Chapter 7

STUDIES ON ARYL AMIDE DERIVATIVES
INTRODUCTION
The characteristic group present in the simple carboxylic amide is CONH$_2$. They are the acyl substitution products of ammonia. Many natural products are amides (-CO-NH-), urea (-NH-CO-NH-) and diamides (-CO-NH-CO-NH) derivatives of carbonic acid. The peptides and proteins are linear structure of cyclic polyamides. The alkaloids of pepper, piperidine and chavicine are N-substituted amides of unsaturated acid. N-isobutyl amides of certain highly unsaturated aliphatic acids occur in plants, shows insecticidal activity. Amides derived from polyacetylenic acid have been isolated from certain fungi.

SYNTHETIC ASPECT
Various methods for the synthesis of aryl amides are described in literature. 1. Marayama, Tatsuya, Suzuki Onda have synthesized arylamide as under.

\[
\begin{align*}
\text{Ph}\text{NH}2 \xrightarrow{\text{Pyridine}} \text{PhNHCOCONHR} \\
\text{Ph} \xrightarrow{\text{PhCl}} \text{PhNHCONHR} \\
\text{Ph} \xrightarrow{\text{PhCl}} \text{PhNHCONHR} \\
\text{Ph} \xrightarrow{\text{PhCl}} \text{PhNHCONHR}
\end{align*}
\]

2. An effective protocol by thermal condensation of carboxylic acids with amines has been reported by L. J. Gooben et al.

\[
\begin{align*}
\text{R}_1\text{OH} + \text{HN}_2\text{R}_2\text{R}_3 \xrightarrow{\text{neat, 160°C}} \text{N-R}_2\text{R}_3
\end{align*}
\]

3. Z. Huang et al. have prepared borane-tetrahydrofuran complex used to generate triacyloxyboranes, which can be effectively reacted with various nucleophiles (alkylamines, arylamines, hydrazides, alcohols, phenols) at reflux temperature in toluene to provide the corresponding amides.

\[
\begin{align*}
\text{R}_1\text{OH} & \xrightarrow{i) 0.35\text{eq. BH}_3\text{-THF, Toluene}} \text{N-R}_2\text{R}_3 \\
\text{R}_1\text{OH} & \xrightarrow{\text{ii) 1.2 eq. R}_2\text{R}_3\text{NH, reflux, 12 hr.}} \text{N-R}_2\text{R}_3
\end{align*}
\]

4. D. J. Hardee and coworkers suggested that the conversion of carboxylic acids to their corresponding acid chlorides occurs rapidly in the presence a tertiary amine base and 3,3-dichlorocyclopropenes via aromatic cation-activated nucleophilic acyl substitution to give the corresponding amides.
5. G. E. Veitch et al.\textsuperscript{14} have used magnesium nitride as a convenient source of ammonia allowing a direct transformation of esters to primary amides. Methyl, ethyl, isopropyl, and tert-butyl esters are converted to the corresponding carboxamides in good yields.

6. C. Larrive-Aboussafy et al.\textsuperscript{15} have synthesized DBU catalyzed corresponding amides derivatives.

7. Multivalent metal salts, such as ferric chloride and sulfate, are active and versatile catalysts for the amidation of aliphatic fatty acids with long-chain aliphatic amines was reported by Y. Terada et al.\textsuperscript{16}

8. J. Bures et al.\textsuperscript{17} have reported 2,2′-dipyridyl diselenide catalyzed direct reaction of carboxylic acids with azides and trimethylphosphine at room temperature.

9. I. Azumaya et al.\textsuperscript{18} have prepared various tertiary benzanilide derivatives in high yields from a broad range substituted benzoic acid and N-monoalkylated anilines using dichlorotriphenylphosphorane in chloroform.
10. Deoxo-Fluor is a versatile and mild reagent for acyl fluoride generation and subsequent one-pot amide coupling. J. M. White et al.\(^ {19} \) have reported the conversion of acids to amides and the use of deoxo-fluor as peptide-coupling reagent. Products were isolated after facile purification in good yields.

\[
\begin{align*}
R^1\text{O} & \quad + \quad F_3S\text{OCH}_3 \quad \xrightarrow{\text{DIPEA}} \quad R^1\text{O} & \quad \xrightarrow{\text{NHR}^3} \quad R^1\text{N} \quad R^4\\
\text{CH}_2\text{Cl}_2
\end{align*}
\]

11. D. M. Shendage et al.\(^ {20} \) have prepared stereoconservative protection and deprotection method of amino and carboxyl groups includes the generation of \(N\)-phthaloyl \(N'\)-alkyl secondary amides from \(N\)-phthaloyl amino acids by using a mixed anhydride method.

\[
\begin{align*}
\text{PGN} & \quad \xrightarrow{(1) \text{ isobutyl chloroformate}, \text{Et}_3\text{N}} \quad \text{PGN} & \quad \xrightarrow{(2) \text{R}^2\text{NH}_2, \text{NaHCO}_3} \quad \text{PGN}\\
R^1 & \quad \text{O} & \quad \text{O} & \quad \text{NHR}^2 & \quad R^1
\end{align*}
\]

**THERAPEUTIC IMPORTANCE**

Amides, aryl amides and heterocyclic aryl amides showed various pharmacological activities. The biological activities of aryl amide derivatives have been reported as under.

1. Anticonvulsant\(^ {21} \)
2. Herbicidal\(^ {22} \)
3. Cardiotonic\(^ {23} \)
4. Antimicrobial\(^ {24,25} \)
5. Analgesic\(^ {26} \)
6. Antiulcer\(^ {27} \)
7. MAO inhibitor\(^ {28} \)
8. Anticancer\(^ {29,30} \)
9. Antiinflammatroy\(^ {31} \)
10. Anti-HIV\(^ {32} \)
11. Sodium channel blockers\(^ {33,34} \)

G. Shattat et al.\(^ {35} \) have synthesized and evaluated anti-hyperlipidemic activity of \(N\)-(benzoylphenyl)-5-fluoro-\(1H\)-indole-2-carboxamide (1) derivatives. H. B. Rubins and coworkers\(^ {36} \) have studied carboxamide derivatives as pharmacological mechanism of
fibrates, including bezafibrate, by the induction of lipoprotein lipase and reduction of apolipoprotein C-III synthesis leading to increased hydrolysis of triglycerides (TG). S. Olgen et al. and G. Liu et al. have studies the potential role for carboxamide derivatives as anti-allergics and antioxidants.

A. K. Mallams has reported arylamide derivatives as antitumor agent. More over S. J. Lauloo et al. and J. Hazarika have prepared some new biologically active arylamide derivatives and reported them as antimicrobial agents. Dhanak Dushyant et al. have synthesized arylamide (2) useful as urotensin-II antagonist. E. J. Sanderson Philip et al. (3) have synthesized aryl amides and studied their biological activity.

C. Kishor Kumar et al. have synthesized some 3-oxoisindoline-5-carboxamides and studied their antioxidant activity.

M. B. Anthony et al. have reported aryl amide derivatives as antiulcer agents. J. E. Foster et al. have synthesized some new amide derivatives as potent anticonvulsant. A. R. Mulik et al. have studied some aryl amides shows antibiotic activity. G. Bridge et al. have screened arylamides as anti-HIV agent. L. Bettinetti and co-workers have prepared arylamides as antibacterial agents. D. W. Hobbs et al. have designed some amides and reported them as MCH-receptor antagonist.

S. Henning et al. have reported carboxamide derivatives (4), as renin inhibitors and renin-angiotensin modulators useful in the treatment of hypertension. C. Zhong et al. have synthesized and reported antitumor activities of some carboxamide derivatives.
R. Aleksandra et al.\textsuperscript{53} have documented rational design, synthesis, and potency of 1\textit{H}-indole-5-carboxamide as potential fructose 1,6-bisphosphatase inhibitors.

![Structure](image)

(4)

S. Tabuchi et al.\textsuperscript{54} have screened arylamide derivatives as novel potent antagonist of human neuropeptide YY\textsubscript{5} receptor. J. H. Chan\textsuperscript{55} has reported substituted benzophenone-arylamide derivatives as inhibitor reverse transcriptase. L. Pieters et al.\textsuperscript{56} have synthesized new diazene carboxamides (5) as anticancer agent. N. J. Anthony and co-workers\textsuperscript{57} have investigated amides for anti-HIV activity. G. Chen et al.\textsuperscript{58} have reported aryl amides (6) as antitumor agents.

![Structure](image)

(5)

G. A. Doherty et al.\textsuperscript{59} have synthesized indole-5-carboxamide derivatives (7) as DP2 receptor modulators for treating immunological diseases. Indole carboxamide derivatives applied as p38\textalpha-selected MAP kinase inhibitor which reduces tumor growth in mouse xenograft models of multiple myeloma and SD-282 reduces inflammation in a subchronic model by S. Medicherla et al.\textsuperscript{60}

![Structure](image)

(7)

CONTRIBUTION FROM OUR LABORATORY

Some new arylamide derivatives bearing benzimidazol moiety (8) were assessed by H. H. Parekh et al.\textsuperscript{61} and evaluated its antimicrobial activity. A. R. Parikh et al.\textsuperscript{62-65}
have synthesized new arylamide derivatives (9), (10) and reported them as antimicrobial agents.

V. H. Shah et al.\textsuperscript{66} have synthesized some new aryl amides (11) and evaluated their antimicrobial activity.

V. N. Patoliya et al.\textsuperscript{67-70} have synthesized and evaluated antimicrobial activity of some aryl amide derivative (12). D. M. Purohit et al.\textsuperscript{159} have reported new aryl amides derivatives having piperazine moiety as a antimicrobial agent.

Looking to the interesting properties of aryl amide derivatives, we have synthesized some aryl amides bearing a chromene moiety, which have been described as under.

**SECTION-I: SYNTHESIS AND BIOLOGICAL SCREENING OF $N'$-(ARYLCARBONYL)-6-FLUORO-3,4-DIHYDRO-2H-CHROMENE-2-CARBOHYDRAZIDE**
SECTION-I
SYNTHESIS AND BIOLOGICAL SCREENING OF $N'$-(ARYLCARBONYL)-6-FLUORO-3,4-DIHYDRO-2H-CHROMENE-2-CARBOHYDRAZIDE

Arylamide derivatives showed different biological activity such as antihistaminic, anti-inflammatory, anticonvulsant, antitubercular, antipyretic, analgesic, antiseptic etc. To get a better therapeutic agent and to evaluate its pharmacological profile, we have synthesized aryl amides of type-(XII) by the condensation of 6-fluoro-3,4-dihydro-2H-chromene-2-carbohydrazide with different aromatic acid in the presence of $N$-[3-(dimethylamino)propyl]-$N'$-ethylcarbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBT) and triethylamine (TEA).

The constitution of the synthesized products have been characterized by using elemental analysis, IR & $^1$H-NMR spectroscopy and further supported by mass spectroscopy.

All the compounds have been evaluated for their in vitro biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards A. niger, C. Albicans and A. Clavatus at a different concentration. The biological activities of synthesized compounds were compared with standard drugs.

**REACTION SCHEME**

![Reaction Scheme Image]
IR SPECTRUM OF 6-FLUORO-N'(PHENYL CARBONYL)-3,4-DIHYDRO-2H-CHROMENE-2-CARBOHYDRAZIDE

Instrument: SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm\(^{-1}\) (KBr disc.)

<table>
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<th>Type</th>
<th>Vibration Mode</th>
<th>Frequency cm(^{-1})</th>
<th>Ref.</th>
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<td>Reported</td>
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<td>C-H str. (sym.)</td>
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<td></td>
<td>C-H def. (sym.)</td>
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<td>1470-1435</td>
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<tr>
<td></td>
<td>C-H def. (asym.)</td>
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<td>1395-1370</td>
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<td>Aromatic</td>
<td>C-H str.</td>
<td>3009</td>
<td>3100-3000</td>
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<td></td>
<td>C=C str.</td>
<td>1535 &amp; 1492</td>
<td>1585-1480</td>
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<td>C-H i.p. def.</td>
<td>1089</td>
<td>1125-1090</td>
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<tr>
<td>Amide</td>
<td>C=O str.</td>
<td>1697 &amp; 1649</td>
<td>1700-1650</td>
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<td>-NH str.</td>
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<td>C-N str.</td>
<td>1101</td>
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<tr>
<td>Ether</td>
<td>C-O-C</td>
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**1H-NMR SPECTRUM OF 6-FLUORO-N’-(PHENYLCARBONYL)-3,4-DIHYDRO-2H-CHROMENE-2-CARBOHYDRAZIDE**

**Internal Standard:** TMS; **Solvent:** CDCl\textsubscript{3} **Instrument:** BRUKER Spectrometer (300MHz)

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<th>Sr. No.</th>
<th>Chemical Shift In δppm</th>
<th>Relative No. of Protons</th>
<th>Multiplicity</th>
<th>Inference</th>
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<td>multiplet</td>
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<td>-</td>
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<td>2.42-2.46</td>
<td>1H</td>
<td>multiplet</td>
<td>-CH\textsubscript{2} (a)</td>
<td>-</td>
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<td>3</td>
<td>2.82-2.90</td>
<td>2H</td>
<td>multiplet</td>
<td>-CH\textsubscript{2} (b)</td>
<td>-</td>
</tr>
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<td>4</td>
<td>4.66-4.70</td>
<td>1H</td>
<td>double doublet</td>
<td>-CH (c)</td>
<td>3.0 &amp; 9.6</td>
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<tr>
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<td>6.77-6.92</td>
<td>3H</td>
<td>multiplet</td>
<td>Ar-H (d,e,f)</td>
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<td>2H</td>
<td>triplet</td>
<td>Ar-H(g,g’)</td>
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<td>triplet</td>
<td>Ar-H(h)</td>
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<td>doublet</td>
<td>Ar-H(i,i’)</td>
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<td>8.82</td>
<td>1H</td>
<td>singlet</td>
<td>-CO-NH</td>
<td>-</td>
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<tr>
<td>10</td>
<td>9.26</td>
<td>1H</td>
<td>singlet</td>
<td>-CO-NH</td>
<td>-</td>
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</table>
EXPANDED $^1$H-NMR SPECTRUM

Chapter-7

Studies on Aryl Amide...
MASS SPECTRUM OF 6-FLUORO-N\(^\prime\)-(PHENYLCARBONYL)-3,4-DIHYDRO-2\(H\)-CHROMENE-2-CARBOHYDRAZIDE

Mol. Wt. = 314.3
\(m/z = 315.2\) (M+1), 332.0 (M+18), 629.4 (2M+1), 646.4 (2M+18)

MASS SPECTRUM OF 6-FLUORO-N\(^\prime\)-((4-METHYLPHENYL)CARBONYL)-3,4-DIHYDRO-2\(H\)-CHROMENE-2-CARBOHYDRAZIDE

Mol. Wt. = 328.3
\(m/z = 329.3\) (M+1), 346.3 (M+18), 657.4 (2M+1), 674.5 (2M+18)
EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF \(N'(\text{arylcarbonyl})\)-6-fluoro-3,4-dihydro-2H-chromene-2-carbohydrazide

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mental. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica gel-G F\(_{254}\) coated aluminum sheet (Merck prepared plates) as stationary phase. 10 % Methanol in chloroform was used as a mobile phase.

[A] SYNTHESIS OF 6-FLUORO-3,4-DIHYDRO-2H-CHROMENE-2-CARBOHYDRAZIDE

See, Chapter-2, Part-B, Section-I, Experimental [B], Page no. 93.

[B] SYNTHESIS OF 6-FLUORO-\(N'(\text{phenylcarbonyl})\)-3,4-dihydro-2H-chromene-2-carbohydrazide

To the stirred solution of benzoic acid (1.22 g, 0.01 mol) in dry DCM (20 ml), HOBl (\(N\)-hydroxybenzotriazole) (1.53 g, 0.01 mol) and EDCI (\(N,N'\)-dicyclohexylcarbodi-imide) (2.87 g, 0.015) was added at 0 °C. The obtained solution was stirred for 15 minute at 0 °C. To this solution 6-fluoro-3,4-dihydro-2H-chromene-2-carbohydrazide (2.10 g, 0.01 mol) was added portionwise, then after 2 minute TEA (2.08 ml 0.015 mol) was added. The reaction mixture was stirred for 10 hour at room temperature (monitored by TLC). The solvent was distillled out, residue was poured into water. The product was extracted with ethylacetate (20 ml \(\times\) 3), and the combined organic layers were washed with water followed by brine and dried over anhydrous Na\(_2\)SO\(_4\). The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel (mesh size: 60-120 (eluent: 2 % methanol in DCM) to obtain pure product. Yield: 79 %, M. P. 203-204 °C, (C\(_{17}\)H\(_{15}\)FN\(_2\)O\(_3\)); Required: C, 64.96; H, 4.81; N, 8.91 %; Found: C, 64.61; H, 4.72; N, 8.85 %).

Similarly, other \(N'(\text{arylcarbonyl})\)-6-fluoro-3,4-dihydro-2H-chromene-2-carbohydrazide were (12a-j) prepared. The physical constants are recorded in Table-12a, Page no. 241.
Studies on Biologically Active...

[C] BIOLOGICAL SCREENING OF N'-ARYL-CARBOXYL-6-FLUORO-3,4-DIHYDRO-2H-CHROMENE-2-CARBOHYDRAZIDE

Antimicrobial testing was carried out as described in Chapter-1, Section-I, Experimental [C], Page no. 37. The results obtained from antimicrobial testing are recorded in Table-12b, Page no. 242.
TABLE-12a: PHYSICAL CONSTANTS OF N’-(ARYLCARBONYL)-6-FLUORO-3,4-DIHYDRO-2H-CHROMENE-2-CARBOHYDRAZIDE

![Chemical Structure](image)

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<tr>
<th>Sr. No.</th>
<th>Substitution R</th>
<th>Molecular Formula/Molecular Weight</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>% Composition Calcd./Found</th>
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<tr>
<td>12a</td>
<td>H</td>
<td>C_{17}H_{15}FN_{2}O_{3} 314.31</td>
<td>203-204</td>
<td>79</td>
<td>C 64.96 4.84 8.91</td>
</tr>
<tr>
<td>12b</td>
<td>4-OMe</td>
<td>C_{18}H_{17}FN_{2}O_{4} 344.34</td>
<td>185-187</td>
<td>73</td>
<td>C 62.79 4.98 8.14</td>
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<tr>
<td>12c</td>
<td>4-CH_{3}</td>
<td>C_{18}H_{17}FN_{2}O_{3} 328.34</td>
<td>197-198</td>
<td>76</td>
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<td>12d</td>
<td>4-NO_{2}</td>
<td>C_{17}H_{14}FN_{3}O_{5} 359.31</td>
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<td>12e</td>
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<td>12f</td>
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<td>C_{17}H_{14}ClFN_{2}O_{3} 348.76</td>
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<td>C_{17}H_{13}ClFN_{3}O_{5} 393.75</td>
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<td>C 51.86 3.33 10.67</td>
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TABLE 12b: BIOLOGICAL SCREENING OF N\(^\text{\textregistered}\)-(ARYLCARBONYL)-6-FLUORO-3,4-DIHYDRO-2H-CHROMENE-2-CARBOHYDRAZIDE

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<th>Antifungal activity</th>
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<th>Minimal fungicidal concentration μg/ml</th>
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MINIMAL INHIBITION CONCENTRATION

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<td>Ciprofloxacin</td>
<td>50</td>
<td>50</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

MINIMAL FUNGICIDAL CONCENTRATION

<table>
<thead>
<tr>
<th>Standard Drugs</th>
<th>C.Albicans</th>
<th>A.Niger</th>
<th>A.Clavatus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nystatin</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Greseofulvin</td>
<td>500</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
ANTIBACTERIAL ACTIVITY:

From screening results, substituted aryl amide 12b (R= 4-OMe) & 12f (R= 4-Cl) against *S.aureus*, 12c (R= 4-Me) against *S.pyogenus* and 12f (R= 4-Cl) against *E.coli* exhibit very good activity compared to ampicillin. While 12c (R= 4-Me) & 12e (R= 4-F) against *S.aureus*, 12e (R= 4-F) against *S.pyogenus*, 12j (R= 2-NO2-5-Cl) against *E.coli* and 12f (R= 4-Cl) against *P.aeruginos*, show moderate activity as compared to ampicillin. The remaining compounds demonstrate moderate to poor activity against all four bacterial species.

ANTIFUNGAL ACTIVITY:

Antifungal screening data shows that substituted aryl amide 12a (R= -H) & 12j (R= 2-NO2-5-Cl) display excellent activity against *C.albicans* as compared to greseofulvin while 12f (R= 4-Cl) exhibit moderate activity against *A.niger* and *A.clavatus*. The remaining compounds show moderate to poor activity against all three bacterial species.
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