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Regioselective Reaction: Synthesis Of Novel Mannich Bases Derived From 5-(4,6-Disubstituted-2-Thiomethyl Pyrimidyl) -1,3,4-Oxadiazole-2-Thiones And Their Biological Properties

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ABSTRACT

A new series of 2-(4,6-disubstituted-2-thiomethyl pyrimidyl)-1,3,4-oxadiazole-5-thiones (5a-c) were synthesized. These oxadiazoles can exist both in the thiol as well as in the thione tautomeric form. However when these compounds were subjected to Mannich reaction, N-Mannich bases (6a-r) were obtained rather than the S-Mannich bases. The structures of the new compounds were confirmed by spectral and analytical data. Few of these Mannich bases were evaluated for their possible antifungal and antibacterial activity. Most of the tested compounds showed significant antifungal and antibacterial activity comparable with that of the standard drug.

KEYWORDS

Pyrimidine;
Oxadiazole;
Biological activity;
Mannich.

INTRODUCTION

The chemistry of pyrimidine and its derivatives has been studied for over a century due to their diverse biological activities[1,2]. They possess antibacterial, antiviral, antitumor, anti-inflammatory activities[3,4]. After the discovery by Mannich, Mannich bases have become important tools for the synthesis of variety of heterocyclic compounds and their derivatives have many attractive applications. However the most important applications are in the field of pharmaceutical products, studies on anti-neoplastic drugs, analgesic drugs, and antibiotic drugs etc.[5,6].

Prompted by the above observations and in continuation of our studies on pyrimidine heterocycles[7], we synthesized a new series of 2-(4,6-disubstituted-

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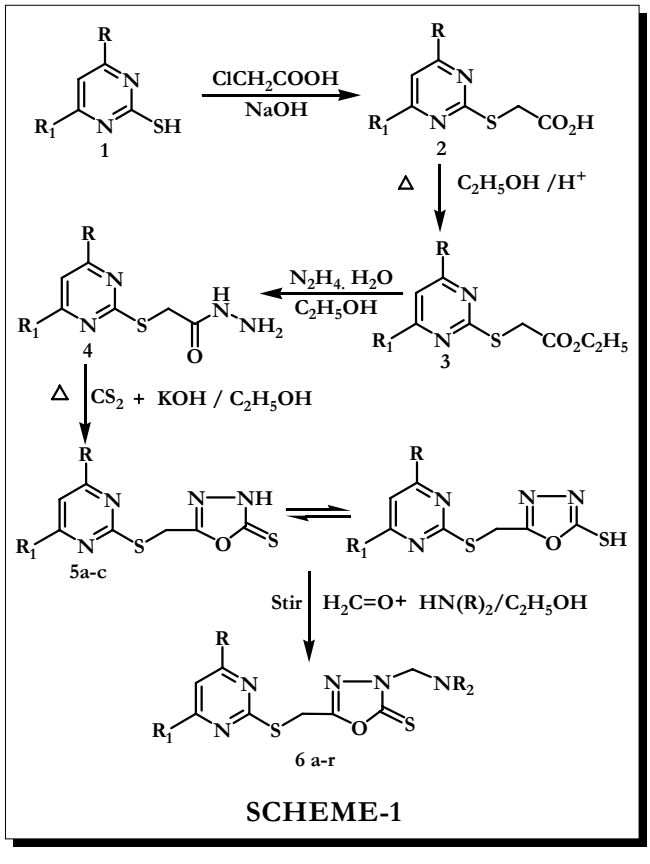
2-thiomethyl pyrimidyl)-1,3,4-oxadiazole-5-thiones **(5a-c)** and subjected for Mannich reaction. The oxadiazole thiones **(5a-c)** can exist both in the thiol as well as in the thione tautomeric form. However the Mannich reaction of these compounds resulted in the formation of N-Mannich bases **(6a-r)** rather than the S-Mannich bases, there by indicating that the reaction is highly regiospecific. Some of the selected Mannich bases from this series were subjected to antibacterial and antifungal activity studies. Among the tested compounds many of them showed significant antibacterial and antifungal activity comparable with that of the standard drugs.

The synthetic route followed for obtaining the title compound is outlined in SCHEME 1. Thus 4,6-disubstituted-prymidine-2-thiol **(1)** on reaction with chloro acetic acid in aqueous sodium hydroxide followed by neutralization with hydrochloric acid gave the 4,6-disubstituted-pyrimidine-2-thioacetic acid **(2)**. 4,6-disubstituted-pyrimidine-2-thioacetic acid **(2)** on esterification with ethyl alcohol gave 4,6-disubstituted-pyrimidine-2-thio ethyl acetate **(3)**. Reaction of **(3)** with hydrazine hydrate in ethanol medium gave 4,6-disubstituted-prymidine-2-thio acethydrazide **(4)**. The hydrazide **(4)** when reacted with carbon disulfide in alcoholic potassium hydroxide gave 5-(4,6-disubstituted-2-thiomethyl pyrimidyl)-1,3,4-oxadiazole-2-thione **(5a-c)**. Reaction of **(5)** with formaldehyde and appropriate secondary amine in ethanol media gave N-Mannich base **(6a-r)** rather than the S-Mannich bases. 4,6-Disubstituted pyrimidine-2-thiol **(1)** was prepared as per the procedure reported in literature[8].



SCHEME-1

RESULTS AND DISCUSSION

The structure of the newly synthesized 2-(4,6-disubstituted-2-thiomethyl pyrimidyl)-1,3,4-oxadiazole-5-thione **(5a-c)** and 3-substituted aminomethyl-5-(4,6-dimethyl-2-thiomethyl-pyrimidyl)-1,3,4-oxadiazole-2-thiones **(6a-r)** were established on the basis of spectral and analytical data. The C, H, N analysis of these compounds were in agreement with the calculated values within the limits of experimental error. In the IR spectra of oxadiazoles the C-H stretching and C=N absorption bands were observed in the region of ≈2900cm^{-1} and 1588-1619cm^{-1} respectively. In a typical example the ^{1}H-NMR spectrum of **(5b)** the methyl protons attached at the 4th position of the pyrimidyl moiety appeared as a singlet at δ, 2.45 integrating for three protons. The S-CH_2 protons appeared as singlet at δ, 4.4. The pyrimidyl 5-H & 6-H protons appeared as two doublets centered at δ, 6.9 and 8.4 each integrating for one proton. The signal due to the NH proton appeared as a broad singlet at δ, 13.4 which is probably due to the thione-thiol tautomerism and gets disappeared on exchange with D_2O. Further the mass spectrum of this compound showed the molecular ion peak at m/z, 241(M^++1 peak) consistent with the molecular formulae $C_8H_8N_4S_2O$. Similarly in the ^{1}H-NMR spectrum of(5c) the signals appeared are assigned as follows; δ, 2.4(s, 6H, 2XCH_3), 4.4(s, 2H, S-CH_2), 6.8(d, 1H, pyrimidine-5H) and 13.6(br, 1H, NH). Mass:m/z, 255(M^++1) consistent with the molecular formulae $C_9H_{10}N_4S_2O$.

When these oxadiazoles were treated with appropriate amine in the presence of formaldehyde in ethanol medium the Mannich reaction occured at the nitrogen rather than the sulphur. Formation of N-

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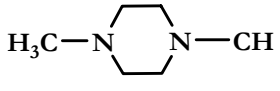
Mannich bases were confirmed by recording the ^{1}HNMR spectra of these compounds. In a typical example the proton NMR spectrum of Mannich base(6m), the 4.6-dimethyl protons of the pyrimidyl group appeared as a singlet at δ, 2.27 integrating for six protons. The signal due to piperazine protons appeared as multiplet in the region of δ, 2.4-2.6 integrating for 8 protons. The S-CH_2 protons came into resonance as a singlet at δ, 4.49 integrating for two protons. The N-CH_2-N protons appeared at δ, 4.85 integrating for two protons. Pyrimidyl-5H appeared as a singlet at δ, 7.0 integrating for one proton. The NH proton appeared at δ, 3.3. The mass spectrum of this compound showed the molecular ion peak at m/z, 352 consistent with the molecular formulae $C_{14}H_{20}N_6S_2O$. The base peak was observed at m/z, 254 due to the formation of parent oxadiazole involving the loss of piperazino methyl radical from the molecular cation. Similarly the ^{1}H-NMR and mass spectral data for few other representative compounds were given below.

(6n): 3-(N-Methyl piperazinomethyl)-5-(4,6-dimethyl-2-thiomethyl-pyrimidyl)-1,3,4-oxadiazole-2-thione

^{1}HNMR($CDCl_3$):δ, 2.41(s, 6H, pyrimidine-2xCH_3), 2.71(s, 3H, N-CH_3), 3.4-3.6(m, 8H, piperazinoprotons), 4.40(s, 2H, S-CH_2), 4.90(s, 2H, N-CH_2) and 6.77(s, 1H, pyrimidine-5H). Mass:m/z, 366 (M^++1) consistent with the molecular formulae $C_{15}H_{22}N_6S_2O$, m/z, 254(Base peak) due to the loss of N-methyl piperazino methyl radical.



(6o): 3-(Morpholinomethyl)-5-(4,6-dimethyl-2-thiomethyl-pyrimidyl)-1,3,4-oxadiazole-2-thione: ^{1}H-NMR($CDCl_3$)

δ, 2.41(s, 6H, Pyrimidine-2xCH_3), 2.72(t, 4H, CH_2-N-CH_2), 3.65(t, 4H, CH_2-O-CH_2), 4.41(s, 2H, S-CH_2), 4.94(s, 2H, N-CH_2) and 6.77(s, 1H, pyrimidine-5H), Mass:m/z, 353(M^++1) consistent with the molecular formulae $C_{14}H_{19}N_5S_2O_2$. The base peak at m/z, 254 is due to the formation of parent oxadiazole cation by the loss of the morpholino methyl radical.

(6r): 3-(Imidazolinomethyl)-5-(4,6-dimethyl-2-thiomethyl-pyrimidyl)-1,3,4-oxadiazole-2-thione: ^{1}H-NMR($CDCl_3$)

δ, 2.43(s, 6H, Pyrimidine-2xCH_3), 4.44(s, 2H, S-CH_2), 5.46(s, 2H, N-CH_2) 6.79(s, 1H, pyrimidine-5H), 7.12(d, 2H, imidazole -4H and -5H) and 7.75 (s, 1H, imidazole-2H). Mass:m/z, 335(M^++1) consistent with the molecular formulae $C_{13}H_{14}N_6S_2O$. Base peak at m/z, 254 is due to the formation of parent oxadiazole cation by the loss of the imidazolomethyl radical from the parent ion.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra(cm^{-1}) were recorded on a Perkin Elmer 577 spectrophotometer in KBr pellets.^{1}HNMR spectra were recorded on a Perkin Elmer(Model RB-12) spectrometer using TMS as an internal standard (chemical shifts are reported in δ scale). Mass spectrum was recorded on LC/MS (API 3000, Applied Biosystems) operating at 70eV. C,H,N analysis was carried out on a Vairo-EL (Elementa) model. Purity of the compounds was checked by TLC on silica gel plates.

Preparation of substituted-pyrimidne-2-thioacetic acid (2)

2-Chloro acetic acid(9.45g, 0.1mole) was taken in a round bottom flask and 50ml water was added, cooled and neutralized by adding a saturated solution of sodium carbonate. A solution of substituted-pyrimidine-2-thiol(0.1mole) (1) and sodium hydroxide(8g 0.2mole) in 50ml water was slowly added to the above solution maintaining the temperature of the reaction mixture at 15-20^{0}C. The contents were further stirred at room temperature for 3-4 hours.

The reaction was monitored by TLC. The contents were cooled and acidified to pH 2-4 using hydrochloric acid. The resulting solid separated was filtered, washed with water, dried and recrystallized from ethanol.

Preparation of substituted-pyrimidine-2-thio ethyl acetate (3)

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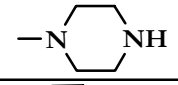
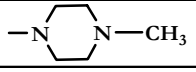
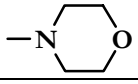
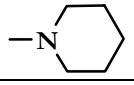
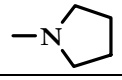
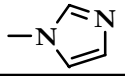
TABLE 1: Characterization data of 2-(4,6-disubstituted-2-thiomethyl pyrimidyl)-1,3,4-oxadiazole-5-thione (5a-c) and 3-substituted aminomethyl-5-(4,6-disubstituted-2-thiomethyl-pyrimidyl) -1,3,4-oxadiazole-2-thiones(6a-r)

Compound No.	R	R^1	$(R)_2$	Mol. Formulae (Mol. Wt)	M.P °C (Yield %)	Colour and crystal nature	Analysis (%) Found (Calculated)		
							C	H	N
5a	H	H	-	$C_7H_6N_4OS_2$ (226)	152-155 (60)	Pale yellow powder	37.11 (37.19)	2.70 (2.65)	24.68 (24.72)
5b	CH_3	H	-	$C_8H_8N_4OS_2$ (240)	157-159 (65)	Yellow powder	40.05 (40.00)	3.29 (3.33)	23.28 (23.33)
5c	CH_3	CH_3	-	$C_9H_{10}N_4OS_2$ (254)	178-182 (70)	Pale yellow Crystals	42.55 (42.50)	3.90 (3.94)	22.04 (21.99)
6a	H	H		$C_{12}H_{16}N_6OS_2$ (324)	147-149 (60)	Off-white powder	44.46 (44.41)	4.90 (4.94)	25.93 (25.89)
6b	H	H		$C_{13}H_{18}N_6OS_2$ (338)	126-128 (65)	Yellow powder	46.10 (46.15)	5.28 (5.32)	24.80 (24.85)
6c	H	H		$C_{12}H_{15}N_5O_2S_2$ (325)	119-121 (71)	White crystals	44.25 (44.31)	4.66 (4.61)	21.48 (21.53)
6d	H	H		$C_{13}H_{17}N_5OS_2$ (323)	116-118 (65)	Yellow powder	48.25 (48.29)	5.21 (5.26)	21.60 (21.67)
6e	H	H		$C_{12}H_{15}N_5OS_2$ (309)	122-125 (68)	Off-white crystals	46.56 (46.60)	4.80 (4.85)	22.61 (22.65)
6f	H	H		$C_{11}H_{10}N_6OS_2$ (306)	132-134 (71)	Yellow crtstals	43.16 (43.13)	3.24 (3.26)	27.42 (27.45)
6g	CH_3	H		$C_{13}H_{18}N_6OS_2$ (338)	158-160 (68)	Orange powder	46.09 (46.15)	5.29 (5.32)	24.89 (24.85)
6h	CH_3	H		$C_{14}H_{20}N_6OS_2$ (352)	134-136 (64)	Yellow crtstals	45.60 (45.65)	5.30 (5.35)	22.82 (22.85)
6i	CH_3	H		$C_{13}H_{17}N_5O_2S_2$ (339)	110-113 (72)	Off-white crystals	46.07 (46.01)	5.03 (5.01)	20.58 (20.61)
6j	CH_3	H		$C_{14}H_{17}N_5OS_2$ (335)	120-124 (63)	Yellow crtstals	49.89 (49.85)	5.62 (5.66)	20.71 (20.77)
6k	CH_3	H		$C_{13}H_{17}N_5OS_2$ (323)	126-129 (62)	Yellow crtstals	48.24 (48.29)	5.25 (5.21)	21.67 (21.69)
6l	CH_3	H		$C_{12}H_{12}N_6OS_2$ (320)	135-137 (60)	Orange powder	44.95 (45.00)	3.71 (3.75)	26.29 (26.25)
6m	CH_3	CH_3		$C_{14}H_{20}N_6OS_2$ (352)	158-161 (65)	Off-white crystals	47.69 (47.72)	5.63 (5.68)	23.89 (23.83)
6n	CH_3	CH_3		$C_{15}H_{22}N_6OS_2$ (366)	100-102 (62)	Yellow crtstals	49.15 (49.18)	6.04 (6.01)	22.90 (22.96)
6o	CH_3	CH_3		$C_{14}H_{19}N_5O_2S_2$ (353)	104-106 (64)	Off-white crystals	47.54 (47.59)	5.40 (5.38)	19.80 (19.84)
6p	CH_3	CH_3		$C_{15}H_{19}N_5OS_2$ (349)	108-111 (66)	Orange powder	51.26 (51.31)	5.97 (5.99)	19.96 (19.93)
6q	CH_3	CH_3		$C_{14}H_{19}N_5OS_2$ (337)	122-124 (65)	Yellow crtstals	49.80 (49.86)	5.63 (5.65)	20.79 (20.75)
6r	CH_3	CH_3		$C_{13}H_{14}N_6OS_2$ (334)	143-146 (64)	Yellow crtstals	46.69 (46.73)	4.17 (4.19)	25.17 (25.13)

Solvent for recrystallization : Ethanol

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A mixture of substituted pyrimidine-2-thioacetic acid 2(0.1mole) was taken in 100ml absolute ethanol and 2.5ml of conc.sulphuric acid was added. The reaction mixture was refluxed for 3hours. Cooled and quenched to 250ml of ice cold water. The pyrimidine-2-thio ethyl acetate was extracted with ethyl acetate, washed with saturated sodium bicarbonate solution and dried over anhydrous sodium sulphate. The organic layer was concentrated under reduced pressure to give yellow oil. This is taken as such for further reaction.

Preparation of substituted-pyrimidine-2-thio acethydrazide (4)

A mixture of pyrimidine-2-thio ethyl acetate (0.1mole) and hydrazine hydrate(5ml, 0.1mole) taken in 100ml ethanol was heated on a water bath for 3 hours. Excess of ethanol was removed by distillation under vacuum. On cooling, white solids gets separated, which was collected by filtration and recrystallized from ethyl alcohol.

Preparation of 5-(4,6-disubstituted-2-thiomethyl pyrimidyl)-1,3,4-oxadiazole-2-thione (5)

A mixture of substituted-pyrimidyl-2-thio-acethydrazide 4(0.1mole), potassium hydroxide (11.2g, 0.2mole) and ethanol (100ml) were taken in a 500ml round bottom flask. Carbon disulphide (15.2g, 0.2mole) was added slowly. After the complete addition of carbon disulphide the contents were refluxed on a water bath for 2 hours. Progress of the reaction was monitored by TLC. After completion of reaction, excess ethanol was removed by distillation. The contents were poured to ice-cold water and acidified with dilute hydrochloric acid. The solid separated was collected by filtration, washed with water, dried and recrystallized from ethanol. The compounds prepared as per this procedure are listed in TABLE 1.

General procedure for the synthesis of 3-substituted aminomethyl-5-(4,6-dimethyl-2-thiomethyl pyrimidyl)-1,3,4-oxadiazole-2-thiones (6)

A solution of 5-(4,6-disubstituted-2-thiomethyl pyrimidyl)-1,3,4-oxadiazole-2-thione 5(0.01mol) in absolute ethanol(20ml) was treated with formaldehyde 40%(3ml). Later, the appropriate amine (0.01mol) in ethanol(10ml) was added with stirring and the reaction mixture was stirred overnight. The precipitated Mannich base was collected by filtration and dried. Further purification was done by recrystallization from ethanol to give compounds(6a-r). Characterization data of these compounds are given in TABLE 1.

BIOLOGICAL ACTIVITY

Antibacterial studies

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *klebesilla* by serial dilution method[9,10]. Serial dilutions of the drug in Muller-Hinton broth were taken in

TABLE 2: Antibacterial activity data of some selected compounds (Zone of inhibition in mm). #

Compound No	*Pseudomonas aeruginosa*	*Escherichia coli*	*Klebesilla*	*Staphylococcus aureus*
6a	6.25(16-20)	6.25(16-20)	6.25(16-20)	6.25(16-20)
6b	6.25(16-20)	6.25(16-20)	6.25(16-20)	6.25(16-20)
6c	12.5 (11-15)	12.5 (11-15)	12.5 (11-15)	12.5 (11-15)
6g	6.25(16-20)	6.25(16-20)	6.25(16-20)	6.25(16-20)
6h	25(<10)	25(<10)	25(<10)	25(<10)
6i	25(<10)	25(<10)	25(<10)	25(<10)
6m	25(<10)	25(<10)	12.5 (11-15)	25(<10)
6n	25(<10)	25(<10)	25(<10)	25(<10)
6o	25(<10)	25(<10)	25(<10)	25(<10)
6r	6.25(16-20)	12.5 (11-15)	12.5 (11-15)	12.5 (11-15)
Std (Ciprofloxacin)	6.25(25-33)	6.25(30-40)	6.25(23-27)	6.25(22-30)

 # The MIC values were evaluated at concentration range 6.25-25 μg/ml. The figures in the table show the MIC values and the corresponding zone of inhibition (in mm).

TABLE 3: Antifungal activity data of some selected compounds. (Zone of inhibition in mm).#

Compound No	MIC in μg/ml and zone of inhibition (in mm)			
	Aspergillus flavus	*Aspergillus fumigatus*	*Candida albicans*	*penicililum*
6a	6.5(16-20)	6.5(16-20)	6.5(16-20)	6.5(16-20)
6b	6.5(16-20)	6.5(16-20)	6.5(16-20)	6.5(16-20)
6c	25(<10)	25(<10)	25(<10)	25(<10)
6g	6.5(16-20)	6.5(16-20)	6.5(16-20)	6.5(16-20)
6h	25(<10)	25(<10)	25(<10)	25(<10)
6i	25(<10)	25(<10)	25(<10)	25(<10)
6m	25(<10)	25(<10)	25(<10)	25(<10)
6n	6.5(16-20)	25(<10)	25(<10)	25(<10)
6o	6.5(16-20)	25(<10)	25(<10)	25(<10)
6r	6.5(16-20)	6.5(16-20)	6.5(16-20)	6.5(16-20)
Std (Ciclopiroxolamine)	6.25(25-30)	6.25(25-30)	6.25(27-33)	6.25(22-27)

 # The MIC values were evaluated at concentration range 6.25-25 μ g/ml. The figures in the table show the MIC values and the corresponding zone of inhibition (in mm).

tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacteria was inoculated and incubated for 16-18 hours at 37^0C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth. Solvent control was also kept. Ciprofloxacin was used as the standard drug[11,12]. The results are summarized in TABLE 2.

Antifungal studies

Newly prepared compounds were screened for their antifungal activity against *Aspergillus flavus*, *Aspergillus fumigates*, *Candida albicans* and *Penicillium* by the serial dilution method[13,14]. Antifungal activity was determined by measuring the diameter of the zone of inhibition. Activity of each compound was compared with that of Ciclopiroxolamine as standard drug. The antifungal activity results showed that the newly prepared Mannich bases have moderate to good activity against the above mentioned organisms and the results are summarized in TABLE 3.

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REFERENCES

[1] (a) J.Wichmann, A.Geo, Koclzewskis, M.Vincent, T. Woletring; Bioorg.Med.Chem.Lett., **9(11)**, 1573 **(1999)**
(b) E.R.El-Bendary, M.A.El-Sherbeny, F.A.Badri; Bull.Chem.Farm., **137(4)**, 115 **(1998)**.

[2] (a) G.Kirpal; U.S.Patent; 5,869,494, Chem.Abstr., **130**, 163202 **(1999)**.
(b) K.Tsuji, H.Ishikawa; Bioorg.Med.Chem.Lett., **4**, 160 **(1994)**.

[3] (a) W.Lie, Y.Tin, P. G Wang; Chemtech., **2**, 23 **(1999)**.
(b) R.S.Varma; Green Chem., **1**, 43 **(1999)**.
(c) M.Kidwai, R.Venkatraman, R.K.Garg, K.R.Bhushan; J.Chem.Res., **5**, 586 **(2000)**.

[4] (a) C.O.Kappe, W.M.F.Fabian, M.A.Semones; Tetrahedron., **53**, 2803 **(1997)**.
(b) G.Lepetil, S.P.A; German Patent, 2,424,670, **(1974)**, Chem.Abstr., **83**, 20628 **(1975)**.
(c) G.E.Hardmann, F.G. Kathawala; U.S.Patent. 4,053,600, **(1997)**, Chem.Abstr., **88**, 22970 **(1978)**.

[5] (a) S.K.Sridhar, S.N.Pandeya, J.P.Stables, A.Ramesh; Eur.J.Pharm.Science, **16(3)**, 129 **(2002)**.
(b) J.R.Dimmock, P.Kumar, Curr.Med.Chem., **4(1)**, 1-22 **(1997)**.
(c) I.A.Poplevskaya, G.N.Kondaurou, K.A.Abdullin, L.K.Shipunova, G.B.Chermanova, O.K.Kabiev; Tr.Inst.Khim.Nauk.Akad.Nauk.Kaz., SSR, **52**, 52 **(1980)**, Chem.Abstr., **94**, 120781 **(1981)**.

[6] (a) P.Cagniant, G.Krisch, M.Wierzbicki, F.Lepage, D.Cagniant, D.Loebenberg, R.Parmergiani; Scherlock, Eur.J.Med.Chem., **15**, 439 **(1980)**.

Full Paper

(b) Korea Inst. of science and technology, Jpn.Kokai Tokkyo Koho, JP, 5, 867, 693 **(1983)**, Chem.Abstr., **99**, 70474a **(1983)**.
(c) J.R.Dimmock, S.K.Raghavan, B.M.Logan, G.E. Bigam; Eur.J.Med.Chem., **18**, 249 **(1983)**.
[7] B.Kalluraya, B.Lingappa, N.Satheesh Rai; Phosphorous Sulphur and Silicon related elements (In press).
[8] G.Donald, V.Robert, R.Berthold, Herbert.E.Johnson; Org.synthesis., **5**, 703; Walter, France and Richard Kraft, Chem.Ber., **86**, 797 **(1953)**.
[9] A.Barry; 5th Ed., Williams and Wilkins, Baltimore, (MD,1) **(1991)**.
[10] D.James, Mac.Lowry, J.Jaqua Marry, T. Selpak Sally; Applied Microbiology, 46-53, July **(1970)**.
[11] H.Fenlon Christine, H.cynamon Michel; Antimicrobial Agents and chemotherapy, 386, March **(1986)**.
[12] R.Davis, A.Markam, J.A.Balfour; Drugs, **6**, 1019. June **(1996)**.
[13] B.A.Arthington-Skaggs, M.Motley, D.W.Warnock, C.J.Morrison; J.Clinical microbiology, 2254-2260 June **(2000)**.
[14] R.S.Varma; Ed.National Academy of chemistry and Biology, Lucknow, India **(1998)**.