 6 | 4 | 3 | 4 |
| 4s | 12 | 17 | 4 | 5 | 2 | 3 | 3 |
| 4t | 15 | 11 | 5 | 5 | 4 | 4 | 3 |
| Ciprofloxacin | 20 | 20 | 0 | 0 | 0 | 0 | 0 |
| Fluconzaole | 0 | 0 | 0 | 29 | 25 | 19 | 15 |
| Methanol | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

* Zone of inhibition in mm

* Concentration of newly synthesized compounds used in 250 mg/mL.

* Concentration of standard drug used is 250 mg/mL.

reaction mixture was stirred for 2 h after completion of the reaction, the solvent was distilled off and the residue thus obtained was washed with water. The m.p. recrystallization solvents and elemental analysis of the compounds are given in Table 2.

**Spectral analysis**

IR (KBr) νmax in $cm^{-1}$: 790 (C-Br), 1030 (C-O-C), 1530 (C-C of aromatic ring), 1680 (C=O),3310(O-H).

$^1$H NMR ($DMSOd_6$) δ in ppm: 3.39 (s, 3H, $OCH_3$), 5.58 (d, 1H, CHBr), 6.26 (s, 1H, $C_3H$ of coumarin ring), 6.35 (d, 1H, CH-Ar), 7.30-8.45 (m, 7H, Ar-H), 11.30 (ss, 1H, OH exchangeable with $D_2O$).

**4-[{2'-(substituted)phenyl}-l', 2'di(substituted) anilinoethyl]-coumarin 4a - 4t**

The solution of compound 3a-3d (0.02 mole) in methanol (80 mL) were refluxed with substituted aniline (0.02 mole) for 7 h. Then, the reaction mixtures were distilled off, cooled, poured into ice cold water, washed with pertroleum ether (40-60º). The m.p. recrystallization solvents and elemental analysis of the compounds are given in table 3.

**Spectral analysis**

IR (KBr) $\nu_{max}$ in $cm^{-1}$: 1120 (C-O-C), 1597 (C-C of aromatic ring), 1675 (C=0), 3310 (N-H), 3475 (O-H).

$^1$H NMR ($CDCl_3$) δ in ppm : 3.41 (s, 9H, 3x $OCH_3$), 5.59 (bs, 2H, 2x CH-NH), 5.45 (d, 1H, NH-CH-Coum.), 6.15 (d, 1H, NH-CH-Ar), 6.35 ($s_7$ 1H, $C_3H$ of coumarin ring), 7.25-8.90 (m, 15H, Ar-H), 11.32 (s, 1H, OH exchangeable). MS:$[M]^+$at m/z 538.

Antibacterial and antifungal activities were performed according to filter paper disc method (Gold and Bowie, 1950)[13].

**Antibacterial activity**

Antibacterial activity of methanolic solution of compound and standard drug was performed by preparing standard size of blank whatmann filter paper-1. discs (6.5 mm). Paper discs sterilized by dry heat at 140°C for 1h. Saturated with the test solution and the known standard reference anti biotic solution separately. These discs were air dried at room temp. to remove any residual solvent which might interfere with the determination. The discs were then placed on the surface of a sterilized agar nutrient medium that had been incubated with the test organism (by using a sterile swab) and air dried to remove the surface moisture. Thickness of the agar medium was kept equal in all petridishes and standard disc (Ciprofloxacin) was used in each plate as a control.

Before incubation petridishes were placed for 1h. In a cold room (5°C) to allow diffusion of the compound from the disc into the agar plate. These discs were now incubated at 37°C for 20-24 h after which the zone of inhibition or depressed growth was measured.

**Antifungal activity**

For antifungal Screening, spare suspension (5 ml) of each test organisms (72 h culture) was added to sterilised patato dextrose agar (PDA) medium at 35 - 40°C by thorough shakking. The peteri dishes were seeded will the mixture and the paper dises of the methanolic solution of compound and the reference antibiotic (Fluconazole) as the control was placed in the same manner as in antibacterial activity determination. There petri dishes were incubated at 30ºC for 48 h. The zone of inhibition was considered as an indicator for the antifungal activity.

## RESULTS AND DISCUSSION

The antimicrobial profile of newly synthesized compounds of scheme is reported in table IV. The table shows the activity of three types of coumarins.

**Antibacterial activity**

The compounds of first step are characterised by the presence of ethylenic double bond at 4-position of coumarin nucleus. Besides this other substitutents are at 2'-position, which are also varied.

Compounds of first step (2a-2d) exhibit no or very little antibacterial .activity ranging from 0 to 7mm but their corresponding dibromo adducts (step

2) exhibit varying degree of protection (4 to 15mm). Compound 3b, which have unsubstituted $C_6H_4$ substitution at 2'-position of coumarin, exhibited 12mm hazy zone against Staph. aureus 209p. On the other hand, compound 3c, bearing m-$N(CH_3)_2C_6H_4$ substitution at 2'-position of coumarin, exhibited 15mm zone of inhibition against Staph. aureus 209p. Compound 3a and 3d elicited less activity.

Furthermore, substitution of various substituted anilines in compounds 3a-3d was found to be fruitful for antibacterial activity. Compound 4c, having p-$OCH_3$ & m-OH $C_6H_4$ substitution at 2'-position of coumarin ring along with p-$OCH_3$ anilino substitution at 1' and 2'-positions of coumarin ring, elicited 19mm hazy zone against Staph. aureus 209p. A hazy zone of 12mm against Staph. aureus 209p was exhibited by compound 4d, having p-$OCH_3$ & m-OH-$C_6H_4$ substitution at 2'-position of coumarin ring along with p-$CH_3$ anilino substitution at 1' and 2'-position of coumarin ring. Compound 4e and 4f showed 11mm hazy zone and 16mm inhibition against Staph. aureus 209p. (substituted with p-$OCH_3$ & m-$OHC_6H_4$ substitution at 2'-position of coumarin ring along with anilino substitution at 1' and 2'-positions of coumarin ring and $C_6H_4$ substitution moiety at 2'-position of coumarin ring along with p-Cl anilino substitution at 1' and 2'-positions of coumarin ring elicited 15mm inhibition against Staph. aureus 209p. Compound 4n (24mm), 4o (11mm) and 4r (15mm) were found to have good percentage of antibacterial activity against Staph. aureus 209p (having p-$N(CH_3)_2C_6H_4$ substitution at 2'-position of coumarin along with o-$CH_3$ anilino moiety at 1' and 2'-positions of coumarin ring, m-$N(CH_3)_2C_6H_4$ substitution at 2'-position of coumarin ring and anilino moiety at 1' and 2'-positions of coumarin ring and o-$CH_3C_6H_4$ substitution at 2'-positions of coumarin ring and o-$OCH_3$ anilino substitution 1' and 2'-positions of coumarin ring respectively). Compounds 4s and 4t having o-$OCH_3C_6H_4$ substitution at 2'-positions of coumarin ring and o-$CH_3$ anilino substitution at 1' and 2'-positions of coumarin ring and o-$OCH_3C_6H_4$ substitution at 2'-positions of coumarin ring and anilino substitution at 1' and 2'-positions of coumarin ring respectively showed 12mm and 15mm protection against Staph. aureus 209p respectively. Compounds 4g (14mm), 4i (19mm), 4s (17mm) and 4t (11mm) also gave good response (in the range of 11mm to 19mm) against E.coli. ESS 2231. Rest of the compounds showed no or very low activity. If we consider the effect of these newly synthesized compounds against both the bacteria i.e. Staph. aureus 209p and E.coli ESS 2231, compound 4i was found to be most potent at it exhibited 15mm hazy zone against Staph. aureus 209p and 19mm hazy zone against E.coli ESS 2231. But at the same time compound 4n was found to give more protection of 24mm against Staph. aureus 209p in comparison to standard drug Ciprofloxacin (20mm hazy zone) and compound 4i gave good activity (19mm) against E.coli ESS 2231.

Hence, it may be concluded from the above discussion that substitution with electron donating groups i.e. $OCH_3$, $CH_3$ at 1' and 2'-positions of coumarin is most beneficial for antibacterial activity particularly against Staph. sureus 209p and E.coli ESS 2231.

**Antifungal activity**

All newly synthesized compounds 2a-2d, 3a-3d, 4a-4t were tested in order to evaluate their antifungal activity. It was observed that styryl products i.e. compounds 2a-2d exhibit very low activity.

Bromination of compounds 2a-2d yielded dibromoadduct and they elicited very low activity. Whereas, 1', 2'-diamino substituted $C_6H_4$ products (compounds 4a-4t) of these dibromo derivatives (compounds 3a-3d) showed hazy zone against various fungi. Compound 4i, bearing $C_6H_4$ substitution at 2'-position of coumarin ring along with o-$CH_3$ anilino substitution at 1' and 2'-positions of coumarin ring, showed 12mm hazy zone against Candida albicans and 10mm hazy zone against Candida krusei $GO_3$-Compound 4j, having $C_6H_4$ moiety at 2'-position of coumarin ring and anilino substitution at 1' and 2'-positions of coumarin ring, elicited 16mm inhibition against Aspergillus fumigatus. Compound 4o, bearing m-$N(CH_3)_2C_6H_4$ substitution at 2'-position of coumarin ring and anilino moiety at 1' and 2'-positions of coumarin ring, showed 11mm hazy zone against Aspergillus fumigatus, 12mm inhibition against Candida

albicans, 13mm protection against Candida albians ATCC 10231 and 12mm. hazy zone against Candida krusei $GO_3$.

The bromination of different substituted arylidenes enhances the antifungal activity (compound 3a-3d) but this enhancement in the biological activity is less than compounds 4a-4t. Among all the compounds of this series, compound 4o was found to be most potent compound, which elicited significant results towards different fungi.

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