Synthesis and Biological Activity Studies of Some Thiazolidinones and Azetidinones

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A series of 4-thiazolidinones and 2-azetidinones have been synthesized by condensation of 4,4'-diaminodiphenylsulphone with various aromatic or heterocyclic aldehydes to yield the Schiff's bases. Cyclocondensation of Schiff's bases with 2-mercaptopropionic acid afforded 4-thiazolidinone derivatives, and cyclocondensation of Schiff's bases with chloroacetylchloride in presence of triethylamine afforded 2-azetidinone derivatives. The structures of the newly synthesized compounds were confirmed by analytical and spectral (IR, NMR, and Mass) data. All these compounds were evaluated for their *in vitro* growth-inhibitory activity against several microbes. Compound 4b and 4c exhibited equipotent antibacterial activity with the reference standard ampicillin against *Bacillus subtilis.*

Dapsone (4,4'-diaminodiphenylsulphone), a sulphone analog, has been proved to be a powerful antimicrobial agent. 4-thiazolidinones are associated with antibacterial[1-7], antifungal[1-7], and antitubercular[8-11] activities and have diverse biological activities. β-lactam compounds are of interest due to the therapeutic significance of penicillin and cephalosporin antibiotics and possess significant antibacterial[3-7,12-19], antifungal[3-7,12-19] and antitubercular activities[12-14]. 4-thiazolidinone and 2-azetidinone derivatives occupy an important place in medicinal chemistry as they show a variety of microbiological activity. Therefore, an attempt was made to study the antibacterial, antifungal and antitubercular activities of 4-thiazolidinone and 2-azetidinone in present investigation.

4,4'-diaminodiphenylsulphone (1) was condensed with various aromatic or heterocyclic aldehydes in ethanol in the presence of concentrated sulphuric acid as a catalyst to yield the Schiff's bases (2a-f). These Schiff"s bases on treatment with 2-mercaptopropionic acid yielded substituted 4-thiazolidinones (3a-f), and on treatment with chloroacetylchloride in the presence of triethylamine gave substituted 2-azetidinones (4a-f). The structural assignment of the products was based on their elemental, IR, NMR and Mass spectral data. The title compounds were screened for their antibacterial and antifungal activity.

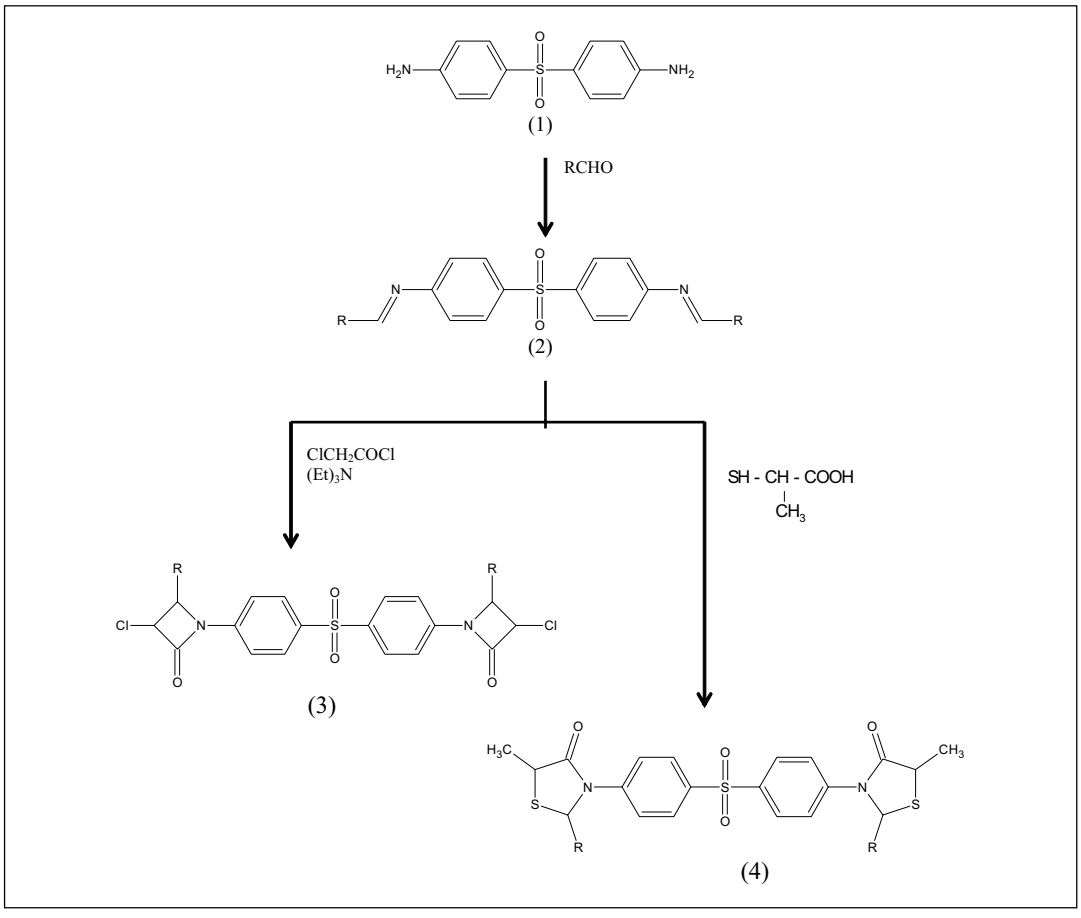
All melting points were taken by open capillary tubes and were uncorrected. IR spectra recorded on a Perkin Elemer IR spectrophotometer, using KBr pellets, NMR on Bruker DRX 300 (300MHZ) NMR spectrophotometer in DMSO using TMS as internal standard and Mass spectra on Jeol SX 102 (FAB) Mass spectrophotometer.

To a mixture of 4,4'-diaminodiphenylsulphone (2.48 g, 0.01 mol) and p-methyl benzaldehyde (2.40 g, 0.02 mol) dissolved in ethanol, one drop of concentrated sulphuric acid was added. The reaction mixture was refluxed for 6 h. The reaction mixture was then poured into crushed ice. Separated solid was filtered, dried and re-crystallized from ethanol to give 4,4'-Bis (4-methylbenzylidene amino) diphenyl sulphone. The reaction was monitored by TLC.

To a mixture of compound 2b (4.52 g, 0.01 mol) in dry dioxane (10 ml), a solution of 2-mercaptopropionic acid (2.17 ml, 0.025 mol) in dry dioxane (10 ml) was added and the reaction mixture was refluxed for 24 h. The reaction mixture was then poured into crushed ice. The separated solid was neutralized by sodium bicarbonate to remove excess of 2-mercaptopropionic acid. Solid compound obtained was crystallized from ethanol to give 4,4'-Bis (2-(4-methyl phenyl)-5-methyl-1, 3-thiazolidin-4-one-3-yl) diphenyl sulphone. IR (KBr)cm^{-1} : 1693 (C=O), 1279 (SO_2, Asymmetrical str.), 1141 (SO_2, Symmetrical str.), 719 (C-S-C), ^{1}H NMR ($CDCl_3$) δ: 3.58 (s, 2H, 2×S-CH-Ar), 3.30-3.50 (s, 6H, 2×Ar-CH_3), 1.40-1.70 (d, 6H, 2×CH-CH_3), 2.10-2.6 (qua, 2H, 2×CH-CH_3), 5.90-8.60 (m,16H, 4×4 Ar-H); MS (m/z) 628 (M^+), 598, 564, 538, 503, 439, 271. Anal Calcd for $C_{34}H_{32}N_2O_4S_3$: C, 64.96; H, 5.09; N, 4.45. Found: C, 64.80; H, 5.03; N, 4.39.

To a mixture of compound 2b (4.52 g, 0.01 mol) in dry dioxane (10 ml), triethylamine (3.49 ml, 0.025 mol), was added chloroacetyl chloride (1.99 ml, 0.025 mol) drop-wise at 5-10°. The reaction mixture was stirred for 6 h. The reaction mixture was then poured into crushed ice. The solid separated was dried and re-crystallized from ethanol to give 4,4'-Bis (3-chloro-4-(4-methyl phenyl)-2-oxo-azetidin-1-yl) diphenyl sulphone. IR (KBr)cm^{-1} : 1683 (C=O), 1340 (SO_2, Asymmetrical str.), 1150 (SO_2, Symmetrical str.), 745 (C-S-C), ^{1}H NMR ($CDCl_3$) δ: 2.48-2.60 (s, 2H, 2×CH-Cl), 4.22-4.40 (s, 2H, 2×CH-Ar), 2.80-2.93 (s, 6H, 2×Ar-CH_3), 7.40-8.50 (m, 16H, 4×4 Ar-H); MS (m/z) 604 (M^+), 589, 575, 543, 534, 480, 423, 273. Anal Calcd for $C_{34}H_{32}N_2O_4S_3$: C, 63.57; H, 4.30; N, 4.63. Found: C, 63.45; H, 4.29; N, 4.27. The synthetic route is represented in Scheme 1, and physical data of the synthesized compound are given in Table 1.

The compounds synthesized were screened for their antibacterial activity[4] using *Staphylococcus aureus,*



Scheme 1: Synthesis of some thiazolidinone and azetidinone from dapsone R = heterocyclic or aromatic aldehyde

TABLE 1: PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS

Compound	R	Molecular Formula	(%) Yield	M.P.(°)
2a	Phenyl	$C_{26}H_{20}N_2O_2S$	75	201-202
2b	P-Methylphenyl	$C_{28}H_{24}N_2O_2S$	70	205-206
2c	P-Nitrophenyl	$C_{26}H_{18}N_4O_6S$	80	215-216
2d	P-Hydroxylphenyl	$C_{26}H_{20}N_2O_4S$	85	96-97
2e	Thiophene	$C_{22}H_{16}N_2O_4S$	70	195-200
2f	Furfural	$C_{22}H_{16}N_2O_4S$	80	220-221
3a	Phenyl	$C_{32}H_{28}N_2O_4S_3$	68	110-112
3b	P-Methylphenyl	$C_{34}H_{32}N_2O_4S_3$	70	120-121
3c	P-Nitrophenyl	$C_{32}H_{26}N_4O_8S_3$	65	113-114
3d	P-Hydroxyphenyl	$C_{32}H_{28}N_2O_6S_3$	72	132-134
3e	Thiophene	$C_{28}H_{24}N_2O_4S_5$	65	168-169
3f	Furfural	$C_{28}H_{24}N_2O_6S_3$	69	169-171
4a	Phenyl	$C_{30}H_{22}N_2O_4SCl_2$	64	172-173
4b	P-Methylphenyl	$C_{32}H_{26}N_2O_4SCl_2$	72	160-161
4c	P-Nitrophenyl	$C_{30}H_{20}N_4O_8SCl_2$	70	163-165
4d	P-Hydroxylphenyl	$C_{30}H_{22}N_2O_6SCl_2$	69	174-175
4e	Thophene	$C_{26}H_{18}N_2O_4S_3Cl_2$	65	180-182
4f	Furfural	$C_{26}H_{18}N_2O_6SCl_2$	69	220-222

concentration. Control experiment was carried out under similar condition by using ampicillin as a standard for comparison. The inhibition zone measure in mm showed that compounds 4b, 4c, 4e and 4f were more active than other compounds tested against the above microbes. Compounds 4b and 4c exhibited equipotent activity with the reference standard ampicillin against *B. subtilis* (Table 2).

The antifungal activity[13] was tested against the fungal species *Aspergilus niger* and *Candida albicans* at 50 mg concentration. The antifungal data revealed that the compounds 3d, 3e, 4b, 4e and 4f were more active than other compounds tested against the above microbes, but none showed better or comparable activity to griseofulvin (Table 2).

The synthesized compounds were screened for antitubercular activity[9,14] at 1 mg, 10 mg and 100 mg concentration against the human strain $H_{37}Rv$ of *M. tuberculosis.* Isoniazid was used as the standard drug for comparison. The antitubercular data revealed that the compound 3e, 4b and 4e showed activity at 10 mg concentration, other compounds showed activity at 100 mg, while none of the compound showed activity at 1 g concentration (Table 2).

TABLE 2: ANTIMICROBIAL ACTIVITY DATA OF THE TITLE COMPOUNDS

Compound	Zone of inhibition in mm						Concentration in µg/ml	
	Bacteria				Fungi		Mycobacterium tuberculosis	
	S. a	B. s	E. c.	P. a.	A. n.	C. a.	100 µg	10 µg
3a	12	11	11	09	09	08	-	+
3b	11	10	14	10	13	14	-	+
3c	13	12	13	10	09	08	-	+
3d	12	10	13	11	11	11	-	+
3e	14	11	15	11	12	13	-	-
3f	15	13	16	12	10	09	-	+
4a	14	12	13	14	08	10	-	+
4b	20	20	18	17	11	12	-	-
4c	20	20	17	12	08	09	-	+
4d	15	14	16	13	09	10	-	+
4e	17	21	15	17	11	10	-	-
4f	16	15	14	14	12	11	-	+
Ampicillin	22	20	21	20	—-	—-	——-	——
Griseofulvin	—-	—-	—-	—-	15	16	——-	——-
Isoniazid	—-	—-	—-	—-	—-	—-	-	+

S. a.- *Staphylococcus aureus*, B. s.- *Bacillus subtilis*, E. c.- *Escherichia coli*, P. a.- *Pseudomonas aeruginosa*, A. n.- *Aspergillus niger*, C. a.- *Candida albicans*, '-'indicates no growth, '+' indicates growth less than 20 colonies,

Escherichia coli, Pseudomonas aeruginosa and Bacillus subtilis as test organism. The activities of these compounds were tested using agar cup-plate method at 50 mg

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