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Synthesis of novel thiazolidinone and acetidinone derivatives and their anti microbial activity

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ABSTRACT

2'-{2"-[(2'",6'"-dichlorophenyl) amino] phenyl}-N-(4-oxo-2-substitutedphenyl (1,3-thiazolidin-3-yl))acetamide 4a-j, 2'-{2"-[2'", 6'"-dichlorophenyl) amino]phenyl}-N-(3-chloro-2-oxo-4-substituted phenylazetidinyl) acetamide 5a-j have been synthesized by the reaction of N-((1E)-1-Aza-2-Substituted phenylvinyl)-2'-{2"-[2'", 6'"-Dichloro Phenyl) Amino] Phenyl} Acetamide 3, with thoglycolic acid,, Chloroacetyl chloride and triethyl amine respectively. The compounds have been screened for their antimicrobial activity against different micro-organisms. The structures of novel synthesized compounds have been established on the basis of elemental analysis, IR, 1H NMR and Mass spectral data.

Key words: Thiozolidinone,, Azetidinone, Antimicrobial activity.

INTRODUCTION

Thiazolidinone and it's derivatives have been reported to possess a variety of pharmacological properties. 4-thioozolidinones are known to exhibit antitubercular[1], antibacterial[2-3], anticonvulsant[4] and antifungal[5] activities and also reported as HIV-1 RT inhibitors [6-7].

Apart from the substructure of widely used antibiotics such as penicillin, cephalosporin, monolactams, etc. the acetidin-2-one (â-lactam) skeleton has been synthetic intermediates and their biological activity[9]. A large number of 3-hloro monocyclic â-lactams possess powerful antibacterial, antimicrobial[10], antiinflammatory[11], anticonvulsant and antitubercular activity. They also function as enzyme inhibitors and are effective on the central nervous system.

4-Thiazolidinone and 2-azetidinone derivatives occupy an important place in medicinal chemistry as they show a variety of microbiological activity.

N-amino-2-{2'[2",6"-dichlorophenyl)amino] phenyl} acetamide 2 was prepared by treating 2-{2'-(2",6"-dichlorophenyl) amino] phenyl} acetic acid 1 with thionyl chloride followed by reaction aldehydes yield N-((1E)-1-Aza-2-Substitutedphenylvinyl)-2'-{2",6"-Dichloro Phenyl) Amino] Phenyl} Acetamide 3. Compound 3 were converted into 2'-{2"',6'"-dichloro phenyl) amino] phenyl}-n-(4-oxo-2-substitutd phenyl (1, 3-thiazolidin-3-yl)) acetamide 4a-j by condensation with thioglycolic acid. Compound 3 on reaction with chloroacetyl chloride in the presence of triethyl amine gave the 2'-{2"-[{2"',6'"-dichlorophenyl)amino] phenyl}-n-(3-chloro-2-oxo-4-substitutedphenylazetidinyl)acetamide 5a-j (Scheme-I). The structures of the compounds synthesized were assigned on the basis of the elemental analysis, IR, 1H NMR and Mass spectral

data. The compounds were evaluated for their antimicrobial activities.

Antimicrobial activity

The synthesized compounds 4a-j and 5a-j were screened for their antibacterial activity against E. coli, p. aeruginosa, S. aureus and bacillus sp. The minimum inhibitory concentration (MIC) was determined using Disk Diffusion method according to the standard procedure at three test concentration, 128 µg/ml, 256 µg/ml and 512 µg/ml. DMF was used as a blank. Standard antibacterial Streptomycin was also screened under the similar conditions for the comparison. Results are presented inTable 2.

Conclusion from Table 2:

All the compounds [4a-j] were found inactive against *E. coli, P. aeruginosa, S. aureus* and *bacillus sp* at 128 µg/ml concentrations.

The Screening data indicated that the compound 4b was found to show mild activity against E. coli., P. aeruginosa, S. aureus and bacillus sp at 256 µg/m. concentration. Compounds 4c and 4j were found to show mild activity against p. aeruginosa, S. aureus and bacillus sp only at 256 µg/ml concentration.

The screening data indicated that all compounds [4a-j] were found to show mild to moderate activity against all bacterial species at 512 µg/ml concentration.

All the compounds [5a-j] were found inactive against E. coli, P. aeruginosa, S. aureus and bacillus sp at 128 µg/ml concentrations.

The screening data indicated that the compounds 5d and 5j were found to show mild activity against all bacterial species at 256 µg/ml concentration. Compound 5e was found to show mild activity against E. coli, and P. aeruginosa only at 256 µg/ml concentration. Compound 5a, 5c, 5e and 5i also found mild activity against bacillus sp at the same test concentration.

The screening data indicated that all the compounds [5a-j] were found to show mild to moderate activity against E. coli, P. aeruginosa, S. aureus and bacillus sp at 512 µg/ml concentration.

EXPERIMENTAL

All the melting points were determined in open capillaries and are uncorrected. The purity of compounds was checked by TLC on silica gel 'G' coated glass plates. IR spectra were recorded in KBr on Shimadzu FT-IR 8300 spectrophotometer and ^{1}H NMR spectra were recorded on Varian 400 MHz and Bruker Avance-II in $CDCl_3$ by using TMS as internal standard. Mass spectra of the synthesized compounds have been recorded on a Joel SX 102/DA-6000 spectrometer. Microwave assisted reactions were carried out in "Q-Pro-M Modified Microwave system". The elemental analysis (%N) was carried out by total Kjeldahl method at Atul Limited, Valsad.

N-amino-2-{2'-[2",6"-dichlorophenyl) amino[phenyl} acetamide (2)

A mixture of 1 (0.01 mole) and thionyl chloride (0.05 mole) was taken in a round bottom flask. The reaction mixture was refluxed for 30 min in a water bath. The acid chloride so obtained was again refluxes with hydrazine hydrate (0.2 mole) in absolute ethanol for 4 to 5 hour. The reaction mixture was then poured into crushed ice with constant stirring. The solid, thus obtained, was filtered, washed with water, and recrystallized from ethanol.m.p. 138°C. Yields 69%.

N-((1E)-1-Aza-2-Substituted phenyl vinyl)-2'-{2"-[2'", 6'"-DihloroPhenyl)Amino[Phenyl}Acetamide(3)

A mixture of 3 (0.0032 mole), various substituted aldehyde (0.0032 mole) and a few drops of conc. HCl in a solvent mixture of DMF + Ethanol was heated under reflux for 8-10 hours. Then the solution was poured into crushed ice. The product thus obtained, was filtered, washed with water, dried and recrystallized from acetone. Yield-(67-75%).

2'-{2"-[2'", 6'"-dihlorophenyl)amino[phenyl}-n-(4-oxo-2-substituted pheynl (1,3-thiazolidin-3-yl))acetamide (4a-j)

A mixture of 3 (0.002 mole) and thioglycollic acid ($SHCH_2COOH$) (0.002 mole) in presence of catalytic amount of Anhy.ZnCl2 in DMF was heated under reflux for 11-12 hours. After the completion of reaction, mixture was poured into ice-

Table 1: Physical data of compound 4a-j & 5a-j

Comps	Mol. Formula (Mol. Wt)	Mol. Formula (Mol. Wt)	Yield (%) (time/hr)	m./p. °C	%N (Required) Found
4a	2-OCH_3	$C_{24}H_{21}O_3N_3Cl_2S$ (502.42)	62 (11-12)	220	(8.36) 8.34
4b	4-OCH_3	$C_{24}H_{21}O_3N_3Cl_2S$ (502.42)	65 (11-12)	167	(8.36) 8.34
4c	-H	$C_{23}H_{19}O_2N_3Cl_2S$ (472.39)	67 (11-12)	120	(8.89) 8.88
4d	3-Br	$C_{23}H_{18}O_2N_3Cl_2BrS$ (551.29)	61 (11-12)	150	(7.62) 7.60
4e	2-Cl	$C_{23}H_{18}O_2N_3Cl_3S$ (506.84)	60 (11-12)	128	(8.29) 8.27
4f	3-NO_2	$C_{23}H_{18}O_4N_4Cl_2S$ (517.39)	66 (11-12)	162	(10.82) 10.81
4g	2-OH	$C_{23}H_{19}O_3N_3Cl_2S$ (488.39)	70 (11-12)	132	(8.60) 8.58
4h	4-N $(CH_3)_2$	$C_{25}H_{24}O_2N_4Cl_2S$ (515.46)	67 (11-12)	185	(10.86) 10.86
4i	3,4-di OCH_3	$C_{25}H_{24}O_4N_3Cl_2S$ (532.45)	69 (11-12)	211	(7.89) 7.87
4j	3-OH,4-OCH_3	$C_{24}H_{21}O_4N_3Cl_2S$ (518.42)	64 (11-12)	190	(8.10) 8.07
5a	2-OCH_3	$C_{24}H_{20}O_3N_3Cl_3$ (504.80)	66 (15-16)	162	(8.32) 8.30
5b	4-OCH_3	$C_{24}H_{20}O_3N_3Cl_3$ (504.80)	69 (15-16)	152	(8.32) 8.31
5c	-H	$C_{23}H_{18}O_2N_3Cl_3$ (474.77)	67 (15-16)	258	(8.85) 8.83
5d	3-Br	$C_{23}H_{17}O_2N_3Cl_3Br$ (553.67)	71 (15-16)	199	(7.58) 7.56
5e	2-Cl	$C_{23}H_{17}O_2N_3Cl_4$ (509.22)	70 (15-16)	168	(8.25) 8.24
5f	3-NO_2	$C_{23}H_{17}O_4N_4Cl_3$ (519.77)	68 (15-16)	213	(10.77) 10.74
5g	2-OH	$C_{23}H_{18}O_3N_3Cl_3$ (490.77)	72 (15-16)	171	(8.56) 8.54
5h	4-N $(CH_3)_2$	$C_{25}H_{23}O_2N_4Cl_3$ (517.84)	67 (15-16)	182	(10.81) 10.81
5i	3,4-di OCH_3	$C_{25}H_{22}O_4N_3Cl_3$ (534.82)	65 (15-16)	214	(7.85) 7.82
5j	3-OH,4-OCH_3	$C_{24}H_{20}O_4N_3Cl_3$ (520.80)	69 (15-16)	193	(8.06) 8.04

cold water. The solid product thus, obtained was filtered, washed with water, dried and recrystallized form mixture of acetone : methanol (1:1). Yield (60-70%).

4e

IR (KBR)-Cl (750), -C=O (amidyl) (1600), -C=O (1750), -CH_2(2950), -NH (3070).

4g

IR (KBR)-Cl (750), -C=O (amidyl) (1610), -C=O (1740), -CH_2(2950), -NH (3080).

4c

^{1}H NMR of compound: δ 2.692 (s, 2H, O=C-CH_2S), 2.850 (s, 2H, -CH_2-Ar), 3.140 (s, 1H, -N-CH), 4.201 (s, 1H, Ar-NH-Ar), 6.993-7.856 (m, 13H, ArH), 8.245 (s, 1H, O=C-NH).

4fM/S (m/z)

517 (M+), 521 (M+4), 294-2H (292) (M^+), 296 (M+4), 161 (M^+), 165 (M+4), 123, 102, 119.

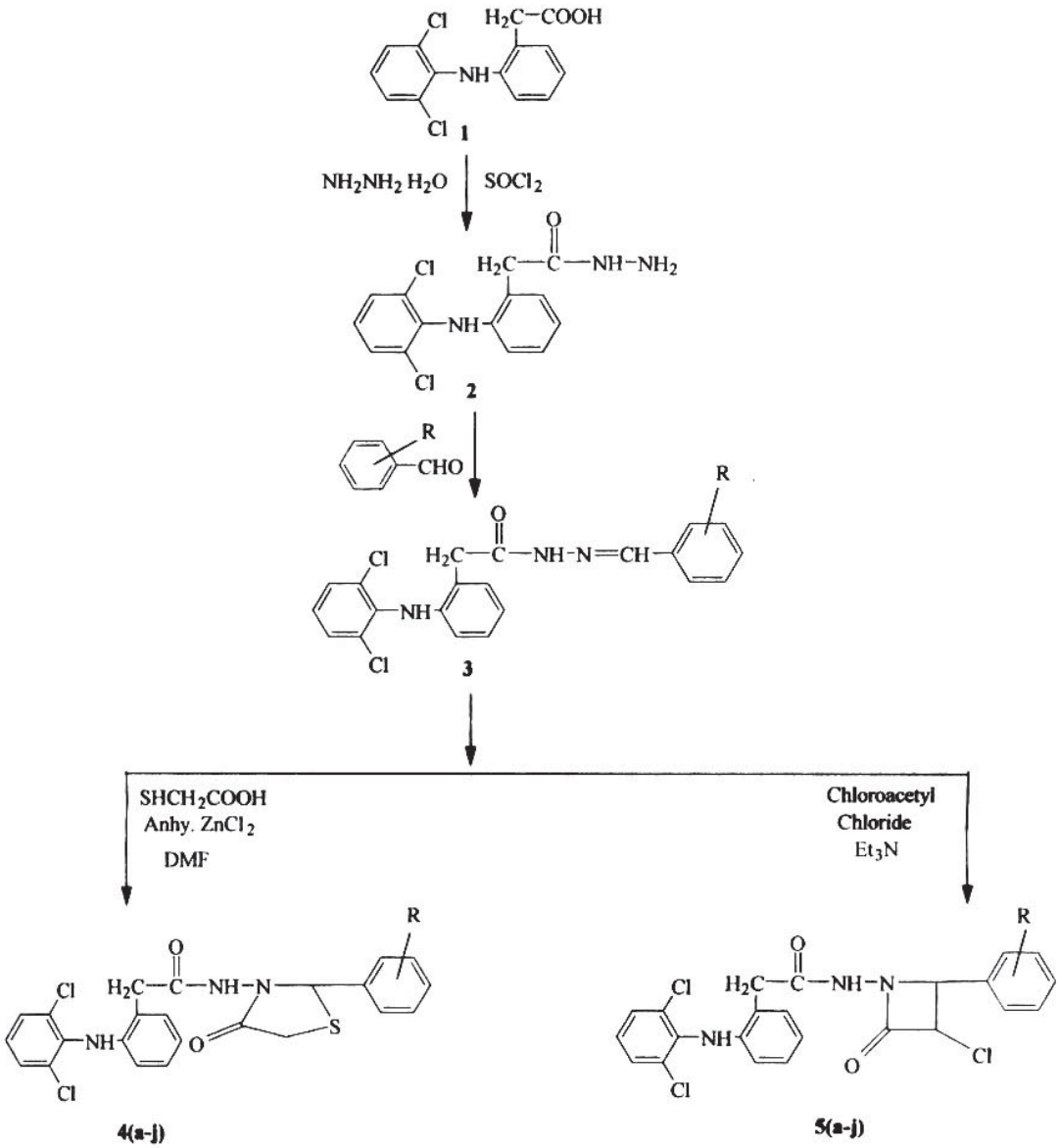
2'-{2"-[2'", 6'"-dihlorophenyl) amino [phenyl}-n-(3-chloro-2-oxo-4-substituted phenylazetidinyl) acetamide (5a-j)

To a stirred solution of 3 (0.002 mole(in 1, 4-dioxane at 0-5°C, chloroacetyl chloride was added drop wise with constant stirring. Then triethylamine (0.002 mole) was added and reaction mixture was heated under reflux for 15 to 16 hours. After completion of reaction, it was poured in ice cold water. The solid thus obtained, was filtered, washed with water, dried and recrystallized from acetone. Yield (65-72%).

Table 2: Antibacterial activity of compound (4a-j) & (5a-j)

Compound	Antibacterial activity											
	E. coli			*P. aeruginosa*			*S. aureus*			*Bacillus* sp		
	128 µg/ml	256 µg/ml	512 µg/ml	128 µg/ml	256 µg/ml	512 µg/ml	128 µg/ml	256 µg/ml	512 µg/ml	128 µg/ml	256 µg/ml	512 µg/ml
4a	-	+	++	-	-	+	-	+	++	-	+	+
4b	-	+	++	-	+	++	-	+	++	-	+	+
4c	-	-	++	-	+	++	-	+	++	-	+	+
4d	-	+	++	-	+	+	-	+	++	-	-	++
4e	-	+	++	-	+	+	-	-	++	-	+	++
4f	-	-	+	-	-	+	-	-	+	-	-	+
4g	-	-	+	-	-	++	-	-	+	-	-	+
4h	-	-	+	-	+	+	-	-	+	-	-	++
4i	-	-	+	-	-	+	-	-	+	-	+	+
4j	-	-	++	-	+	++	-	+	++	-	+	++
5a	-	+	++	-	-	+	-	-	+	-	+	+
5b	-	+	++	-	+	+	-	+	+	-	-	++
5c	-	-	+	-	-	++	-	+	++	-	+	++
5d	-	+	++	-	+	++	-	+	++	-	+	++
5e	-	+	++	-	+	++	-	-	++	-	+	+
5f	-	-	+	-	-	+	-	-	+	-	-	+
5g	-	-	+	-	-	++	-	+	+	-	-	+
5h	-	-	++	-	+	+	-	-	+	-	-	+
5i	-	-	+	-	-	+	-	-	+	-	+	+
5j	-	+	++	-	+	++	-	+	++	-	+	+
strepto Mycin	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++

The inhibition diameter in nm (-)< 6mm, (+=7-10mm, (++) = 11-15mm, (+++) = 16-21mm (++++) = 22-28mm



R = 2-OCH_3, 4-OCH_3, -H, 3- Br, 2-Cl, 3- NO_2, 2- OH, 4-$N(CH_3)_2$, 3,4-di OCH_3, 3-OH-4- OCH_3

Scheme

5f

IR (KBR)-Cl (750), -C=O (amidyl) (1620), -C=O (1750), -CH_2(2950), -NH (3100).

5j

IR (KBR)-Cl (750), -OCH_3 (1040), -C=O (amidyl) (1620), -C=O (1750), -CH_2(2950), -NH (3100).

5c ^{1}H NMR of compound: δ 2.696 (s, 2H, -CH_2-Ar), 3.787 (s, 1H, Ar-NH-Ar), 4.356 (D, 1H, -CH-Cl), 5.2 (d, 1H, -Ch-Ar), 6.417-8.018 (m, 12H, ArH), 8.335 (s, 1H, O=C-NH).

5h: M/S (m/z)

518 (M+), 524 (M+6), 294-2H (292) (M^+), 296 (M+4), 224 (M^+), 226 (M+2), 181 (M^+), 183 (M+2), 161 (M^+), 165 (M+4).

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