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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF SOME NEW 2-AZETIDINONES

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ABSTRACT

A series of 1 - [4'- (6"-methoxy - naphthalen-2"-yl) - 6'- (2"- hydroxy - 4" - methoxy phenyl) pyrimidin - 2' - yl - ureido] - 4 -(phenyl / substituted phenyl / 2'-furyl) - 3 - chloro - 2 -azetidinone **(4a-j)** were prepared. The structures of compounds were confirmed on the bases of elemental analysis, IR and ^{1}H NMR. The compounds were screen for antibacterial activity.

KEYWORDS: 2-azetidinones, schiff base, antibacterial activity, heterocyclic synthesis.

INTRODUCTION

The β-lactam antibiotics are used to treat a wide range of bacterial infection in both the community and hospital environment. There is also considerable market in veterinary field. The cephalosporins are among the most frequently employed β-lactam[1]. Cephalosporins have withstood the onslaught of microorganisms and have come to physician's arsenal in combating a wide range of microbial infections.

2-Azetidinone derivatives have been reported to possess anti-flammatory[2-3], anticonvulsant[4], fungicidal[5] and antibiotic activity[6]. 2-Azetidinones is also associated with pharmacological activity namely, hypnotic, antiviral, anesthetic, analegasic etc.[7-8]

In this study 6-methoxy-2-acetyl naphthalene on condensation with 2- hydroxy 4-methoxy benzaldehyde according to claisen-schemidt condensation[9-11] gave chalcone, which was converted to 2-amino-4-(6'-methoxy-naphthalen -2'-yl) - 6 - (4'-methoxty-2'-hydroxy pheynyl) – pyrimidine **(1),** by the treatment of guanidine nitrate and 25% KOH solution. This compound **(1)** on reaction with methyl chloroformate followed by treatment with hydrazine hydrate (80%) to give 2-(n-amido-ureido)-4-(6'-methoxy- naphthalen-2'-yl) - 3 - (4'-methoxty-2'-hydroxy phenyl) – pyrimidine **(2).** The resulting compound **(2)** on condensation with different aromatic aldehydes yielded corresponding 1-phenyl / substituted phenyl / 2'-furyl-4-[4'- (6"-methoxy –naphthalen-2"-yl) - 6' - (2"- hydroxy - 4" - methoxyphenyl) pyrimidin - 2'- yl] semicarbazide **(3a-j)** (Schiff Bases). This different Schiff bases on cyclo condensation with chloroacetylchloride gave substituted 2-azetidinones**(4a-j).**

RESULT AND DISCUSSION

The structures of all compounds were confirmed on the basis of their elemental analysis, IR spectra and ^{1}H NMR spectra. The IR spectrum of **4a-j** exhibited a band due to =CH str. (3100-3000cm^{-1}), C=C str. (1635-1495 cm^{-1}), C-H bending [1,2,4,5-substituted (900-860 cm^{-1})], C-H bending [1,4-substituted (840-800 cm^{-1})], C-Cl str. (750-700 cm^{-1}), C-F str. (1100-1000 cm^{-1}), C=N (ring) (1650-1580 cm^{-1}) stretching vibration which indicates the presence of pyrimidine ring and β-lactam ring C=O (1742 cm^{-1}).

Appearance of a signal at ^{1}H NMR ($CDCl_3$); δ: 2.7 {6H, s, -N(CH_3)$_2$}, 4.12(1H, s, -CHCl), 6.9(1H, s, -CH, pyrimidine ring), δ: 4.0 (s, 1H, >CHCl), 8.43(s, 1H, -CO-NH-), confirms the presence of 2-azetidinone ring.

Table. I: Formulas, melting points, yields and analytical data of 2-azetidinone 4a-j.

No	R	Molecular formula	Melting point °C	Yield	Elemental analysis		
					% of C	% of H	% of N
					Found (Caled)	Found (Caled)	Found (Caled)
4a	4-Methoxy-2-hydroxyphenyl	$C_{33}H_{28}N_5O_7Cl$	148	52	61.71 (61.73)	4.41 (4.40)	10.92 (10.91)
4b	4-Methoxyphenyl	$C_{33}H_{28}N_5O_6Cl$	175	48	63.33 (63.31)	4.52 (4.51)	11.17 (11.19)
4c	3-Nitrophenyl	$C_{32}H_{25}N_6O_7Cl$	152	44	59.94 (59.96)	3.94 (3.93)	13.11 (13.11)
4d	4-Hydroxyphenyl	$C_{32}H_{26}N_5O_6Cl$	163	51	62.82 (62.80)	4.27 (4.28)	11.42 (11.44)
4e	4-N,N-dimethylaminophenyl	$C_{34}H_{31}N_6O_5Cl$	130	55	63.92 (63.90)	4.91 (4.89)	13.18 (13.15)
4f	3-Methoxy 4-Hydroxyphenyl	$C_{33}H_{28}N_5O_7Cl$	140	43	61.70 (61.73)	4.38 (4.40)	10.95 (10.91)
4g	4-Florophenyl	$C_{32}H_{25}N_5O_5ClF$	137	57	62.61 (62.59)	4.11 (4.10)	11.44 (11.41)
4h	2,4,6-Trimethoxyphenyl	$C_{35}H_{32}N_5O_8Cl$	158	59	61.28 (61.27)	4.73 (4.70)	10.22 (10.21)
4i	2-Chloropenyl	$C_{32}H_{25}N_5O_5Cl_2$	149	55	60.95 (60.96)	4.02 (4.00)	11.13 (11.11)
4j	2-Furnayl	$C_{30}H_{25}N_5O_6Cl$	166	57	61.22 (61.20)	4.08 (4.05)	11.90 (11.85)

Compd.	Spectra
1	IR (KBr): 1574 (C=C str.), 1645(C=N str. (Pyrimidine moiety)), 3050 (-OH), 3416(-NH_2). ^{1}H NMR ($CDCl_3$); δ: 5.1(s,2H, -NH_2), and 6.8-7.6 (m, 10H, Ar-H)
2	IR (KBr): 1642(C=N str. (Pyrimidine moiety)), 1660 (C=O, amide), 3048(-OH), 3378, 3352(-$NHNH_2$): ^{1}H NMR ($CDCl_3$); δ: 4.4 (2H, s, -NH_2), 6.76-7.4 (m, 11H, Ar-H and NH), 8.5 (m, 1H, -CONH)
3e	IR(KBr):: 1575(C=N), 1630(-CH=N), 1663(C=O, amide), 3042(-OH). ^{1}H NMR ($CDCl_3$); δ:3.86 (s, 6H, OCH_3), 4.40 (m, 1H, -CH=N), 6.7-7.8(m, 15H, Ar-H and NH), 8.46 (s, 1H, -CO-NH-).
4a	IR(KBr):: 1651 (C=O, amide), 3041(-OH). ^{1}H NMR ($CDCl_3$);δ: 3.95(s,9H, OCH_3), δ: 6.75-7.91(m, 14H, Ar-H and NH), δ: 9.88(s, 1H, -CO-NH-).
4b	IR(KBr):: 1642 (C=O, amide), 3049(-OH). ^{1}H NMR ($CDCl_3$); δ: 3.96(s, 9H, OCH_3), δ: 7.19-7.89(m, 15H, Ar-H and NH), δ: 9.86(s, 1H, -CO-NH-).
4c	IR(KBr):: 1348 & 1542 (NO_2)1648 (C=O, amide), 3051(-OH). ^{1}H NMR ($CDCl_3$); δ: 3.19(d, 1H,>CH-Ar), δ:3.92(s, 6H, OCH_3), δ: 6.87-7.58(m, 15H, Ar-H and NH), δ: 9.92(s, 1H, -CO-NH-).
4d	IR(KBr):: 1638 (C=O, amide), 3038(-OH). ^{1}H NMR ($CDCl_3$); δ:3.88(s, 6H, OCH_3 δ: 6.91-7.61(m, 15H, Ar-H and NH), δ: 9.83(s, 1H, -CO-NH-).
4e	IR(KBr): 1312(N(CH_3)), 1641 (C=O, amide), 3044(-OH). ^{1}H NMR ($CDCl_3$); δ:2.83(s, 6H, N(CH_3)), δ:3.86(s, 6H, OCH_3),δ:3.86(s, 6H, OCH_3)δ: 6.70-7.43(m, 15H, Ar-H and NH), δ:9.80(s, 1H, -CO-NH-).
4f	IR(KBr):: 1643 (C=O, amide), 3053(-OH). ^{1}H NMR ($CDCl_3$); δ: 3.96(s, 9H, OCH3), δ: 7.01-8.12(m, 14H, Ar-H and NH), δ: 9.91(s, 1H, -CO-NH-).
4g	IR(KBr):: 1639 (C=O, amide), 3050(-OH), 1080 (C-F). ^{1}H NMR ($CDCl_3$); δ: 3.97(s, 6H, OCH_3), δ: 7.36-8.10(m, 15H, Ar-H and NH), δ: 9.86(s, 1H, -CO-NH-).
4h	IR(KBr):: 1645 (C=O, amide), 3039(-OH). ^{1}H NMR ($CDCl_3$); δ: 3.91(s, 6H, OCH_3), δ: 6.88-7.36(m, 13H, Ar-H and NH), δ: 9.85(s, 1H, -CO-NH-).
4i	IR(KBr):: 748(C-Cl), 1649 (C=O, amide), 3035(-OH). ^{1}H NMR ($CDCl_3$); δ: 3.80(s, 6H, OCH_3), δ: 5.05 (s, 1H, >CHCl), δ: 7.01-7.81(m, 14H, Ar-H and NH), δ: 9.9(s, 1H, - CO-NH-).

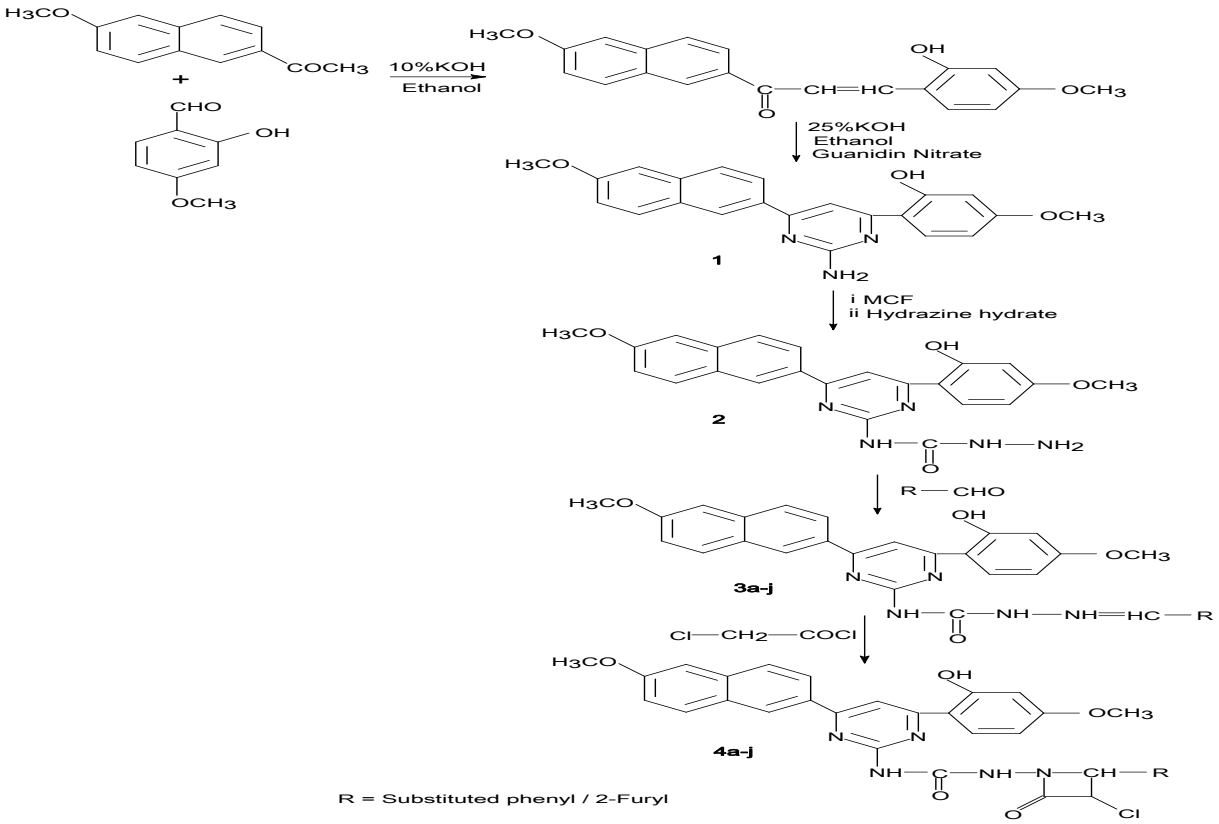
Experimental Section

General Procedures: All melting points were determined in an open capillary tube and are uncorrected. Infra Red (IR) Spectra were recorded on a FTIR-8400 Shimadzu with KBr. The Proton Nuclear Magnetic Resonance (1H NMR) spectra were recorded on a Brüker Avance dpx-200 (at 200 MHz) using TMS as internal standard. All regents were of the highest purity commercially available. The chemical shift are expressed in part per million (ppm) downfield from the internal standard. Elemental analysis of C, H, and N done by CDRI, Lucknow and results are within ± 0.4 % of the theoretical value. Thin layer chromatography was carried out using Kieselgel 60 F-254 (Merck) to monitor the

reaction, using a mixture of CHCl3: CH3OH (8:2) as a mobile phase and are visualized with UV (254 nm) or iodine to check the purity of the compounds.

Preparation of 2-amino-4-(6'-methoxy-naphthalen-2'-yl) - 6 - (4'-methoxty-2'-hydroxy phenyl) - pyrimidine (1).

6-Methoxy-2-acetyl naphthalene (0.01 mol) and 2-hydroxy-4-methoxy benzaldehyde (0.01 mol) in ethanol (50 ml) were stirred at 32^{o}C for 30 min. Then, 10% KOH (3mL) was added and the reaction mixture was stirred for 4hrs and then the reaction mixture kept for 24h at room temperature. The reaction mixture was then poured in to ice-cold water and acidified with dil HCl. The formed precipitates was filtered off, washed with water and recrystallised from ethanol to give chalcone. This chalcone (0.01 mol), guanidine nitrate (0.01 mol) and 25% KOH (2 ml) were refluxed for 20 h in ethanol (50 ml). Then the reaction mixture was cooled to room temperature and poured on to crushed ice. The separated solid was filtered, washed with water, dried and recrystallised from ethanol to give the title compound **(1)**. M.P. 160^{o}C, Yield 65.0%, (Found: C: 70.78; H: 5.12; N: 11.29%, Calculated for $C_{22}H_{19}O_3N_3$; C: 70.76; H: 5.13; N: 11.25%). confirms the presence of compound **(1).**



Preparation of 4-[4'- (6'‘-methoxy –naphthalen-2''-yl) - 6' - (2''- hydroxy - 4'' - methoxyphenyl) pyrimidin - 2'- yl] semicarbazide (2).

A mixture of 2-amino-4-(6'-methoxy-naphthalen-2'-yl)-6-(4'-methoxy-2'-hydroxy phenyl) – pyrimidine (0.01 mol) and methyl chloroformate (0.02 mol) in presence of triethylamine was refluxed for 10 hrs in ethanol (50 ml). The reaction mixture was then poured into ice-cold water, acidified with dilute HCl, filtered, washed with water and dried. The dried crude was again refluxed with hydrazine hydrate in toluene for 7 hrs. Then evaporated out toluene under vacuum to dryness, washed material with water till neutral pH and dried to give resulting compound **(2).** The dried crude was recrystallised using methanol. M.P. 188^{o}C. Yield 61.0%. (Found: C: 64.01; H: 4.93; N: 16.20%, Calculated for $C_{23}H_{21}O_4N_5$; C: 64.03; H: 4.91; N: 16.23%).

Preparation of 1-phenyl / substituted phenyl / 2'-furyl-4-[4'- (6''-methoxy –naphthalen-2''-yl) - 6' - (2''- hydroxy - 4'' - methoxyphenyl) pyrimidin - 2'- yl] semicarbazide (3e)

A mixture of 4-[4'- (6'‘-methoxy –naphthalen-2"-yl) - 6' - (2"- hydroxy - 4" – methoxy phenyl) pyrimidin - 2'- yl] semicarbazide **(2)** (0.01 mol) and 4-N, N dimethyl amino benzaldehyde (0.01 mol) were refluxed in dry benzene (60 ml) for 10 hrs using dean-stark separator. During the course of the reaction the water was removed continuously. The excess benzene was distilled, the solid product was filtered and recrystallised from chloroform. M.P. 195oC, Yield 71.0%, (Found: C: 68.29; H: 5.39; N: 14.91%, Calculated for C32H30N6O4; C: 68.31; H: 5.37; N: 14.94%) All substituted Schiff base 3a-j were prepared in similar manner.

Preparation of 1 - [4'- (6''-methoxy - naphthalen-2''-yl) - 6'- (2''- hydroxy - 4'' - methoxy phenyl) pyrimidin - 2' - yl - ureido] - 4 -(phenyl / substituted phenyl / 2'-furyl) - 3 - chloro - 2 -azetidinone (4e)

A solution of compound **(3e)** (Schiff base) in dry 1,4-dioxan (50 ml) and triethylamine (0.012 mol) was added chloro acetyl chloride (0.012mol) drop wise with well stirring at 0o-5oC .The reaction mixture was stirred for 9 hrs and kept for 2 days at room temperature. Then the reaction mass poured ice-cold water. The separated solid was filtered, washed with water, dried and recrystallised from ethanol. All substituted compound 4a-j were prepared in similar manner.

Antibacterial Activity

The synthesised compounds were tested for their antibacterial activity by measuring the zone of inhibition using cup plate method12 against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Salmonella typhi* as test organisms.

Table-II .Antibacterial activity of the compound 4a-j.

Compound	Antibacterial activity			
	Diameter of zone inhibition (in mm)			
	S.aureus	***B.subtilis***	***E.coli***	***S.typhi***
4a	10	9	11	11
4b	15	16	13	7
4c	14	13	14	16
4d	11	14	14	8
4e	8	10	10	9
4f	10	11	11	11
4g	12	8	8	13
4h	11	12	11	13
4i	9	8	8	15
4j	11	10	10	12
Streptomycin	29	31	28	30

The result of antibacterial screening indicate that good activity was shown by compounds 4b,4c against *S. aureus*, compounds 4b,4d against *B. subtilis*, compounds 4c, 4d against *E.coli*, compounds 4c,4j shown good activity against *S.typhi*. while compounds 4e, 4i were less active against *S. aureus*, compounds 4g, 4i against *B. Subtilis*, compounds 4f, 4g against *E.coli*, compounds 4b,4d were less active against *S.typhi*. Other compounds showed moderate activity against both bacterial strains (Table-II). However, no specific structure-activity relationship could be established.

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REFERENCES

1. Klein, N. C.; Cunha, A.; Advance in Therapy, 1995; 21: 83.
2. Desai, K. G.; Desai, K. R.; Indian J. Chem., 2005; 44B: 2093.
3. Shah S K; Peter B L; Eur Pat Appl EP 199, 1986, 360; Chem Abstr, 1974; 17: 541.
4. Koniya T: Lres L; Chem Abstr, 1977; 86: 1656a.
5. Mistry K.; Desai, K. R.; Chemistry an Indian Journal, 2005; 12(3): 47.
6. Desai, J. M.; Shah, V. H.; Indian J. Chem., 2003; 42B: 631.
7. Srivastava, S. K.; Srivastava, S; Srivastava, S. D.; Indian J. Chem., 1999; 38B:183.
8. Chiain Ho L K; Leung H C H; Hunf K; Chem Abstr, 1983; 99: 53672w.
9. Dawey, W; Tivey, D. J.; J. chem. Soc., 1958; 1320.
10. Kohler, H. M.; Chadwell, H.; Gilman, H.; Blatt, A. H.; (Eds.) Organic Synthesis p.78 (Coll.Vol.I), Wiley, New York 1967.
11. Mehra, H. S.; J. Indian Chem. Soc., 1968; 45: 178.
12. Barry, A. L.; The Antimicrobial Susceptibility Test: Principle and Practices, edited by Illusle & Febiger, (Philadelphia Pa USA), (976 p.180,. [Biol. Abstr., 1977; 64: 25183].