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# SYNTHESIS AND ANTIMICROBIAL STUDIES OF INDOLYL PYRIMIDINES

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**Abstract :** Many classes of chemotherapeutic agents containing pyrimidine nucleus are in clinical use such as antibacterial (Sulfadiazine,sulfamerazine and sulfamethazine), anticancer (5- fluorouracil and ftorafur), antiviral ( iodoxuridine, trifluridine and zidovudine)agents. The reaction of indolyl chalcone with urea or thiourea gave indolyl pyrimidines derivatives. All the synthesized compounds have been characterized by elemental and spectral (IR, PMR and Mass) analyses. All representative compounds have been evaluated for their antibacterial and antifungal activities.

**Keyword:** Indolyl pyrimidines, thiourea , indoles

## Introduction

The indole derivatives are known to posses anticancer , antioxidant , antirheumatoidal and anti HIV activities. indolyl pyrimidines systems as antioxidants, DNA cleavage and cytotoxic agents . In continuation if our interest on drug like molecules. The evaluation of the novel indolyl pyrimidine analogues for antimicrobial activities to generate novel molecular templates which are likely to exhibit interesting biological properties.

Pyrimidine present an interesting group of compounds many of which possess widespread pharmacologic properties such as antimicrobial [1], analgesic, antiviral, anti-inflammatory [2], anti HIV[3], antitubercular[4], antitumor[5], antineoplastic[6], antimalerial[7], diuretic[8], cardiovascular [9] agents, hypnotic drugs for the nervous system [10], calcium sensing receptor antagonists [11] and also for antagonists of the human $A_{2A}$ adenosine receptor[12]. Several drugs have been developed as anticancer agents which contain pyrimidine moieties, such as clofarabine,capeitabine, cytarabine,fludarabine,gemcitabine,decitabine [13] and floxuridine [14,15].

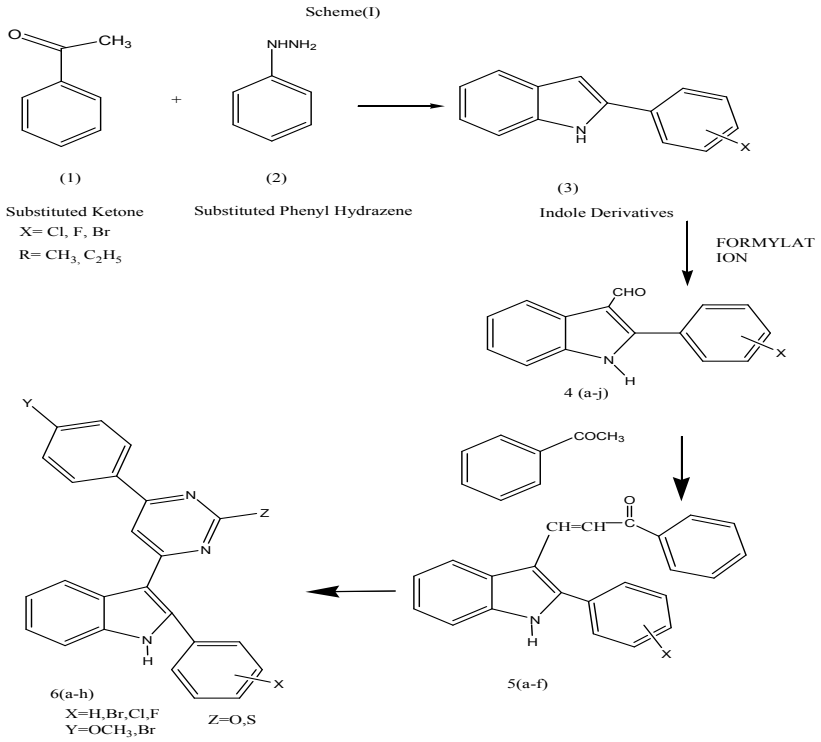
Pyrimidine based heterocycles are potential bioactive molecules and exhibit antibacterial, anti-inflammatory, cytotoxic[16], antitumoral , analgesic, antitubercular and antiviral , antihypertensive, anticonvulsant , antimicrobial agents and also act as enzyme inhibitors . Many classes of chemotherapeutic agents containing pyrimidine nucleus are in clinical use such as antibacterial (Sulfadiazine,sulfamerazine and sulfamethazine), anticancer (5- fluorouracil and ftorafur), antiviral ( iodoxuridine, trifluridine and zidovudine), antifungal

(flucytocine) and antimalarial (pyrimethamine)agents. Nitrogen containing heterocycles such as pyrimidine and indole is a promising structural moiety for drug designing.

## Experimental

Substituted 2-phenyl indoles were prepared by Fischer-indole synthesis and by the method of Joshi et al. Substituted 2-phenyl indoles was subjected to Vilsmeier – Haack formylation [a] with $POCl_3$ and N, N- dimethylformamide to give 2-arylindole-3- carboxaldehyde (4) was reacted with substituted acetophenones in ethanolic NaOH to obtain chalcone **(5 a-f),** which were condensed with urea and thiourea in presence of cyclising agent, concentrated hydrochloric acid to obtain substituted pyrimidines **( 6a-h)** respectively. The title compound gave a single spot on TLC in different solvent system. The synthetic sequence leading to the formation of targeted compounds is depicted in Scheme – I

Scheme(I)




## Materials and Methods

Characterization of synthesized compounds has been done on the basis of elemental analyses, IR and $^1H$ NMR studies. C and H analyses of compounds has been done using coleman C and H analyzer .Nitrogen analyses has been done using coleman N-analyses 29. Melting point were determined in open glass capillaries and are uncorrected. IR (4000-400 $cm^{-1}$) were recorded on Perkin Elmer model 557 and Nicholet magna model 750 spectrophotometer in KBr pallets at central Drug Research Institute (CDRI), Lucknow .$^1H$ NMR spectra were recorded on spectrometer (300 mHz) using $CDCl_3$ /DMSO as solvent.TMS was taken as standard. The chemical shift are in δppm .The purity of compounds was checked by TLC using silica gel-G as adsorbent in various solvent system. Visualization was accomplished by U.V light or iodine adsorption.

**1- (4- substituted phenyl ) -3-(2'- aryl indolyl) -2- propen-1-one ( 5a-f)**

Equimolar quantities (0.01 M) of 2-arylindole-3- carboxaldehyde and substituted acetophenones were taken in 100 ml conical flask and dissolved in 20ml of ethanol to this (.03mol) of NaOH in minimum quantity of water was added . The mixture was stirred on magnetic stirrer and the reaction was monitored with TLC . Reaction mixture was diluted with water and acidified with concentrated hydrochloric acid . The precipitated chalcon was filtered and recrystallized from absolute ethanol. The purity of the chalcones was tested with thin layer chromatography using solvent system (50% benzene and 50% petroleum ether). Compounds are white and pale yellow. The physical and analytical characteristics are given in **Table-1**

**4- ( 2-arylindol-3- yl)-6-(4- substituted phenyl) -2- substituted pyrimidines (6a-h)**

Chalcone (0.01mol) and urea or thiourea (.01mol) were dissolved in absolute alcohol (20ml) few drops of concentrated HCl were added and the reaction mixture was refluxed and the reaction was monitored by TLC. After completion of reaction it was poured into 250ml of ice cold water and kept for some time. The crude solid was filtered and subjected to column chromatography. Elution with solvent system ethyl acetate / petroleum ether (60-80$^{o}$). The compounds were blue in colour. The physical and analytical characteristics are given in **Table-2**

**Result and Discussion**

Substituted 2-phenyl indoles were prepared by Fischer indole synthesis and by the method of Joshi et al. (**Scheme-I)**.The IR spectra of 2-arylindole showed absorption band at 3450-3350 $cm^{-1}$ which is attributed to >N-H stretching vibration, In the IR spectra of the compounds (4a-j) >N-H absorption band appears at 3417-3400 $cm^{-1}$ and aromatic C-H str. Absorption peak appears at 3060-3051 $cm^{-1}$. Aliphatic C-H stretching Vibration is observed at 2839 $cm^{-1}$ ,aromatic C=C absorption band is observed at 1604 $cm^{-1}$ and HC=O absorption appears at 1750 $cm^{-1}$ .Absorption band due to C-Br appears at 548 $cm^{-1}$.The $^{1}$H NMR spectra of 2-arylindole revealed the presence of a broad resonance signal in the region of δ 7.8-8.0ppm .which is attributed to >N-H proton, a methine resonance signal (=C-H, at C-3) appears as a sharp singlet at δ 6.4ppm. In the $^{1}$H NMR spectra of all compounds (4a-j) , the disappearance of resonance signal from δ 6.4ppm due to methine =C-H proton at C-3 position of indole moiety, supports the formation of formyl indole. In the IR spectra of ( 5a-f) shows the disappearance of >C=O absorption band at 1750 $cm^{-1}$ supports the formation of 1- (4-substituted phenyl ) -3-(2'- aryl indolyl) -2- propen-1-one. The IR and $^{1}$HNMR spectra of the title compounds are given in **Table-3.**

**Antibacterial and Antifungal Activities**

All the synthesized compounds were screened for their antimicrobial activity against bacteria *Escherichia coli* and *Bacillus subtilis* and fungi ***Candida albicans***, *fuserium oxysporium* at different concentration by disc diffusion method. Streptomycin and Ketokenazole are used as standard for evaluating antibacterial and antifungal activities respectively. Some compounds show prominent results. The antibacterial and antifungal activities are listed in **Table-4 & 5.**

**Table – 1**

**Physical characteristics and analytical Characteristics of 1- (4- substituted phenyl ) -3- (2'- aryl indolyl) -2- propen-1-one ( 5a-f)**

| Compd.No. | X | Y aniline | M.P.(°C) | M.F. | C (%) | | H (%) | | N (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cal. | Obs. | Cal. | Obs. | Cal. | Obs. |
| 5a | H | Br | 180 | $C_{23}H_{16}$ Br N O | 68.65 | 68.62 | 3.98 | 3.93 | 3.48 | 3.43 |
| 5b | Br | Br | 250 | $C_{23}H_{15}$ $Br_2$ N O | 57.38 | 57.34 | 3.11 | 3.10 | 2.91 | 2.90 |
| 5c | Cl | Br | 270 | $C_{23}H_{15}$ Br Cl N O | 63.23 | 63.21 | 3.43 | 3.40 | 3.20 | 3.19 |
| 5d | H | $OCH_3$ | 258 | $C_{24}H_{19}$ N $O_2$ | 81.58 | 81.53 | 5.38 | 5.34 | 3.96 | 3.92 |
| 5e | Br | $OCH_3$ | 258 | $C_{24}H_{18}$ Br N $O_2$ | 66.66 | 66.62 | 4.16 | 4.14 | 3.24 | 3.21 |
| 5f | F | Br | 268 | $C_{23}H_{15}$ Br FN O | 65.71 | 65.70 | 3.57 | 3.53 | 3.33 | 3.31 |

**Table –2**

**Physical characteristics and analytical Characteristics of 4- ( 2-arylindol-3- yl)-6-(4-substituted phenyl) -2- substituted pyrimidines (6a-h)**

| Compd.No. | X | Y aniline | Z | M.P.(°C) | M.F. | C (%) | | H (%) | | N (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Cal. | Obs. | Cal. | Obs. | Cal. | Obs. |
| 6a | Br | Br | O | 180 | $C_{24}H_{15}$ $Br_2N_3$ O | 55.27 | 55.21 | 2.87 | 2.82 | 8.06 | 8.02 |
| 6b | Cl | Br | O | 182 | $C_{24}H_{15}$ Br Cl $N_3$ O | 60.44 | 60.42 | 3.14 | 3.11 | 8.81 | 8.80 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 6c | H | $OCH_3$ | O | 184 | $C_{25}H_{19}N_3O_2$ | 76.33 | 76.30 | 4.83 | 4.80 | 10.68 | 10.63 |
| 6d | H | Br | O | 240 | $C_{24}H_{16}BrN_3O$ | 65.15 | 65.13 | 3.61 | 3.60 | 9.50 | 9.49 |
| 6e | Br | $OCH_3$ | O | 260 | $C_{25}H_{18}BrN_3O_2$ | 63.55 | 63.51 | 3.81 | 3.80 | 8.89 | 8.84 |
| 6f | F | Br | O | 265 | $C_{24}H_{15}BrFN_3O$ | 62.60 | 62.59 | 3.26 | 3.23 | 9.13 | 9.10 |
| 6g | Br | Br | S | 265 | $C_{25}H_{15}Br_2N_3S$ | 54.64 | 54.62 | 2.73 | 2.70 | 7.65 | 7.61 |
| 6h | Cl | Br | S | 250 | $C_{25}H_{15}BrClN_3S$ | 59.46 | 59.42 | 2.97 | 2.92 | 8.32 | 8.30 |

**Table- 3**
**Spectral data of 4- ( 2-arylindol-3- yl)-6-(4- substituted phenyl) -2- substituted pyrimidines (6a-h)**

| **Compd. No** | **IR(KBr) $\nu_{max}$ $cm^{-1}$** | **$^1$HNMR($CDCl_3$) δ ppm** | **FEB mass m/z** |
|---|---|---|---|
| 6a | 3403 (NH str.), 3050 (Aromatic C-H Str.), 2839 (Aliphatic C-H Str.), 1750 (C=O), 1657(aromatic C=C Str.), 1601( C=C Str.). | 11.2{s,1H,OH),10.9(s,1H,NH,), 8.3-7(m,5H,Ar-H),7.6(s,1H Pyrimidine proton), 7.3(s,1H,Indolylproton),7.1-6.7(M,8H,Ar-H), | 521/523/525 isotopic cluster |
| 6c | 3416 (NH str.), 3049 (Aromatic C-H ), 2839 (Aliphatic C-H Str.), 1716 (C=O), 1657(aromatic C=C Str.), 1602( C=C Str.). | 11.3(s,1H, OH),10.8(S,1H,NH.), 8.4-7.7(m,4H,Ar-H), 7.5(S,1H,Pyrimidine proton ), 7.3(S,1H,Indolyl proton), 7.1-6.7(M,8H,Ar-H), 5.2(S,2H,NH), | 393 ( Molecular ion ) |
| 6g | 3323 (NH str.), 2961 (Aromatic C- H ), 2826 (Aliphatic C-H Str.), 1750 (C=O), 1598 (aromatic C=C Str.), 748(C-Cl Str. ), 499 (C-Br Str. ). | 10.7(S,1H,NH,Exchangeable), 8.4(S,1H,Pyrimidine proton ), 8.3-7.4(M,4H,Ar-H), 7.3(S,1H,Indolyl proton ), 7.0-6.6(m,8HAr-H), | 549/551/ 553 isotopic cluster |

**Table- 4**

**Antibacterial activity of 4- ( 2-arylindol-3- yl)-6-(4- substituted phenyl) -2- substituted pyrimidines (6a-h)**

| compounds | Mean value of area of inhibition in mm **(400ppm)** | | Mean value of area of inhibition in mm **(800ppm)** | | Mean value of area of inhibition in mm **(1000ppm)** | |
|---|---|---|---|---|---|---|
| | ***E.coli*** | ***Bacillus subtilis*** | ***E.coli*** | ***Bacillus subtilis*** | ***E.coli*** | ***Bacillus subtilis*** |
| **Streptomycin** | 3 | 6 | 5 | 7 | 10 | 12 |
| 6a | NIL | NIL | NIL | **20mm** | **8mm** | **6mm** |
| 6b | NIL | NIL | NIL | NIL | **4mm** | NIL |
| 6c | **6mm** | **14mm** | **10mm** | NIL | **10mm** | NIL |
| 6d | **6mm** | **NIL** | **6mm** | NIL | **12mm** | **16mm** |
| 6e | **10mm** | NIL | NIL | NIL | NIL | NIL |
| 6f | NIL | NIL | NIL | NIL | **10mm** | NIL |
| 6g | NIL | NIL | NIL | NIL | NIL | NIL |
| 6h | NIL | NIL | NIL | NIL | NIL | **8mm** |

**Table- 5**

**Antifungal activity of 4- (2-arylindol-3- yl-)-6-(4- substituted phenyl) -2- substituted pyrimidines (6a-h)**

| Compounds | Mean value of area of inhibition in mm **(400ppm)** | | Mean value of area of inhibition in mm **(800ppm)** | | Mean value of area of inhibition in mm **(1000ppm)** | |
|---|---|---|---|---|---|---|
| | ***Candida albicans*** | ***Fuserium oxysporium*** | ***Candida albicans*** | ***Fuserium oxysporium*** | ***Candida albicans*** | ***Fuserium oxysporium*** |
| Ketokenazole | 8mm | 22mm | 10mm | 20mm | 18mm | 22mm |
| 6a | 7mm | Nil | 4mm | 10mm | 12mm | Nil |
| 6b | Nil | 2mm | 4mm | 6mm | 14mm | Nil |
| 6c | 3mm | 4mm | 6mm | 4mm | 14mm | 4mm |
| 6d | 4mm | 8mm | 15mm | 10mm | 20mm | 6mm |
| 6e | Nil | Nil | 4mm | 12mm | 30mm | Nil |
| 6f | 2mm | **4mm** | **Nil** | **10mm** | **20mm** | Nil |
| 6g | **2mm** | Nil | Nil | **Nil** | **Nil** | **6mm** |
| 6h | Nil | Nil | Nil | **Nil** | **Nil** | **6mm** |

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