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A facile synthesis and antibacterial screening of some new 4-Thiazolidinone derivatives

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Abstract: *Efficient syntheses of 4-thiazolidinone are affected by reaction of 6-methoxy-2-acetyl naphthalene and 4-methoxy-2-hydroxy benzaldehyde to give chalcone. This on further reaction with guanidine nitrite gives Amino Pyrimidine derivative. This amino Pyrimidine derivative treated with methyl chloroformate, hydrazine hydrate and various substituted aromatic aldehydes respectively yielded various Schiff bases. The reaction of various substituted Schiff bases with thioglycolic acid gives corresponding 4-thiozolidinone derivatives*
The various synthesized compounds were assigned on the bases of elemental analysis, IR and ^{1}H NMR spectral data. The compounds are evaluated for their antibacterial activity.

Keywords: *Chalcones, Schiff base, 4-Thiozolidinone, Antibacterial Activity.*

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I. Introduction:

In recent years, several new methods for preparation of thiazolidinone derivatives and reaction have been reported in the literature. The chemistry of 4- thiazolidinone ring system in area of interest for many research groups due to actual and potential biological activity of many derivatives. 4-thiazolidinones play a vital role owing to their wide range of biological activity [1-5]. 4-thiazolidinone is known to exhibit antitubecular[6], antibacterial [8-10] antifungal[11] and antitheraputic[12-14] activities.

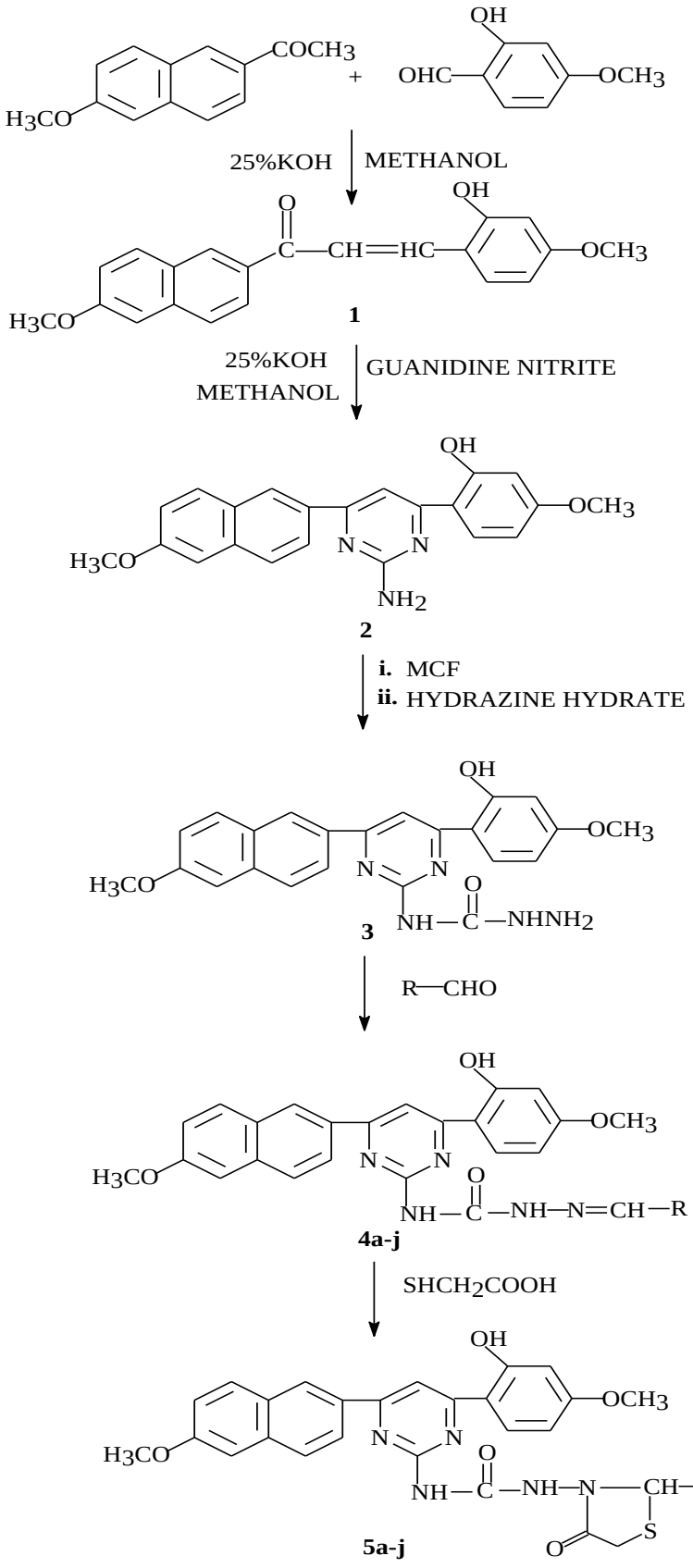
The reaction 6-Methoxy-2- Acetyl Naphthalene with 4-Methoxy 2- Hydroxy Benzaldehyde in present of Methanol and 10% KOH (2-3 ml) to give chalcone **(1)** Which was convert to {4-(6' Methoxy-2' Naphthyl) 6- (2'Hydroxy-4' Methoxy Phenyl)} 2-Amino Pyrimidine **(2)** by treatment with guanidine nitrate & 40% KOH (2-3 ml) in methanol. This compound **(2)** on further reaction with Methyl Chloro Formate & Hydrazine Hydrate to give N-acetyl hydrazine {4-(6'Methoxy-2'-Naphthyl) 6-(2'-Hydroxy-4'-MethoxyPhenyl)}-2-Amino Pyrimidine **(3).**

This compound **(3)** was Condensed with different Aromatic aldehydes to obtain corresponding N-ureido- 4 -(Substituted Aromatic aldehydes){4'-(6"-Methoxy-2"-Naphthyl)-6'-(2"-Hydroxy-4"-Methoxy Phenyl)}-2-Amino Pyrimidine **(4_{a-j})** (Schiff Base). This different Schiff Base on Cyclo condensation with Thioglycolic acid gives substituted 4-Thiozolidinine derivatives **(5_{a-j})**.

II. Experimental Section:

All melting points were determine in an open capillary tube and are uncorrected. Infra Red (IR) Spectra were recorded on a FTIR-8400 Shimadzu with KBr. Proton Nuclear Magnetic Resonance (^{1}H NMR) Spectra were recorded on a Brüker Avance dpx-200 (at 200 MHz) with $CHCl_3$ as a solvent using TMS as internal reference (Chemical shift in δ ppm). Elemental analysis of C, H, and N done by CDRI, Lucknow and results are within ± 0.4 % of the theoretical value. Silica gel thin layer chromatography was carried out using Kieselgel 60 (Merck) to monitor the reaction and to check the purity of compounds. The eluent was a mixture of benzene and methanol in different proportion (70:30) and spots were located by iodine.
Activity of the compound has also been screened against *E.coil, P.areyginosu, S.aureus, and B.mycodies*

SCHEME:


COCH3
H3CO
+
OH
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25%KOH
METHANOL
O
C—CH═HC
1
25%KOH
METHANOL
GUANIDINE NITRITE
N
NH2
2
i. MCF
ii. HYDRAZINE HYDRATE
NH—C—NHNH2
3
R—CHO
NH—C—NH—N═CH—R
4a-j
SHCH2COOH
NH—C—NH—N—CH—R
S
5a-j

Preparation of 2-Amino-4-(6'-methoxy-2'-naphthyl)-6-(2'-hydroxy-4'-methoxy phenyl) Pyrimidine (2).
A mixture of **(1)** (0.01 mole), guanidine nitrate (0.01 mole) and 25% KOH (2ml) in ethanol (50 ml) was refluxed for 20 hours. Then the reaction mixture was cooled to room temperature and poured into crushed ice and acidified with dilute HCl. The solid separated out was filtered, washed with water, dried and recrystallised from suitable solvent to give the title compound. M.P. 167^{o}C. Yield 70.0%. (Found: C: 76.73; H: 5.12; N: 11.30%, Calculated for $C_{22}H_{19}O_3N_3$; C: 76.77; H: 5.09; N: 11.26%). IR (KBr): C=C str. (1574 cm^{-1}), C=N str. (Pyrimidine moiety, 1645cm^{-1}),-NH_2 (3416 cm^{-1}). ^{1}H NMR ($CDCl_3$); δ: 5.14(2H, s, -NH_2), δ: 2.6 (1H, s, Pyrimidine -CH), and δ: 6.8-7.6 (m, 4H, Ar-H) confirms the presence of compound **(2).**

Preparation of 2-(N-Amino-Ureido)-4-(6'-methoxy-2'-naphthyl)-6-(2'-hydroxy-4'-methoxy phenyl) Pyrimidine (3).
A mixture of compound **(2)** (0.01 mole) and methyl chloroformate (0.02 mole) 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 till neutral pH and dried to give resulting compound **(3).** The dried crude was recrystallised using a suitable solvent. M.P. 188^{o}C. Yield 70.0%. (Found: C: 64.11; H: 4.81; N: 16.20%, Calculated for $C_{23}H_{21}O_4N_5$; C: 64.03; H: 4.87; N: 16.24%). IR (KBr): C=N str. (Pyrimidine moiety, 1642cm^{-1}),-NH2 (3418 cm^{-1}), -NH-CO-NH- (1610 cm^{-1}, urea), C=O str. (1660 cm^{-1}), C-S-C Str. (754 cm^{-1}). ^{1}H NMR ($CDCl_3$); δ: 5.1(2H, s, -NH_2), δ: 9.8(1H, s, -NH), δ: 2.7 (1H, s, Pyrimidine -CH), and δ: 7.1-7.5 (m, 4H, Ar-H) confirms the presence of compound **(3).**

Synthesis of N-ureido-4'- (4'-N, N Dimethyl Amino Phenyl) {4' (6"-methoxy-2"-naphthyl)-6'-(2"-hydroxy-4"-methoxy phenyl)} –2-amino pyrimidine (4e)
In 250 ml R.B.F. mixture of (4) (0.01 mole) and 4'-N,N Dimethyl amino benzaldehyde (0.01 mole) in benzene (60 ml) was taken dean-stark was attached to it and started reflux for 10 hours. During the course of the reaction the water was removed continuously. The benzene was distilled off to get (4e). The solid product was filtered and recrystallised from suitable solvent. All substituted Schiff base 4a-j were prepared in similar manner. M.P. 195^{o}C. Yield 71.0%. (Found: C: 68.27; H: 5.39; N: 14.90%, Calculated for $C_{32}H_{30}N_6O_4$; C: 68.33; H: 5.34; N: 14.95%). IR: C=O (1716 cm^{-1}), CONH (1662cm^{-1}), O-H (3042 cm^{-1}), -N=CH- (1632 cm^{-1}). ^{1}H NMR ($CDCl_3$); δ: 8.0 (m, 1H, -CH=N), δ: 9.8 (s, 1H, CONH), δ: 3.86 (s, 3H, OCH_3).

Synthesis of 2-(4'-N, N Dimethyl Amino)-3-{-4'-(6"-methoxy-2"-naphthyl)-6'-(2"-hydroxy-4"-methoxyphenyl)-2-pyrimidyl}-N-ureido-4-thiazolidinone (5e)
In 250 ml R.B.F. mixture of Schiff base (5e) (0.01) mole in benzene was taken dean struck apparatus was attached to it and thioglycolic acid in benzene (0.01 mole) was added slowly then it was reflux for 15 hours. During the course of the reaction the water was removed continuously. The benzene was distilled of to get 4-thiazolidinone (5e). The solid product was filtered and recrystalised from suitable solvent. M.P. 241^{o}C. Yield 63.0%. (Found: C: 64.25; H: 4.84; N: 13.18, Calculated for $C_{34}H_{31}N_6O_5S$; C: 64.23; H: 4.88; N: 13.22%). IR: C=O (1710 cm^{-1}), CONH (1659cm^{-1}), O-H (3036 cm^{-1}), -N-CH-S (2960 cm^{-1}). ^{1}H NMR ($CDCl_3$); δ: 3.21(s, 1H, -CH-S) δ: 9.8 (s, 1H, CONH), δ: 3.86 (s, 3H, OCH_3), δ: 3.6(S, 2H, $COCH_2$)

Table –I Formulas, melting points, yield and analytical data of 4-Thiazolidinones

No.	R	M. F.	% Y	M. P. °C	Elemental Analysis		
					% of C Found (Cal.)	% of H Found (Cal.)	% of N Found (Cal.)
5a	4-methoxy-2-hydroxyphenyl	$C_{33}H_{29}N_5O_7S$	53	163	62.01 (61.96)	4.58 (4.57)	10.97 (10.95)
5b	4-methoxyphenyl	$C_{33}H_{29}N_5O_6S$	50	158	63.54 (63.55)	4.72 (4.69)	11.21 (11.23)
5c	2-nitrophenyl	$C_{32}H_{26}N_6O_7S$	55	164	60.22 (60.18)	4.13 (4.10)	13.19 (13.16)
5d	4-hydroxyphenyl	$C_{32}H_{27}N_5O_6S$	59	143	63.08 (63.04)	4.42 (4.46)	11.51 (11.49)
5e	4-N,N-dimethylaminophenyl	$C_{34}H_{32}N_6O_5S$	63	154	64.15 (64.14)	5.10 (5.07)	13.18 (13.20)
5f	3-methoxy 4-hydroxyphenyl	$C_{33}H_{29}N_5O_7S$	66	135	61.92 (61.96)	4.55 (4.57)	10.97 (10.95)
5g	4-fluorophenyl	$C_{32}H_{26}N_5O_5FS$	58	151	62.87 (62.84)	4.29 (4.28)	11.41 (11.45)
5h	2,4,6-trimethoxyphenyl	$C_{35}H_{33}N_5O_8S$	49	178	61.50 (61.48)	4.88 (4.86)	10.25 (10.24)
5i	2-chlorophenyl	$C_{32}H_{26}N_5O_5ClS$	51	171	61.21 (61.19)	4.18 (4.19)	11.17 (1115)
5j	3-chlorophenyl	$C_{32}H_{25}N_5O_5ClS$	53	162	61.18 (61.19)	4.21 (4.17)	11.19 (11.15)

III. Results And Discussion:

Structures of compound synthesized have been confirmed by elemental analysis, IR Spectra, ^{1}H NMR Spectra. 4-thiozolidizole compound shows Infra red (KBr) a band at C=0 (1720-1615cm^{-1}), NH-C-NH (1650-1560cm^{-1}), -C-O-C-, Asymmetric (700-600 cm^{-1}), C-N (1020-1226cm^{-1}), 1,4 substitution (840-800cm^{-1}), -C-O-C-, Symmetric (1260-1220cm^{-1}).

^{1}H NMR (CDCl3): δ: 2.6 (S, 3H, CH_3), δ: 2.7 (-N- (CH_3) 2), δ: 7.0 –7.5 (m, 4H, AR-H), δ: 3.9 (O-CH_3) proves the presence of 4-thiazolidinone ring.

ANTIBACTERIAL ACTIVITY:

All the synthesized compounds were screened for their in vitro anti bacterial activity against *E.coli* & *P.areyginosu* (gram negative) and *S.aureus* & *B.mycodies* (gram positive) bacteria. Screening was carried out in acetone solution at concentration of 100 µg/ml. Cup plate method[15] was employed using nutrient agar culture medium. Streptomycin was used as reference compound for comparison. The anti bacterial Screening results are given in Table-II all compounds were active against both gram positive and gram-negative bacteria at concentration of 100 µg/ml. The degree of inhibition varied with the test compound as well as with bacterium.

The Screening result indicates that compounds 5e & 5i shows high activity and compound 5a & 5j shows low activity against *E.coli*. Compound 5g& 5h high activity and compound 5a & 5c shows low activity against *P.areyginosu*. Compound 5e & 5h shows high activity and compound 5a & 5j shows low activity against *S.aureus*. Compound 5g & 5h shows high activity and compound 5a & 5c shows low activity against *B.mycodies*.

The zone of inhibition of reference compound Streptomycin (25mm). The result indicates that presence of methyl and chloro group shows good antibacterial activity. Howe ever no specific structure activity relationship could be established.

Table-II Antibacterial activity of 4- thiazolidinones 5a-j

No.	R	Antibacterial Activity			
		Diameter of zone of inhibition (in mm)			
		S. aureus	*S. paratyphi-A*	*E. coli*	*B. subtilis*
5a	4-methoxy-2-hydroxyphenyl	9	8.5	8.5	9
5b	4-methoxyphenyl	13.5	10	11	11
5c	3-nitrophenyl	16	9	10	9.5
5d	4-hydroxyphenyl	11.5	10	11.5	10
5e	4-N,N-dimethylaminophenyl	17	14.5	18	21
5f	3-methoxy 4-hydroxyphenyl	15	10.5	17	11
5g	4-fluorophenyl	12	21	11	17
5h	2,4,6-trimethoxyphenyl	16.5	19	13	15
5i	2-chloropenyl	18	15	13.5	20
5j	3-chlorophenyl	19	18	15	17
Std	*Streptomycin*	39	33	34	36

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