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Synthesis, Characterization and Antimicrobial Activity of 3-(Pyrimidinyl)-1-(4-Fluorophenyl)-5-(Aryl)-5, 6-Dihydro-1H-Pyrano [2, 3-D] Pyrimidine-2, 4, 7(3H)-Triones

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ABSTRACT

The synthesis of 3-(pyrimidinyl)-1-(4-fluorophenyl)-5-(aryl)-5,6-dihydro-1H-pyrano[2,3-d] pyrimidine-2,4,7(3H)-trione [C1-C12] were carried out by the reaction of substituted ureas 3a-c with malonic acid to produce pyrimidines 4a-c which on treatment with various aldehydes 5a-d and meldrum acid to produce final products C1-C12 (Scheme 3.I)

Keywords: Pyrimidine derivatives, malonic acid, substituted urea derivatives, meldrum acid.

INTRODUCTION

The fused pyrimidines are an important class of compounds as chemotherapeutic agents for their antibacterial [1], antiviral [2] and cytotoxic [3] properties. The pyranofused pyrimidine showed a broad range of biological activities such as antitubercular, antimicrobial [4,5], antiplatelet [6], antifungal [7], antiviral [8], analgesic as well as anticonvulsant activities and also showed effects against amphetamine induced stereotypy and on potentiation of pentobarbitone sodium hypnosis [9]. Moreover, all the compounds which have a uracil moiety in the skeleton of an organic molecule showed antitumor, antibacterial, bronchodilator, vasodilator, antihypertensive, cardiotonic, hepatoprotective, and antiallergic activities; some of them also exhibit antimalarial, analgesic, antifungal, and herbicidal properties [10,11,12].

One of the most important factors in drug design is that fluorine is much more lipophilic than hydrogen; so incorporating fluorine atom in a molecule will make it more fat soluble. This means it percolates into membranes much more readily, and hence the fluorinated molecule has a higher bioavailability. In a view of the above facts, aim is to synthesize novel fluorinated pyranofused pyrimidine derivatives.

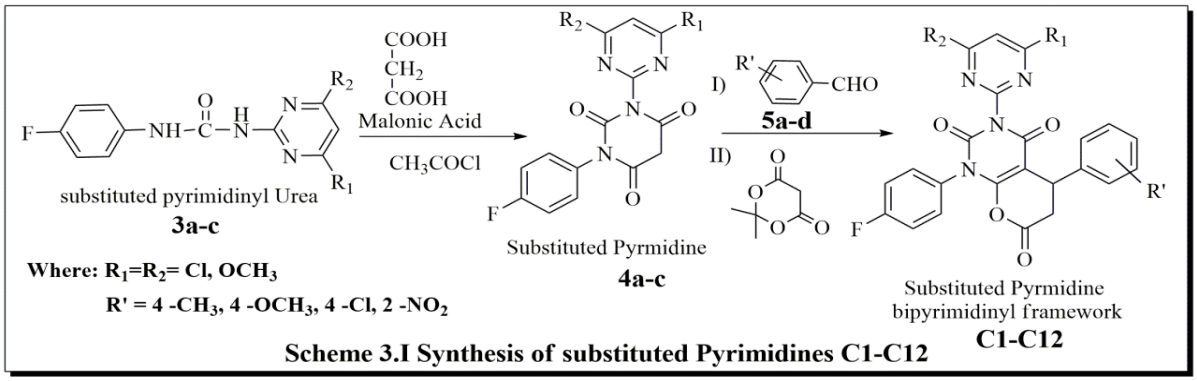
MATERIALS AND METHODS

Synthesis of 1-(4-chloropyrimidin-2-yl)-3-(4-fluorophenyl) pyrimidine-2,4,6(1H,3H,5H)-trione [4a]: In a 250 mL round bottom flask,1-(4-chloropyrimidin-2-yl)-3-(4-fluoro phenyl) urea 3a (0.01mol) was heated with Malonic acid (0.0115mol) and acetyl chloride (20 mL) under reflux temperature for 2-3 h. Cooled mass was then poured into crushed ice under vigorous stirring and stirred for 1 h. The formed precipitates were filtered out, washed and crystallized by MeOH to give 4a. Similarly, other compounds [4b-c] were prepared and characterized (Scheme1).

Synthesis of 3-(4-chloropyrimidin-2-yl)-1-(4-fluorophenyl)-5-(4-methoxyphenyl)-5,6-dihydro-1H-pyrano[2,3-d] pyrimidine-2,4,7(3H)-trione [C1]: In a 250 mL round bottom flask, A mixture of 4a (0.01mol), 4-methoxybenzaldehyde 5a (0.01mol), meldrum acid (0.01mol) and catalytic amount of piperidine in 20 mL ethanol was refluxed for 3-4 h. The reaction mass was cooled to room temperature, separated solid was filtered out and recrystallized by ethanol to give C1. Similarly, other compounds [C2-C12] were prepared and characterized (Scheme1).

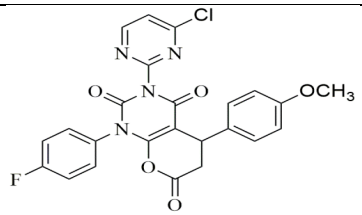
Characterization of Compounds C1-C12: Melting points (M P.) were measured using µ-ThermoCal$_{10}$ (Analab scientific Pvt. Ltd.) melting point apparatus & are uncorrected. TLC was carried out using silica gel 60 F_{254} precoated with aluminum sheets. ^{13}C NMR and ^{1}H NMR spectra were recorded on a Bruker Avance 400 spectrophotometer operating at 100 MHz for NMR and 400 MHz for ^{1}H ^{13}C NMR under solutions in DMSO-d_6. Chemical shifts (δ) are deginated in ppm and referenced to the residual protic solvent. FT-IR spectra were measured using Shimadzu FT-IR 8401 spectrophotometer with KBr disc, and are written in wave numbers (cm^{-1}). The mass spectra (LCMS) were measured using Shimadzu LCMS-2010 spectrometer.

Reaction Scheme for the Synthesis of Compounds [C1-C12]:

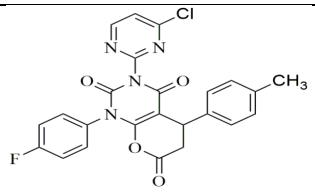


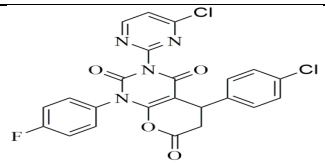
Scheme 3.I Synthesis of substituted Pyrimidines C1-C12

Spectral data analysis of some selected compounds:

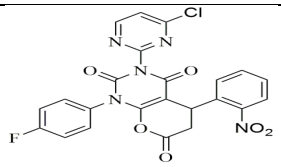
Compound code: C1	
Molecular formula: $C_{24}H_{16}ClFN_4O_5$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, CH_2, d), 3.6 (3H, OCH_3, s), 4.2 (1H, CH, t), 6.86-7.40 (10H, Ar-H, m).

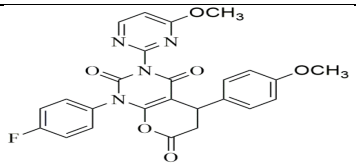
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.4, 35.2, 39.6, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168, 170
IR cm^{-1} (KBr):	3032 (C-H Aromatic stretch.), 1770 (C=O Aliphatic Ester), 1750 (C=O Cyclic Ester), 1644 (C=O amide Stretch.), 1600 (C=C Aliphatic stretch.), 1515 (C-F bend)., 1560 (C=C Ar. Stretch.), 753 (Ar C-H bend).
Mass (M+1):	494.0
Elemental analysis:	**Calculated (%):** C: 58.25; H: 3.26; N:11.32 **Found (%) :** C:58.12; H: 3.76; N:11.36

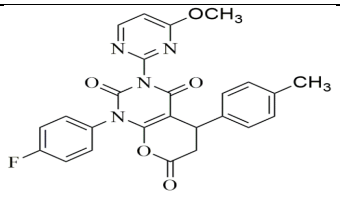
Compound code: C2	
Molecular formula: $C_{24}H_{16}ClFN_4O_4$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	2.6 (3H, CH_3, s), 3.2 (2H, CH_2, d), 4.2 (1H, CH, t), 6.86-7.40 (10H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.4, 35.2, 36.0, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168, 170
IR cm^{-1} (KBr):	3031 (C-H Aromatic stretch.), 1770 (C=O Aliphatic ester), 1750 (C=O Cyclic Ester), 1642 (C=O amide Stretch.), 1600 (C=C Aliphatic stretch.)1515 (C-F bend)., 1560 (C=C Ar. Stretch.), 756 (Ar C-H bend).
Mass (M+1):	478.0
Elemental analysis:	**Calculated (%):** C: 60.20; H: 3.37; N:11.70 **Found (%) :** C:60.80; H: 3.86; N:11.76

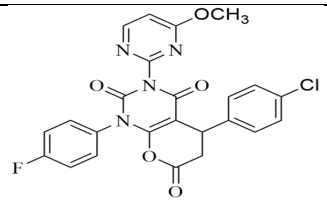
Compound code: C3	
Molecular formula: $C_{23}H_{13}Cl_2FN_4O_4$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, CH_2, d), 3.8 (1H, CH, t), 6.86-7.40 (10H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 35.2, 36.0, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168, 170
IR cm^{-1} (KBr):	2950 (C-H Aromatic stretch.), 1765 (C=O Aliphatic Ester), 1750 (C=O Cyclic Ester), 1642 (C=O amide Stretch.), 1600 (C=C Aliphatic stretch.)1515 (C-F bend)., 1560 (C=C Ar. Stretch.), 748 (Ar C-H bend).
Mass (M+1):	498.0

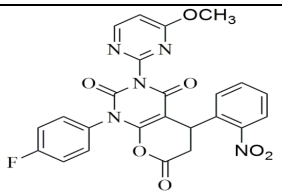
Elemental analysis:	**Calculated (%):** C: 55.33; H: 2.62; N:11.22 **Found (%) :** C:55.21; H: 2.76; N:11.36

Compound code: C4	
Molecular formula: $C_{23}H_{13}ClFN_5O_6$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, CH_2, d), 3.8 (1H, CH, t), 6.86-7.40 (10H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 35.2, 36.0, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168.2, 171
IR cm^{-1} (KBr):	3000 (C-H Aromatic stretch.), 1770 (C=O Aliphatic Ester) 1750 (C=O Cyclic Ester), 1645 (C=O amide Stretch.), 1620 (N=O Stretch.), 1600 (C=C Aliphatic stretch.), 1515 (C-F bend)., 1558 (C=C Ar. Stretch.), 750 (Ar C-H bend).
Mass (M+1):	509.0
Elemental analysis:	**Calculated (%):** C: 54.18; H: 2.57; N:13.74 **Found (%) :** C:54.29; H: 2.99; N:13.78

Compound code: C5	
Molecular formula: $C_{25}H_{19}FN_4O_6$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, CH_2, d), 3.6 (6H, OCH_3, s), 3.8 (1H, CH, t), 6.86-7.40 (10H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.4, 35.2, 39.6, 40.1, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168, 170
IR cm^{-1} (KBr):	3050 (C-H Aromatic stretch.), 1765 (C=O Aliphatic Ester), 1750 (C=O Cyclic Ester), 1644 (C=O amide Stretch.), 1600 (C=C Aliphatic stretch.), 1515 (C-F bend)., 1560 (C=C Ar. Stretch.), 754 (Ar C-H bend).
Mass (M+1):	490.0
Elemental analysis:	**Calculated (%):** C: 61.22; H: 3.90; N:11.42 **Found (%) :** C:61.32; H: 3.76; N:11.36

Compound code: C6	
Molecular formula: $C_{25}H_{19}FN_4O_5$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	2.6 (3H, CH_3, s), 3.2 (2H, CH_2, d), 3.6 (3H, OCH_3, s), 3.8 (1H, CH, t), 6.86-7.40 (10H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.4, 35.2, 36.0, 39.6, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168, 170
IR cm^{-1} (KBr):	3031 (C-H Aromatic stretch.), 1770 (C=O Aliphatic Ester), 1750 (C=O Cyclic Ester), 1644 (C=O amide Stretch.), 1602 (C=C Aliphatic stretch.)1515 (C-F bend)., 1560 (C=C Ar. Stretch.), 753 (Ar C-H bend).
Mass (M+1):	474.0
Elemental analysis:	**Calculated (%):** C: 63.29; H: 4.04; N:11.81 **Found (%) :** C:63.32; H: 4.16; N:11.72

Compound code: C7	
Molecular formula: $C_{24}H_{16}FClN_4O_5$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, CH_2, d), 3.6 (3H, OCH_3, s), 3.8 (1H, CH, t), 6.86-7.40 (10H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 35.2, 36.0, 39.6, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168, 170
IR cm^{-1} (KBr):	3010 (C-H Aromatic stretch.), 1760 (C=O Aliphatic Ester), 1750 (C=O Cyclic Ester), 1644 (C=O amide Stretch.), 1610 (C=C Aliphatic stretch.), 1515 (C-F bend)., 1560 (C=C Ar. Stretch.), 753 (Ar. C-H bend).
Mass (M+1):	494.0
Elemental analysis:	**Calculated (%):** C: 58.25; H: 3.26; N:11.32 **Found (%) :** C:58.21; H: 3.36; N:11.38

Compound code: C8	
Molecular formula: $C_{24}H_{16}FN_5O_7$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, CH_2, d), 3.6 (3H, OCH_3, s), 3.8 (1H, CH, t), 6.86-7.40 (10H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 35.2, 39.6, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.8. 158.0, 168.2, 171
IR cm^{-1} (KBr):	3015 (C-H Aromatic stretch.), 1770 (C=O Aliphatic Ester), 1750 (C=O Cyclic Ester), 1644 (C=O amide Stretch.), 1602 (C=C Aliphatic stretch.), 1515 (C-F bend)., 1560 (C=C Ar. Stretch.), 745 (Ar C-H bend).
Mass (M+1):	505.0
Elemental analysis:	**Calculated (%):** C: 57.03; H: 3.19; N:13.86 **Found (%) :** C:57.07; H: 3.59; N:13.78

RESULTS AND DISCUSSION

Table 1 show the various condensation products C1-C12 derived from substituted pyrimidinyl urea (3a-c). It clearly revels that the compounds bearing electron withdrawing group are prepared in less time as compared to compound bearing electron donating group. Compounds C4, C8 and C12 bearing electron withdrawing were synthesized in 5 h. as shorter time as compared to compound C1, C5 and C9 bearing electron donating group in 7 h.

Table 1. Characteristic data of synthesized compounds C1-C12 from substituted pyrimidinyl urea (3a-c).

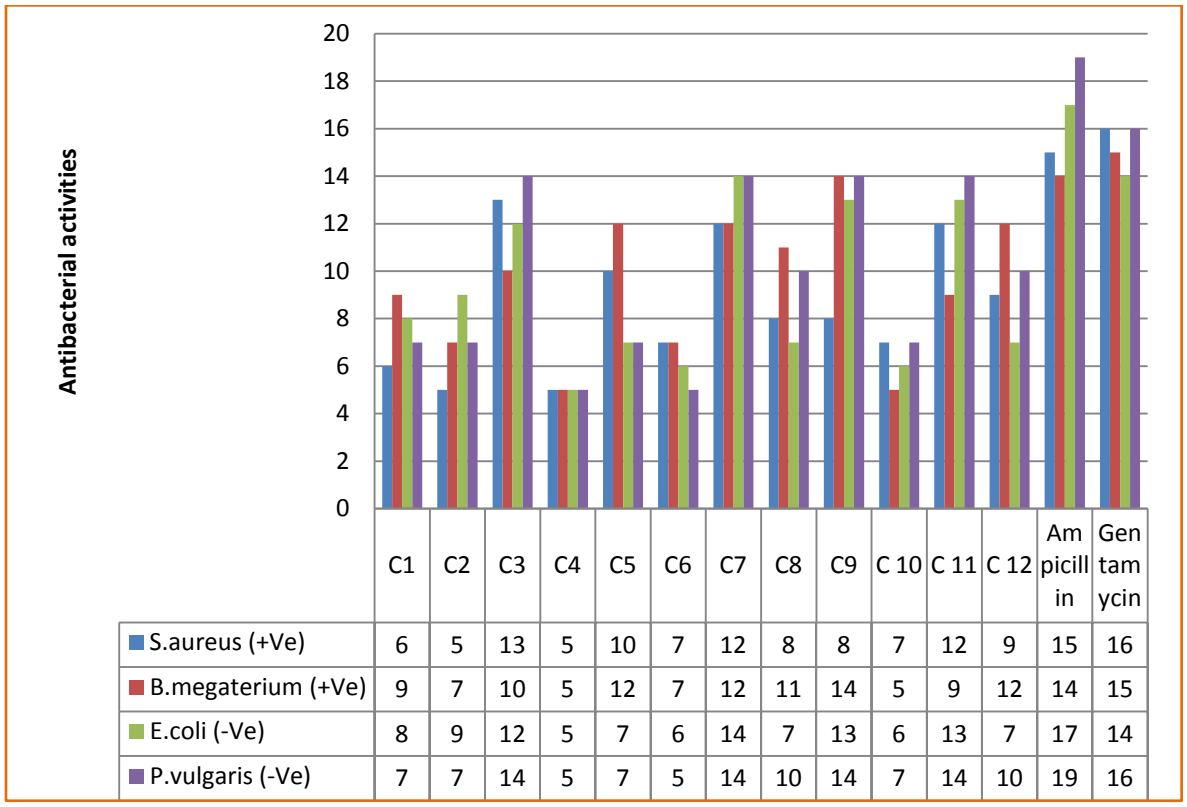
Sr.No.	Compounds Code	R'	R1	R2	Reaction Time[a] (hr.)	% Yield[b]
1	C1	4-OCH_3	-Cl	-H	7	65
2	C2	4-CH_3	-Cl	-H	6.5	68
3	C3	4-Cl	-Cl	-H	6	70
4	C4	2-NO_2	-Cl	-H	5	75
5	C5	4-OCH_3	-OCH_3	-H	7	65
6	C6	4-CH_3	-OCH_3	-H	6.5	66
7	C7	4-Cl	-OCH_3	-H	6	70
8	C8	2-NO_2	-OCH_3	-H	5	78
9	C9	4-OCH_3	-Cl	-OCH_3	7	65
10	C10	4-CH_3	-Cl	-OCH_3	6.5	67
11	C11	4-Cl	-Cl	-OCH_3	6	70
12	C12	2-NO_2	-Cl	-OCH_3	5	74

[a]Reaction is monitored by TLC. [b]Isolated yield

All the compounds were crystallized from hot ethanol and percentage yield was calculated after crystallization step. All the synthesized compounds have been characterized by melting point, ^{1}H NMR, ^{13}C NMR, IR and Mass spectroscopy. All the data were in agreement with the cited literature.

APPLICATIONS

Biological Evaluations: The antibacterial potency of the drugs was screened by disc plate process [13].The test discs were having 50 µg per disc of the examination drugs. The potency was revealed next to gram +ve bacteria are *Bacillus megaterium* [MTCC (121)], *Staphylococcus aureus* [MTCC (96)] and gram –ve bacteria *Proteus vulgaris* [MTCC (1771)], *Escherichia coli* [MTCC (443)].



	C1	C2	C3	C4	C5	C6	C7	C8	C9	C 10	C 11	C 12	Ampicillin	Gentamycin
S.aureus (+Ve)	6	5	13	5	10	7	12	8	8	7	12	9	15	16
B.megaterium (+Ve)	9	7	10	5	12	7	12	11	14	5	9	12	14	15
E.coli (-Ve)	8	9	12	5	7	6	14	7	13	6	13	7	17	14
P.vulgaris (-Ve)	7	7	14	5	7	5	14	10	14	7	14	10	19	16

Against *Staphylococcus aureus*: Maximum activity were found in compounds (C3, C7, C11) zone of inhibition-13.0 mm. and minimum activity were found in compounds (C2, C4) zone of inhibition -5.0 mm.

Against *Bacillus megaterium*: Maximum activity were found in compounds (C5, C7, C9, C12) zone of inhibition -14.0 mm whereas minimum activity were found in compound (C4, C10) zone of inhibition -5.0 mm.

Against *Escherichia coli*: Maximum activity were found in compounds (C7, C9, C11) zone of inhibition -14.0 mm and minimum activity were found in compounds (C4) zone of inhibition -5.0 mm

Against *Proteus vulgaris*: Maximum activity were found in compound (C3, C7, C9, C11) zone of inhibition -14.0 mm (near to standard drug) and minimum activity were found in compounds (C4, C6) zone of inhibition -4.0 mm.

CONCLUSIONS

In conclusion, we have synthesized of novel fluorinated 5, 6-dihydro-1H-pyrano [2, 3-d] pyrimidine-2, 4, 7(3H)-triones as potential antimicrobial agents.

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REFERENCES

[1] B.S. Holla, B. Kalluraya, K.R. Sridhar, E. Drake, L.M. Thomas, K.K. Bhandary, M.J. Levine, *Eur. J. Med. Chem*, **1994**.
[2] P.Molina, E. Aller, A. Lorenzo, P. López-Cremades, I. Rioja, A. Ubeda, M.C. Terencio, M.J. Alcaraz, *J. Med. Chem*, **2001**, 44, 1011.
[3] S.S.Chobe, B.S. Dawane, K.M. Tumbi, P.P. Nandekar, A.T. Sangamwar, *Bioorg. Med. Chem. Lett*, **2012**, 22,7566; (b) M.T. Di Parsia, C. Suarez, M.J. Vitolo, V.E. Marquez, B. Beyer, C. Urbina, I. Hurtado, *J. Med. Chem*, **1981**, 24, 117.
[4] N.R.Kamdar, D.D. Haveliwala, P.T. Mistry, S.K. Patel, *Eur.J. Med. Chem*, **2010**, 45, 5056.
[5] (a) Abdel Fattah, M. E., Atta, A. H., Abdel Gawad, I. I., Mina, S.M, *Orient. J. Chem*, **2004**, *20*, 257; (b) M.M. Ghorab, A.Y. Hassan, *Phosphorus, Sulfur Silicon Relat. Elem*, **1998**, 141, 251.
[6] O. Bruno, C. Brullo, A. Ranise, S. Schenone, F Bondavalli, E.Barocelli, V.Ballabeni, M. Chiavarini, M. Tognolini, M. Impicciatore, *Bioorg. Med. Chem. Lett*, **2001**, 11, 1397.
[7] V.K. Akluwalia, M. Bala, *Indian J. Chem, Sect. B*, **1996**, 35B, 742.
[8] A.H. Shamroukh, M.E.A. Zaki, E.M.H. Morsy, F.M. Abdel-Motti, F.M. E. Abdel-Megeid, *Arch. Pharm*, **2007**, 340, 236.
[9] K.C. Joshi, R. Jain, K. Sharma, *J. Indian Chem. Soc*, **1988**, 45,202.
[10] (a)*The pyrimidines*; D. Fenn, *Ed.; Wiley: New York* **1994**; (b) D. Heber, C. Heers, U. Ravens, *Pharmazie* **1993**, *48*, 537; (c) E.M. Grivasky, S. Lee, C.W. Sigal, D.S. Duch, C.A.Nichol, *J. Med. Chem*, **1980**, *23*, 327; (d) A.D.Broom, J.L. Shim, G.L. Anderson, *J. Org. Chem*, **1976**, 41, 1095.
[11] M.M. Ghorab, A.Y. Hassan, *Phosphorus, Sulfur Silicon Relat.Elem*, **1998**, 141, 251; (b) S. Furuya, T. Ohtaki, *Eur. Patent*, **1994,** 6, 085,65; (c) W. J. Coates, *Eur. Patent*, **1990**, 3,510, 58.
[12] (a) N. Kitamura, A. Onishi, *Eur. Patent* **1984**, 1,635,99; (b) J. Davoll, J. Clarke, E.F. Elslager, *J. Med. Chem*, **1972**, 15,837; (c) G. Levitt, *U. S. Patent*, **1982**, 4, 339, 267.
[13] S.A. Walksman, *Microbial Antagonism and Antibiotic Substances, Commonwealth Fund, N.Y., 2nd edition*, **1945,** 72.

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