INTERNATIONAL JOURNAL OF ADVANCES IN PHARMACY, BIOLOGY AND CHEMISTRY

Research Article

# Microwave assisted synthesis and antimicrobial screening of novel 9-(N-phenyl) - 4, 5-(2", "'-methoxyphenol)-9H-1,3,6,8,9-hexa-azo-fluorene-2,7-diamine derivatives using bis-heterocyclic chalcones

**R. S. Dhivare[1], S. S. Rajput[2]***

[1] Department of Chemistry, J.J.T. University, Rajasthan, India.

[2]Department of Chemistry, SVS's Dadasaheb Rawal College, Dondaicha, (MS), India.

**ABSTRACT**

Amino-pyrimidine derivatives were synthesized by simple and clean single pot method using bis-chalcones of different substituted phenyl glutarimides and guanidine nitrate with neutral alumina irradiated under the microwave supported solvent less condition is demonstrated. All the compounds were screened their antimicrobial activities and showed moderate activities. But certain amino-pyrimidines exhibited synergistic and significant activities against *Candida albicans* and *Aspergillus niger* fungal genres.

**Keywords:** N-Phenyl Glutarimides, Bis-heterocyclic chalcones, Amino-pyrimidines and Antimicrobial activity.

## INTRODUCTION

The heterocyclic compounds containing nitrogen groups unusually involved in the pastresearches of heterocyclic chemistry with the development of synthetic methods. Chalcones and cyclic imides perform a significant starring role in the heterocyclic synthesis containing nitrogen groups. Cyclic imides[1]resembling succinimides[2, 3], maleimides[4], phthalimides[5] and glutarimide[6] showed antibacterial[7] and antifungal shielding activities. The substituted heterocyclic imides were developed from cyclic anhydrides[8], trifluoroacetylation[9] and bis-heterocyclic analogs[10] by microwave synthesis. Bis-chalcones are prepared by the condensation[11] of the substituted ketones and aldehyde groups[12]. They are synthesized by utilizing a number of synthetic routes like solid phase cross-aldol condensation, acid catalyst[13], coupling reaction[14] and microwave assisted synthesis[15, 16].

The amino-pyrimidine derivative has been developed by chalcones intermediates with nitrate, chlorides of guanidine cyclized by ring extension of N-C-N groups. A variety of novel amino-pyrimidines[17], imidopyrimidines[18], pyrido-pyrimidines[19] and substituted pyrimidines from the chalcone intermediates[20, 21] shown the significant antibacterial and antifungal activities[22]. Several amino-pyrimidine derivatives exhibited the significant antimicrobial[23], antioxidant[24], anti-inflammatory[25], anticancer[26], anti-plasmodial[27], anti-proliferative leukemia[28], anti-hyperlipidemic[29], breast carcinoma cells[30], analgesic[31], hypoglycemic activities[32], apoptosis inducing activities[33] and non-nucleoside pyrimidine exhibits HIV-1: RT preventive[34] activities. The synthesis of pyrimidine and amino-pyrimidine derivatives are prepared by conventional method using Claisen-Schmidt condensation coordinating by chalcones[35], cyclization of guanidine hydrochloride[36], guanidine[37] palladium catalyst[38], pyrimidines and fused pyrimidines[39], malononitriles[40], formamides[41], thiosemicarbazide[42], hydroxylamine[43] and guanidine nitrate[44] by using clean, solvent free microwave synthesis[45].

## EXPERIMENTAL SECTION

### Material methods:

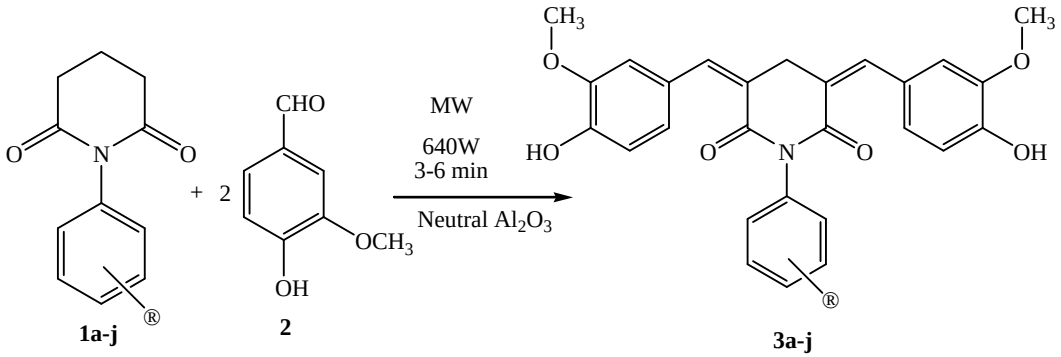
Melting points of all the synthesized compounds were inscribedand uncorrectedby using open glass capillaries. IR spectra were verified on Shimadzu FTIR-8400Ṡ and ATR Brucker alpha FT-IR spectrophotometer.$^{1}$H NMR spectra were recorded on 500.13 MHz by Brucker spectrophotometer. The completion of reaction was observed by thin layer chromatography practicing done on silica glaze aluminium plates by diethyl ether and ethyl acetate 7:3 proportion ratio. All the compounds **5a-j** was synthesized in the microwave oven in hours from bis-chalcones, guanidine nitrate, neutral alumina.

### General procedure for the synthesis of bis-chalcones derived from N-phenyl glutarimides:

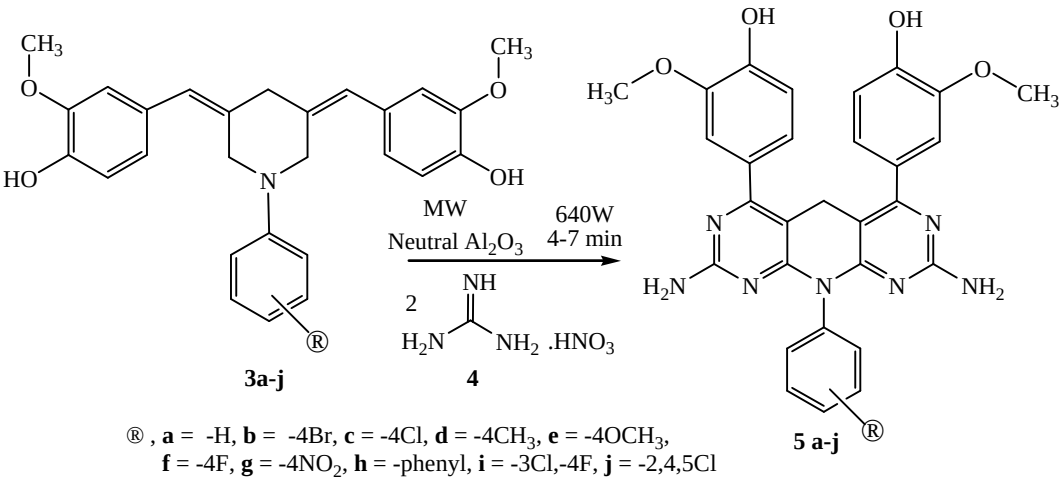
The bis-chalcones **(3a-j)** derivatives were synthesized by the mixture of 0.1 mole of N-phenyl glutarimides **(1a-j)** and 0.2 moles of 4-hydroxy-3-methoxy benzaldehyde in 2 gm of neutral $Al_2O_3$ under microwave supported solvent free condition on 640W power for 3-6 min. The developed compounds were recrystallized from ethanol **(Scheme – I)**

### (3Z,5Z)-3,5-bis(4-hydroxy-3-methoxybenzylidene)-1-phenylpiperidine-2,6-dione (3a):

Yellowish White Solid; Molecular Formula: $C_{27}H_{23}NO_6$; Molecular Weight: 457.47; Yield: 79.91%; Melting Point (ºC): 78-80 ºC; Elemental Analysis:C, 71.06; H, 6.98; N, 3.24; FTIR (KBr): >C=O (2-Peaks): 1595 $cm^{-1}$ and 1672 $cm^{-1}$, =C-H: 2968 $cm^{-1}$, aromatic ring (3-Peaks): 1455 $cm^{-1}$, 1513 $cm^{-1}$ and 1541 $cm^{-1}$, Ar-$OCH_3$: 1157 $cm^{-1}$, Ar-OH: 3320 $cm^{-1}$; $^{1}$H NMR (200.13 MHz, $CDCl_3$, δ ppm): 6.26-7.40 (m, 8H, Ar-H and =CH), 9.87 (s, 1H, -OH), 3.70 (s, 3H, -$OCH_3$), 2.46 (s, 2H, -$CH_2$)




**Scheme -I:** (3Z,5Z)-3,5-bis(4-hydroxy-3-methoxybenzylidene)-N-phenylpiperidine-2,6-dione




**Scheme -II:** 9-(N-phenyl)-4,5-(2","'-methoxyphenol)-9H-1,3,6,8,9-hexa-azo-fluorene-2,7-diamine (5a-j)

**(3Z,5Z)-3,5-bis(4-hydroxy-3-methoxybenzylidene)-1-(4-bromophenyl)piperidine-2,6-dione (3b):**
Dark Yellow Solid; Molecular Formula: $C_{27}H_{22}BrNO_6$; Molecular Weight: 536.37; Yield: 94.37%; Melting Point (ºC): 94-96 ºC; Elemental Analysis:C, 60.88; H, 4.25; N, 2.75; FTIR (KBr): >C=O (2-Peaks): 1667 $cm^{-1}$ and 1689 $cm^{-1}$, =C-H: 3032 $cm^{-1}$, aromatic ring (3-Peaks): 1462 $cm^{-1}$, 1514 $cm^{-1}$ and 1590 $cm^{-1}$, Ar-$OCH_3$: 1172 $cm^{-1}$, Ar-OH: 3294 $cm^{-1}$, Ar-Br: 1072 $cm^{-1}$

**(3Z,5Z)-3,5-bis(4-hydroxy-3-methoxybenzylidene)-1-(4-chlorophenyl)piperidine-2,6-dione (3c):**
Yellow Solid; Molecular Formula: $C_{27}H_{22}ClNO_6$; Molecular Weight: 491.92; Yield: 82.25%; Melting Point (ºC): 76-78 ºC; Elemental Analysis:C, 66.42; H, 4.68; N, 2.99; FTIR (KBr) (Spectra No.-51): >C=O (2-Peaks): 1667 $cm^{-1}$ and 1742 $cm^{-1}$, =C-H: 3030 $cm^{-1}$, aromatic ring (3-Peaks): 1462 $cm^{-1}$, 1512 $cm^{-1}$ and 1590 $cm^{-1}$, Ar-$OCH_3$: 1170 $cm^{-1}$, Ar-OH: 3287 $cm^{-1}$, Ar-Cl: 1026 $cm^{-1}$

**(3Z,5Z)-3,5-bis(4-hydroxy-3-methoxybenzylidene)-1-p-tolylpiperidine-2,6-dione (3d):**
Yellow Solid; Molecular Formula: $C_{28}H_{25}NO_6$; Molecular Weight: 471.5; Yield: 83.98%; Melting Point (ºC): 95-97 ºC; Elemental Analysis:C, 71.86; H, 5.73; N, 3.55; FTIR (KBr): >C=O (2-Peaks): 1594 $cm^{-1}$ and 1675 $cm^{-1}$, =C-H: 2946 $cm^{-1}$, aromatic ring (3-Peaks): 1459 $cm^{-1}$, 1514 $cm^{-1}$ and 1596 $cm^{-1}$, Ar-$OCH_3$: 1171 $cm^{-1}$, Ar-OH: 3280 $cm^{-1}$; $^1$H NMR (500.13 MHz, DMSO-$d^6$, δ ppm): 6.97-7.48 (m, 5H, Ar-H and =CH), 9.78 (s, 1H, -OH), 3.70 (s, 3H, -$OCH_3$), 2.71 (s, 2H, -$CH_2$)

**(3Z,5Z)-3,5-bis(4-hydroxy-3-methoxybenzylidene)-1-(4-ethoxyphenyl)piperidine-2,6-dione (3e):**
Yellow Solid; Molecular Formula: $C_{28}H_{25}NO_7$; Molecular Weight: 487.5; Yield: 69.41%; Melting Point (ºC): 68-70 ºC; Elemental Analysis:C, 69.09; H, 5.72; N, 3.20; FTIR (KBr): >C=O (2-Peaks): 1596 $cm^{-1}$ and 1677 $cm^{-1}$, =C-H: 2971 $cm^{-1}$, aromatic ring (3-Peaks): 1460 $cm^{-1}$, 1514 $cm^{-1}$ and 1596 $cm^{-1}$, Ar-$OCH_3$: 1171 $cm^{-1}$, Ar-OH: 3466 $cm^{-1}$

**(3Z,5Z)-3,5-bis(4-hydroxy-3-methoxybenzylidene)-1-(4-fluorophenyl)piperidine-2,6-dione (3f):**
Yellow Solid; Molecular Formula: $C_{27}H_{22}FNO_6$; Molecular Weight: 475.47; Yield: 90.84%; Melting Point (ºC): 85-87 ºC; Elemental Analysis:C, 68.81; H, 4.93; N, 3.33; FTIR (KBr): >C=O (2-Peaks): 1594 $cm^{-1}$ and 1672 $cm^{-1}$, =C-H: 3089 $cm^{-1}$, aromatic ring (3-Peaks): 1426 $cm^{-1}$, 1513 $cm^{-1}$ and 1594 $cm^{-1}$, Ar-$OCH_3$: 1158 $cm^{-1}$, Ar-OH: 3316 $cm^{-1}$, Ar-F: 1126 $cm^{-1}$

**(3Z,5Z)-3,5-bis(4-hydroxy-3-methoxybenzylidene)-1-(4-nitrophenyl)piperidine-2,6-dione (3g):**
Pale Yellow Solid; Molecular Formula: $C_{27}H_{22}N_2O_8$; Molecular Weight: 502.47; Yield: 78.33%; Melting Point (ºC): 93-95 ºC; Elemental Analysis:C, 64.76; H, 4.65; N, 5.85; FTIR (KBr): >C=O (2-Peaks): 1668 $cm^{-1}$ and 1711$cm^{-1}$, =C-H: 3078 $cm^{-1}$, aromatic ring (3-Peaks): 1460 $cm^{-1}$, 1512 $cm^{-1}$ and 1590 $cm^{-1}$, Ar-$OCH_3$: 1170 $cm^{-1}$, Ar-OH: 3269 $cm^{-1}$, Ar-$NO_2$: 1512 $cm^{-1}$

**(3Z,5Z)-3,5-bis(4-hydroxy-3-methoxybenzylidene)-1-(naphthalen-1-yl)piperidine-2,6-dione (3h):**
Whitish Brown Solid; Molecular Formula: $C_{31}H_{25}NO_6$; Molecular Weight: 507.53; Yield: 91.74%; Melting Point (ºC): 88-90 ºC; Elemental Analysis:C, 73.79; H, 5.02; N, 2.98; FTIR (KBr): >C=O (2-Peaks): 1667 $cm^{-1}$ and 1704 $cm^{-1}$, =C-H: 3078 $cm^{-1}$, aromatic ring (3-Peaks): 1429 $cm^{-1}$, 1460 $cm^{-1}$, 1511 $cm^{-1}$, 1589 $cm^{-1}$ and 1667 $cm^{-1}$, Ar-$OCH_3$: 1172 $cm^{-1}$, Ar-OH: 3178 $cm^{-1}$

**(3Z,5Z)-3,5-bis(4-hydroxy-3-methoxybenzylidene)-1-(3-chloro-4-fluorophenyl)piperidine-2,6-dione (3i):**
Dark Yellow Solid; Molecular Formula: $C_{27}H_{21}ClFNO_6$; Molecular Weight: 509.91; Yield: 82.23%; Melting Point (ºC): 74-76 ºC; Elemental Analysis:C, 63.91; H, 4.69; N, 2.86; FTIR (KBr): >C=O (2-Peaks): 1595 $cm^{-1}$ and 1674 $cm^{-1}$, =C-H: 3027 $cm^{-1}$, aromatic ring (3-Peaks): 1459 $cm^{-1}$, 1511 $cm^{-1}$ and 1544 $cm^{-1}$, Ar-$OCH_3$: 1172 $cm^{-1}$, Ar-OH: 3309 $cm^{-1}$, Ar-F: 1172 $cm^{-1}$, Ar-Cl: 1056 $cm^{-1}$

**(3Z,5Z)-3,5-bis(4-hydroxy-3-methoxybenzylidene)-1-(2,4,5-trichlorophenyl)piperidine-2,6-dione (3j):**
Pinkish White Solid; Molecular Formula: $C_{27}H_{20}Cl_3NO_6$; Molecular Weight: 560.81; Yield: 83.03%; Melting Point (ºC): 103-105 ºC; Elemental Analysis:C, 58.58; H, 3.84; N, 2.87; FTIR (KBr): >C=O (2-Peaks): 1669 $cm^{-1}$ and 1694 $cm^{-1}$, =C-H: 3027 $cm^{-1}$, aromatic ring (3-Peaks): 1459 $cm^{-1}$, 1512 $cm^{-1}$ and 1580 $cm^{-1}$, Ar-$OCH_3$: 1170 $cm^{-1}$, Ar-OH: 3276 $cm^{-1}$, Ar-2,4,5Cl: 1078 $cm^{-1}$; $^1$H NMR (500.13 MHz, DMSO-$d^6$, δ ppm): 6.96-8.10 (m, 5H, Ar-H

and =CH), 9.77 (s, 1H, -OH), 3.40 (s, 3H, -$OCH_3$), 2.30 (s, 2H, -$CH_2$)

**General procedure for the synthesis of amino-pyrimidines (5a-j):**

Amino-pyrimidine **(5a-j)** derivatives were synthesized by the mixture of 0.2 moles of previously prepared bis-chalcones **(3a-j)** and 0.4 moles of guanidine nitrate in 2 gm of neutral $Al_2O_3$ under microwave supported solvent free condition on 640W power for 4-7 minutes. The synthesized compounds were recovered by ethyl acetate and recrystallized by ethanol **(Scheme-II)**

**9-(1-phenyl)-4,5-(2″,‴-methoxyphenol)-9H-1,3,6,8,9-hexa-azo-fluorene-2,7-diamine (6a):**

Brownish Yellow Solid; Molecular Formula: $C_{29}H_{25}N_7O_4$; Molecular Weight: 535.55; Yield: 80.45%; Melting Point (ºC): 89-91 ºC; Elemental Analysis: C, 65.19; H, 4.71; N, 18.95; FTIR (KBr): -$NH_2$ (2-Peaks): 3303 cm-1 and 3365 $cm^{-1}$, aromatic ring (3-Peaks): 1532 $cm^{-1}$, 1595 $cm^{-1}$ and 1665 $cm^{-1}$, Ar-$OCH_3$: 1293 $cm^{-1}$, Ar-OH: 3509 $cm^{-1}$

**9-(4′-bromophenyl)-4,5-(2″,‴-methoxyphenol)-9H-1,3,6,8,9-hexa-azo-fluorene-2,7-diamine (6b):**

Yellowish Orange Solid; Molecular Formula: $C_{29}H_{24}BrN_7O_4$; Molecular Weight: 614.45; Yield: 76.54%; Melting Point (ºC): 99-101 ºC; Elemental Analysis: C, 56.89; H, 4.21; N, 16.31; FTIR (KBr): -$NH_2$ (2-Peaks): 3417 cm-1 and 3461 $cm^{-1}$, aromatic ring (3-Peaks): 1532 $cm^{-1}$, 1595 $cm^{-1}$ and 1665 $cm^{-1}$, Ar-$OCH_3$: 1293 $cm^{-1}$, Ar-OH: 3593 $cm^{-1}$, Ar-Br: 1024 $cm^{-1}$; $^1$H NMR (500.13 MHz, DMSO-$d^6$, δ ppm): 6.96-7.56 (m, 5H, Ar-H), 9.77 (s, 2H, -$NH_2$), 10.27 (s, 1H, -OH), 3.80 (s, 3H, $OCH_3$), 3.41 (s, 2H, $CH_2$)

**9-(4′chlorophenyl)-4,5-(2″,‴-methoxyphenol)-9H-1,3,6,8,9-hexa-azo-fluorene-2,7-diamine (6c):**

Yellowish Solid; Molecular Formula: $C_{29}H_{24}ClN_7O_4$; Molecular Weight: 570.00; Yield: 83.03%; Melting Point (ºC): 88-90 ºC; Elemental Analysis: C, 61.38; H, 4.67; N, 17.73; FTIR (KBr): -$NH_2$ (2-Peaks): 3300 cm-1 and 3370 $cm^{-1}$, aromatic ring (3-Peaks): 1461 $cm^{-1}$, 1596 $cm^{-1}$ and 1623 $cm^{-1}$, Ar-$OCH_3$: 1268 $cm^{-1}$, Ar-OH: 3493 $cm^{-1}$, Ar-Cl: 1028 $cm^{-1}$

**9-(p-tolyl)-4,5-(2″,‴-methoxyphenol)-9H-1,3,6,8,9-hexa-azo-fluorene-2,7-diamine (6d):**

Whitish Yellow Solid; Molecular Formula: $C_{30}H_{27}N_7O_4$; Molecular Weight: 549.58; Yield: 79.12%; Melting Point (ºC): 108-110 ºC; Elemental Analysis: C, 65.85; H, 5.15; N, 17.98; FTIR (KBr): -$NH_2$ (2-Peaks): 3402 cm-1 and 3456 $cm^{-1}$, aromatic ring (3-Peaks): 1459 $cm^{-1}$, 1515 $cm^{-1}$ and 1592 $cm^{-1}$, Ar-$OCH_3$: 1297 $cm^{-1}$, Ar-OH: 3600 $cm^{-1}$

**9-(4′-methoxyphenyl)-4,5-(2″,‴-methoxyphenol)-9H-1,3,6,8,9-hexa-azo-fluorene-2,7-diamine (6e):**

Yellowish Green Muddy Solid; Molecular Formula: $C_{30}H_{27}N_7O_5$; Molecular Weight: 565.58; Yield: 67.25%; Melting Point (ºC): 88-90 ºC; Elemental Analysis: C, 63.86; H, 4.98; N, 17.75; FTIR (KBr): -$NH_2$ (2-Peaks): 3316 cm-1 and 3394 $cm^{-1}$, aromatic ring (3-Peaks): 1513 $cm^{-1}$, 1594 $cm^{-1}$ and 1667 $cm^{-1}$, Ar-$OCH_3$: 1296 $cm^{-1}$, Ar-OH: 3600 $cm^{-1}$

**9-(4′-fluorophenyl)-4,5-(2″,‴-methoxyphenol)-9H-1,3,6,8,9-hexa-azo-fluorene-2,7-diamine (6f):**

Yellow Solid; Molecular Formula: $C_{29}H_{24}FN_7O_4$; Molecular Weight: 553.54; Yield: 80.00%; Melting Point (ºC): 91-93 ºC; Elemental Analysis: C, 63.72; H, 4.49; N, 17.98;FTIR (KBr): -$NH_2$ (2-Peaks): 3313 cm-1 and 3392 $cm^{-1}$, aromatic ring (3-Peaks): 1513 $cm^{-1}$, 1594 $cm^{-1}$ and 1668 $cm^{-1}$, Ar-$OCH_3$: 1296 $cm^{-1}$, Ar-OH: 3500 $cm^{-1}$, Ar-F: 1158 $cm^{-1}$

**9-(4′-nitrophenyl)-4,5-(2″,‴-methoxyphenol)-9H-1,3,6,8,9-hexa-azo-fluorene-2,7-diamine (6g):**

Yellow Solid; Molecular Formula: $C_{29}H_{24}N_8O_6$; Molecular Weight: 580.55; Yield: 70.68%; Melting Point (ºC): 123-125 ºC; Elemental Analysis: C, 60.28; H, 4.67; N, 19.75; FTIR (ATR): -$NH_2$ (2-Peaks): 3254 cm-1 and 3355 $cm^{-1}$, aromatic ring (3-Peaks): 1461 $cm^{-1}$, 1594 $cm^{-1}$ and 1672 $cm^{-1}$, Ar-$OCH_3$: 1265 $cm^{-1}$, Ar-OH: 3600 $cm^{-1}$, Ar-$NO_2$: 1513 $cm^{-1}$;$^1$H NMR (500.13 MHz, $CDCl_3$, δ ppm): 6.96-8.20 (m, 5H, Ar-H), 9.77 (s, 2H, -$NH_2$), 10.27 (s, 1H, -OH), 3.80 (s, 3H, $OCH_3$), 3.38 (s, 2H, $CH_2$)

**9-(napthy-4-yl)-4,5-(2″,‴-methoxyphenol)-9H-1,3,6,8,9-hexa-azo-fluorene-2,7-diamine (6h):**

Greyish Brown Solid; Molecular Formula: $C_{33}H_{27}N_7O_4$; Molecular Weight: 585.61; Yield: 64.60%; Melting Point (ºC): 103-105 ºC; Elemental Analysis: C, 67.76; H, 4.69; N, 16.99; FTIR (KBr): -$NH_2$ (2-Peaks): 3299 cm-1 and 3393 $cm^{-1}$, aromatic ring (3-Peaks): 1459 $cm^{-1}$, 1513 $cm^{-1}$, 1535 $cm^{-1}$, 1594 $cm^{-1}$ and 1669 $cm^{-1}$, Ar-$OCH_3$: 1265 $cm^{-1}$, Ar-OH: 3600 $cm^{-1}$

**9-(3′-chloro-4′-fluorophenyl)-4,5-(2″,‴-methoxyphenol)-9H-1,3,6,8,9-hexa-azo-fluorene-2,7-diamine (6i):**

Brownish Solid; Molecular Formula: $C_{29}H_{23}ClFN_7O_4$; Molecular Weight: 587.99; Yield: 72.60%; Melting Point (ºC): 84-86 ºC; Elemental Analysis: C, 59.38; H, 3.89; N, 16.85; FTIR (KBr): -$NH_2$ (2-Peaks): 3254 cm-1 and 3324 $cm^{-1}$, aromatic

ring (3-Peaks): 1543 $cm^{-1}$, 1595 $cm^{-1}$ and 1675 $cm^{-1}$, Ar-$OCH_3$: 1293 $cm^{-1}$, Ar-OH: 3501 $cm^{-1}$, Ar-F: 1158 $cm^{-1}$, Ar-Cl: 1028 $cm^{-1}$

**9-(2′,4′,5′-trichlorophenyl)-4,5-(2″,‴-methoxyphenol)-9H-1,3,6,8,9-hexa-azo-fluorene-2,7-diamine (6j):**

Whitish Pink Solid; Molecular Formula: $C_{29}H_{22}Cl_3N_7O_4$; Molecular Weight: 638.89; Yield: 72.10%; Melting Point (ºC): 128-130 ºC; Elemental Analysis: C, 54.82; H, 3.38; N, 15.78; FTIR (KBr) (Spectra No.-86): -$NH_2$ (2-Peaks): 3246 cm-1 and 3286 $cm^{-1}$, aromatic ring (3-Peaks): 1512 $cm^{-1}$, 1590 $cm^{-1}$ and 1671 $cm^{-1}$, Ar-$OCH_3$: 1296 $cm^{-1}$, Ar-OH: 3500 $cm^{-1}$, Ar-2,4,5Cl: 1078 $cm^{-1}$; $^1$H NMR (500.13 MHz, DMSO-$d^6$, δ ppm): 6.97-8.07 (m, 5H, Ar-H), 9.69 (s, 2H, -$NH_2$), 9.77 (s, 1H, -OH), 3.70 (s, 3H, $OCH_3$), 3.40 (s, 2H, $CH_2$)

## RESULT AND DISCUSSION

### Chemistry:

The starting compounds of bis-chalcones **3a-j** were prepared by the reaction of substituted N-phenyl-piperidine-2,6-dione**1a-j** using 4-hydroxy-3-methoxy Benzaldehyde **2**. The series of amino-pyrimidines or 9-(1-phenyl)-4,5-(2"',"'-methoxyphenol)-9H-1,3,6,8,9-hexa-azo-fluorene-2,7-diamine **(6a-j)** were synthesized in reasonable yields by the microwave irradiation of bis-chalcones **3a-j** with guanidine nitrate **4** in presence of neutral alumina by solvent free state. The structure of amino-pyrimidines was confirmed by elemental, IR and $^1$HNMR analysis.

**Table 1**
**Antimicrobial activities of Bis-chalcones and amino-pyrimidines**

| Compd Code | Zone diameter calculated in mm and tabulated by (Mean±S.D.) | | | |
|---|---|---|---|---|
| | ***Bacillus subtilis*** | ***Escherichia coli*** | ***Candida albicans*** | ***Aspergillusniger*** |
| | 100 µg/ml | 100 µg/ml | 100 µg/ml | 100 µg/ml |
| **3a** | -- | -- | 16.31 ± 0.33 ** | 16.46 ± 0.27 ** |
| **3b** | -- | 2.33±4.04 ** | 17.80 ± 0.16 ** | 17.36 ± 0.31 ** |
| **3c** | 8.33±0.57 ** | 8.33±0.57 ** | 22.42 ± 0.39 ** | 21.69 ± 0.18 ** |
| **3d** | 7.33±0.57 ** | 4.66±4.04 ** | 21.41 ± 0.25 ** | 19.50 ± 0.45 ** |
| **3e** | -- | -- | 14.53 ± 0.41 ** | 16.56 ± 1.75 ** |
| **3f** | 8.33±0.57 ** | 8.33±0.57 ** | 16.15 ± 0.22 ** | 18.57 ± 0.32 ** |
| **3g** | -- | 2.33±4.04 ** | 20.43 ± 0.16 ** | 17.12 ± 0.12 ** |
| **3h** | -- | -- | 19.04 ± 0.08 ** | 15.89 ± 1.72 ** |
| **3i** | -- | -- | 17.71 ± 0.22 ** | 16.31 ± 0.22 ** |
| **3j** | 7.66±1.15 ** | 2.33±4.04 ** | 19.94 ± 0.15 ** | 21.67 ± 0.48 ** |
| **5a** | 6.33±0.57 ** | 7.66±0.57 ** | -- | 10.23 ± 0.38 ** |
| **5b** | 6.66±1.15 ** | 8±1 ** | 22.57 ± 0.27 ** | 16.72 ± 0.20 ** |
| **5c** | 7.33±1.52 ** | 8.66±0.57 ** | 13.83 ± 0.22 ** | 12.56 ± 0.08 ** |
| **5d** | 7.33±1.52 ** | 7.66±1.15 ** | -- | 19.13 ± 0.06 ** |
| **5e** | 6.66±0.57 ** | 7.33±0.57 ** | 8.69 ± 0.39 ** | 15.36 ± 0.30 ** |
| **5f** | 7.66±0.57 ** | 8.33±0.57 ** | 9.34 ± 0.34 ** | 15.71 ± 0.29 ** |
| **5g** | 7.33±0.57 ** | 8.66±0.57 ** | 16.57 ± 0.40 ** | 19.54 ± 0.39 ** |
| **5h** | 7.33±0.57 ** | 4.66±4.04 ** | 8.86 ± 0.22 ** | 12.56 ± 0.13 ** |
| **5i** | 6.33±0.57 ** | 7±0 ** | 11.30 ± 0.32 ** | 18.59 ± 0.20 ** |
| **5j** | 6.33±0.57 ** | 7.33±0.57 ** | 8.40 ± 0.04 ** | 20.73 ± 0.44 ** |
| **Ctrl** | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| **Std** | 18.33±0.57 | 18.33±0.57 | 12.40 ± 0.43 | 10.45 ± 0.11 |

***Keynote:*** *Zone of inhibition measured in mm (Mean±S.D.) (N=3) ('--' means no zone)*

**Antimicrobial activities (3a-j and 5a-j):**

The entire synthesized compounds **3a-j** and **5a-j** were screened for their antibacterial activity against gram positive bacteria *Bacillus subtilis* (MCMB-310) and gram negative bacteria *Escherichia coli* (MCMB-301) using DMF solvent. And antifungal activities against *Candida albicans* (NCIM-3471) and *Aspergillus niger* (NCIM-545) strains using DMSO solvent. Ampicillin for antibacterial activities and Amphotericin-B for antifungal activities were used as a standard. All the results of synthesized compounds were carried out by the triplicate format N=3 with Mean ± SD. The statistical significance was carried out by one way ANOVA and confirmed by Dunnett multiple comparisons test performed the standard drugs against synthesized compounds. P value < 0.05 was considered as statistically significant remarked by *p<0.05, **p<0.01, ***p<0.001 compared to standard groups. The calculated data were enlisted in the table-1;

## CONCLUSION

An entire new series of amino-pyrimidine containing 4-hydroxy-3-methoxy benzylidene root have been synthesized in one pot and facile manner from bis-heterocyclic chalcones in good yield. A good number of the synthesized bis-chalcone **3a-j** and amino-pyrimidines **5a-j** showed superior and synergistic antifungal activities against *Candida albicans* and *Aspergillus niger* fungal strains.

## REFERENCES


1. Al-Azzawi M and Hamd AS. Synthesis, Characterization and Evaluation of Biological Activity of Novel Cyclic Imides Containing Heterocycles Based on 2, 5-disubstituted-1,3,4-thiadiazoles, Al-Anbar J. Vet. Sci., 2011; 4(2): 152-164.
2. Rajput SS. Synthesis and Characterization of Bis-heteroyclic Derivatives of 1-(3-Chlorophenyl)-Pyrrolidine-2,5-Dione, International Journal of Advances in Pharmacy, Biology and Chemistry, 2012;1(2): 242-246.
3. Patil MM and Rajput SS. Succinimides: Synthesis, reaction and biological activity, International Journal of Pharmacy and Pharmaceutical Sciences, 2014; 6(11): 8-14.
4. AL-AzzawiAM and Rhahman Mahdi SA. Synthesis and Evaluation of Antimicrobial Activity of Several New Maleimides to BenzothiazoleMoiety, J. of Baghdad for Sci., 2013;10(3): 658-672.
5. Amin K M, El-masry AH, Mohamed NA, Awad GEA and Habib BS. Synthesis, Characterization and Antimicrobial Activity of Some Novel Isoindole-1,3-Dione Derivatives, Der Pharma Chemica, 2013;5(5): 97-108.
6. Dhivare RS and Rajput SS. Synthesis, Characterization and Antimicrobial Evolution of Six Membered CyclicImides, International Journal of Chemistry and Pharmaceutical Sciences, 2015;3(8): 1877-1880.
7. Dhivare RS and Rajput SS. Synthesis and antimicrobial activity of five Membered cyclic imide derivatives of mono, di and tri substituted aromatic amines and napthylamine, World Journal of Pharmaceutical Research, 2015;4(6): 1650-1658.
8. Kmetani T, Fitz T and Watt DS, A synthesis of succinimides and glutarimides from cyclic anhydrides, Tetrahedron Letters, 1986;27(8): 919-922.
9. Kartrizky AR, Yang B, Qiu G and Zhang ZA. A convenient Trifluoroacetylation Reagent: N-(Trifluoroacetyl) succinimide, Center of Heterocyclic compounds, University of Florida, Gainesville, 1998; 55-57.
10. Shaker RM. Synthesis of 1,4-Phenylene Bridged Bis-Heterocyclic Compounds, ARKIVOC, 2012;i: 1-44.
11. Voskiene A, Mickevicius V and Mikulskiene G. Synthesis and structural characterization of products condensation 4-carboxy-1-(4-styrylcarbonylphenyl)-2-pyrrolidinones with hydrazines,ARKIVOC, 2007;XV: 303-314.
12. Patil CB, Mahajan SK and Katti SA. Chalcone: A versatile molecule, Journal of Pharmaceutical Science and Research, 2009; 1(3): 11-22.
13. Rajput SS and Patole SS. Synthesis and uses of chalcone in hetrocyclic synthesis, World Journal of Pharmaceutical Research, 2015; 4(7): 1566-1591.
14. Suwito H, Jumina, Mustofa, Kristanti AN and Puspaningsih NNT. Chalcones: Synthesis, structure diversity and pharmacological aspects,Journal of Chemical and Pharmaceutical Research, 2014;6(5):1076-1088.
15. Dhivare RS and Rajput SS. Synthesis and antimicrobial evaluation of some novel bis-heterocyclic chalcones from cyclic imides under microwave irradiation, Chemical Science Review and Letters, 2015; 4(15): 937-944.
16. Thirunarayanan G and Vanangamudi G. Synthesis of some 4-bromo-1-naphthyl

chalcones using silica-sulfuric acid reagent under solvent free conditions, ARKIVOC, 2006;xii: 58-64.
17. Sandhirakasu V and Mannathuswamy G. Synthesis, characterization and antimicrobial screening of novel bis-2-aminopyrimidines, Journal of Pharmacy Research, 2014; 8(4): 548-551.
18. Rathod AK. QSAR Studies of Imidazole Based Pyrimidine Derivatives with Microbial Activity, International Journal of Research in Pharmaceutical and Biomedical Sciences, 2012;3(1): 352-360.
19. Kheder NA, Mabkhot YN and Farag AM. A convenient access to new pyrido[4,3-*d*]pyrimidine, thiazolo[3,4-*c*]pyrimidine and pyrimido[4,5-*d*]pyridazine derivatives,ARKIVOC, 2008;xvii: 107-116.
20. Jyothi MV, Prasad YR, Venkatesh P and Sureshreddy M. Synthesis and Antimicrobial Activity of Some Novel Chalcones of 3-Acetyl Pyridine and their pyrimidine Derivatives,Chemical Science Transactions, 2012;1(3): 716-722.
21. Ghosh R and Das A. Synthesis and biological activities of chalcones and their heterocyclic derivatives: a review, World Journal of Pharmacy and Pharmaceutical Sciences, 2014;3(3): 578-595.
22. Gontijo FA, Pascon RC, Fernandes L, Machado Jr J, Alspaugh JA and Vallim M. A. The role of the de novo pyrimidine biosynthetic pathway in Cryptococcus neoformans high temperature growth and virulence, Fungal Genetics and Biology, 2014; 70: 12–23.
23. Dangar VR, Borkhataria KN and Shah VR. Synthesis, characterization and antimicrobial activity of pyrazoline and amino cyanopyridine derivatives of with vanillin,Sci. Revs. Chem. Commun., 2014;4(1): 31-37.
24. Himaja M, Rout PK, Karigar AA, Das P and Munirajasekhar D. Synthesis and antioxidant activity of 4,6-diphenylpyrimidin-2-amine and its derivatives, Universal Journal of Pharmacy, 2012;01(01): 72-77.
25. Bahekar SS and Shinde DB. Synthesis and anti-inflammatory activity of some 2-amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydropyrimidine-5-yl_-acetic acid derivatives, Acta Pharm., 2003;53: 223–229.
26. Schenone S, Zanoli S, Brullo C, Crespan E and Maga G. Current Advances in the Development of Anticancer Drugs Targeting Tyrosine Kinases of the SrcFamily, Current Drug Therapy, 2008;3: 158-176.
27. Singh K, Kaur H, Chibale K, Balzarini J, Little S., Bharatam P. V. 2-Aminopyrimidine based 4-aminoquinoline anti-plasmodial agents. Synthesis, biological activity, structure-activity relationship and mode of action studies, European Journal of Medicinal Chemistry, 2012; 52: 82-97.
28. Chang S, Yin S, Wang J, Jing Y and Dong J. Design and synthesis of novel 2-phenylaminopyrimidine (pap) derivatives and their antiproliferative effects in human chronic myeloid leukemia cells, Molecules, 2009;14(10): 4166-4179.
29. Khedkar VM, Arya N, Coutinho EC, Shishoo CJ and Jain KS. Docking study of novel antihyperlipidemicthieno [2,3-d] pyrimidine; LM-1554, with some molecular targets related to hyperlipidemia – an investigation into its mechanism of action, Springer Plus, 2014;3(628): 1-12.
30. Abd El-Moneim M. Synthesis, Mass Spectra Investigation and Biological Activity of Some Pyrimidine Derivatives, IOSR Journal of Applied Chemistry, 2014;7(1): 67-76.
31. Chaudhary A, Sharma PK, Verma Pand Dudhe R. Synthesis of novel pyrimidine derivative and its biological evaluation, AnaleleUniversitaNii din Bucuresti – Chimie (serienoua), 2011;20(02): 123-140.
32. Mokale SN, Elgire RD, Sakle NS, and Shinde DB. Microwave-Assisted Synthesis, Hypolipidemic and Hypoglycemic Activity of Some Novel 2-(4-(2-Amino-6-(4-substituted phenyl)-pyrimidin-4-yl)-phenoxy)-2-methyl Propanoic Acid Derivatives,Arch. Pharm. Chem. Life Sci., 2012;345: 22-27.
33. Singh B, Synthesis, antiproliferative and apoptosis-inducing activity of thiazolo [5,4-d]pyrimidines, European Journal of Medicinal Chemistry, 2013;70: 864-874.
34. Petricci E. Towards new methodologies for the synthesis of biologically interesting 6-substituted pyrimidines and 4(3H)-pyrimidinones, ARKIVOC, 2006;vii: 452-478.
35. Khdur Radhiya A. Synthesis of novel heterocyclic derivatives containing di aze, International Journal of Pharmaceutical Chemistry, 2013;2(2), 2278-8700.
36. Solankee A, Patel R and Patel K. Synthesis and evaluation of some novel *S*-triazine based chalcones and their derivatives, Der PharmaChemica, 2011;3(6): 317-324.

37. Mohsin HF. Synthesis of some new pyrimidines from chalcone containing an imingroup, International Journal of Pharmaceutical Chemistry Research, 2013;2(1), 23-35.
38. El-Deeb IM, Ryu JC and Lee SH. Synthesis of new *n*-arylpyrimidin-2-amine derivatives using a palladium catalyst, Molecules, 2008;13(4): 818-830.
39. Theivendren PS, Caiado RJ, Phadte VD and Silveira KV. A mini review of pyrimidine and fused pyrimidine marketed drugs, Research in Pharmacy, 2012;2(4): 01-09.
40. Al-Issa SA. A facile microwave-assisted synthesis of some fused pyrimidine derivatives, Oriental Journal of Chemistry, 2014;30(2): 469-477.
41. Ismail M. Synthesis and cyclization reactions of 2-(6-methylquinolin-4-yl) malononitriles and ethyl 2-cyano-2-(6-methylquinolin-4-yl)acetates, J. Serb. Chem. Soc., 2006; 71 (7): 721-732.
42. Tiwari U. Clean and efficient microwave assisted synthesis of some new pyrimidine, pyrazoline and isoxazoline derivatives from 3-(3-nitrophenyl)-nphenyl-Prop-2-enamide, European Chem. Bull., 2013;2(5): 242-246.
43. Asiri AM and Khan SA. Synthesis and Anti-Bacterial Activities of a Bis-Chalcone Derived from Thiophene and Its Bis-Cyclized Products, Molecules, 2011; 16(1): 523-531.
44. Kanagarajan V, Thanusu J and Gopalakrishnan M. Design, Synthesis and Spectral Characterization of Novel 2-morpholino-*N*-(4,6-diarylpyrimidin-2-yl)acetamides, Journal of the Korean Chemical Society, 2010;54(1): 49-54.
45. Dhivare RS and Rajput SS, Microwave Assisted Synthesis and Microbial Screening of Novel Amino-pyrimidine Derivatives using Bis-chalcones, Journal of Chemistry and Chemical Sciences, 2015; 5(10): 550-556.