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Synthesis, Mass Spectra Investigation and Biological Activity of Some Pyrimidine Derivatives

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Abstract: *2,6-Disubstituted-5-cyano-4-hydroxypyrimidines (3 and 4) have been prepared via cyclocondensation of ethyl-β-(3-bromo-4-methoxy phenyl)-α-cyanoacrylate (2) with guanidine hydrochloride and thiourea in presence of anhydrous potassium carbonate. Treatment of 3 with acetic anhydride, ethyl chloroacetate, methyl acrylate and 4-methylphenacyl bromide afforded the corresponding N-acetyl (6), N-alkyl (9) and fused pyrimidines (7, 8). The electron impact (EI) ionization mass spectral fragmentations of some synthesized compounds are discussed. Some of the synthesized compounds were tested for their antimicrobial and inhibitory activities against Breast carcinoma cells (MCF-7) cell line.*

I. Introduction

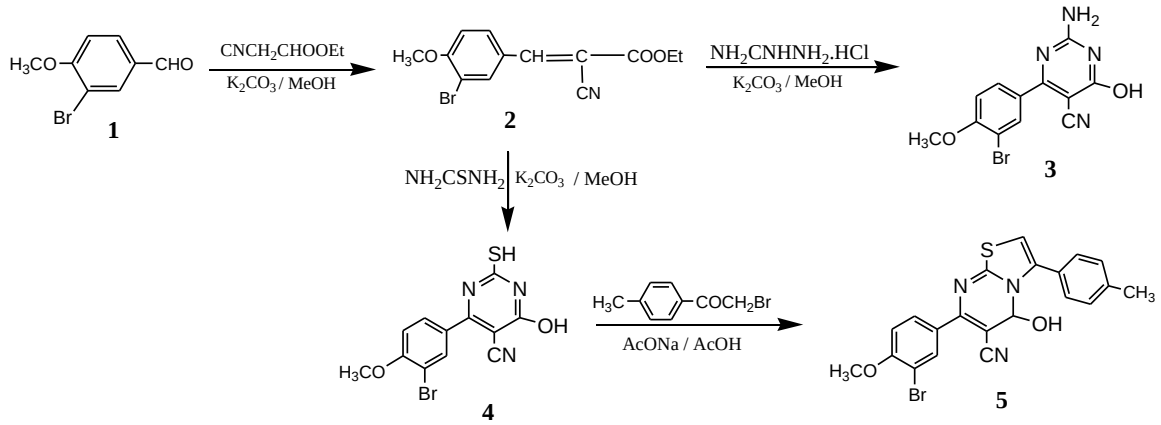
Because of their interesting biological activities, low molecular weight heteroycles have attracted enormous attention in medicinal chemistry. Nitrogen-containing heterocycles have recently received a significant importance because of their diverse pharmacological properties [1-5]. Of these heterocycles, the synthesis, reactions and biological activities of pyrimidine containing molecules stands as an ever expanding area of research in hetero aromatic chemistry. However, the synthesis of some substituted pyrimidines by the treatment of α,β-unsaturated esters with thiourea and guanidine in the presence of anhydrous potassium carbonate were reported [6]. The literature indicated that compounds having pyrimidine nucleus possesses broad range of biological activity like anticancer, antiviral, anti-HIV, antibacterial, antihypertensive, anticonvulsant, antithyroid, and antibiotics [7].The electron Impact (EI) ionization mass spectral fragmentation of some of the synthesized 2-aminopyrimidine and 2-mercaptopyrimidine derivatives were described.

II. Results and Discussion

1) Chemistry

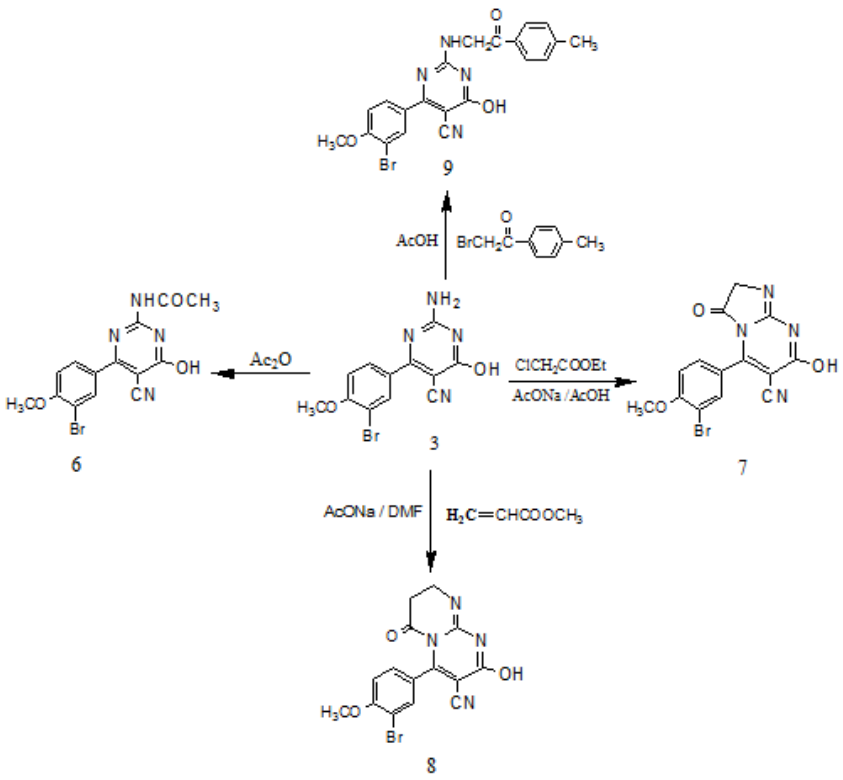
Condensation of 3-bromo-4-methoxybenzaldehyde (1) with ethylcyanoacetate in the presence of anhydrous potassium carbonate led to the formation of ethyl β-(3-bromo-4-methoxyphenyl)-α-cyanoacrylate (2). The reaction of ester derivative (2) with guanidine hydrochloride and thiourea in methanol in presence of anhydrous potassium carbonate under reflux, yielded the corresponding 6-(3-bromo-4-methoxyphenyl)-5-cyano-4-hydroxy-2-aminopyrimidine (3) and 6-(3-bromo-4-methoxyphenyl)-5-cyano-4-hydroxy-2-mercaptopyrimidine (4, Scheme 1).

Treatment of 2-mercaptopyrimidine (4) with 4-methylphenacyl bromide in presence of fused sodium acetate in acetic acid under reflux afforded the corresponding 6-(3-bromo-4-methoxyphenyl)-5-cyano-4-oxo-3-(p-methylphenyl)-thiazolo[2,3-b]pyrimidine (5; Scheme 1).



Scheme 1

Acetylation of 2-aminopyrimidine (3) with acetic anhydride under reflux led to the formation of 6-(3-bromo-4-methoxyphenyl)5-cyano-4-hydroxy-2-(acetylamino)pyrimidine (6). Treatment of 2-aminopyrimidine (3) with ethylchloroacetate in acetic acid afforded the corresponding 6-hydroxy-5-cyano-4-imidazolidino[2,1-b] pyrimidin-3-one (7). The reaction of methyl acrylate in dimethylformamide in presence of fused sodium acetate gave the corresponding 5-(3-bromo-4-methoxyphenyl)-6-cyano-7-hydroxy-2,3-dihydropyrimidino[2,1-b]pyrimidin-4-one (8). Alkylation of 2-aminopyrimidine (3) with 4-methylphenacylbromide in acetic acid under reflux yielded the corresponding 2-(*p*–methylbenzoyl)methylamino-4-hydroxy-5-cyano-6-(3-bromo-4-methoxyphenyl)pyrimidine (9, Scheme 2).



Scheme 2

2) Mass Spectrometry

The mass spectral decomposition modes [6-10] of the prepared 2-mercaptopyrimidine and 2-aminopyrimidine derivatives have been investigated. Table 1 lists the m/z (relative abundance, %) values of the principle fragment of synthesized compounds, while figures 1,2,3,4,5 and 6 illustrated the mass spectra of compounds 3,4,5,6,8 and 9 respectively.

Compound 3

The mass spectrum of compound 3 (Fig.1) showed the molecular ion peaks at m/z 320/322 corresponding to the molecular formula $C_{12}H_9N_4BrO_2$. The base peaks of compounds 3 was found at m/z 322 (M+2) along with the molecular ion peak due to the presence of isotope of bromine atom present in this compounds. The molecular ion of compound 3 fragmented further and involved two pathways as illustrated in table 1 (Scheme 3). The molecular ion of m/z 320 fragmented via pathway A to give peak at m/z 279 by losing NH-CN group. The peak at m/z 279 underwent fragmentation to produce a peak at m/z 212. It further underwent loss of NH, HBr, C_2 and CH_2O to give peaks at m/z 197, 117, 93 and m/z 63 respectively. Accordingly, the same molecular ion of m/z 320 fragmented via the pathway B by the cleavage of isocyanate group (NCO) to give peak at m/z 278, which lose NH-CN group to give a peak at m/z 237. Then lose of formaldehyde and bromine atom to a peak at m/z 128. It further underwent loss of CH=CHN molecule to give a peak at m/z 76.

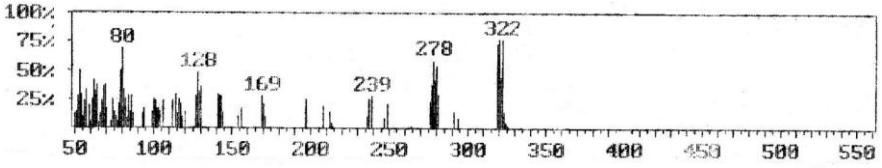
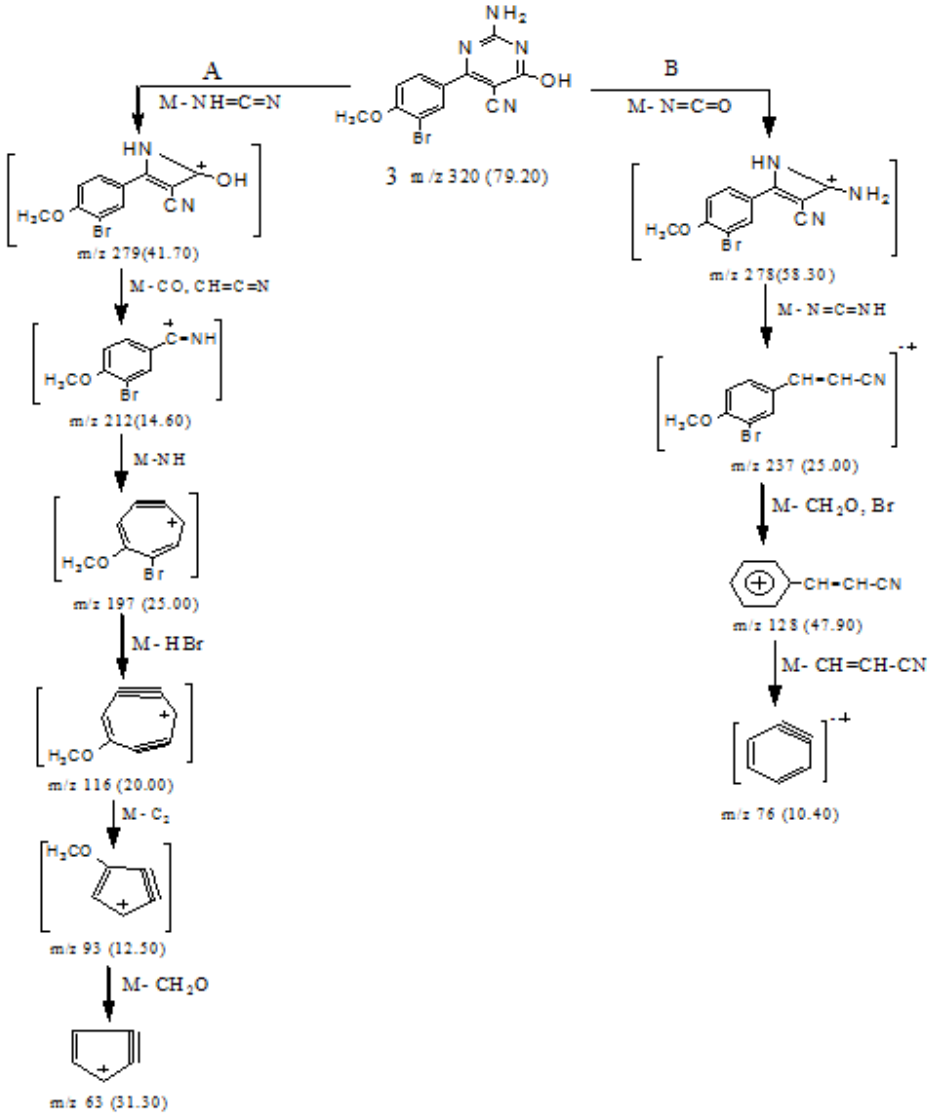


Figure 1: 70 eV mass spectrum of compd 3



Scheme 3: Main fragmentation pathway of compd.3

Compound 4:

The mass spectrum of compound 4 (Fig. 2) showed the molecular ion peak at m/z 337/339 corresponding to the molecular formula $C_{12}H_8N_3BrO_2$. The base peak of compounds 4 was found at 339 (M+2). From the study of mass spectra of compound 4, it had fragmented to the ion of m/z 256 via the pathway A. The ion of m/z 256 underwent fragmentation to produce a peak at m/z 211 by losing thioformyl group (CHS). The ion at m/z 211 underwent loss of CN, OCH_3, Br and C_2 to give peaks at m/z 185, 154, 75 and 51 respectively. The molecular ion of compound 4 was also found to undergo fragmentation via the pathway B to produce the ion of m/z 278. The ion of m/z 278 broked to gave an ion at m/z 236 which lose isocyanate group (NCO). The ion at m/z 236 fragmented to gsve an ion at m/z 210 which lose cyano group (CN). Also the ion at m/z 210 underwent loss of hydrogen bromide, formaldehyde and acetylene molecules to give peaks at m/z 130, 100 and m/z 74 respectively (Scheme 4).

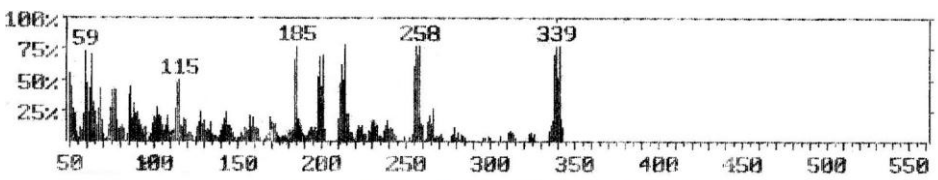
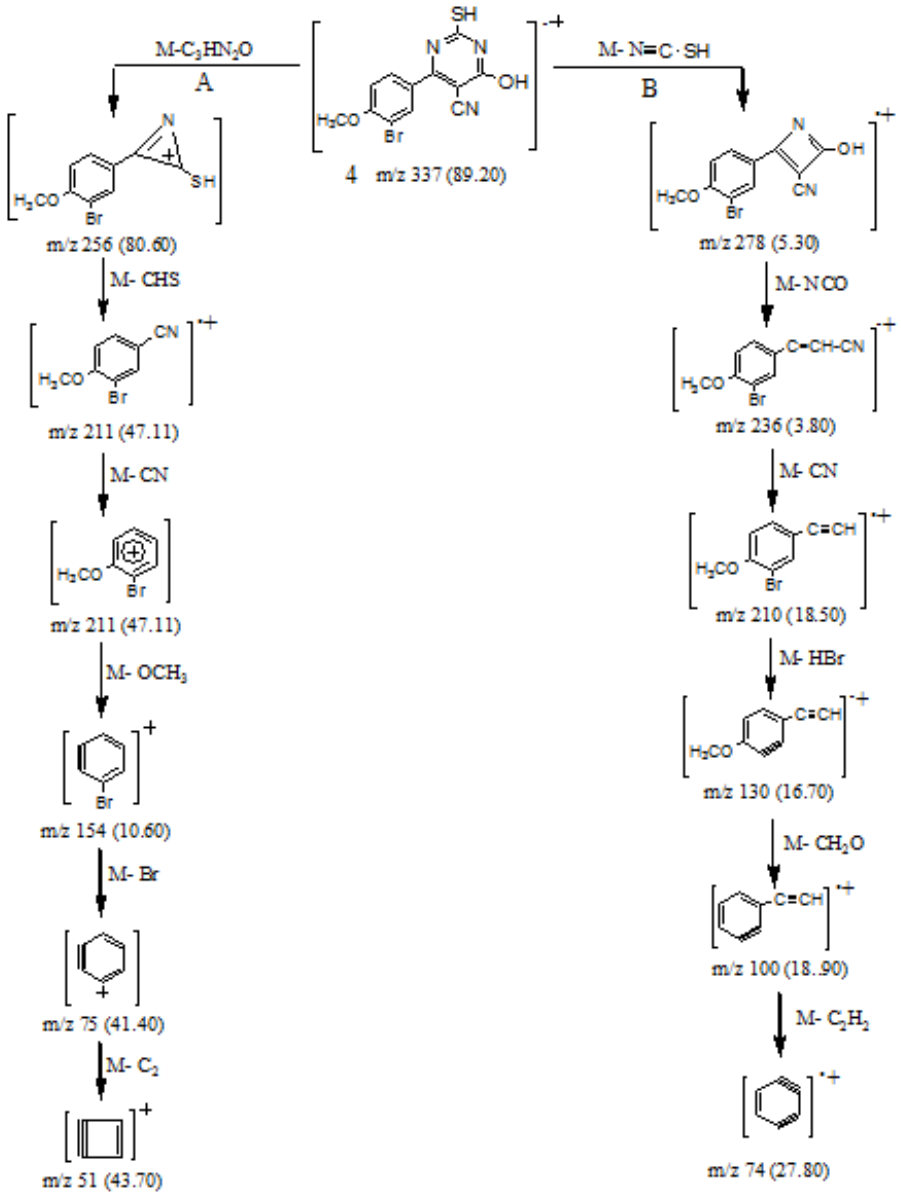


Figure 2: 70 eV mass spectrum of compd 4



Scheme 4: Main fragmentation pathway of compd.4

Compound 5:

From the mass spectrum of compound 5 (Fig.3), it was concluded that the molecular ion at m/z 451/453. The ion of m/z 451 underwent fragmentation via the pathway A to give a peak at m/z 263. The ion at m/z 263 broke to give stable fragment at m/z 185. The base ion of m/z 185 underwent loss of methyl group (CH_3), carbon monoxide (CO) and bromine atom to give peaks at m/z 170, 142 and m/z 63. Also, the same molecular ion peak at m/z 451 undergo fragmentation via the pathway B to produce the ion of m/z 188, which lose (N=C=N) group to give the ion of m/z 148. The ion at m/z 148 underwent loss of sulphur atom (S), methyl group (CH_3) and acetylene molecule to give peaks at m/z 116, 101 and 75 respectively (Scheme 5).

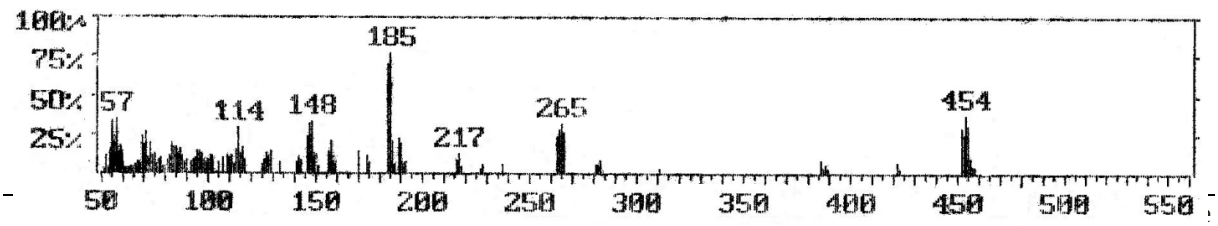
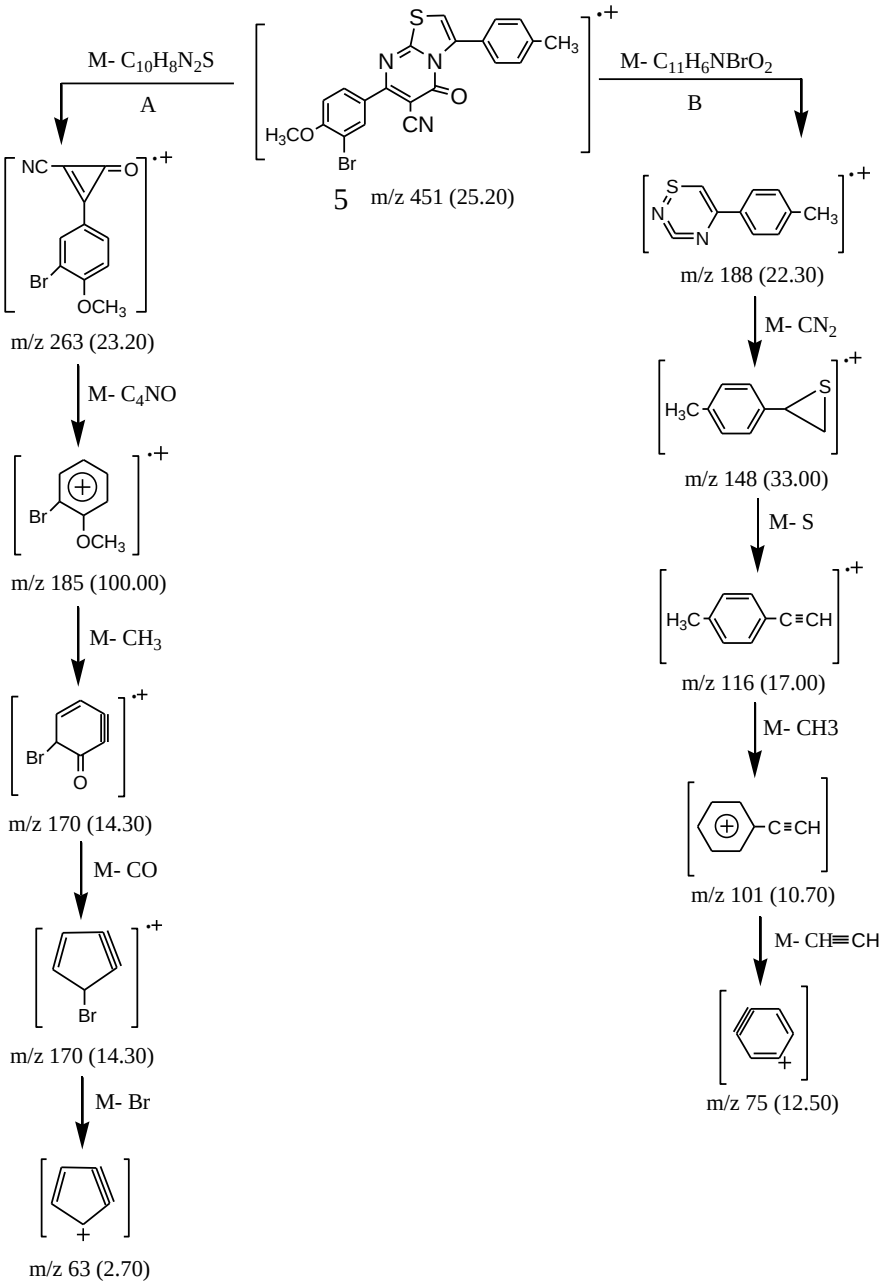


Figure 3: 70 eV mass spectrum of compd 5



Scheme 5: Main fragmentation pathway of compd.5

Compound 6, 8 and 9:

The mass spectra of compounds 6 (Fig. 4), 8 (Fig. 5) and 9 (Fig. 6) shows relatively small molecular ions peaks typical of a cleavage and rearrangement processes type fragmentation. From the study of the mass spectra of compounds 6, 8 and 9, it was found that the molecular ion for all these compounds fragmented further and involved two various pathways as illustrated by Table 1.

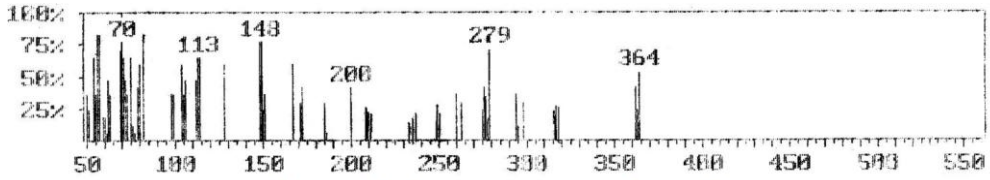


Figure 4: 70 eV mass spectrum of compd 6

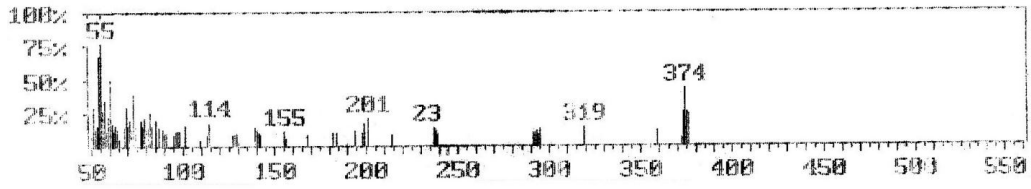


Figure 5: 70 eV mass spectrum of compd 8

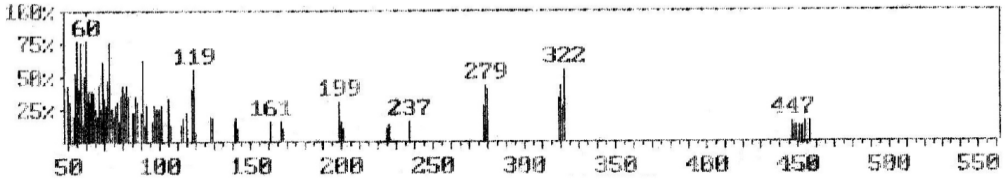


Figure 6: 70 eV mass spectrum of compd 9

Table 1: EI mass spectra (70eV) of compounds 1- 6, 8 and 9 m/z (relative intensity, %)

Compd	M^+	Pathway A		Pathway B		Other Ions
		-M	m/z	-M	m/z	
3	$[C_{12}H_9N_4BrO_2]^+$ 320(79.20)	NHCN CO,C_2HN NH HBr C_2 CH_2O	$[C_{11}H_8N_2BrO_2]^+$ 279(41.70) $[C_8H_7NBrO]^+$ 212(14.60) $[C_8H_6NBrO]^+$ 197(25.00) $[C_8H_5O]^+$ 117(20.80) $[C_6H_5O]^+$ 93(12.50) $[C_5H_3]^+$ 63(31.30)	NCO CN_2H Br, CH_2O C_3H_2N	$[C_{11}H_9N_3BrO]^+$ 278(58.30) $[C_{10}H_8NBrO]^{\cdot +}$ 237(25.00) $C_9H_6N]^+$ 128(42.90) $[C_6H_4]^{\cdot +}$ 76(10.40)	322(M^++2,100), 321(M^++1,43.60), 319(M^+-1,72.92), 294(8.30), 291(14.60), 281(29.50), 280(54.20), 277(37.50), 276(22.90), 249(20.80), 247(8.30), 239(27.10), 236(10.40), 214(2.10), 208(18.80), 171(10.40), 170(20.80), 169(27.10), 156(16.70), 154(10.40), 144(14.60), 143(.80), 169(27.10), 156(16.70), 154(10.40), 144(14.60), 143(27.10), 142(27.10), 141(29.20), 130(35.20), 129(31.30), 127(27.10), 118(10.40), 116(25.00), 114(29.20), 112(22.90), 106(22.90), 103(16.70), 101(22.90), 100(25.00), 93(12.50), 87(12.50), 86(27.10), 80(68.80), 79(50.00), 78(20.80), 64(37.20), 53(50.00), 52(27.10)
4	$[C_{12}H_8N_3BrO_2S]^+$ 337(89.20)	C_3HN_2O CHS CN OCH_3 Br C_2	$[C_9H_7N_3BrOS]^+$ 256(80.60) $[C_8H_6NBrO]^{\cdot +}$ 211(47.11) $[C_7H_6N_3BrO]^+$ 185(84.60) $[C_6H_3Br]^+$ 154(10.60) $[C_6H_3]^+$ 75(41.40) $[C_6H_3]^+$ 75(41.40)	CHNS NCO CN HBr CH_2O C_2H_2	$[C_{11}H_7N_2BrO_2]^{\cdot +}$ 278(5.30) $[C_{10}H_7NBrO]^{\cdot +}$ 236(3.80) $[C_9H_7BrO]^{\cdot +}$ 210(18.50) $[C_9H_6O]^{\cdot +}$ 130(16.70) $[C_8H_6O]^{\cdot +}$ 100(18.90) $[C_6H_2]^{\cdot +}$ 74(27.80)	339(M^++2, 100), 338(M^++1, 53.20), 336(M^+-1, 68.20), 299(4.40), 297(3.10), 296(3.50), 281(6.60), 279(10.60), 266(26.40), 265(13.70), 264(20.70), 263(15.20), 258(82.40), 257(69.60), 255(60.80), 253(13.20), 231`(16.30), 230(15.00), 224(11.909), 222(12.80), 216(22.50), 214(78.90), 2143(50.20), 212(62.10), 201(70.00), 200(44.10), 199(69.20), 198(52.00), 187(10.60), 186(18.50), 172(19.60), 170(15.90), 159(19.80), 157(20.70), 145(12.80), 143(23.30), 132(10.10), 103(20.70), 102(28.20), 90(23.80), 88(30.00), 76(44.109), 65(22.90), 64(31.30), 63(70.50),

						62(42.70)
5	$[C_{21}H_{14}N_3BrO_2S]^{\cdot+}$ 451(25.20)	$C_{10}H_8N_2S$ C_4NO CH_3 CO Br	$[C_{11}H_6NBrO_2]^{\cdot}$ 263(23.20) $[C_7H_6BrO]^+$ 185(100.00) $[C_6H_3BrO]^{\cdot+}$ 170(14.30) $[C_5H_3Br]^{\cdot+}$ 142(9.80) $[C_5H_3]^+$ 63(2.70)	$C_{10}H_8NBrO_2$ CN_2 S CH_3 C_2H_2	$[C_{10}H_8N_2S]^{\cdot+}$ 188(22.30) $[C_9H_8S]^{\cdot+}$ 148(33.30) $[C_9H_8]^{\cdot+}$ 116(17.00) $[C_8H_5]^+$ 101(10.70) $[C_6H_3]^+$ 75(12.50)	453(M^++2, 25.00), 452(28.60), 423(3.60), 422(7.10), 283(8.00), 282(6.30), 281(5.40), 266(25.90), 265(31.30), 264(27.70), 217(12.50), 192(7.10), 190(8.80), 189(22.30), 186(20.50), 184(70.50), 174(0.70), 149(10.70), 147(31.30), 146(23.20), 133(7.10), 129(13.40), 127(12.50), 115(12.50), 114(28.30), 111(10.70), 109(11.60), 102(10.70), 100(9.90), 96(13.40), 95(14.30), 88(11.60), 87(15.20), 86(11.80), 74(10.70), 73(19.60), 71(26.80), 64(23.20), 57(33.90), 55(33.00), 52(10.70)
6	$[C_{14}H_{11}N_4BrO_3]^{\cdot+}$ 362(41.20)	CH_2CO, NH-CN $C_4H_2N_2O$ Br CH_3O	$[C_{11}H_8N_2BrO_2]^+$ 279(70.60) $[C_7H_6BrO]^+$ 185(29.90) $[C_7H_6O]^+$ 106(47.10) $[C_6H_3]^+$ 75(64.70)	CH_2CO NCO NH-CN CN C_2H_2 CH_2O	$[C_{12}H_9N_4BrO_2]^{\cdot+}$ 320(25.30) $[C_{11}H_9N_3BrO]^+$ 320(25.30) $[C_{10}H_8NBrO]^{\cdot+}$ 237(19.20) $[C_9H_8BrO]^{\cdot+}$ 211 (26.50) $[C_7H_6BrO]^{\cdot+}$ 125(29.40) $[C_6H_4Br]^{\cdot+}$ 155(16.20)	364(M^++2, 52.90), 363(M^++1,23.50), 298(29.60), 295(11.80), 294(35.30), 276(4.20), 275(23.50), 263(29.40), 260(35.30), 200(41.20), 186(5.90), 172(41.20), 171(29.60), 167(58.80), 151(35.30), 150(23.50), 149(94.10), 148(94.10), 128(58.80), 114(64.70), 113(64.40), 112(47.10), 104(68.80), 99(35.50), 98(35.50), 88(82.40), 80(59.9), 79(41.20), 73(35.80), 71(64.10), 70(100), 69(70.60), 63(35.30), 57(82.40), 57(82.40), 56(82.40)
8	$[C_{15}H_{11}N_4BrO_3]^+$ 374(42.20)	C_3H_3O CN NH_2, CO CH_2O, HBr CN C_2H_2	$[C_{12}H_8N_4BrO_2]^+$ 319(14.10) $[C_{11}H_8N_3BrO_2]^+$ 293(10.90) $[C_{10}H_8N_2BrO]^{\cdot+}$ 237(14.20) $[C_9H_5N]^{\cdot+}$ 127(7.80) $[C_8H_5]^+$ 101(15.60) $[C_6H_3]^+$ 75(15.60)	$C_{10}H_6NBrO$ NCO CN	$[C_5H_5N_3O_2]^+$ 139(14.20) $[C_4H_5N_2O_2]^+$ 96(10.90) $[C_3H_5NO]^{\cdot+}$ 73(39.10)	376(M^++2, 23.4), 375(M^++1, 25.00), 372(6.30), 359(10.90), 292(9.40), 295(12.50), 294(4.80), 248(7.80), 247(6.30), 239(7.80), 238(0.90), 213(7.8), 201(20.30), 199(17.20), 198(9.40), 155(10.90), 142(7.80), 140(10.90), 128(7.80), 114(17.20), 98(10.90), 96(10.90), 89(12.90), 87(14.10), 85(18.50), 80(4.10), 79(20.30), 77(18.80), 72(12.50), 64(12.50), 63(15.60), 60(50.00), 59(21.90), 56(26.60), 55(100), 54(67.20)
9	$[C_{21}H_{17}N_4BrO_3]^{\cdot+}$ 452(15.20)	C_9H_8O NH-CN NCO C_2N OCH_3	$[C_{12}H_9N_4BrO_2]^+$ 320(42.50) $[C_{11}H_8N_2BrO_2]^+$ 279(42.50) $[C_{10}H_8NBrO]^+$ 237(15.50) $[C_8H_8BrO]^+$ 199(30.00)	$C_{12}H_9N_4BrO_2$ CH=C=O CH_3 C_2H_2	$[C_9H_8O]^+$ 132(12.20) $[C_7H_7]^+$ 91(62.50) $[C_6H_4]^+$ 76(25.50) $[C_4H_2]^+$ 50(42.50)	454(M^++2, 13.20), 453(M^++1, 6.20), 322(55.00), 321(27.50), 319(32.50), 280(40.00), 278(27.50), 235(12.20), 226(12.50), 201(10.00), 200(15.00), 168(15.00), 167(15.00), 161(15.00), 143(10.00), 142(17.50), 141(15.20), 129(37.50), 128(20.00), 119(55.50), 118(40.00), 115(22.50), 106(12.50), 105(32.50), 101(27.50), 100(25.00),

		HBr C_2	$[C_8H_8Br]^{\cdot+}$ 168(10.00) $[C_7H_4]^{\cdot+}$ 88(30.00) $[C_5H_4]^{\cdot+}$ 64(37.50)			99(25.00), 98(25.00), 97(27.50), 88(30.00), 87(35.50), 80(42.50), 79(35.50), 77(30.00/0, 75(20.00), 73(75.00), 72(47.50), 70(32.50), 68(60.20), 59(50.00), 57(75.00), 51(30.00)

III. Biological activity

1) Antimicrobial activity

Using paper disc agar diffusion technique [11, 12] all the newly synthesized compounds were tested in vitro for antibacterial activity against sever at strains of bacteria such as Bacillus subtilis, Straphylocouus aureas, Streptococcus pneumonia, Escherichia coli and Pseudomonas solanarium. Also these compounds were tested in vitro against some fungi such as Aspergillus Nigar and Penicillium. The selectivity of compounds 3, 4, 5, 6 and 9 were tested at 100µg/ml concentration and the activity was determined by measuring Zone of inhibition. The screening results given in Table 2 indicated that all the compounds exhibited antibacterial and antifungal activities against one or the other type of bacteria and fungi. From the results obtained, it is clear that compound 3 showed mild activity against the tested bacteria and fungi. Compound 4 showed high activity toward the test bacteria and moderate activity toward the tested fungi. Compounds 5 and 9 showed moderate activity against the test bacteria and high activity against the tested fungi. Compound 6 showed moderate activity towards both the test bacteria and fungi.

Table 2: Antimicrobial Activity

Compd No	Antibacterial Activity					Antifungal Activity	
	Gram Positive Bacteria			Gram Negative Bacteria			
	Bacillus Subtilis	Staphylococcus Aureas	Streptococcus Penumonia	Escherichia Coli	PesudomonasSolanarium	AspergillusNigaer	Penicillium
3	+	+	+	+	-	+	+
4	+++	+ ++	++	++	++	++	+
5	+ +	+ +	+	+++	+++	+++	+ + +
6	++	+	+++	++	++	++	++
9	+	++	++	+ + +	++	+ + +	+ + +

- No antimicrobial activity, + Mild activity, ++ Moderate activity, +++ Marked activity

2) Anticancer evaluation

The cytotoxicity and antitumor activity of the prepared compounds 3, 4, 5 and 6 wereevaluated of cytotoxicity against MCF-7 cell line according to the method of Masmann [13] and Vrjayen [14]. Inhibitory activity against Breast carcinoma cells (MCF-7 cell line) was detected by using different concentrations of the tested compounds from (0-50 μg) and viability % was detected. Also, inhibitory concentration fifty (IC_{50}) for compounds 3, 4, 5 and 6 were calculated from figures 7- 10 respectively. Inhibitory activity concentrations fifty (IC_{50}) detected under the experimental conditions were to be 9.5μg for compound 6, 10.42 for compound 3, 11.8 μg for compound 5 and 17.1 $\mu g$for compound 4. These results revealed that, all the tested compounds have cytotoxic and antitumor activities against Breast carcinoma cells with superiority of the prepared compound 6 with inhibitory concentration fifty (IC_{50}) equal to 9.5μg.

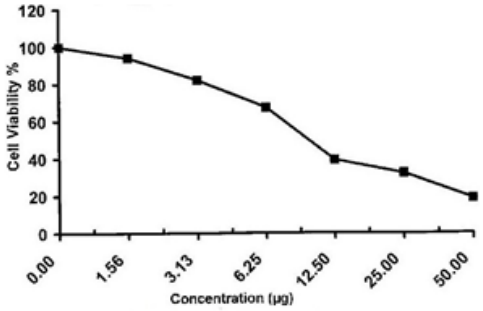


Figure 7: For compd 3

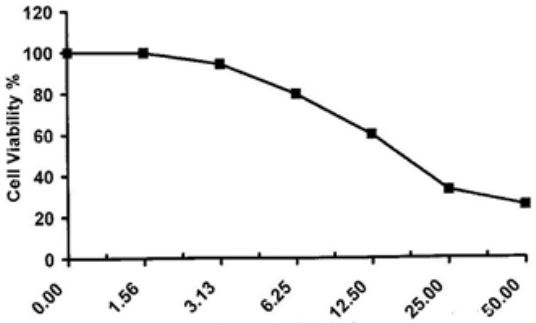


Figure 8: For compd 4

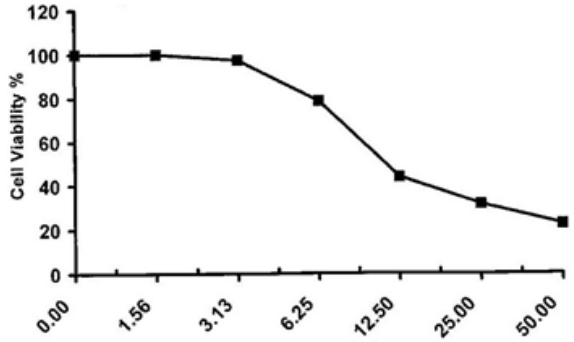


Figure 9: For compd 5

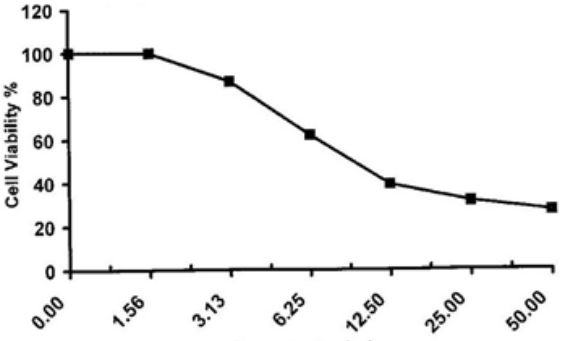


Figure 10: For compd 6

IV. Experimental

Melting points were determined in capillaries with a Thomas-Hover Uni-Melt apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 1420 spectrometer and a Biorad FTS7 (KBr). Proton NMR spectra were recorded on a general electric QE 300 instrument and chemical shifts are given with respect to TMS. Mass spectra were recorded on a Jeol JMS D-300 spectrometer operating at 70 eV. Microanalyses were conducted using an elemental analyzer 1106.

Ethyl-β-(3-bromo-4-methoxyphenyl)-α-cyanoacrylate (2)

A mixture of 3-bromo-4-methoxybenzaldehyde (0.01 mole), ethyl cyanoacetate (0.01 mole) and anhydrous potassium carbonate (0.03 mole) in methanol (50 ml) was heated under reflux for 2hrs, then cooled and poured into water. The resulting solid was filtered off, washed with water, dried and purified with ethanol to give 2 as colorless crystals, yield 87%, mp: 130^{o}C, IR(KBr): 2225 (CN), 1748 (C=O), 1589 (C=C), 1215, 1078 (C-O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.3 (t, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.36 (q, 2H, OCH_2)6.98- 7.71(m, 4H, Ar-H and H-olefinic) ppm. Anal. Found: C, 50.37; H, 3.66; N, 4.46. $C_{13}H_{12}NBrO_3$ requires: C, 50.48; H, 3.88; N, 4.53.

6-(3-Bromo-4-methoxyphenyl)-5-cyano-4-hydroxy-2-substituted-pyrimidines (3 and 4)

A mixture of 2 (0.01 mole), guanidine hydrochloride or thiourea (0.01mole) in methanol (50 ml) in presence of anhydrous potassium carbonate (0.03 mole) was heated under reflux for 4 hrs, then cooled and poured into ice-dilute hydrochloric acid (1N). The resulting solid was filtered off, washed with water, dried and purified by recrystallization from suitable solvent to give 3 and 4.

6-(3-Bromo-4-methoxyphenyl)-5-cyano-4-hydroxy-2-amino-pyrimidine(3**)** as pale yellow crystals, yield 63%, mp: 320^{o}C, IR(KBr): 3351, 3158 (NH_2), 3398- 2850 (br. OH), 2223 (CN), 1625 (C=N), 1608, 1581 (C=C), 1251, 1083 (C-O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 3.88(s, 3H, OCH_3), 7.40- 7.91(m, 3H, Ar-H), 8.50 (s, 2H, NH_2), 10.98 (s, 1H, OH) ppm. Anal. Found: C, 44.91; H, 2.68; N, 17.35. $C_{12}H_9N_4BrO_2$ requires: C, 45.00; H, 2.81; N, 17.50.

6-(3-Bromo-4-methoxyphenyl)-5-cyano-4-hydroxy-2-mercapto--pyrimidine(4**)** as pale yellow crystals, yield 67%, mp: 220^{o}C, IR(KBr): 3389-2850 (br. OH), 2227 (CN), 1628 (C=N), 1608, 1589 (C=C), 1213, 1121, 1083 (C-O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 3.89(s, 3H, OCH_3), 7.31-7.81 (m, 3H, Ar-H), 9.21 (s, 1H, SH), 10.83(s, 1H, OH) ppm. Anal. Found: C, 42.57; H, 2.26; N, 12.33; S, 9.28. $C_{12}H_9N_4BrO_2$ requires: C, 42.73; H, 2.37; N, 17.46; S, 9.49.

6-(3-Bromo-4-methoxyphenyl)-5-cyano-3-(*p*-tolyl)-thiazolo-[3,2-b]-pyrimidin-4-one (5)
A mixture of 4 (0.01 mole) and 4-methyl phenacylbromide (0.01 mole) in acetic acid (30 ml) in presence of fused sodium acetate (0.03 mole) was heated under reflux for 4 hrs, then cooled and poured into water. The crude product obtained was filtered off, washed with water, dried and purified by recrystallization from ethanol to give 5 as a yellow crystals, yield 71%, mp: 170^{o}C, IR(KBr): 2225 (CN), 1695 (C=O), 1627 (C=N), 1606, 1588 (C=C), 1271, 1075 (C-O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.23(s, 3H, CH_3), 3.88(s, 1H, $COCH_3$), 7.12- 7.89 (m, 8H, Ar-H and thiazole) ppm. Anal. Found: C, 55.71; H, 2.98; N, 9.11; S, 7.02. $C_{21}H_{14}N_3BrO_2S$ requires: C, 55.88; H, 3.10; N, 9.31; S, 7.09.

6-(3-Bromo-4-methoxyphenyl)-5-cyano-3-hydroxy-2-acetylamino)-pyrimidine (6)
A solution of 3 (0.01 mole) in acetic anhydride (20 ml) was refluxed for 2 hrs., then cooled and poured into ice-water. The solid obtained was filtered off, washed with water, dried and purified by ethanol to give 6 as pale yellow crystals, yield 56%, mp: 245^{o}C. IR(KBr): 3341-2450 (br. OH), 3212 (NH), 2225 (CN), 1605, 1589 (C=C), 1212, 1083 (C-O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.25 (s, 3H, $COCH_3$), 3.89 (s, 3H, OCH_3), 7.32- 7.68 (m, 3H, Ar-H), 10.20(s, 1H, NH), 11.20 (s, 1H, OH) ppm. Anal. Found: C, 46.23; H, 3.01; N, 15.47. $C_{14}H_{11}N_4BrO_3$ requires: C, 46.41; H, 3.04; N, 15.47.

6-Hydroxy-5-cyano-4-(3-bromo-4-methoxyphenyl)-imidazolidino-[2,1-b]-pyrimidin-3-one (7)
A mixture of 3 (0.01 mole) and ethyl chloroacetate (0.01 mole) and fused sodium acetate (0.03 mole) in acetic acid (30 ml) was heated under reflux for 4 hrs, then cooled and poured into ice-water. The crude product obtained was filtered off, washed with water, dried and purified by recrystallization from ethanol to give 7 as a yellow crystals, yield 62%, mp: 260^{o}C, IR(KBr): 3396-2850 (br. OH), 2226 (CN), 1698 (C=O), 1629 (C=N), 1608, 1591 (C=C), 1263, 1075 (C-O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 3.88 (s, 3H, OCH_3), 4.25 (s, 2H, NCH_2CO), 7.31- 7.71 (m, 3H, Ar-H), 11.21 (s, 1H, OH) ppm. Anal. Found: C, 46.46; H, 2.33; N, 15.36. $C_{14}H_9N_4BrO_3$ requires: C, 46.67; H, 2.50; N, 15.55.

7-Hydroxy-6-cyano-5-(3-bromo-4-methoxyphenyl)-2,3-dihydropyrimidino[2,1-b]-pyrimidin-4-one (8)
A mixture of 3 (0.01 mole), methyl acrylate (0.01 mole) and fused sodium acetate (0.03 mole) in dimethylformamide (25 ml) was refluxed for 6 hrs, then cooled and poured into ice-water. The resulting solid was filtered off, washed with water, dried and purified by recrystallization from acetic acid to give 8 as a colorless crystals, yield 62%, mp: 290^{o}C, IR(KBr): 3385-2920 (br. OH), 2221 (CN), 1701 (C=O), 1629 (C=N), 1608, 1587 (C=C), 1218, 1120, 1083 (C-O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.65 (t, 2H, OCH_2), 3.25 (t, 2H, NCH_2), 3.89 (s,3H, OCH_3), 7.31- 7.68 (m, 3H, Ar-H), 11.21 (s, 1H, OH) ppm. Anal. Found: C, 48.02; H, 2.81; N, 14.74. $C_{15}H_{11}N_4BrO_3$ requires: C, 46.13; H, 2.94; N, 14.97.

2-(*P*-methylbenzoyl)methylamino-5-cyano-6-(3-bromo-4-methoxyphenyl)-4-hydroxy-pyrimidine (9)
A mixture of 3 (0.01 mole) and 4-methyl-phenylacylbromide (0.01 mole) in acetic acid (25 ml) was refluxed for 2 hrs, then cooled and poured into ice-water. The solid formed was filtered off, washed with water, dried and purified by recrystallization from ethanol to give 9 as a yellow crystals, yield 67%, mp: 300^{o}C, IR(KBr): 3381-2910 (br. OH), 2225 (CN), 1703 (C=O), 1625 (C=N), 1605, 1583 (C=C), 1212, 1085 (C-O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.31 (s, 2H, CH_3), 3.31 (s, 2H, NCH_2CO), 3.89 (s,3H, OCH_3), 7.12- 7.81 (m, 7H, Ar-H), 11.02 (s, 1H, OH) ppm. Anal. Found: C, 55.57; H, 3.62; N, 12.18. $C_{21}H_{17}N_4BrO_3$ requires: C, 55.75; H, 3.76; N, 12.39.

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