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Facile Access to Polyfunctionalized Thiazolidinones and their Antimicrobial Evaluation

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ABSTRACT

Novel 4 - (4-cyanophenylamino) – 2 - (4-methylpiperazin-1-yl) – 5 - (5-(arylidene)-4-oxo-2-phenylthiazolidin-3-yl) benzoic acids were synthesized. The chemical structures of all the synthesized 4-Thiazolidinones were elucidated using IR, Mass and ^{1}H NMR spectroscopy.
The compounds were screened for their *in vitro* anti-microbial activity.
Keywords: Polyfunctionalized, Thiazolidinones, Arylidene, Antimicrobial Activity

I. INTRODUCTION

Resistance to existing antibiotics and antimicrobial agents has given rise to public health crisis. Therefore, development of new compounds to fight the resistant microbes is currently the need of time.

Thiazolidinones have attracted number of researchers due to their wide spectrum of biological activities [1] namely antimicrobial [2], anticancer [3], antimalarial [4], antiviral [5], fungicidal [6], antitubercular [7] activities etc.

Keeping in view the above observations, and in continuation to our research in developing novel bioactive compounds [8], new series of polyfunctionalized Thiazolidinones were synthesized and screened for their antimicrobial activity.

II. METHODS AND MATERIALS

All reagents were of analytical grade and used directly. All the melting points were determined in open glass capillary and are uncorrected. Progress of reaction was monitored by thin layer chromatography (TLC) using silica gel-G coated aluminium plates (0.5 mm thickness, Merck) and spots were visualized under UV radiation. The synthesized compounds were purified by recrystalization and/or column chromatography. The IR spectra were recorded on BRUKER TENSOR Series using KBr pellets. ^{1}H NMR spectra were recorded on 300MHz BRUKER ULTRASHIELD using DMSO-d_6 as a solvent and TMS as an internal reference and chemical shift values were expressed in δ ppm.

Preparation of 5-amino-4-(4-cyano-phenylamino)-2-(-4-N-methyl-piperazin-1-yl)-benzoic acid (2)

4-(4-cyano-phenylamino)-2-(4-N-methyl-piperazin-1-yl)-5-nitro- benzoic acid **(1)** (8.0 g, 0.0209 mol) was suspended in water (10 ml) containing acetic acid (2.6 ml, 0.0418 mol) at 70 ˚C and Iron dust (2.3 g, 0.0418 mol) in ethanol (4.7 ml, 0.0836 mol) was added portion wise. The progress of reaction was monitored by TLC using toluene: methanol (6:4) as eluent. After the completion of reaction, the refluxed content was poured into crushed ice. The solid product obtained was filtered and dried. The crude product was purified by crystallization from ethanol to get the title compound. M.P: 110 -112 ˚C

3.5. Preparation of 5-(benzylidene-amino)-4-(4-cyano-phenylamino)-2-(4-*N*-methyl-piperazin-1-yl)-benzoic acid (3a)

To a well-stirred solution of Compound **2** (10.0 g, 0.0284 mol) in ethanol (20 ml), Benzaldehyde (6.2 ml, 0.0568 mol) and acetic acid (1.0 ml) were added. The reaction mixture was refluxed for 4 h at 70-80 ˚C. The progress of reaction was monitored by TLC using toluene: acetone (8:2) as eluent. After the completion of reaction, the refluxed content was dumped in to water. The pH was adjusted to neutral. The crude product was purified by crystallization from ethanol to get the title compound. M.P: 180-200 ˚C.

Preparation of 4-(4-cyano-phenylamino)-2-(4-methyl-piperazin-1-yl)-5-(4-oxo-2-phenyl-thiazolidin-3-yl)-benzoic acid (4a)

Compounds **(3a)** (10 g, 0.0227 mol), thioglycolic acid (5.4 ml, 0.0454 mol) in DMF (20 ml) and anhydrous zinc chloride (6.0 g, 0.0454 mol) were refluxed for 6-8 h. The progress of reaction was monitored by TLC using hexane: ethyl acetate (8:2) as eluent. After the completion of reaction it was poured in to crushed ice. The product obtained was washed with $NaHCO_3$ to remove unreacted acid, filtered, dried and recrystallized from ethanol to get the title compounds. M.P.: 160-162 ˚C

Preparation of 4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)-5-(5-(substituted benzylidene)-4-oxo-2-phenylthiazolidin-3-yl)benzoic acid (5a-5j)

A mixture of Compound **(4a)** (10.0 g, 0.0194 mol) in glacial acetic acid (20.0 ml) buffered with sodium acetate and substituted benzaldehyde (4.5 ml, 0.0388 mol) was refluxed for 4-6 h. The progress of reaction was monitored by TLC using a toluene: acetone (6:2) as eluent. After the completion of reaction, it was poured into crushed ice. The resulting product was filtered and washed with water until neutrality. The crude product was crystallized from methanol to get the title compound.

(5-(5-benzylidene-4-oxo-2-phenylthiazolidin-3-yl)-4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)benzoic acid (5a)

^{1}H NMR: 2.75 (s, 3H), 2.85 (t, 4H), 3.03 (t, 4H), 4.60 (s, 1H), 5.43 (s, 1H), 6.91-7.65 (m, 17H), 9.52 (s, 1H). **IR (KBr cm^{-1}):** 3433 (-OH), 3223 (-NH), 3053 (-CH), 2985-2873 (-CH), 1730, 1666 (-2CO), 1642 (-C=C-), 724 (-C-S). **MS (m/z):** 602.42 (M^+). **Anal. Calcd. For** $C_{35}H_{31}N_5O_3S$: C, 69.80; H, 5.31; N, 11.63, **Found:** C, 69.76; H, 5.28; N, 11.60, **m.p.** 162 ˚C, **Yield:** 73 %.

5-(5-(2-chlorobenzylidene)-4-oxo-2-phenylthiazolidin-3-yl)-4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)benzoic acid (5b)

^{1}H NMR: 2.71 (s, 3H), 2.83 (t, 4H), 3.07 (t, 4H), 4.56 (s, 1H), 5.40 (s, 1H), 6.90-7.69 (m, 16H), 9.59 (s, 1H). **IR (KBr cm^{-1}):** 3431 (-OH), 3223 (-NH), 3052 (-CH), 2980-2872 (-CH), 1734, 1660 (-2CO), 1640 (-C=C-), 825 (C-Cl), 722 (-C-S). **MS (m/z):** 637.22 (M^+). **Anal. Calcd. For** $C_{35}H_{30}ClN_5O_3S$: C, 66.02; H, 4.71; N, 11.00, **Found:** C, 66.05; H, 4.70; N, 11.04, **m.p.** 150 ˚C, **Yield:** 58 %.

5-(5-(3-chlorobenzylidene)-4-oxo-2-phenylthiazolidin-3-yl)-4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)benzoic acid (5c)

^{1}H NMR: 2.73 (s, 3H), 2.84 (t, 4H), 3.05 (t, 4H), 4.52 (s, 1H), 5.45 (s, 1H), 6.96-7.67 (m, 16H), 9.57 (s, 1H). **IR (KBr cm^{-1}):** 3438 (-OH), 3229 (-NH), 3048 (-CH), 2985-2870 (-CH), 1739, 1654 (-2CO), 1641 (-C=C-), 824 (C-Cl), 722 (-C-S). **MS (m/z):** 637.31 (M^+). **Anal. Calcd. For** $C_{35}H_{30}ClN_5O_3S$: C, 66.02; H, 4.73; N, 11.00, **Found:** C, 66.07; H, 4.75; N, 11.01, **m.p.** 147 ˚C, **Yield:** 63 %.

5-(5-(4-chlorobenzylidene)-4-oxo-2-phenylthiazolidin-3-yl)-4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)benzoic acid (5d)

^{1}H NMR: 2.76 (s, 3H), 2.81 (t, 4H), 3.07 (t, 4H), 4.55 (s, 1H), 5.42 (s, 1H), 6.89-7.72 (m, 16H), 9.58 (s, 1H). **IR (KBr cm^{-1}):** 3430 (-OH), 3225 (-NH), 3054 (-CH),

2986-2871 (-CH), 1739, 1662 (-2CO), 1647 (-C=C-), 823 (C-Cl), 725 (-C-S). **MS (m/z):** 637.28 (M^+). **Anal. Calcd. For** $C_{35}H_{30}ClN_5O_3S$: C, 66.02; H, 4.71; N, 11.00, **Found:** C, 66.01; H, 4.66; N, 11.03, **m.p.** 142 °C, **Yield:** 65 %.

4-(4-cyanophenylamino)-5-(5-(2-methylbenzylidene)-4-oxo-2-phenylthiazolidin-3-yl)-2-(4-methylpiperazin-1-yl)benzoic acid (5e)

^{1}H NMR: 2.20 (s, 3H), 2.73 (s, 3H), 2.87 (t, 4H), 3.07 (t, 4H), 4.66 (s, 1H), 5.45 (s, 1H), 6.92-7.66 (m, 16H), 9.52 (s, 1H). **IR (KBr cm^{-1}):** 3437 (-OH), 3225 (-NH), 3058 (-CH), 2987-2877 (-CH), 1735, 1668 (-2CO), 1648 (-C=C-), 728 (-C-S). **MS (m/z):** 616.90 (M^+). **Anal. Calcd. For** $C_{36}H_{33}N_5O_3S$: C, 70.15; H, 5.35; N, 11.36, **Found:** C, 70.12; H, 5.32; N, 11.31, **m.p.** 148 °C, **Yield:** 78 %.

4-(4-cyanophenylamino)-5-(5-(3-methylbenzylidene)-4-oxo-2-phenylthiazolidin-3-yl)-2-(4-methylpiperazin-1-yl)benzoic acid (5f)

^{1}H NMR: 2.25 (s, 3H), 2.73 (s, 3H), 2.86 (t, 4H), 3.02 (t, 4H), 4.68 (s, 1H), 5.43 (s, 1H), 6.87-7.62 (m, 16H), 9.58 (s, 1H). **IR (KBr cm^{-1}):** 3434 (-OH), 3227 (-NH), 3051 (-CH), 2987-2874 (-CH), 1736, 1668 (-2CO), 1647 (-C=C-), 723 (-C-S). **MS (m/z):** 616.84 (M^+). **Anal. Calcd. For** $C_{36}H_{33}N_5O_3S$: C, 70.15; H, 5.35; N, 11.36, **Found:** C, 70.12; H, 5.30; N, 11.32, **m.p.** 144 °C, **Yield:** 72 %.

4-(4-cyanophenylamino)-5-(5-(4-methylbenzylidene)-4-oxo-2-phenylthiazolidin-3-yl)-2-(4-methylpiperazin-1-yl)benzoic acid (5g)

^{1}H NMR: 2.23 (s, 3H), 2.71 (s, 3H), 2.84 (t, 4H), 3.07 (t, 4H), 4.64 (s, 1H), 5.48 (s, 1H), 6.97-7.63 (m, 16H), 9.57 (s, 1H). **IR (KBr cm^{-1}):** 3433 (-OH), 3227 (-NH), 3057 (-CH), 2984-2878 (-CH), 1732, 1667 (-2CO), 1644 (-C=C-), 721 (-C-S). **MS (m/z):** 616.89 (M^+). **Anal. Calcd. For** $C_{36}H_{33}N_5O_3S$: C, 70.15; H, 5.35; N, 11.36, **Found:** C, 70.10; H, 5.31; N, 11.39, **m.p.** 145 °C, **Yield:** 70 %.

4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)-5-(5-(2-nitrobenzylidene)-4-oxo-2-phenylthiazolidin-3-yl)benzoic acid (5h)

^{1}H NMR: 2.71 (s, 3H), 2.84 (t, 4H), 3.03 (t, 4H), 4.63 (s, 1H), 5.46 (s, 1H), 6.89-8.13 (m, 16H), 9.50 (s, 1H). **IR (KBr cm^{-1}):** 3435 (-OH), 3223 (-NH), 3058 (-CH), 2984-2876 (-CH), 1733, 1666 (-2CO), 1642 (-C=C-), 1548, 1370 (N-O), 724 (-C-S). **MS (m/z):** 647.92 (M^+). **Anal. Calcd. For** $C_{35}H_{30}N_6O_5S$: C, 64.94; H, 4.63; N, 12.98, **Found:** C, 64.90; H, 4.61; N, 12.95, **m.p.** 160 °C, **Yield:** 69 %.

4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)-5-(5-(3-nitrobenzylidene)-4-oxo-2-phenylthiazolidin-3-yl)benzoic acid (5i)

^{1}H NMR: 2.75 (s, 3H), 2.82 (t, 4H), 3.01 (t, 4H), 4.69 (s, 1H), 5.41 (s, 1H), 6.85-8.10 (m, 16H), 9.54 (s, 1H). **IR (KBr cm^{-1}):** 3432 (-OH), 3226 (-NH), 3055 (-CH), 2987-2873 (-CH), 1732, 1669 (-2CO), 1641 (-C=C-), 1546, 1373 (N-O), 723 (-C-S). **MS (m/z):** 647.89 (M^+). **Anal. Calcd. For** $C_{35}H_{30}N_6O_5S$: C, 64.94; H, 4.63; N, 12.98, **Found:** C, 64.92; H, 4.62; N, 12.92, **m.p.** 166 °C, **Yield:** 65 %.

4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)-5-(5-(4-nitrobenzylidene)-4-oxo-2-phenylthiazolidin-3-yl)benzoic acid (5j)

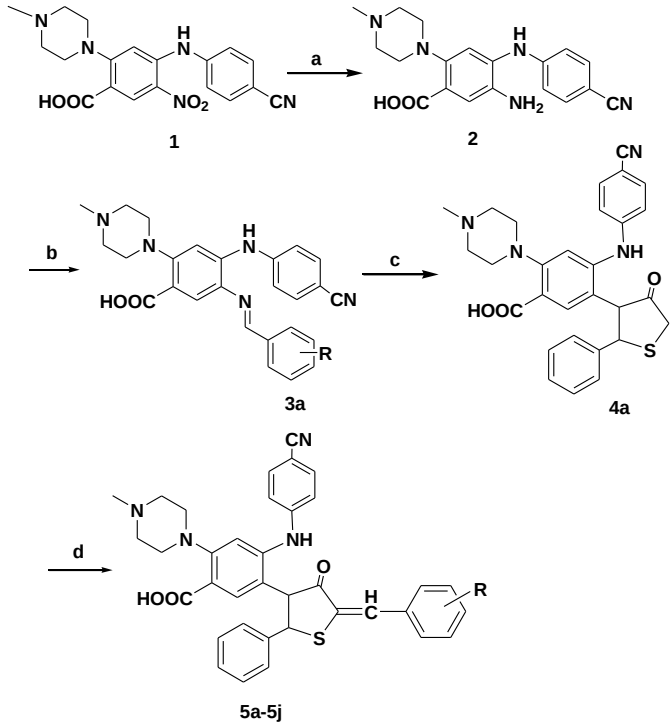
^{1}H NMR: 2.76 (s, 3H), 2.84 (t, 4H), 3.02 (t, 4H), 4.66 (s, 1H), 5.42 (s, 1H), 6.89-8.13 (m, 16H), 9.51 (s, 1H). **IR (KBr cm^{-1}):** 3432 (-OH), 3221 (-NH), 3056 (-CH), 2982-2878 (-CH), 1732, 1664 (-2CO), 1640 (-C=C-), 1542, 1377 (N-O), 723 (-C-S). **MS (m/z):** 647.92 (M^+). **Anal. Calcd. For** $C_{35}H_{30}N_6O_5S$: C, 64.94; H, 4.63; N, 12.98, **Found:** C, 64.90; H, 4.60; N, 12.94, **m.p.** 159 °C, **Yield:** 68 %.

III. RESULTS AND DISCUSSION

Chemistry

Reaction of compound 4-(4-cyano-phenylamino)-2-(4-N-methyl-piperazin-1-yl)-5-nitro- benzoic acid **(1)**

with Fe in acetic acid in ethanol yielded 5-amino-4-(4-cyano-phenylamino)-2-(-4-N-methyl-piperazin-1-yl)-benzoic acid **(2)**. Compound **(2)** reacted with benzaldehyde in presence of acetic acid to form 5-(benzylidene-amino)-4-(4-cyano-phenylamino)-2-(4-N-methyl-piperazin-1-yl)-benzoic acid **(3a)**, which on reaction with thioglycolic acid in presence of zinc chloride in DMF yielded 4-(4-cyano-phenylamino)-2-(4-methyl-piperazin-1-yl)-5-(4-oxo-2-substituted phenyl-thiazolidin-3-yl)-benzoic acid **(4a)**. Compound **(4a)** was refluxed with substituted benzaldehydes in glacial acetic acid in presence of sodium acetate to yield the title compounds 4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)-5-(5-(substituted benzylidene)-4-oxo-2-phenylthiazolidin-3-yl)benzoic acid **(5a-5j) (Scheme 1)**.



Scheme 1. **(a)** Fe/CH_3COOH, Ethanol, 80 ℃ **(b)** Benzaldehyde, Ethanol, 70 ℃ **(c)** Thioglycolic acid, Anhydrous $ZnCl_2$, DMF **(d)** Substituted aryl benzaldehydes, Glacial acetic acid, CH_3COONa, Reflux.

Structures of thiazolidinones **(5a-5j)** were elucidated by IR, ^1H NMR, mass spectroscopy and elemental analysis. The spectra were in full agreement with the proposed structure.

Biological Evaluation

Antibacterial Activity

The minimum inhibitory concentration (MIC) of the synthesized compound were tested against two representative Gram-positive (*Staphylococcus aureus* MTCC 443 and *Staphylococcus pyogenus* MTCC 443) and two Gram-negative (*Escherichia coli* MTCC 442 and *Pseudomonas aeruginosa* MTCC 443) and assayed *in vitro* using broth micro dilution method by standard gradual dilution starting from (250, 200, 125, 100, 50, 25, 12.5, 6.25, 3.125) µg/mL.

Ciprofloxacin and Chloramphenicol were used as reference antibacterial agents. Solution of the test compounds and reference drugs were dissolved in DMSO. The *in vitro* results of the antibacterial activity of the newly synthesized compounds are presented in **Table 1**.

The antibacterial potency of the synthesized compounds was compared with broad spectrum antibiotics, Ciprofloxacin & Chloroamphenicol. From the table, it is observed that some of the compounds displayed moderate to good antibacterial activity in the range of 62.5-125 µg/ml.

Table 1. Antibacterial activity of title compounds.

Compd.	ANTIBACTERIAL ACTIVITY TABLE				
	MINIMUM INHIBITORY CONCENTRATION				
	-R	*E.c* µg/ml	*P.a* µg/ml	*S.a*µg/ml	*S.p* µg/ml
5a	-H	200	500	100	125
5b	2-Cl	500	250	125	200
5c	3-Cl	200	250	125	500
5d	4-Cl	100	125	250	62.5
5e	2-CH_3	250	200	500	500
5f	3-CH_3	200	250	250	250
5g	4-CH_3	200	250	200	125
5h	2-NO_2	500	200	500	500
5i	3-NO_2	250	500	100	250

5j	4-NO_2	200	62.5	200	200
Ciprofloxacin		25	25	50	50
Chloramphenicol		50	50	50	50

Antifungal Activity

The minimum inhibitory concentration (MIC) of the synthesized compound was tested against fungi (*Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323) and assayed *in vitro* using broth micro dilution method standards with gradual dilution starting from (250, 200, 125,100, 50, 25, 12.5, 6.25, 3.125) µg/mL. Nystatin and Greseofulvin were used as reference antibacterial agents. Solution of the test compounds and reference drugs were dissolved in DMSO. The *in vitro* results of the antifungal activity of the newly synthesized compounds are presented in **Table 2**.

Table 2. Antifungal activity of title compounds

Compd.	ANTIFUNGAL ACTIVITY TABLE			
	MINIMUM INHIBITORY CONCENTRATION			
	-R	*C.a.* µg/ml	*A.n.* µg/ml	*A.c.* µg/ml
5a	-H	200	500	1000
5b	2-Cl	500	1000	500
5c	3-Cl	1000	1000	250
5d	4-Cl	1000	500	250
5e	2-CH_3	500	1000	200
5f	3-CH_3	250	500	250
5g	4-CH_3	250	500	500
5h	2-NO_2	500	1000	1000
5i	3-NO_2	250	1000	500
5j	4-NO_2	200	250	500
Nystatin		100	100	100
Griseofulvin		500	100	100

IV. CONCLUSION

A facile method for the synthesis of diversely functionalized thiazolidinones was developed. The newly synthesized thiazolidinones exhibited good to moderate antibacterial and antifungal activity. Further structural modifications of the compounds may prove as lead structures for the development of agents with higher antimicrobial activity.

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