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Synthesis of Novel 1,2,3,4-Tetrahydro-N-(Substitutedphenyl)-6-Methyl-4-(4-(Phenoxymethyl)Phenyl)-2-Thioxopyrimidine-5-Carboxamide and Study of their Antimicrobial Activity

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ABSTRACT

During the last two decades, several pyrimidine derivatives have been developed as chemotherapeutic agents and have found wide clinical applications. We synthesize some pyrimidines by Biginelli condensation method. Novel 1,2,3,4-tetrahydro-N-(substitutedphenyl)-6-methyl-4-(4-(phenoxymethyl)phenyl)-2-thioxopyrimidine-5-carboxamide (AB116 to AB130) are synthesized and characterized by FT-IR, ^{1}H NMR, Mass spectra, TLC and elemental analysis. The newly synthesized compounds were screened for antimicrobial activities(MIC) *in vitro* against two strains of gram –ve and two strains of gram +ve bacteria and three fungi by broth dilution method. Few of the compounds show excellent antimicrobial activity.

KEYWORDS

1,2,3,4-tetrahydro pyrimidine, Antimicrobial activity.

INTRODUCTION

Heterocyclic compounds have drawn special attention in organic chemistry because of their abundance in natural products and their diverse biological properties.[1] Pyrimidine and its derivatives have been recognized as important heterocyclic compounds due to their variety of chemical and biological significance to medicinal chemistry.[2,3,4] Pyrimidine antagonists belong to the group of antimetabolite anti-cancer drugs and show structural resemblance with naturally occurring nucleotides. Their action is accomplished through incorporation as false precursor in DNA or RNA or through inhibition of proteins involved in nucleotide metabolism.

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The most commonly used pyrimidine antagonists are 5-fluorouracil, gemcitabine and cytarabine. Newer oral variants of 5-fluorouracil are capecitabine and tegafur. 5-Fluorouracil and its analogues are used e.g. in the treatment of colorectal-breast- head and neck cancer.[5,6,7] whereas gemcitabine is especially prescribed for non-small cell lung cancer and pancreatic cancer.[8,9] Cytarabine is administrated in the treatment of leukaemia.[10] The pyrimidine nucleus is embedded in a large number of alkaloids, drugs, antibiotics, agrochemicals and antimicrobial agents[11]. In the past decades, a broad range of biological effects, including antiviral, antitumor, antibacterial and anti-inflammatory activities, has been ascribed to partly reduced pyrimidine(DHPM) derivatives. More recently, appropriately functionalized DHPMs have emerged as eg. orally active antihypertensive agents[12]. Some other researchers[13,14] also prepared pyrimidine

derivatives and tested their antitumor and anticancer activities. As a result of remarkable pharmacological activity of pyrimidine derivatives, in continuous of our earlier work[15,16] we have synthesized 1,2,3,4-tetrahydro pyrimidine derivatives and studied their antimicrobial activity.

MATERIAL AND METHOD

Melting points were determined in open capillary tubes and are uncorrected. 0.5 mm thickness and spots were located by iodine. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using potassium bromide (KBr) pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in DMSO-d_6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

EXPERIMENTAL

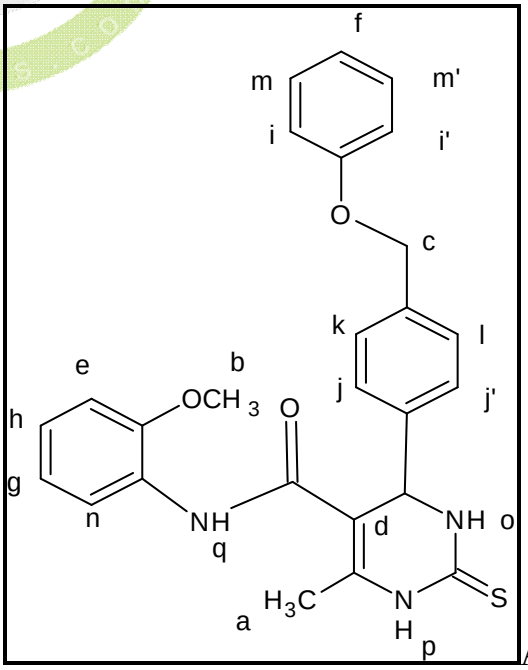
Syntheses of N-(substituted phenyl)-3-oxobutanamides were achieved using previously published methods[17,18].

General procedure for the synthesis of 1,2,3,4-tetrahydro-N-(substitutedphenyl)-6-methyl-4-(4-(phenoxymethyl)phenyl)-2-thioxopyrimidine-5-carboxamide (AB-116 to130)

A mixture of *N*-(substituted phenyl)-3-oxobutanamides (0.01 M), 4-(phenoxymethyl)benzaldehydes (0.01 M), thiourea (0.015 M) and catalytic amount of conc. acid in ethanol (30 ml) was heated under reflux condition for 11 to 12 hrs. The reaction mixture was kept at room temperature for 24 hrs. The crystalline product obtained and recrystallized from ethanol.

1. 1,2,3,4-tetrahydro-N-(2-methoxyphenyl)-6-methyl-4-(4-(phenoxymethyl)phenyl)-2-thioxopyrimidine-5-carboxamide (AB-116)

Yield: 68%; mp 221ºC; Anal. Calcd. for $C_{26}H_{25}N_3O_3S$: C, 67.95; H, 5.48; N, 9.14; O, 10.44; S, 6.98; Found: C, 67.64; H, 5.21; N, 9.01; O, 10.12; S, 6.34%; IR (cm^{-1}): 3363 (N-H stretching of amide), 3109 (C-H stretching of aromatic ring), 2955 (C-H asymmetrical stretching of CH_3 group), 2871 (C-H symmetrical stretching of CH_3 group), 1703 (C=O stretching of amide), 1662 (C=O stretching of cyclic) 1597 (N-H deformation of pyrimidine ring), 1523 (C=C stretching of aromatic ring), 1423 (C-H asymmetrical deformation of CH_3 group), 1342 (C-H symmetrical deformation of CH_3 group), 1342 (C-N-C stretching vibration of pyrimidine ring), 1269 (C-N stretching), 1246 (C-O-C asymmetrical stretching OCH_3), 1070 (C-H in plane deformation of aromatic ring), 1014 (C-O-C symmetrical stretching OCH_3) 823 (para-substituted); MS: *m/z* 460; ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (s, 3H, Ha), 3.32 (s, 3H, Hb), 5.17 (s, 2H, Hc) 5.43 (s, 1H, Hd), 7.07-7.11 (m, 4H, He-h), 7.24-7.26 (dd', 2H, Hii', *J* = 8.80 Hz), 7.40-7.42 (dd', 2H, Hjj', *J* = 8.80 Hz), 7.54-7.57 (m, 2H, Hkl), 7.68 (s, 2H, Hmm'), 8.45-8.46 (m,1H, Hn), 8.81 (s, 1H, Ho), 8.86-8.89 (d, 1H, Hp), 9.65 (s, 1H, Hq).



AB-116

2. N-(3-chlorophenyl)- 6-methyl-1,2,3,4-tetrahydro- 4-(4-(phenoxymethyl)phenyl)-

2-thioxopyrimidine-5-carboxamide (AB-117)

Yield: 65%; mp 213ºC; Anal. Calcd. for $C_{25}H_{22}ClN_3O_2S$: C, 64.72; H, 4.78; Cl, 7.64; N, 9.06; O, 6.90; S, 6.91; Found: C, 64.24; H, 4.12; Cl, 7.22; N, 8.56; O, 6.72; S, 6.46%; MS: m/z 464.

3 . N-(2-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-4-(4-(phenoxymethyl)phenyl)-

2-thioxopyrimidine-5-carboxamide (AB-118)

Yield: 67%; mp 201ºC; Anal. Calcd. for $C_{25}H_{22}FN_3O_2S$: C, 67.10; H, 4.95; F, 4.25; N, 9.39; Found: C, 66.62; H, 4.72; F, 4.01; N, 9.10%; MS: m/z 448.

4. N-(3-chloro-4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-4-(4-phenoxymethyl)phenyl)-2-thioxopyrimidine-5-carboxamide (AB-119)

Yield: 63%; mp 204ºC; Anal. Calcd. For $C_{25}H_{21}ClFN_3O_2S$: C, 62.30; H, 4.39; Cl, 7.36; F, 3.94; N, 8.72; Found: C, 62.04; H, 4.15; Cl, 7.13; F, 3.67; N, 8.54%; MS: m/z 482.

5. 1,2,3,4-tetrahydro-N-(4-methoxyphenyl)-6-methyl-4-(4-(phenoxymethyl)- phenyl)-2-thioxopyrimidine-5-carboxamide (AB-120)

Yield: 70%; mp 205ºC; Anal. Calcd. for $C_{26}H_{25}N_3O_3S$:C, 67.95; H, 5.48; N, 9.14; Found: C, 67.80; H, 5.20; N,9.00%; MS: m/z 460.

6. N-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-4-(4-(phenoxymethyl)phenyl)-

2-thioxopyrimidine-5-carboxamide (AB-121)

Yield: 71%; mp 220ºC; Anal. Calcd. for $C_{25}H_{22}ClN_3O_2S$: C, 64.72; H, 4.78; Cl, 7.64; N, 9.06; Found: C, 64.33; H, 4.42; Cl, 7.12; N, 9.00%; MS: m/z 464;

7. 1,2,3,4-tetrahydro-6-methyl-4-(4-(phenoxymethyl)phenyl)-2-thioxo-N-ptolylpyrimidine-5-carboxamide (AB-122)

Yield: 66%; mp 197ºC; Anal. Calcd. for $C_{26}H_{25}N_3O_2S$: C, 70.40; H, 5.68; N, 9.47; Found: C, 70.01; H, 5.31; N,9.12%; MS: m/z 444.

8. N-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-4-(4-(phenoxymethyl)phenyl)-2-thioxopyrimidine-5-carboxamide (AB-123)

Yield: 57%; mp 195ºC; Anal. Calcd. for $C_{25}H_{22}FN_3O_2S$: C, 67.10; H, 4.95; F, 4.25; N, 9.39; Found: C, 67.01; H,4.23; F, 4.05; N, 9.12%; MS: m/z 448.

9. N-(2-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-4-(4-(phenoxymethyl)phenyl)-

2-thioxopyrimidine-5-carboxamide (AB-124)

Yield: 69%; mp 188ºC; Anal. Calcd. for $C_{25}H_{22}ClN_3O_2S$: C, 64.72; H, 4.78; Cl, 7.64; N, 9.06; Found: C, 64.26; H, 4.29; Cl, 7.28; N, 8.79%; MS: m/z 464.

10. N-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-6-methyl-4-(4-(phenoxymethyl-) phenyl)-2-thioxopyrimidine-5-carboxamide (AB-125)

Yield: 72%; mp 211ºC; Anal. Calcd. For $C_{25}H_{21}Cl_2N_3O_2S$: C, 60.24; H, 4.25; Cl, 14.23; N, 8.43;

Found: C, 60.00; H, 4.01; Cl, 14.02; N, 8.07%; MS: m/z 498.

11. 1,2,3,4-tetrahydro-N-(3-methoxyphenyl)-6-methyl-4-(4-(phenoxymethyl)phenyl)-2-thioxopyrimidine-5-carboxamide (AB-126)

Yield: 58%; mp 186ºC; Anal. Calcd. for $C_{26}H_{25}N_3O_3S$: C, 67.95; H, 5.48; N, 9.14; Found: C, 67.56; H, 5.33; N,9.01%; MS: m/z 460.

12. 1,2,3,4-tetrahydro-6-methyl-N-(2,4-dimethylphenyl)-4-(4-(phenoxymethyl)-phenyl)-2-thioxopyrimidine-5-carboxamide(AB-127)

Yield: 61%; mp 187ºC; Anal. Calcd. for $C_{27}H_{27}N_3O_2S$: C, 70.87; H, 5.95; N, 9.18; Found: C, 70.64; H, 5.75; N, 9.01%; MS: m/z 458.

13. N-(4-bromophenyl)-1,2,3,4-tetrahydro-6-methyl-4-(4-(phenoxymethyl)-phenyl)-2-thioxopyrimidine-5-carboxamide (AB-128)

Yield: 68%; mp 205ºC; Anal. Calcd. for $C_{25}H_{22}BrN_3O_2S$: C, 59.06; H, 4.36; Br, 15.72; N, 8.26; Found: C, 58.88;H, 4.10; Br, 15.23; N, 8.11%; MS: m/z 508.

14. N-(3-bromophenyl)-1,2,3,4-tetrahydro-6-methyl-4-(4-(phenoxymethyl)-phenyl)-2-thioxopyrimidine-5-carboxamide (AB-129)

Yield: 70%; mp 214ºC; Anal. Calcd. for $C_{25}H_{22}BrN_3O_2S$: C, 59.06; H, 4.36; Br, 15.72; N, 8.26; Found: C, 58.67; H, 4.13; Br, 15.43; N, 8.10%; MS: m/z 508.

15. 1,2,3,4-tetrahydro-6-methyl-4-(4-(phenoxymethyl)phenyl)-N-phenyl-2-thioxopyrimidine-5-carboxamide (AB-130)

Yield: 64%; mp 224ºC; Anal. Calcd. for $C_{25}H_{23}N_3O_2S$: C, 69.91; H, 5.40; N, 9.78; O, 7.45; Found: C, 69.43; H,5.10; N, 9.24; O, 7.21%; MS: m/z 430.

BIOLOGICAL EVALUATION

Antimicrobial evaluation

All of the synthesized compounds **(AB- 116 to 130)** were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method [19-21] with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes* MTCC 443, two Gram-negative bacteria *Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 441 and three fungal strains *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282, *Aspergillus clavatus* MTCC 1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and gresiofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh, India. The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro dilution broth method according to NCCLS standards[19].

Minimal Inhibition Concentration [MIC]

The main advantage of the 'Broth Dilution Method' for MIC determination lies in the fact that it can readily be converted to determine the MIC as well.

1. Serial dilutions were prepared in primary and secondary screening.

2. The control tube containing no antibiotic is immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37^0 C overnight.

3. The MIC of the control organism is read to check the accuracy of the drug concentrations.

4. The lowest concentration inhibiting growth of the organism is recorded as the MIC.

5. The amount of growth from the control tube before incubation (which represents the original inoculums) is compared.

Methods used for primary and secondary screening

Each synthesized drug was diluted obtaining 2000 µg mL^{-1} concentration, as a stock solution. Inoculum size for test strain was adjusted to 10^8 cfu (colony forming unit) per milliliter by comparing the turbidity.

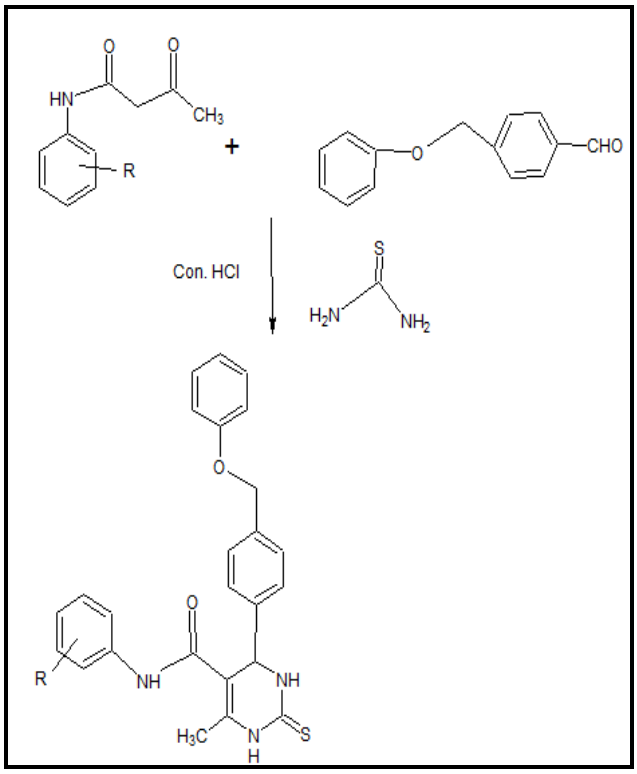
Primary screen: In primary screening 1000 µg mL^{-1}, 500 µg $mL^{-1}$and 250 µg mL^{-1} concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms.

Secondary screen: The drugs found active in primary screening were similarly diluted to obtain 200 µg mL^{-1}, 100 µg mL^{-1}, 50 µg mL^{-1}, 25 µg mL^{-1}, 12.5 µg mL^{-1}, and 6.250 µg mL^{-1} concentrations.

Table 1:- *In vitro* Antimicrobial Screening Results for AB-116 to AB-130

Code	**Minimal inhibition concentration (µg mL^{-1})**						
	Gram-positive species		**Gram-negative species**			**Fungal species**	
	S. a.	*S. p.*	*E. c.*	*P.a.*	*C.a.*	*N. a.*	*A. c.*
AB-116	200	200	200	250	500	500	500
AB-117	200	200	100	200	250	500	500
AB-118	100	100	250	500	500	250	250
AB-119	1000	500	1000	500	500	500	500
AB-120	250	1000	1000	500	1000	1000	1000
AB-121	250	500	500	250	500	500	500
AB-122	100	500	200	250	250	200	200
AB-123	250	62.5	500	250	100	250	250
AB-124	100	250	500	500	200	▪ 1000	▪ 1000
AB-125	250	500	200	1000	500	500	500
AB-126	62.5	500	250	250	250	▪ 1000	▪ 1000
AB-127	200	200	100	100	250	▪ 1000	▪ 1000
AB-128	150	200	250	150	1000	500	500
AB-129	62.5	500	500	1000	1000	500	1000
AB-130	250	500	1000	1000	250	1000	1000
Gentamycin	0.25	0.50	0.05	1	-	-	-
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Iprofloxacin	50	50	25	25	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Gresiofulvin	-	-	-	-	500	100	100

Reaction Scheme



AB-101 to AB-115, Where, R=

AB-116,R=2-OCH_3-

AB-117,R=3-Cl

AB-118,R=2-F

AB-119,R= 3-Cl 4-F

AB-120, R= 4-OCH_3

AB-121,R= 4-Cl

AB-122,R= 4-CH_3

AB-123,R= 4-F

AB-124,R= 2-Cl

AB-125,R= 3,4-DiCl

AB-126,R= 3-OCH_3

AB-127,R= 2,4-diCH_3

AB-128,R= 4-Br

AB-129,R= 3-Br

AB-130,R= H

Reading Result: The highest dilution showing at least 99 % inhibition zone is taken as MIC. The result of this is much affected by the size of the inoculums. The test mixture should contain 10^8 organism/mL.

The results obtained from antimicrobial susceptibility testing are depicted in Table 1.

RESULT AND DISCUSSION

All the synthesized compounds have shown sharp melting points and melts clearly. Their elemental analysis result reveals that they are in well agreement with their structure. In spectral studies all the peaks are in the range of their value according to the structure assigned. The assignment of the infrared bands were made by comparing the spectra of the compounds with reported literature values on similar systems[22]. By the antimicrobial study of the compounds we conclude that most of compounds are good antimicrobial agents, very few of them are less or moderate active as compared to standard drugs. All the compounds possess better antifungal activity than antibacterial so most of the compounds are more toxic to fungi. Compounds AB-119 and AB-120 are active against all the strains of bacteria and fungi where as compounds AB-128, AB-129 and AB-130 show good activity against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli* and *Pseudomonas aeruginosa*, but it is excellent against three fungal strains *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus* and AB-125 are also toxic for *Streptococcus pyogenes* and *Pseudomonas aeruginosa*. Compounds AB-124, AB-126 and AB-127 are excellent against fungi. In general it is observed that compounds having functional group $–OCH_3$ and halogen are good antimicrobial agents and would be useful as pesticides.

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