RESEARCH PAPER

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Synthesis of new 4-thiazolidinones and 2-azitidiones with their in vitro biological activities

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A series of 2-aryl-3-[(3'5'-dinitrobenzamido)]-thiazolidin-4-ones and N-[3'5'-dinitrobenzamido]-3-chloro-4-(aryl substituted) azetidin-2-ones have been prepared and examined for antibacterial and antifungal activity *in vitro* against E.coli (gram negative), S.aurus (gram positive) and A.niger, A. flavous respectively. The reaction of 3,5-dinitrobenzoic acid with thienyl chloride in the presence of dry methanol yields 3,5-dinitro-benzoate, on condensation with various aromatic aldehyde gave 2-(3'5'- dinitrobenzoyl) hydrazones, which on cycle-addition with thioglycollic acid and chloroacetyl chloride gave 2-aryl-3-[(3'5'-dinitrobenzamido)]-thiazolidin-4-ones and N-[3,5,- dinitrobenzamido]-3-chloro-4-(aryl substituted)-azetidine-2-ones respectively.

THE biological and therapeutic properties of thiazolidinone and azetidinones have greatly initiated the synthesis of immense derivatives of these moieties. 4-Thiazolidinone derivatives are known to possess a variety of pharmacological properties such as anticonvulsant[1,2], sciatic nerve block, spinal anesthetic[3], CNS stimulant[4], local anesthetic[5], analgesic, choleretic[6], sedative[7], antiphlogestic[8] and antifungal[9-11].

The β-lactam ring is associated with a large number of antibiotics such as penicillins, and Cephalosporins. [12-14]. Schiff's bases also show diverse biocidal activities[15] by virtue of a toxopheric C=N linkage. This prompted us to construct a novel molecule containing both these structural features. An efficient one pot synthesis of 2- azetidinones and also 4-thiazolidinone have been achieved from the reaction between respective Schiff's bases with chloroacetyl chloride in the presence of triethylamine and thioglycollic acid in the presence of $ZnC1_2$ respectively. The pharmacological testing has been done against gram positive and gram negative bacteria in different concentrations using Griseofulvin as a standard compound. The compounds Va-f showed 50 to 65% inhibition against **A.niger** and **A. flavous** at concentrations of 25 $\mu g\text{-}cm^{-3}$ and 50 $\mu g\text{-}\ cm^{-3}$. Compounds VIa-f, showed antibacterial activity against **E.coli** and **S.aureus**.

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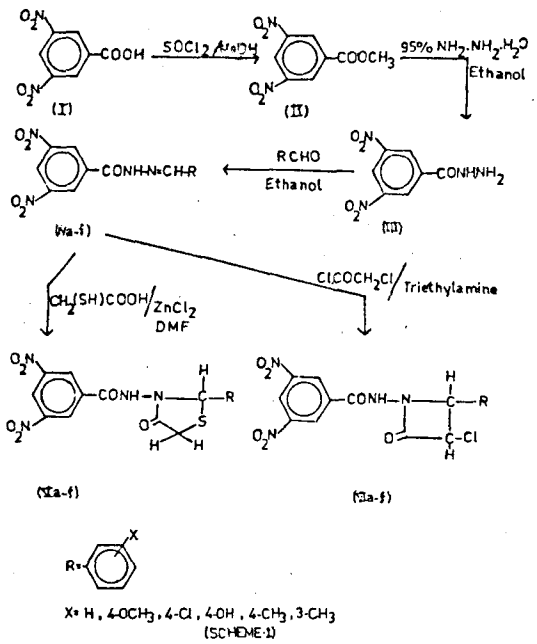
Chemistry

The starting material 3,5-dinitrobenzoic acid I is commercially available whereas its ester derivative II was synthesized by esterification of I with thionyl chloride in methanol. Treatment of II with 95% hydrazine hydrate gave the hydrazide product of the acid III, Condensation of 3,5-dinitrobenzoyl hydrazide III with different aromatic aldehydes gave the corresponding substituted 2-(3'5'-dinitro-benzoyl) hydrazones IVa-f.

Compounds IVa-f on treatment with thioglycollic acid in dimethyl formamide in the presence of anhydrous $ZnC1_2$ afforded 2- aryl-3-[(3',5'-dinitrobenzamido)]-thiazolidin-4-ones Va-f in 65-80% yield **(Scheme I)**. On the other hand the reaction of IVa-f with chloroacetyl chloride in dioxane in the presence of triethylamine yielded N-[3',5'-dinitrobenzamido]-3-chloro-4(aryl substituted) azetidine-2-



(SCHEME-I)

ones VIa-f in 65-84% yield (Scheme-I). The infrared and NMR spectroscopic data of the compounds is given in Table 1,2,3.

Experimental Procedure

3,5-Dinitrobenzoate II:

To a stirred solution of absolute methanol (100 cm^3) was added thionyl chloride (72.9 cm^3; 12 mmol) dropwise at 0°C over 30 minutes. After completion of $SOCl_2$ addition, 3,5-dinitrobenzoic acid (2.21 g, 1 mmol) was added into the above mixture and stirring continued for a further one hour.The reaction mixture was then refluxed for 8-10 hours. Completion of reaction was monitored by TLC. The solvent was removed **in vacuo.** The residue was cooled, diluted with 100 ml of water and neutralized with sodium bicarbonate at 5-10°C. The crude ester thus obtained was filtered and dried (m.p. 110- 111°C, lit.[16] m.p. 112°C).

3,5-Dinitrobenzoic acid hydrazide III:

3,5-Dinitrobenzoate (2.5 g, 10 mm°l) and hydrazine hydrate 95% (3.6 cm^3, 20 mmol) was refluxed for 10-12 hours. Excess of solvent was removed **in vacuo** and the crude hydrazide was recrystallised from ethanol (m.p. 155-157°C, lit.[16] m.p. 158°C).

General procedure for the preparation of substituted-2-(3',5'- dinitrobenzoyl) hydrazones IVa-f:

A mixture of 3,5-dinitrobenzoic acid hydrazide III (2.5 g, 10 mmol) and aromatic substituted aldehydes (10 mmol) was refluxed on a steam bath for 3-5 hours. The excess of solvent evaporated **in vacuo** and the resultant semisolid treated with water. The separated solid was filtered and recrystallized from ethanol. The compounds thus obtained are recorded in **Table 1** along with their spectral data and elemental data are given in microanalysis table.

General procedure for the preparaton of 2-aryl-3-[3',5'- dinitrobenzamido)]-thiazolidin-4-ones Va-f:

To a stirred solution of substituted 2-(3',5'-dinitrobenzoyl) hydrazones (10 mmol) was added thioglycollic acid (0.028~ 0.0321 cm^3, 1 mmol). The reaction mixture was refluxed for a period of 8-12 hrs, then cooled and poured into cold water. The resultant solid was filtered, washed, dried and recrystallized from benzene-petroleum ether (1:1) and ethanol. The compounds thus syhthesized are recorded in **Table 2.**

General procedure for the preparation of synthesis of N-(3',5'- dinitrobenzamido)-3-chloro-4-(aryl sustituted) azetidin-2-one VIa-f:

To a stirred solution of substituted 2-(3',5'-dinitrobenzoyl) hydrazones (2 mmol) and triethylamine (0.126 ml ~ 0.140 ml, 2 mmol) in dry dioxane (25 cm^3) was added chloroacetyl chloride (0.10 ml–0.11 ml, 2 mmol) dropwise. The temperature was maintained at 0 to 5°C during the reaction. After the addition was over, the reaction mixture was stirred at room temperature for 4-5 hrs and then refluxed for 8 hrs. The insoluble triethylamine hydrochloride was then filtered off. The excess solvent was removed **in vacuo** and reaction mixture poured into

Table 1 : Physical and spectral data of compound IVa-f.

Compd. No.	R =	Yield %	m.p (°C)	IR ν_{max} (Nujol) (cm^{-1})	^1H NMR ($CDCl_3$ /DMSO) (δ ppm) Aromatic	Others
IVa	H	80	132	3300(NH), 1630 (C=O), 1610 (C=N) 1540 (NO_2, asym), 1360(NO_2, sym).	7.8.-7.9(m)	8.9-9.5(1H, b, CONH) 8.0-8.2(1H, s, CH=N)
IVb	4-OCH_3	85	130	3250(NH), 1640(C=O), 1615(C=N), 1520(NO_2, asym), 1365(NO_2, sym), 1265, 1080(C-O-C).	7.9-8.0(m)	9.0-9.3(1H, b, CONH) 8.1-8.3(1H, s, CH=N) 3.8 (3H, s, OCH_3)
IVc	4-C1	77	228	3270(NH), 1660(C=O), 1615(C=N), 1520(NO_2, asym), 1325(NO_2, sym).	7.2-8.1(m)	9.1-9.4(1H, b, CONH) 8.2-8.4(1H, s, CH=N)
IVd	4-CH	65	208	3280(NH), 1630(C=O), 1610(C=N), 1510(NO_2, asym), 1340(NO_2, sym).	7.0-7.8(m)	9.0-9.5(1H, b, CONH) 8.1-8.0 (1H, s, CH=N) 10.2-10.5(1H, b, OH)
IVe	4-CH_3	92	236	3200(NH), 1640(C=O), 1600(C=N), 1520(NO_2, asym), 1365(NO_2, sym), 1450, 1370(C-H deformation of CH_3).	7.4-7.7(m)	9.1-9.4(1H, b, CONH) 8.4-8.9(1H, s, CH=N) 2.2 (3H, s, -CH_3)
IVf	3-CH_3	88	220	1380(NH), 1655(C=O), 1605(C=N), 1520(NO_2, asym), 1350(NO_2, sym), 1465, 1360(CH deformation of CH_3).	7.3-7.5(m)	9.2-9.6(1H, b, CONH) 8.5-9.0(1H, s, CH=N) 2.1 (3H, s, -CH_3)

Table II: Physical and spectral data of compounds Va-f.

Compd. No.	R =	Yield %	m.p. °C	IR ν_{max} (Nujol) cm-1	^{1}HNMR ($CDCl_3$/DMSO) (δ, ppm) Aromatic	Others
Va	H	80	295	3200(NH), 2820(CH_2 str), 1720 (C=O cyclic), 1660(C=O acyclic), 1550(NO_2, asym), 1365(NO_2 sym), 710(subst. benz).	7.3-7.5(m)	3.2(1H, s, CH-N) 3.8(2H, s, -CH_2-S)
Vb	4-OCH_3	65	280	3240(NH), 2815(CH_2 str), 1710(C=O cyclic), 1675, (C=O acyclic), 1545 (NO_2 asym), 1355(NO_2 sym), 1265 (C-O-C str), 760(subst. benz).	7.4-7.7(m)	3.1(1H, s, -CH-N) 3.5(2H, s, -CH_2-S) 3.9(3H, s, OCH_3)
Vc	4-Cl	55	238	3255(NH), 2825(CH_2 str), 1710 (C=O cyclic), 1660(C=O acyclic), 1535(NO_2 asym), 1365(NO_2 sym), 755(subst. benz).	7.4-7.7(m)	3.0(1H, s, -CH-N) 3.6(2H, s, -CH_2-S)
Vd	4-OH	68	195	3260(NH), 2805(CH_2 str), 1715(C=O cyclic, 1665(C=O acyclic), 1520 (NO_2 asym), 1360(NO_2 sym), 760 (subst. benz).	7.4-7.9(m)	3.3.(1H, s, -CH-N) 3.6(2H, s, -CH_2-S) 10.2-10.6(1H, b, -OH)
Ve	4-CH_3	72	255	3200(NH), 2820(CH_2 str), 1710 (C=O cyclic), 1670(C=O acyclic), 1530(NO_2 asym), 1370(NO_2 sym), 1475(CH def. of CH_3 group), 755(subst. benz).	7.2-7.4(m)	3.2(1H, s, -CH-N) 3.6(2H, s, -CH_2-S) 2.2(3H, s, -CH_3)
Vf	3-CH_3	75	240	3210(NH), 2825(CH_2 str), 1715 (C=O cyclic), 1665(C=O acyclic) 1535(No_2 asym), 1360(NO sym) 1475(CH def. of CH_3 group).	7.3-7.5(m)	3.3(1H, s, -CH-N) 3.6(2H, s, -CH_2-S) 2.1(3H, s, -CH_3)

Table III : Physical and spectral data of compound VIa-f.

Compd. No.	R =	Yield %	m.p. °C	IR ν_{max} (Nujol) cm^{-1}	^{1}HNMR ($CDCl_3$ / DMSO) (δ, ppm) Aromatic	Others
VIa	H	75	245	3295(NH), 1730(C=O cyclic), 1630(C=O acyclic), 1540(NO_2, asym, 1360(NO_2 sym), 720 (subst. benz).	6.7-8.0(m)	5.5(1H, d, N-CH) 6.5(1H, d, CO-CHCl) 8.6(1H, b, CO-NH)
VIb	4-OCH_3	84	135	3250(NH), 1710(C=O cyclic), 1645(C=0 acyclic), 1520 (NO_2asym), 1360(NO_2 sym), 1265, 1095(C-O-C str), 760(subst. benz).	6.9-8.0 (m)	5.2 (1H, D, N-CH) 6.2(1H, d, CO-CHCl) 8.2(1H, b, CONH) 3.9(3H, s, OCH_3)
VIc	4-Cl	68	210	3270(NH), 1720(C=O cyclic) 1660(C=O acyclic), 1515 (No_2 asym), 1320(NO_2 sym), 755 (subst. benz).	6.8-7.8(m)	5.6(1H, d, N-CH), 6.4(1H, d, CO-CHCl) 8.5(1H, b, CO-NH)
VId	4-OH	65	272	3280(NH), 1715(C=O cyclic), 1650(C=O acyclic, 1510(NO_2 asym), 1345(NO_2 sym), 750 (subst. benz).	7.0-8.0(m)	5.2(1H, d, N-CH) 6.3(1H, d, CO-CHCl) 8.2(1H, b, CONH) 10.1-10.6(1H, b, 3H)
VIe	4-CH_3	80	220	3200(NH), 1730(C=O cyclic) 1640(C=O acyclic, 1455(No_2 asym), 1370(NO_2 sym), 1455, 1370(CH def. of CH_3 group, 750(subst. benz).	7.2-8.1(m)	5.5(1H, d, N-CH) 6.6(1H, d, CO-CHCl) 8.4(1H, b, CO-NH) 2.2(3H, s, CH_3)
VIf	3-CH_3	65	238	3280(NH), 1725(C=O Cyclic) 1655(C=O acyclic), 1520(NO_2, asym), 1350(NO_2 sym), 1460, 1375(CH def. of CH group 760(subst. benz).	7.3-8.2(m)	2.15(3H, s, CH_3) 6.6(1H, d, CO-CHCl) 8.3(1H, b, CONH) 2.2(3H, s, -CH_3)

Table IV: Antifungal activity of compounds va-f at different concentration

Compd. No.	R = X =	Aspergillus niger		Aspergillus flavous	
		25 μg-cm^{-3}	50 μg-cm^{-3}	25 μg-cm^{-3}	50 μg-cm^{-3}
Va	H	76.25	76.82	53.84	51.92
Vb	4-OCH_3	81.87	80.00	55.76	50.64
Vc	4-Cl	72.50	78.12	58.33	51.28
Vd	4-OH	83.12	80.00	64.1	56.41
Ve	4-CH_3	73.75	76.87	53.84	60.25
Vf	3-CH_3	88.12	73.12	58.97	58.97

Table V : Antibacterial activity of compounds VIa-f at different concentration

Compd. No.	R= X =	Escherichia coli		Staphylococcous aureus	
		25 μg-cm^{-3}	50 μg-cm^{-3}	25 μg-cm^{-3}	50 μg-cm^{-3}
VIa	H	—	+	+	+
VIb	4-OCH_3	+	+	+	+
VIc	4-Cl	+++	+++	++	+
VId	4-OH	—	+	—	—
VIe	4-CH_3	+	+	+	+
VIf	3-Ch_3	++	+	+	+
Ampicillin		+++	+++		
Vancomycin				++	++

Each (+) indicates a difference of 2 mm in the diameter of the zone of inhibition.

(-) indicates the no zones of inhibition.

ice cold water. The resulting solid was washed and recrystallized from ethanol. The physical and spectral data of synthesised compounds is given in Table 3.

Pharmacological Screening:

All the synthesised compounds, Va-f, mentioned in table-4 have been screened for antifungal activity. They showed 70-85% inhibition against **Apergillus niger** at both concentrations (25 μg-cm^{-3} and 50 μg-cm^{-3}) tested. These compounds also showed 50-65% inhibition against **Aspergillus flavous** at both the concentrations. The standard compound Griseofulvin has shown 71.6% inhibition at 50 μg-cm^{-3} and 58.4% inhibition at 25 μg-cm^{-3} against **Aspergillus flavous**. Inhibition of 70-85% was observed against **Aspergillus niger** at 50 μg-cm^{-3} and 25 μg-cm^{-3} respectively.

Microanalysis

Compd. No.	Molecular formula	Found (%)/(Calcd) C	H	N
Substituted-2-(3',5'-dinitrobenzoyl) hydrazones IVa-f.				
IVa	$C_{14}H_{10}N_4O_5$	53.49 (53.50)	3.16 (3.18)	17.80 (17.83)
IVb	$C_{15}H_{12}N_4O_6$	52.32 (52.32)	3.48 (3.48)	16.27 (16.27)
IVc	$C_{14}H_{19}N_4O_5Cl$	48.19 (48.20)	2.56 (2.58)	16.03 (16.06)
IVd	$C_{14}H_9N_4O_6$	52.77 (52.78)	2.62 (2.67)	13.40 (13.42)
IVe	$C_{15}H_{12}N_4O_5$	54.83 (54.87)	3.63 (3.65)	17.05 (17.07)
IVf	$C_{15}H_{12}N_4O_5$	54.85 (54.87)	3.64 (3.65)	17.06 (17.07)
2-Aryl-3[3',5'-dinitrobenzamido]-thiazolidin-4-ones Va-f.				
Va	$C_{16}H_{12}N_4O_6S$	49.47 (49.48)	3.10 (3.09)	14.42 (14.43)
Vb	$C_{16}H_{14}N_4O_7S$	47.28 (47.29)	3.41 (3.42)	13.77 (13.79)
Vc	$C_{16}H_{11}N_4O_6SCl$	45.40 (45.44)	2.59 (2.60)	13.25 (13.23)
Vd	$C_{15}H_{12}N_4O_7S$	45.90 (45.91)	3.05 (3.06)	14.27 (14.28)
Ve	$C_{17}H_{14}N_4O_6S$	50.73 (50.74)	3.47 (3.48)	13.92 (13.93)
Vf	$C_{17}H_{14}N_4O_6S$	50.73 (50.74)	3.47 (3.48)	13.94 (13.93)
N-[3',5'-dinitrobenzamido] -3-chloro-4-(aryl substituted) azeditin-2-ones VIa-f.				
VIa	$C_{16}H_{11}N_4O_6Cl$	43.34 (43.36)	3.16 (3.18)	15.94 (15.97)
VIb	$C_{17}H_{13}N_4O_7Cl$	48.6 (48.8)	3.30 (3.34)	12.36 (13.39)
VIc	$C_{16}H_{10}N_4O_6Cl_2$	45.40 (45.44)	2.58 (2.60)	13.23 (13.25)
VId	$C_{16}H_{11}N_4O_7Cl$	47.50 (47.52)	2.95 (2.97)	13.85 (13.86)
VIe	$C_{17}H_{13}N_4O_6Cl$	50.40 (50.43)	3.20 (3.21)	13.82 (13.83)
VIf	$C_{17}H_{13}N_4O_6Cl$	50.40 (50.43)	3.20 (3.21)	13.82 (13.84)

Compounds VIa-f were tested for their antibacterial activity **in vitro** against the microorganisms **Staphylococcous aureus** and **Escherichia coli** in nutrient agar medium. The results of the antibacterial screening of all the compounds at two different concentrations 25 $\mu g\text{-}cm^{-3}$ and 50 $\mu g\text{-}cm^{-3}$ are given in Table 4. The zones of inhibition formed were measured and compared with that of dimethylformamide to evaluate the zone of inhibition due to the test compound. The activity of the compounds are represented by (+), (++), (+++) depending upon the diameter and clarity of the zone of inhibition. Each (+) indicates a difference of 2 mm in the diameter of the zone of inhibition. When there were no zones of inhibition the results have been indicated by (-) in the **Table 5.**

RESULTS AND DISCUSSION

In vitro studies of 2-aryl-3-[(3',5'-dinitrobenzamido)]- thiazolidin-4-ones(Va-f) have showed 50-65% inhibition against **Aspergillus flavous** and 70-85% inhibition against inhibition against **Aspergillus niger.**

N-[3',5'-dinitrobenzamido]-3-chloro-4-(aryl substituted)azetidin- 2-ones (VIa-f) have generally showed antibacterial activity against the species **E.coli** at 25 $\mu g\text{-}cm^{-3}$ and 50 $\mu g\text{-}^{-3}$. However, these compouds exhibit only moderate activity against **S. aureus** at 25 $\mu g\text{-}cm^{-3}$ and 50 $\mu g\text{-}\ cm^{-3}$.

REFERENCES

1. Ensor, C.R. and Chain, G., **Arch. Neurol Pshychial.,** 1948, 62, 857.
2. Troutman, H.D. and Long, L.M., **J. Am. Chem. Soc.,** 1948, 70, 3436.
3. Surrey, A.R., **J. AM. Chem. Soc.,** 1949, 71, 3354.
4. French, G., Atti, Soc. Polorifanic sci., Fis. Mat. Nat., 1965, 11, 117, **Chem. Abstracts.,** 1966, 65, 4439.
5. Surrey, A.R. **J. Am. Chem. Soc.,** 1949, 71, 3105.
6. Saitzinger, G., U.S. Pat. 3,072,671, **Chem. Abstracts, 1963, 59, 12571.**
7. Knusle, E., **Gen. Chim. Ital.,** 1949, 79, 621.
8. Lambert, W., Pharmaceutical Co. Ger. Pat., 1,168,912, **Chem. Abstracts.,** 1964, 61, 4361.
9. Rao, R.P., **J. Ind. Chem. Soc.,** 1958, 35, 576.
10. Rout, M.K. and Pujari, H.K., **J. Sc. Ind. Res.,** 1955, 14B, 13.
11. Chandra, S., **Bull. Chem. Soc., Japan.,** 1967, 40, 2422.
12. Lemke, P.A., Brannon, D.R. and Flynn, E.H., **"Cephalosporins and Penecillins",** Academic Press, New York, 1972.
13. Sammes, P.C., **Chem, Rev.,** 1976, 76, 113.
14. Bose, A.K., Manhas, M.S., **Heterocyclic Chem.,** 1976, 3, 43.
15. Hondnett, E.M. and Dunn, W.J., **J. Med. Chem.,** 1970, 13, 768; Dutt, M.M., Goswami, B.N. and Kataky, **J. Heterocyclic Chem.,** 1986, 23, 793; Patel, J.M., Dave, M.P., Langalia, N.A. and Thaker, K.A., **J. Indian Chem. Soc.,** 1985, 62, 254.
16. Blestein, **Organischem. Chemie,** 1926, 9.