Synthesis and Antimicrobial Activities of Some New Azetidin-2-ones and Thiazolidin-4-ones

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Desai, *et al.*: New Azetidin-2-ones and Thiazolidin-4-ones: Synthesis and Evaluation

Various (4-substituted) phenyl-3-β-[(N-benzenesulphonyl/tosyl)-4-(un)substituted anilino]propionylamido-1,3-thiazolidine-4-ones (3a–x) and 1-β-[(N-benzenesulphonyl/tosyl)-4-(un)substituted anilino]-propionylamido-3-chloro-4-(4-substituted)phenyl-azetidin-2-ones (4a–x) have been synthesised by the cyclocondensation of Schiff bases (2a-x) with thioglycolic acid and chloroacetyl chloride, respectively. The structures of the newly synthesised compounds have been established on the basis of their spectral data and elemental analysis. All compounds were evaluated for antimicrobial activities against *Escherichia coli*, *Bacillus cirroflagellosus*, *Aspergillus niger* and *Colletotrichum capsici*. Most compounds investigated exhibited significant antifungal activity against *Colletotrichum capsici*, comparable to that of fluconazole, the standard used.

Key words: Azetidinones, antimicrobial activity, sulfonamide moiety, thiazolidinones

Survey of the recent literature shows that intensive and indiscriminate use of antibiotics has lead to drug resistant microbial pathogens necessitating the need for the search for new antimicrobial agents with reduced resistance to pathogens and better activity.

Sulfonamides possess diverse biological and pharmacological activities from antimicrobial[1] to antitumor[2] activities. 4-Thiazolidinones are associated with antibacterial[3] antifungal[4], antitubercular[5] and anticonvulsant[6] activities. β-Lactam compounds e.g., penicillin and cephalosporin are well known antibiotics. Azetidinones are also reported to possess antimicrobial[7], antiinflammatory[8,9], analgesic[9] and CNS depressant[9] activities. Encouraged by these observations, it was contemplated to incorporate the biologically active 'sulfonamide' moiety. To enable further evaluation of the potential usefulness of thiazolidinones, azetidinones, and in continuation of our search for nitrogen heterocycles of pharmacological importance[10-13], we report herein the synthesis of some new thiazolidinones (3a-x) and azetidinones (4a-x) with a view to achieve

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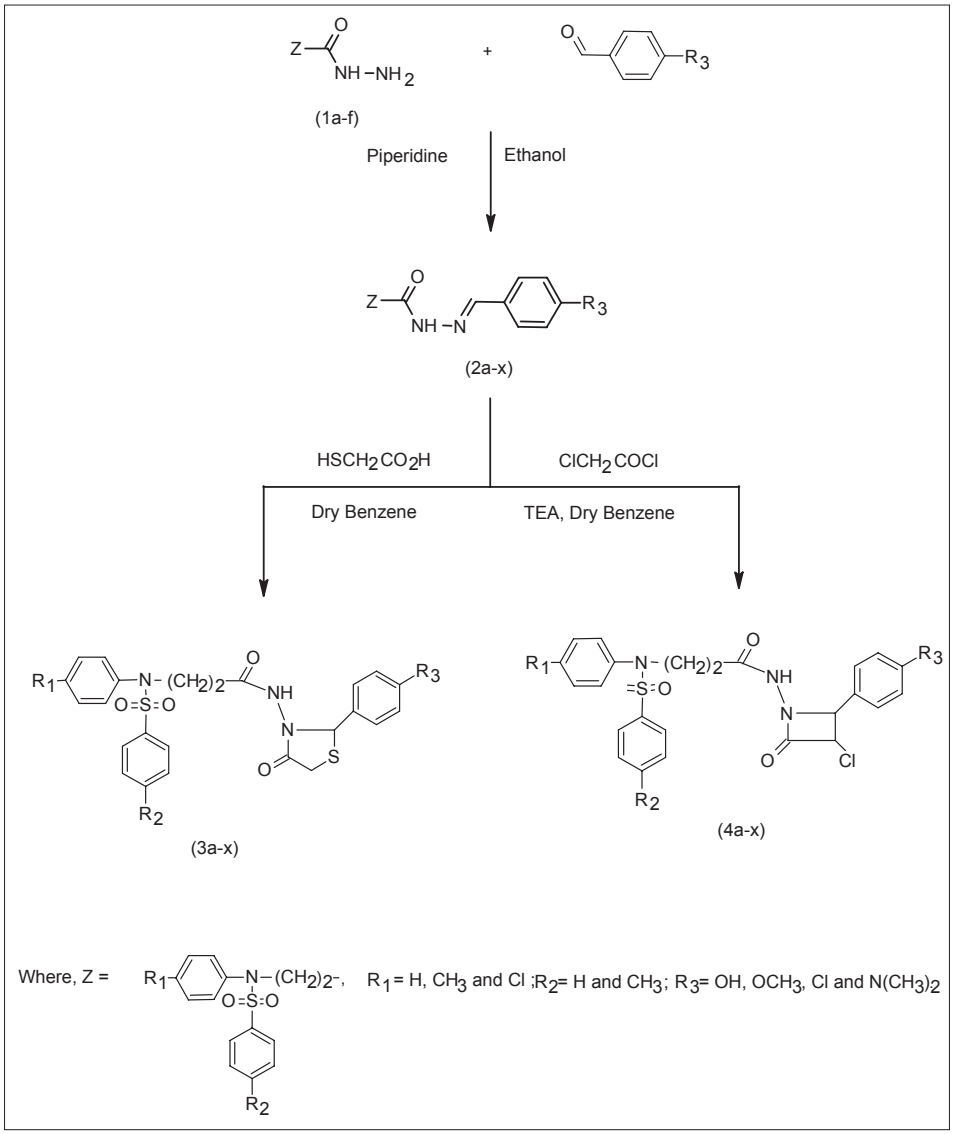
better antimicrobial activity. All the compounds were evaluated for antimicrobial activities against *Escherichia coli*, *Bacillus cirroflagellosus, Aspergillus niger* and *Colletotrichum capsici.* The synthetic route for the title compounds is depicted in Scheme 1.

In the present investigation, Schiff bases (2a-x), were obtained by refluxing β-[(N-benzenesulphonyl/tosyl)-4-(un) substituted anilino]propionic acid hydrazides[14] (1a-f), with 4-substituted benzaldehydes in the presence of piperidine. Schiff bases (2a-x) on cyclocondensation with thioglycolic acid in dry benzene, yielded thiazolidinones (3a-x). Azetidinones (4a-x) were obtained by the cyclocondensation of Schiff bases (2a-x) with chloroacetyl chloride in presence of triethyl amine. The structures of the newly synthesised compounds were confirmed by elemental and spectral (IR, ^{1}HNMR and mass) analysis. After establishing the physicochemical analysis, all the compounds were evaluated for their antimicrobial activities.

Melting points were determined in open capillaries and are uncorrected. IR spectra in KBr were recorded on a Perkin Elmer spectrophotometer and ^{1}HNMR spectra on a Varian 300 MHz NMR spectrometer using TMS as an internal standard (chemical shifts in δ ppm). Mass spectra were recorded on Finnegan Mat 8230 spectrometer. The starting β-[(N-benzenesulphonyl/tosyl)-4-(un) substituted anilino] propionic acid hydrazides (1a-f) were prepared by the literature method[14]. The observed melting points



Scheme 1: Synthesis of title compounds
3a-x are (4-substituted) phenyl-3-β-[(N-benzenesulphonyl/tosyl)-4-(un)substituted anilino]propionylamido-1,3-thiazolidine-4-ones and 4a-x are 1-β-[(N-benzenesulphonyl/tosyl)-4-(un)substituted anilino]propionylamido-3-chloro-4-(4-substituted)phenyl-azetidin-2-ones

were consistent with the melting points reported in the literature.

Preparation of 1-β-[(N-benzenesulphonyl)anilino] propionylamido-2-(4-hydroxy) benzylidene hydrazine (2a): A mixture of 1-β-[(N-benzenesulphonyl)anilino] propionic acid hydrazide (1a**,** 3.19 g, 0.01 mol) and 4-hydroxy benzaldehyde (1.22 g, 0.01 mol) in 30 ml ethanol with 3–4 drops of piperidine was refluxed for 1 h. The solid separated was filtered, washed with cold ethanol, dried and crystallised from ethanol. Various Schiff bases (2b-x) were prepared by adopting the above procedure. Yields and melting points of all the schiff bases are enumerated in Table 1. 2f**:** IR (KBr) cm^{-1}: 3200 (b), (NH), 2970 (s) (-CH_2-), 1610 (s) and 1570 (m) (>C=C< and >C=N-), 1450 (m) (>C-N), 1680 (s) (>C=O) and 1350 (s) (SO_2); 2q**:** IR KBr) cm^{-1}: 3190 (b), (NH), 2930 (s) (-CH_2-), 1610 (s) and 1580 (m) (>C=C< and >C=N-), 1450 (m) (>C-N), 1660 (s) (>C=O) and 1340 (s) (SO_2). 2f: ^{1}HNMR (DMSO-d6): δ 2.20 (s, 3H, CH_3), 2.40 (s, 3H, OCH_3), 9.60 (s, 1H, -CONH-), 3.0 (t, 2H, CH_2), 3.80 (t, 2H, CH_2), 8.10 (s, 1H, -N=CH-) and 6.90–7.70 (m, 12H, ArH); 2k: ^{1}HNMR (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 10.6 (s, 1H, -CONH-), 3.30 (t, 2H, CH_2), 3.90 (t, 2H, CH_2), 8.90 (s, 1H, -N=CH-) and 6.92–7.85 (m, 13H, ArH).

Preparation of 2-(4-hydroxy)phenyl-3-β-[(N-benzenesulphonyl)anilino]propionyl amido-1,3,-

TABLE 1: PHYSICOCHEMICAL DATA

Comp. No.,	R_1	R_2	R_3	MP (°)	Yield (%)	Comp. No.,	R_1	R_2	R_3	MP (°C)	Yield (%)
2a	H	H	OH	110-12	70	3m	CH_3	CH_3	OH	180-81	80
2b	H	H	OCH_3	153-55	65	3n	CH_3	CH_3	OCH_3	164-65	75
2c	H	H	Cl	184-86	68	3o	CH_3	CH_3	Cl	174-75	80
2d	H	H	$N(CH_3)_2$	228-29	69	3p	CH_3	CH_3	$N(CH_3)_2$	>300	76
2e	H	CH_3	OH	132-33	68	3q	Cl	H	OH	>300	80
2f	H	CH_3	OCH_3	172-74	70	3r	Cl	H	OCH_3	175-176	80
2 g	H	CH_3	Cl	165-66	78	3s	Cl	H	Cl	162-63	70
2h	H	CH_3	$N(CH_3)_2$	240-41	76	3t	Cl	H	$N(CH_3)_2$	230-31	80
2i	CH_3	H	OH	183-84	75	3u	Cl	CH_3	OH	194-95	70
2j	CH_3	H	OCH_3	168-69	78	3v	Cl	CH_3	OCH_3	172-73	75
2k	CH_3	H	Cl	185-86	80	3w	Cl	CH_3	Cl	110-11	80
2l	CH_3	H	$N(CH_3)_2$	210-11	79	3x	Cl	CH_3	$N(CH_3)_2$	230-31	69
2m	CH_3	CH_3	OH	132-33	80	4a	H	H	OH	130-32	75
2n	CH_3	CH_3	OCH_3	158-59	75	4b	H	H	OCH_3	125-26	65
2o	CH_3	CH_3	Cl	178-79	80	4c	H	H	Cl	150-51	68
2p	CH_3	CH_3	$N(CH_3)_2$	190-91	76	4d	H	H	$N(CH_3)_2$	159-60	75
2q	Cl	H	OH	140-41	80	4e	H	CH_3	OH	102-03	60
2r	Cl	H	OCH_3	145-46	85	4f	H	CH_3	OCH_3	165-66	70
2s	Cl	H	Cl	155-56	75	4 g	H	CH_3	Cl	156-57	70
2t	Cl	H	$N(CH_3)_2$	208-09	80	4h	H	CH_3	$N(CH_3)_2$	163-64	75
2u	Cl	CH_3	OH	105-06	80	4i	CH_3	H	OH	98-99	70
2v	Cl	CH_3	OCH_3	92-93	75	4j	CH_3	H	OCH_3	103-04	75
2w	Cl	CH_3	Cl	148-49	80	4k	CH_3	H	Cl	168-69	75
2x	Cl	CH_3	$N(CH_3)_2$	200-01	69	4l	CH_3	H	$N(CH_3)_2$	189-90	75
3a	H	H	OH	168-69	75	4m	CH_3	CH_3	OH	115-16	80
3b	H	H	OCH_3	165-66	65	4n	CH_3	CH_3	OCH_3	138-39	75
3c	H	H	Cl	176-77	68	4o	CH_3	CH_3	Cl	150-51	80
3d	H	H	$N(CH_3)_2$	173-74	70	4p	CH_3	CH_3	$N(CH_3)_2$	148-49	76
3e	H	CH_3	OH	160-61	70	4q	Cl	H	OH	120-21	80
3f	H	CH_3	OCH_3	154-55	80	4r	Cl	H	OCH_3	117-18	75
3g	H	CH_3	Cl	105-06	78	4s	Cl	H	Cl	136-37	70
3h	H	CH_3	$N(CH_3)_2$	175-76	76	4t	Cl	H	$N(CH_3)_2$	150-51	71
3i	CH_3	H	OH	173-74	75	4u	Cl	CH_3	OH	134-35	75
3j	CH_3	H	OCH_3	140-41	78	4v	Cl	CH_3	OCH_3	105-06	70
3k	CH_3	H	Cl	118-19	75	4w	Cl	CH_3	Cl	132-33	75
3l	CH_3	H	$N(CH_3)_2$	235-36	70	4x	Cl	CH_3	$N(CH_3)_2$	160-61	70

All the compounds were analysed for C, H and N. The experimental values were within ±0.04% of the calculated value. All the compounds were crystallised from aq ethanol

thiazolidine-4-one (3a):1-β-[(N-benzenesulphonyl) anilino]propionylamido-2-(4-hydroxy)benzylidene hydrazine (2a**,** 4.23 g, 0.01 mol), thioglycoloic acid (0.9 g, 0.015 mol) in dry benzene was refluxed for 8–10 h. Excess of solvent was removed under reduced pressure. The residue was washed with saturated solution of sodium bicarbonate followed by water. The powder separated was filtered, washed repeatedly with water, dried and crystallized from ethanol.

The above procedure was followed to prepare 2-(4-OH/OCH_3/Cl/N,N-dimethyl amino)phenyl-3-β-[(N-benzenesulphonyl/tosyl)-4-(un) substituted anilino] propionylamido-1,3-thiazolidin-4-ones (3b-x). Yield and melting points of other compounds in the same series are given in Table 1.

3f**:** IR (KBr) cm^{-1}: 3220 (b) (NH), 2960 (s) (CH_2), 1610 (s) and 1510 (m) (>C=C< and >C=N-), 650 (s) and 700 (sh) (-C-S-C-), 1450 (m) (>C-N), 1720 (m) (>C=O of ring), 1675 (s) (>C=O of side chain) and 1390 (s) of SO_2; 3p: 3120 (b) (NH), 2920 (s) (CH_2), 1615 (s) and 1450 (m) (>C=C< and >C=N-), 660 (s), 690 (sh) (-C-S-C), 1470 (m) (-C-N), 1670 (w) (>C=O of ring), 1620 (w) (>C=O of side chain) and 1400 (w) (SO_2). 3a: ^{1}HNMR: (DMSO-d6): δ 10.5 (s, 1H, OH), 9.40 (s, 1H, >CONH), 2.95 (t, 2H, CH_2), 3.5 (s, 1H, N-CH), 3.75 (s, 2H, -S-CH_2), 3.95 (t, 2H, CH_2), 6.95-7.70 (m, 14H, ArH). 3p: MS (m/z, Rel. Abund): 553 (M^+, 13), 508 (63), 274 (50), 179 (52), 157 (85), 137 (63), 120 (66) 101 (66) 79 (100) and 23 (31). Physicochemical properties of all the thiazolidinones are enumerated in Table 1.

Preparation of 1-β-[(N-benzenesulphonyl)anilino] propionylamido-3-chloro-4-(4-hydroxy) phenyl-azetidine-4-one (4a): To a mixture of 1-β-[(N-benzenesulphonyl)anilino]propionylamido-2-(4-hydroxy)benzylidene hydrazine (2a**,** 4.23 g, 0.01 mol) and triethylamine (0.5 g, 0.005 mol) dissolved in dry benzene (80 ml), chloroacetyl chloride (0.569 g, 0.005 mol) in benzene (50 ml) was added drop wise with stirring for 1 h and the reaction mixture was stirred further for 2 h. Triethylamine hydrochloride thus separated was filtered off and the filtrate was concentrated under reduced pressure. Viscous liquid thus obtained was digested with a mixture of n-hexane and diethyl ether (1:1; 3×30 ml). The resulting solid was then digested with ethanol for 1 h, the solution was concentrated, treated with animal charcoal and filtered. On standing crystals of azetidinone were separated. The above procedure was used to prepare remaining azetidinones (4b-x). Yield and melting points of all the azetidinones are enumerated in Table 1. 4f**:** IR (KBr) cm^{-1}: 3200 (b) (NH), 2985 (s) (CH_2), 1610 (s) and 1570 (m) (>C=C< and >C=N), 1450 (m) (>C=N), 1680 (>C=O of ring), 1610 (s) (>C=O of side chain) and 1350 (s) (SO_2); 4q: IR (KBr) cm^{-1}: 3190 (b) (NH), 2980 (s) (CH_2), 1620 (s) and 1580 (m) (>C=C< and >C=N-), 1450 (m), (-C-N-), 1760 (s) (>C=O of ring), 1670 (s) (>C=O of side chain) and 1350 (w) (SO_2). 4b: ^{1}HNMR (DMSO-d6): δ 2.2 (s, 3H, OCH_3), 9.80 (s, 1H, CONH), 3.0 (t, 2H, CH_2), 3.85 (t, 2H, CH_2), 2.60 (d, 1H, Cl-CH-), 4.0 (d, 1H, Cl-C-CH) and 6.80–7.76 (m, 14H, ArH); 4q: 10.5 (s, 1H, OH), 9.40 (s, 1H, CONH), 2.95 (t, 2H, CH_2), 3.90 (t, 2H, CH_2), 2.60 (d, 1H, Cl-CH-), 4.30 (d, 1H, Cl-C-CH) and 6.9–7.70 (m, 13H, ArH). 4q: MS (m/z, Rel. Abund): 534 (M^+, 42), 530 (100), 532 (48), 388 (33), 154 (94), 136 (79), 102 (92), 77 (44), and 39 (15).

Evaluation of antimicrobial activity: All the newly synthesised compounds were evaluated for their antimicrobial activity against Gram negative bacterium *Escherichia coli*, Gram positive bacterium *Bacillus cirroflagellosus* and fungi *Aspergillus niger* and *Colletotrichum capsici* by cup plate method[15]. Cotrimoxazole (Ciplin DS containing trimethoprim 500 mg and sulphamethoxazole 800 mg) and fluconazole were used as standards and DMF as solvent control. All the test samples and the standards were tested at a concentration of 100 µg. The results are expressed as relative percent inhibitions (with respect to the standard, values given in parenthesis).

Amongst the compounds tested, all the compounds have shown minimal antibacterial activity against *Bacillus cirroflagellosus* (in the range of 15–30%), except 2k (57.82) and 2r (48.97). Some of the compounds exhibited moderate to significant antibacterial activity against *Escherichia coli.*, 2k (100), 2p (67.68), 3e (100), 3g (67.7), 3m (67.7), 3o (79.9), 4k (93.06), 4o (93.06). Rest of the compounds were moderate with (40–60%). Some of the compounds exhibited moderate to significant antifungal activity against *Aspergillus niger,* 2b (72.2), 2h (59.84), 2n (72.2), 2q (78.7), 2u (72.2), 2v, 2w and 2x (78.76), 3i (78.7), 4m (78.7), 4v (78.7). Remaining compounds exhibited minimum to moderate activity (25–48%).

Most compounds exhibited significant antifungal activity against *Colletotrichum capsici.,* Amongst all the compounds, 2v has exhibited maximum activity 944.44%. Enumerating in the decreasing order of their activities, 2f, 4e, 4f and 4o (302.02); 3v (299.39); 4n and 4s (261); 3s (242.42); 2c, 2i, 3i, 4c and 4m (206.2); 3b, 4a (188.88); 2l, 2r, 3o and 4g (156.56); 2q, 2u, 3p, 3j and 4v (126.7); 2x, 3a, 3e, 3w and 4K (100). Rest of the compounds exhibited moderate activity (45–75%).

Conversion of hydrazides (1a-f) into schiff bases (2a-x), decreased the antifungal activity. No significant change in the antimicrobial activity of thiazolidinones (3a-x). However the conversion of schiff bases into azetidinones (4a-x) enhanced the antifungal activity against *Colletotrichum capsici* noticeably. From the observations, it is concluded that, most of the compounds exhibited most significant antifungal activity against *C. capsici* comparable to that of the standard, fluconazole.

ACKNOWLEDGEMENTS

The authors thank the Chairman, Department of Chemistry, Karnatak University, Dharwad, for providing the necessary facilities. The authors also thank the Heads of RSIC-CDRI, Lucknow, TIFR-Mumbai, RSIC-IIT, Mumbai for spectral analysis. Authors SRD and UVL are thankful to UGC and CSIR respectively for the financial help in the form of FIP and SRF.

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Accepted 28 August 2011
Revised 23 July 2011
Received 13 April 2010
Indian J. Pharm. Sci., 2011, 73 (4): 478-482