Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(7):784-790

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of 2-phenyl-*3H*-dipyrimido[1,2-a] pyrimidin-4(*5H*)-one derivatives and their antifungal activity

Shrikant V. Hese[1], Rahul D. Kamble[1], Pratima P. Mogle[1], Sonali S. Kamble[2], Madhav J. Hebade[1], Ajay N. Ambhore[1], Shiddhodan N. Kadam[1], Rajesh N.Gacche[2] and Bhaskar S. Dawane[1]*

[1]*Organic Research Laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded (M.S) India*
[2]*School of Life Sciences, Swami Ramanand Teerth Marathwada University, Nanded (MS), India*

ABSTRACT

Some 2-phenyl 3H-dipyrimido[1,2-a] pyrimidin -4(5H)-one derivatives were synthesised by the reaction of pyrido[1,2-a]pyrimidine 3-carbonitrile with benzoic acid in the presence of catalytic amount of Amberlyst 15–wet (strongly acidic) in green reaction medium i.e. PEG-400. The structural elucidation of the compounds was performed by spectral analysis. All the synthesized compounds were screened for their antifungal activity. Most of compounds show excellents activity .

Keywords: 2-phenyl 3H-dipyrimido[1,2-a]pyrimidin-4(5H)-one derivatives, PEG-400; Amberlyst 15-wet (Strongly Acidic); Antifungal activity.

INTRODUCTION

In the past 25 years, the incidence of microbial infection has increased to alarming levels over the world as a result of antimicrobial resistance. A growing number of immune-compromised patients are as a result of cancer chemotherapy, organ transplantation and HIV infection, which are the major factors contributing to this increase. The health problem demands to search and synthesize a new class of antimicrobial compounds and antifungal compounds effective against pathogenic micro-organisms that developed resistance to the antibiotics used in the current regimen [1-5].

Heterocyclic ring systems remains part of many powerful scaffolds holding several pharmacopores that can act as potent and selective drugs for many diseases [6]. Pyrimido-pyrimidine derivatives are well known as bronchodilators [7], vasodilators [8], anti-allergic [9], antihypertensive [10], and anticancer agents [11]. Therefore, a lot of efforts have been made towards the synthetic manipulation of pyrimido-pyrimidine derivatives, which usually requires forcing conditions, long reaction times and complex synthetic pathways [12]. Various methods have been reported [13-17], for the synthesis of pyrimido-pyrimidines 4(5H)-one derivatives. However, many of these methods have several disadvantages such as the need for a prolonged reaction time, high temperature, and use of volatile and toxic organic solvents and occurrence of side products.

Heterogeneous catalyst have been gained attention in the field of organic synthesis due to its advantages over the homogenious catalyst such as, easy isolation, transportation and disposal of catalyst. Among the heterogeneous catalyst Amberlyst-15 is now routinely used in organic synthesis as heterogeneous reusable acid catalysts for various selective transformations of simple and complex molecules [18].

In continuation of our efforts to develop a simple and economical methodology for the synthesis of target compounds of biological interests, we developed the new method by using Amberlyst-15 (strongly acidic) as

heterogeneous catalyst. In corresponding, use of green solvent mediated reactions is a promote relate to in sustainable enlargement. Due to these concerns, polyethylene glycol-400 (PEG-400) has arriving significant awareness above the most recent two decades due to its unique, environmentally benign characteristics [19-25], fascinating our use of PEG-400 as a substitute green solvent in the present study.

EXPERIMENTAL SECTION

Chemistry

All reagents were obtained from commercial suppliers and used without further purification. The substituted pyrido[1,2-a]pyrimidine 3-carbonitrile were prepared by reported methodes [20]. Reaction progress was monitored through thin layer chromatography (TLC) on pre-coated Merck alu-foil plate (silica gel 60F-254, 0.25 mm thickness) visualized by iodine vapors. Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded (in KBr pallets) on Schimadzu spectrophotometer or Perkin Elimer spectrum version.^{1}H NMR spectra were recorded on Avance/Bruker 300/400 MHz spectrophotometer using TMS as an internal standard. All NMR spectra were obtained in DMSO d_6/deuterated chloroform ($CDCl_3$); chemical shifts are reported in parts per million, and coupling constant in hertz (Hz). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), m (multi-plate). The mass spectrum was recorded on GC–MS SHIMDZU (Q2010 PLUS) in the EI mode spectrometer and mass values are reported in m/z.

General experimental procedure for the synthesis of pyrimido[5,4-e]pyrimidin-4(5H)-one derivatives (6a-j);

A mixture of **(4a-j)** (5 mmol) and benzoic acid (5 mmol) **(5),** was stirred in 20 ml PEG-400 in the presence of Amberlyst-15 strongly acidic catalyst (10 wt %) at 70-80^{o}C for 2-4 hrs. The progress of the reaction is monitored on (TLC) after completion of reaction, the catalyst was filtered by simple filtration and further reused for 2-3 times. The reaction mixture was extracted with diethyl ether (2×20 ml). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was recrystallized from chloroform to afford the pure product (**6a-j**)

Spectral data of selected compounds

5-(4-chlorophenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one **(6a);**

Yellow crystals, ($CHCl_3$), mp 240-243^{o}C; IR (KBr, cm^{-1}) νmax; 3328 (N-H), 1691 (C=O), 1580 (C=N), 1495 (C=C), 784 (C-Cl); ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ ppm; 8.04 (s, 1H, NH), 7.84-7.54 (m, 13H, Ar-H), 3.96 (s, 1H, methine); ^{13}CNMR (DMSO-d_6, 100 MHz, 25 °C) δ ppm; 166.2, 161.6, 158.1, 148.0, 135.8, 135.0, 130.6, 125.2, 123.6, 115.3, 55.1; ESI-MS: m/z: 386 [M]$^+$ Chemical Formula : $C_{22}H_{15}ClN_4O$.

5-(4-nitrophenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one **(6b);**

Pale brown solid, ($CHCl_3$), mp 245-248^{o}C; IR (KBr, cm^{-1}) νmax; 3369 (N-H), 1737 (C=O), 1598 (C=N), 1505 (C=C), 1348 (C-NO_2); ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ ppm; 8.14 (s, 1H, NH), 7.85-7.55 (m, 13H, Ar-H), 4.03 (s, 1H, methine); ^{13}CNMR (DMSO-d_6, 100 MHz, 25 °C) δ ppm; 166.2, 161.1, 158.3, 147.3, 134.7, 132.7, 129.0, 127.0, 126.9, 117.0, 54.8; ESI-MS: m/z 397.12 [M]$^+$ Chemical Formula : $C_{22}H_{15}N_5O_3$.

5-(4-flurophenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one **(6c);**

Pale brown solid, ($CHCl_3$), mp 242-245^{o}C; IR (KBr, cm^{-1}) νmax; 3354 (N-H), 3237 (C-H), 1699(C=O), 1604 (C=N), 1562 (C=C), 834 (C-F); ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ ppm; 8.04 s, (1H, NH), 7.85-7.56 (m, 13H, Ar-H), 3.93 (s, 1H, methine); ^{13}CNMR (DMSO-d_6, 100MHz, 25 °C) δ ppm; 166.6, 161.2, 148.3, 147.3, 134.7, 132.7, 129.0, 127.0, 126.9, 124.7,122.8, 120.9, 117.0, 52.0; ESI-MS: m/z 370.12 [M]$^+$ Chemical Formula : $C_{22}H_{15}N_4OF$.

5-(3-nitrophenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one **(6d);**

Pale yellow solid, ($CHCl_3$), mp 247-250^{o}C; IR (KBr, cm^{-1}) νmax; 3238 (N-H), 1690 (C=O), 1586 (C=N), 1550 (C=C); ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ ppm; 8.10 (s, 1H, NH), 7.85-7.26 (m, 13H, Ar-H), 4.12 (s, 1H, methine); ^{13}CNMR (DMSO-d_6, 100 MHz, 25 °C) δ ppm; 166.3, 161.4, 158.3, 147.3, 134.7, 132.7, 129.0, 127.0, 126.9, 122.09, 121.09, 120.09, 117.0, 52.0; ESI-MS: m/z 397.12 [M]$^+$ Chemical Formula : $C_{22}H_{15}N_5O_3$.

5-(2-chlorophenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one **(6e);**

Yellow crystals, ($CHCl_3$), mp 241-243^{o}C; IR (KBr, cm^{-1}) νmax; 3318 (N-H), 1685 (C=O), 1598 (C=N), 1509 (C=C), 736 (C-Cl); ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ ppm; 8.04 (s, 1H, NH), 7.65-7.56 (m, 13H, Ar-H), 4.31 (s, 1H, methine); ^{13}CNMR (DMSO-d_6, 100 MHz, 25 °C) δ ppm; 166.3, 161.4, 148.7, 146.3, 135.7, 130.7,128.0, 126.0, 125.9, 116.0, 52.0; ESI-MS: m/z 386 [M]$^+$ Chemical Formula : $C_{22}H_{15}ClN_4O$.

5-(2-hydroxyphenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one **(6f);**
Yellow crystals, ($CHCl_3$), mp 260-262^oC; IR (KBr, cm^{-1}) νmax; 3423 (O-H), 3318 (N-H), 2916 (C-H), 1670 (C=O), 1589 (C=N), 1509 (C=C); ^1H NMR (DMSO-d_6, 400 MHz, 25 °C) δ ppm; 10.04 (s,1H,OH), 8.04 (s, 1H, NH), 7.67-7.55 (m, 13H, Ar-H), 4.31 (s, 1H, methine), $^{13}CNMR$ (DMSO-d_6, 100 MHz, 25 °C) δ ppm; 166.0, 161.8, 158.3, 148.3, 146.3, 135.7, 130.7, 128.0, 126.0, 125.9, 116.0, 41.0; ESI-MS: m/z 368.13 $[M]^+$ Chemical Formula: $C_{22}H_{16}N_4O_2$.

2,5-diphenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one **(6g);**
Pale yellow crystals, ($CHCl_3$), mp 250-252^oC; IR (KBr, cm^{-1}) νmax; 3318 (N-H), 2916 (C-H), 1690 (C=O), 1587 (C=N), 1499 (C=C); ^1H NMR (DMSO-d_6, 400 MHz, 25 °C) δ ppm; 8.00 (s, 1H, NH), 7.85-7.56 (m, 13H, Ar-H), 4.11 (s, 1H, methine); $^{13}CNMR$ (DMSO-d_6, 100 MHz, 25 °C) δ ppm; 166.2, 162.3, 158.3, 148.3, 146.3, 135.7, 130.7, 128.0, 126.0, 125.9, 116.0, 100.9, 41.0; ESI-MS: m/z 352.39 $[M]^+$ Chemical Formula: $C_{22}H_{16}N_4O$.

5-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one **(6h);**
Brown solids crystals, ($CHCl_3$), mp 278-280^oC; IR (KBr, cm^{-1}) νmax; 3027 (N-H), 2917 (C-H), 1674 (C=O), 1598 (C=N), 1512 (C=C), 786 (C-Cl); ^1H NMR (DMSO-d_6, 400 MHz, 25 °C) δ ppm; 7.97 (s, 1H, NH), 7.49-7.00 (m, 16H, Ar-H), 4.91 (s, 1H, methine), 2.31 (s, 3H, CH_3); $^{13}CNMR$ (DMSO-d_6, 100 MHz, 25 °C) δ ppm; 166.7, 164.7, 162.3, 158.3, 148.3, 146.3, 135.7, 130.7, 128.0, 126.0, 125.9, 124.4, 123.3, 122.2, 121.1, 120.0, 119.0, 118.0, 117.0, 116.0, 100.9, 41.0, 21.0; ESI-MS: m/z 466.92$[M]^+$ Chemical Formula : $C_{26}H_{19}N_6OCl$.

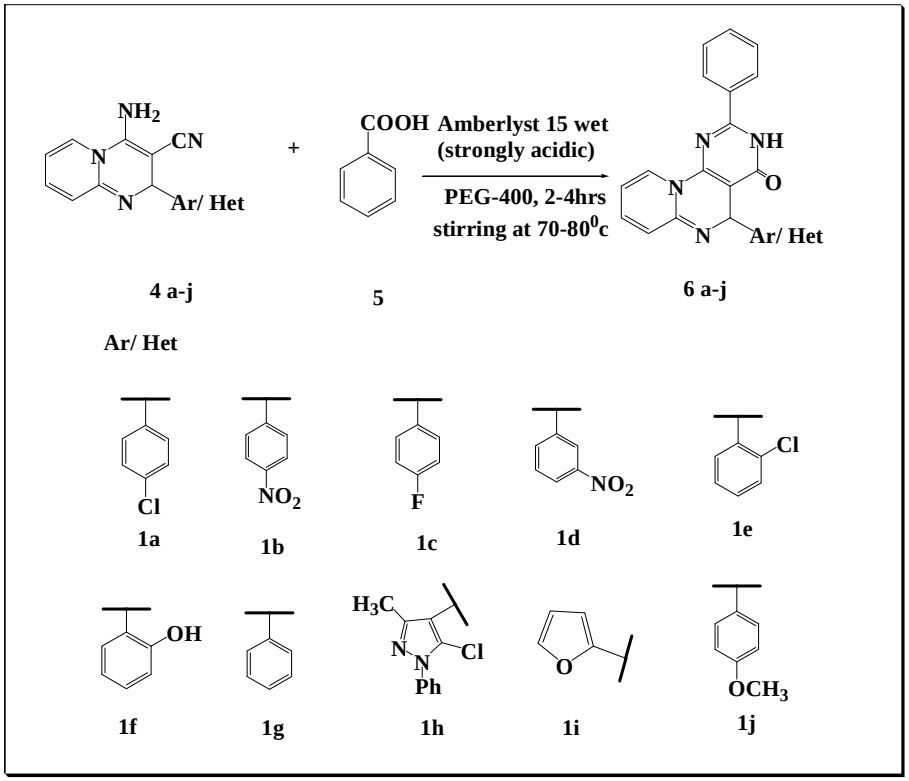
5-(furan-2-yl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one **(6i);**
White solids crystals, ($CHCl_3$), mp 270-273^oC; IR (KBr, cm^{-1}) νmax; 3174 (N-H), 3069 (C-H), 1694(C=O), 1581 (C=N), 1533 (C=C), 1301 (C-O-C);^1H NMR (DMSO-d_6, 400 MHz, 25 °C) δ ppm; 8.31 (s, 1H, NH), 7.46-6.55 (m, 12H, Ar-H), 3.73 (s, 1H, methine); $^{13}CNMR$ (DMSO-d_6, 100 MHz, 25 °C) δ ppm; 166.2, 164.5, 162.3, 158.3, 148.3,146.3, 135.7, 128.0, 126.0, 124.4, 122.2, 120.0, 118.0, 116.0, 41.0; ESI-MS: m/z 466.92 $[M]^+$ Chemical Formula: $C_{20}H_{14}N_4O_2$.

5-(4-methoxyphenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one **(6j);**
Yellow solids crystals, ($CHCl_3$), mp 250-253^oC; IR (KBr, cm^{-1}) νmax; 3318 (N-H), 2910 (C-H), 1695 (C=O), 1598 (C=N), 1509 (C=C); ^1H NMR (DMSO-d_6, 400 MHz, 25 °C) δ ppm; 7.87 (s, 1H, NH) 7.85-7.56 (m, 13H, Ar-H), 4.11 (s, 1H, methine), 3.98 (s, 3H,OCH_3), $^{13}CNMR$ (DMSO-d_6, 100 MHz, 25°C) δ ppm; 166.3, 164.5, 162.3, 158.3, 148.3, 146.3, 135.7, 128.0, 126.0, 124.4, 122.2, 120.0, 118.0, 116.0, 100.9, 60.0, 41.0; ESI-MS: m/z 382.41 $[M]^+$ Chemical Formula :$C_{23}H_{18}N_4O_2$.

Biology
The synthesized compounds (**6a-j)**, in measured quantities, were dissolved in dimethyl sulphoxide (DMSO) in a final concentration of 50 µg ml. The synthesized compounds were evaluated for antifungal activity by disc diffusion method [26]. The fungal (48 h) cultures from the slants were diluted with sterile water and mixed thoroughly to prepare a clear homogeneous suspension. These suspensions were spread on solidified agar, potato dextrose agar for fungi. The filter paper disks prepared by only DMSO (as a negative control) and with a solution of 50 µg/ml concentrations of test compounds (**6a-j)** as well as standard compounds Nystatin as positive control were carefully placed over the spread cultures and incubated the at 28-30 ^oC for 48 h for fungi. After the incubation period, the plates were examined for the zone of inhibition. The diameter for the zones of inhibition was measured, including the diameter of the disk also. All the concentrations were made in triplicate for each of the compounds and the average value was taken. The antifungal activity was evaluated against *A. Niger*, *C. albicans*, *A. Flavus* (fungal strains) using Nystatin as the standard drug.

RESULTS AND DISCUSSION

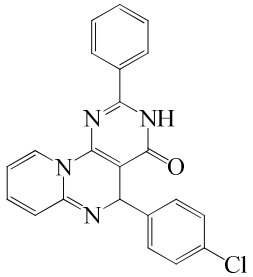
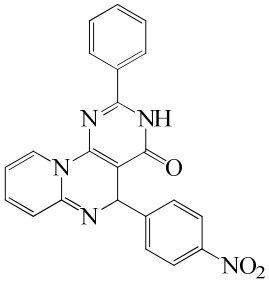
Chemistry
The pyrido[1,2-a]pyrimidine 3-carbonitrile derivatives were synthesized by one pot multi-component reaction as reported in [20]. Furthermore, pyrido[1,2-a]pyrimidine 3-carbonitrile derivatives on reaction with benzoic acid in the presence of catalytic amount of Amberlyst 15–wet (strongly acidic) in green reaction medium i.e. PEG-400 with stirring at 70-80^oC for 2-4 hrs. The synthesis of *5-(3/4 substituted phenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one* gives good yields via condensation–cyclization reaction of benzoic acid in PEG-400 and commercially available Amberlyst-15 (strongly acidic) has been used as acidic catalyst. At ambient temperature as shown in **scheme 1.1.**

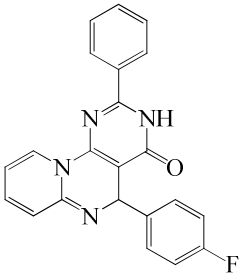
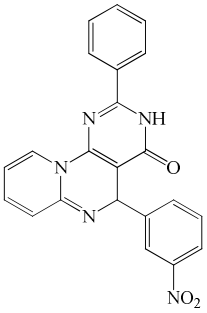
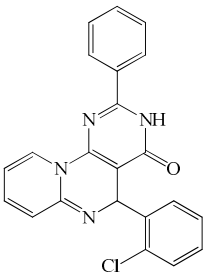
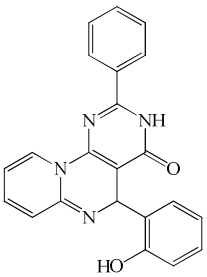
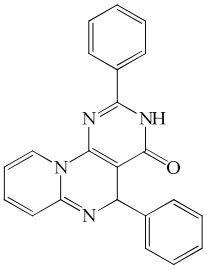
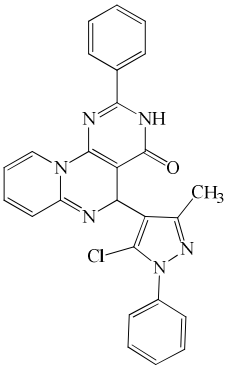


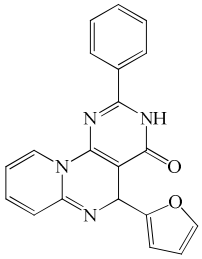
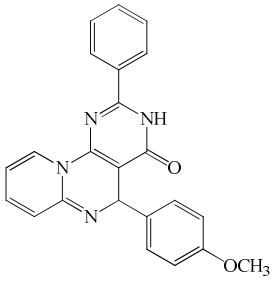
Scheme 1.1: Green synthetic protocol of pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one derivatives

The structure of the entire synthesized compound was confirmed by spectral analysis (IR, ^{1}HNMR, ^{13}C-NMR, Mass). The IR spectrum of compound **(6a)** shows that absence of C≡N peak in 2250 $cm^{-1}$and presence 3328 $cm^{-1}$for NH group and 1691 $cm^{-1}$for C=O of the carbonyl group indicates the formation of **6a**. In ^{1}H NMR the characteristic peak observed as a singlet for NH proton at δ 8.01 ppm and as a singlet for methine proton at δ 4.01 ppm and all other protons were observed in the respective aromatic region (δ 7.65-7.56) ppm. The mass spectrum of the compound showed a M+ ion peak at m/z 386.09 for the molecular formula $C_{22}H_{15}ClN_4O$. The synthetic procedure and characterization data of compounds (**6a-j)** are presented in the experimental section.

Table 1.1: Physiochemical data of (4/3 substituted phenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one derivatives (6a-j)

Entry	Products	Time (min)	Yield (%)[a]	Temp ^{o}C
6a		120	90	70
6b		120	85	80

6c		150	80	75
6d		120	80	70
6e		120	84	70
6f		160	80	70
6g		140	87	75
6h		150	80	70

6i		140	85	80
6j		135	84	70

[a]*Yields on isolated basis*

BIOLOGY

The antifungal activity of the synthesized (4/3 substituted phenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one derivatives (**6a-j)** (50µg/mL concentration) was compared with the standard drug Nystatin. The results of the investigation have been presented in **Table (1.2.)**. It is observed that all the (4/3 substituted phenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one derivatives (**6a-j)** exhibited excellent antifungal activity against standard drug antifungal (Nystatin, 50 µg/ml concentration). The preliminary antifungal screening of (4/3 substituted phenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one derivatives (**6a-j)** revealed that most of the compounds in the series showed potent activity. Therefore, the present study is useful in the light of development of new leads for antifungal research.

Table 1.2: Antifungal activity of (4/3 substituted phenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one derivatives (6a-j)

Sr .NO		*Fungi*		
	Compound Code	*A.niger*	*C.albicans*	*A.flavus*
1	**6a**	21	20	18
2	**6b**	19	22	21
3	**6c**	23	21	20
4	**6d**	18	18	21
5	**6e**	12	14	12
6	**6f**	10	12	09
7	**6g**	13	14	14
8	**6h**	18	17	19
9	**6i**	20	23	21
10	**6j**	19	21	17
11	**Nystatin**	24	24	24

An-Aspergillus niger; Af- Aspergillus flavus; Ca-Candia albicans; Nystatin (conc.50µg/mL)

CONCLUSION

The present study describes the synthesis of new (4/3 substituted phenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one derivatives **(6a-j)** by green methods i.e PEG-400 as green solvents and Amberlyst -15 strongly acidic is used as heterogeneous recyclable catalyst. The (4/3 substituted phenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one derivatives have been evaluated for antifungal activity, viz. *A. niger*, *C. albicans*, *A. Flavus* (fungal strains) using Nystatin as standard drug for antifungal activity. It is observed that most of the (4/3 substituted phenyl)-2-phenyl-3H-pyrido[1,2-a]pyrimido[5,4-e]pyrimidin-4(5H)-one derivatives (**6a-d)** show excellent antifungal activity and **(6e-g)** show moderate antifungal activity and **(6h-j)** show equipotent antifungal activity.

Acknowledgements

The authors PPM and RDK are sincerely grateful to the UGC-CSIR, New Delhi for JRF Award no. F. 17-3/2007 (SA-I) and SRF. Author SVH acknowledge the financial support (RA) from SRTM University, Nanded.

REFERENCES

[1] MS Benedetti; M Bani; *Drug Metab. Rev*., **1999,** 31, 665- 717.
[2] M Koca; S Servi; C Kirilmis; M Ahmedzad; C Kazaz; OG Zbek; OG Tuk, *Eur. J. Med. Chem*., **2005,** 40,1351-1358.
[3] C Bonde; N J Gaikwad, *Bioorg. Med. Chem*., **2004,** 12, 2151-2161.
[4] D Yu; G Huiyuan, *Bioorg. Med. Chem. Lett*., **2002**, 12,857- 859.
[5] VJ Ram, *J. Heterocycl. Chem*., **1988,** 25,253- 256.
[6] (a) YF Li; ZQ Liu; *Free Radical Biol. Med*. **2012,** 52, 103-8. (b) E Gordon; RW Barrett; WJ Dower; SP Foder, *J. Med. Chem*., **1994,** 37,1471-1485.
[7] E Tas; A Kilic; M Durgun; L Kupecik,; I Yilmaz; S Asslam, *Spectrochim. Acta Part A*., **2010**, 75, 811-818.
[8] WJ Coates, *European Patent 351058***, 1990**, 113.
[9] EC Taylor; RJ Knopf; RF Meyer; A Holmes; ML Hoefle, *J. Am. Chem.Soc*. **1960,** 82, 5711-5718.
[10] N Kitamura; A Onishi, *European Patent 163599*, **1984**, 104.
[11] P Raddatz; R Bergmann; *Ger. Pat. 360731*, **1988**, 109.
[12] D Prajapati; M Gohain; AJ Thakur, *Bioorg. Med. Chem. Lett***., 2006,** 16, 3537-40.
[13] VS Dinakaran; B Bomma; KK Srinivasan, *Pharm. Chem***. 2012**, 4, 255-265.
[14] C Jerzy; P Jansuz; G Olaf, *Acta poloniae pharmaceuctia-Drug Research*., **2003,** 60, 487-492.
[15] P Nagender; GM Reddy ;R Naresh Kumar; A C Reddy; VL Reddy; PJ Rajesh; *Bioorganic &Medicinal Chemistry Letters*. **2014,** 24, 2905-2908.
[16] P Sharma; N Rane; VK Gurram, *Bioorganic & Medicinal Chemistry Letters.* **2004,** 12, 4185-90.
[17] T Yakaiah; BV Lingaiah; B Narsaiah; PP Kumar; US Murthy; *European Journal of Medicinal Chemistry*., **2008,** 43, 341-347.
[18] R Pal; T Sarkar; S Khasnobis, *Arkivoc*. **2012**,570- 609
[19] SV Hese; RD Kamble; PP Mogle; AP Acharya; MV Gaikwad; SN Kadam; BS Dawane; *Indo American Journal of Pharm Research*.**2014**:4(01).278-282.
[20] SVHese; RD Kamble; PP Mogle; SS Kadam; MJ Hebade; AN Ambhore; BS. Dawane, *Der Pharma Chemica*, **2015.,** 7(4):249-256.
[21] AN Ambhore; VD Surywanshi; RD Kamble; SV Hese; PP Mogle; SS Kadam; BS. Dawane , *Der Pharma Chemica*, **2015,** 7(4):278-283.
[22] RD Kamble; SV Hese; R J Meshram ; JR Kote ; RN Gacche; BS Dawane; *Med Chem Res* **(2015)** 24:1077–1088.
[23] PP Mogle; RD Kamble; SV Hese; BS Dawane, *Res Chem Intermed* **2014** DOI 10.1007/s11164-014-1842-z
[24] MV Gaikwad; RD Kamble, SV Hese; A P Acharya; PP Mogle; SN Kadam; BS Dawane, *Res Chem Intermed* **(2015)** 41:4673–4678.
[25] AP Acharya; R D Kamble; SD Patil ; SV Hese; OS Yemul; B S. Dawane *Res Chem Intermed* **2013** DOI 10.1007/s11164-013-1403-x
[26] RD Biljana; SR Niko; SD Vidoslav; RD Vukicevic; RM Palic; *Molecules*. **2010,** 15, 2246-2256.