Asian Journal of Chemistry; Vol. 31, No. 9 (2019), 1913-1918

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2019.22002

Design and Synthesis of *Bis*-pyrimidines Linked with Thiazolidin-4-one as New Antibacterial Agents

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Received: 15 February 2019; *Accepted*: 9 April 2019; *Published online*: 31 July 2019; AJC-19476

A series of novel 3-4-[2-hydroxy-5-(4-hydroxy-3-2-[2-(aryl)-4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinylbenzyl)phenyl]-6-phenyl-2-pyrimidinyl-2-(aryl)-1,3-thiazolan-4-ones **5(a-j)** have been synthesized and assayed for their antibacterial activity against *B. subtilis*, *B. sphaericus, S. aureus, P. aeruginosa*, *K. Aerogenes* and *C. violaceum.* The inhibition zones and minimal inhibitory concentrations were measured and compared with the streptomycin. The antibacterial screening data reveal that the compounds containing 4-nitrophenyl (**5c**), 3-nitrophenyl (**5d**), 4-dimethylaminophenyl (**5g**) and 1,3-benzodioxole (**5j**) moiety at 2-position of the thiazolidin-4-one ring exhibited potent inhibitory activity towards all the tested microorganism, which is higher than streptomycin. The other compounds also showed moderate to good activity.

Keywords: *Bis*-heterocycles, Thiazolidin-4-one, Pyrimidine, Antibacterial activity.

INTRODUCTION

The heterocyclic compounds participate in important biochemical processes and are the constituents of main substances in living cells [1] and comprises the core of the active moiety or pharmacophore. An especially more attention is given to nitrogen and sulphur containing heterocyclic compounds, as they possess a broad spectrum of biological activities and are used in various fields of pharmacy [2]. Various natural products and biologically active synthetic compounds have five member, nitrogen and sulphur containing heterocyclic ring in their structures [3], such important class of compound is thiazolidn-4-one [4], this nucleus appears in the structure of thiamine [5], penicillin [6], antibiotics such as micrococcin [7], compounds possessing cardiac and glycemic benefit such as troglitazone [8] and many metabolic products of fungi and primitive marine animals, including 2-(aminoalkyl)-thiazole-4-carboxylic acids [9]. This moiety can also be found in various well known drugs with the desired therapeutic uses [10] and shows considerable physiological effects such as sedative [11], antiinflammatory [12], antibacterial [13], antifungal [14], antitubercular [15], analgesic and hypothermic [16], local [17] and spinal [18] anesthetic, CNS stimulant [19], anti-HIV [20] and nematicidal [21]. Further, thiazolidinones have also been used for the treatment of cardiac diseases [22], diabetic complications like cataracts, nephropathy and neuropathy [23] and selective antiplatelet activating factor [24].

Similarly, pyrimidine and its derivatives have a unique place and have contributed significantly to biological and medicinal fields [25] such as antitubercular [26], calcium channel blockers [27] and also many pyrimidines have displayed diverse pharmaceutical activities [28] depending upon the geometry and type of substituents attached to the ring [29]. 3-Azido-3-deoxythymidine (AZT) [30] a pyrimidine derivative has been found to be a potent antiviral agent against HIV type 1 *in vitro* and has found to decrease mortality and opportunistic infections in patients with AIDS.

Further, inspite of a large number of antibiotics and chemotherapeutic agents available for medical use, but the treatment of infectious diseases still challenging problem [31] because of emerging infectious diseases [32] and the microbial pathogens have turning out to be more resistant towards antibiotics/chemotherapeutics [33], resulted a significant universal health failure [34]. Therefore, the broad spectrum potency is preferred for newly found antimicrobial agents. The recent efforts have been made towards the investigation of more potential anti-

microbial agents [35]. Further, the synthesis of a variety of *bis*-heterocyclic compounds has received great attention [36] not only as main chain polymers but also because of many biologically active natural [37] and synthetic products have molecular symmetry [38]. Thus, *bis*-heterocyclic compounds may avoid the microbial resistance. In the synthesis of *bis*-heterocyclics, researchers have tried to extend various existing methods by using a broad range of protocols to improve the scope and limitations regarding their yield, purity and biological applications [39].

Owing to the immense importance and varied biological activities exhibited by thiazolidin-4-one and pyrimidine and in continuation of our ongoing research on biologically active *bis*-heterocyclic compounds [39-41], it was considered to synthesize the *bis*-heterocyclic compounds containing thiazolidin-4-one and pyrimidine moieties in one molecule for enhancing biological activity (Fig. 1). In the present study, the synthesis of novel 3-4-[2-hydroxy-5-(4-hydroxy-3-2-[2-(aryl)-4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinylbenzyl)phenyl]-6-phenyl-2-pyrimidinyl-2-(aryl)-1,3-thiazolan-4-ones **5(a-j)** with a view to explore their potential biological activity. The antibacterial activity of the compounds has also been evaluated.

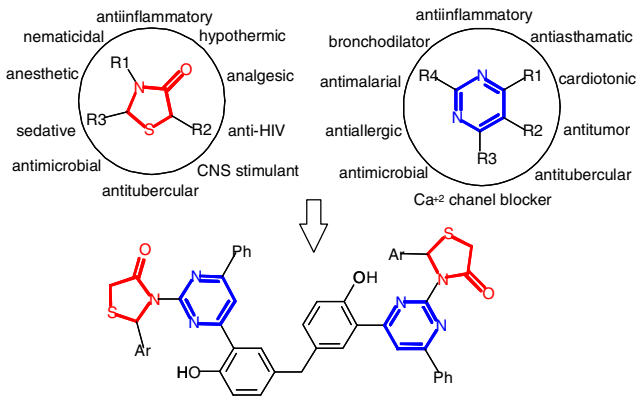


Fig. 1. Title compounds containing thiazolidin-4-one and pyrimidine moieties

EXPERIMENTAL

All the chemicals and solvents were of commercial grade and were used as supplied or were prepared according to procedures described in literature. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel F_{254} plates from Merck and compounds visualized either by exposure to UV light. Melting points were determined in open capillary tube on a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded using KBr disk on a Perkin-Elmer FTIR spectrometer. The NMR spectra were recorded on a Varian Gemini spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C NMR. Mass spectra were recorded on a VG micro mass 7070H spectrometer. Structures of all the newly synthesized compounds were assigned on the basis of their spectral data.

Preparation of 5-(3-formyl-4-hydroxybenzyl)-2-hydroxybenzaldehyde (2): Trioxane (0.2 mol) was dissolved to the solution of salicylaldehyde (**1**) (0.65 mol in 50 mL of glacial acetic acid). To this a mixture of 0.5 mL of conc. sulfuric acid and 2.5 mL of glacial acetic acid was added slowly with stirring in a nitrogen atmosphere at a temperature of ≈ 90 °C. This temperature was maintained for 24 h, while stirring solution. The reaction mixture was then poured into ice-cold water and allowed to stand overnight. The deposited solid was filtered and extracted twice with ether and the solid obtained was purified by crystallization in acetone to give pure compound **2** as white solid in 62 % yield, m.p.132-134. IR (KBr, ν_{max}, cm^{-1}): 3435, 2736, 1665, 843, 813; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.99 (s, 2H, CH_2), 7.32 (m, 4H, ArH), 7.40 (d, J = 8.1 Hz, 2H, ArH), 9.93 (s, 2H, CHO), 10.9 (s, 2H, OH); MS: *m/z* 256 (M^+), 227, 181, 152, 135, 77.

Preparation of (*E*)-3-(2-hydroxy-5-4-hydroxy-3-[(*E*)-3-oxo-3-phenyl-1-propenyl]benzylphenyl)-1-phenyl-2-propen-1-one (3): A solution of compound **2** (0.01 mol) and acetophenone (0.02 mol) in 20 mL of ethanol was treated with 20 mL of 60 % KOH solution at 5-10 °C. The reaction mixture was stirred at room temperature for 5 h. It was then diluted with water (50 mL) and extracted with diethyl ether (3 × 20 mL). The aqueous solution was acidified with dilute HCl. The solid obtained was filtered, washed thoroughly with water, dried the crude product and purified by crystallization from benzene: MeOH (3:2) to give pure **3** in 70 % of yield, m.p. 108-109 °C. IR (KBr, ν_{max}, cm^{-1}): 3439, 3055, 1641, 1571, 1487, 1223; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.84 (s, 2H, CH_2), 7.15 (d, J = 16.4 Hz, 2H, α-H), 7.65-7.85 (m, 16H, ArH), 8.04 (d, J = 16.4 Hz, 2H, b-H), 10.18 (s, 2H, OH); MS: *m/z* 460 (M^+).

Preparation of 2-(2-amino-6-phenyl-4-pyrimidinyl)-4-[3-(2-amino-6-phenyl-4-pyrimidinyl)-4-hydroxybenzyl]-phenol (4): A solution of compound **3** (0.01 mol) and guanidine hydrochloride (0.03 mol) in 20 mL ethanol was added 5 mL of aqueous NaOH (0.02 mol). The reaction mixture was refluxed. TLC (EtOAc:petroleum-ether, 2:1) showed that the reaction was complete in 6 h. The reaction mixture was poured in 50 mL of 10 % cold HCl solution and the precipitate was filtered, washed with water, until free from acid and on recrystallized from benzene-ethanol to give pure compound **4** in 69 % of yield, m.p. 211-213 °C. IR (KBr, ν_{max}, cm^{-1}): 3320, 3025, 2587, 1641, 1487; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.10 (s, 2H, CH_2), 4.85 (bs, 2H, OH), 5.95 (bs, 4H, NH_2), 6.98 (s, 2H, ArH), 7.00 (d, J = 8.4 Hz, 2H, ArH), 7.30 (d, J = 8.4 Hz, 2H, ArH), 7.50-7.60 (m, 10H, ArH), 7.90 (d, J = 7.6 Hz, 2H, ArH); MS: *m/z* 538 (M^+).

General procedure for the synthesis of 3-4-[2-hydroxy-5-(4-hydroxy-3-2-[2-(aryl)-4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinylbenzyl)phenyl]-6-phenyl-2-pyrimidinyl-2-(aryl)-1,3-thiazolan-4-one 5(a-j): To a stirred mixture of compound **4** (0.01 mol), aryl/heteryl aldehyde (0.02 mol) and thioglycolic acid (0.02 mol) in dry toluene (20 mL), $ZnCl_2$ (0.02 mol) was added and refluxed for 5 h at 110 °C. After cooling, the filtrate was concentrated to dryness under reduced pressure and the residue was taken-up in ethyl acetate. The ethyl acetate layer was washed with brine, 5 % sodium bicarbonate solution and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness at reduced pressure; the crude product thus obtained was purified by column chromatography on silica gel with hexane-ethyl acetate as eluent to get the pure compounds.

3-4-[2-Hydroxy-5-(4-hydroxy-3-2-[2-(4-methylphenyl)-4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinylbenzyl)-

phenyl]-6-phenyl-2-pyrimidinyl-2-(4-methylphenyl)-1,3-thiazolan-4-one (5a): Yield: 52 %, m.p. 149-151 °C; IR (KBr, ν_{max}, cm^{-1}): 3345, 3037, 2970, 1675, 1496, 783, 674; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.18 (s, 6H, CH_3), 3.50-3.60 (m, 4H, CH_2-S), 3.98 (s, 2H, CH_2), 5.20 (s, 2H, OH), 5.82 (s, 2H, N-CH-S), 6.70 (s, 2H, ArH), 7.20-7.40 (m, 22H, ArH), 7.60 (s, 2H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 31.0, 34.3, 42.1, 57.4, 110.8, 111.4, 118.1, 122.5, 123.1, 124.2, 128.1, 130.8, 131.0, 134.7, 141.9, 149.0, 152.7, 158.3, 162.7, 174.7; MS: *m/z* 892 (M^+).

2-(4-Chlorophenyl)-3-4-[5-(3-2-[2-(4-chlorophenyl)4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinyl-4-hydroxybenzyl)-2-hydroxyphenyl]-6-phenyl-2-pyrimidinyl-1,3-thiazolan-4-one (5b): Yield: 49 %, m.p. 160-162 °C; IR (KBr, ν_{max}, cm^{-1}): 3340-3300, 3032, 1698, 1603, 1597, 712, 687; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.67-3.70 (m, 4H, CH_2-S), 4.12 (s, 2H, CH_2), 5.20 (s, 2H, OH), 5.86 (s, 2H, N-CH-S), 6.84 (s, 2H, ArH), 7.20-7.35 (m, 16H, ArH), 7.55-7.60 (m, 8H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.3, 42.1, 67.5, 110.7, 111.6, 118.9, 126.3, 127.7, 128.1, 128.9, 130.5, 131.8, 132.0, 134.7, 138.4, 141.2, 154.3, 157.3, 158.3, 162.2, 173.6; MS: *m/z* 932 (M^+).

3-4-[2-Hydroxy-5-(4-hydroxy-3-2-[2-(4-nitrophenyl)-4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinylbenzyl)-phenyl]-6-phenyl-2-pyrimidinyl-2-(4-nitrophenyl)-1,3-thiazolan-4-one (5c): Yield: 45 %, m.p. 195-197 °C; IR (KBr, ν_{max}, cm^{-1}): 3340-3300, 3035, 1699, 1603, 1596, 1520, 1370, 710, 686; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.67-3.70 (m, 4H, CH_2-S), 4.12 (s, 2H, CH_2), 5.09 (s, 2H, OH), 5.86 (s, 2H, N-CH-S), 6.84 (s, 2H, ArH), 7.20-7.35 (m, 12H, ArH), 7.55-7.60 (m, 12H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.4, 42.2, 67.5, 110.8, 111.5, 117.4, 122.3, 127.1, 127.9, 128.7, 130.8, 131.0, 137.5, 141.8, 142.0, 144.8, 154.3, 157.3, 158.3, 162.2, 174.1; MS: *m/z* 954 (M^+).

3-4-[2-Hydroxy-5-(4-hydroxy-3-2-[2-(3-nitrophenyl)-4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinylbenzyl)-phenyl]-6-phenyl-2-pyrimidinyl-2-(3-nitrophenyl)-1,3-thiazolan-4-one (5d): Yield: 54 %, m.p. 190-192 °C; IR (KBr, ν_{max}, cm^{-1}): 3342-3300, 3062, 2980, 1689, 1600, 1595, 1517, 1365, 714, 685; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.67-3.70 (m, 4H, CH_2-S), 4.10 (s, 2H, CH_2), 5.11 (s, 2H, OH), 5.94 (s, 2H, N-CH-S), 6.84 (s, 2H, ArH), 7.20-7.35 (m, 10H, ArH), 7.55-7.60 (m, 10H, ArH), 8.00-8.05 (m, 4H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.4, 42.1, 67.1, 110.8, 111.7, 118.1, 119.8, 122.4, 126.1, 127.1, 130.8, 131.0, 132.1, 132.9, 138.0, 139.0, 141.9, 147.2, 154.3, 157.3, 158.9, 161.2, 173.5; MS: *m/z* 954 (M^+).

3-4-[2-Hydroxy-5-(4-hydroxy-3-2-[2-(4-hydroxyphenyl)-4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinylbenzyl)-phenyl]-6-phenyl-2-pyrimidinyl-2-(4-hydroxyphenyl)-1,3-thiazolan-4-one (5e): Yield: 42 %, m.p. 182-184 °C; IR (KBr, ν_{max}, cm^{-1}): 3400-3320, 3047, 2922, 1695, 1603, 1595, 715, 689; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.67-3.70 (m, 4H, CH_2-S), 4.11 (s, 2H, CH_2), 5.17 (s, 2H, OH), 5.27 (s, 2H, OH), 5.85 (s, 2H, N-CH-S), 6.84-6.90 (m, 6H, ArH), 7.20-7.35 (m, 12H, ArH), 7.55-7.60 (m, 8H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.4, 42.1, 67.0, 111.8, 112.4, 115.1, 118.1, 126.1, 127.7, 128.1, 129.9, 130.5, 131.0, 137.6, 141.9, 154.3, 157.3, 157.7, 158.3, 161.2, 173.4; MS: *m/z* 896 (M^+).

3-4-[2-Hydroxy-5-(4-hydroxy-3-2-[2-(2-hydroxyphenyl)-4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinylbenzyl)-phenyl]-6-phenyl-2-pyrimidinyl-2-(2-hydroxyphenyl)-1,3-thiazolan-4-one (5f): Yield: 47 %, m.p. 180-182 °C; IR (KBr, ν_{max}, cm^{-1}): 3400-3300, 30427, 2922, 1696, 1600, 1592, 717, 685; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.67-3.70 (m, 4H, CH_2-S), 4.12 (s, 2H, CH_2), 5.20 (s, 2H, OH), 5.87 (s, 2H, OH), 5.96 (s, 2H, N-CH-S), 6.84-6.90 (m, 6H, ArH), 7.20-7.35 (m, 12H, ArH), 7.55-7.60 (m, 8H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.5, 42.1, 60.7, 110.4, 111.4, 117.2, 118.1, 121.2, 122.0, 125.8, 126.0, 126.7, 128.1, 130.8, 132.0, 138.7, 141.2, 152.8, 154.3, 157.3, 157.2, 161.2, 174.1; MS: *m/z* 896 (M^+).

2-[4-(Dimethylamino)phenyl]-3-(4-5-[3-(2-2-[4-(dimethylamino)phenyl]-4-oxo-1,3-thiazolan-3-yl-6-phenyl-4-pyrimidinyl)4-hydroxybenzyl]2-hydroxyphenyl-6-phenyl-2-pyrimidinyl)1,3-thiazolan-4-one (5g): Yield: 55 %, m.p. 196-198 °C; IR (KBr, ν_{max}, cm^{-1}): 3400-3300, 3042, 2965, 1698, 1599, 1592, 716, 686; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.91 (s, 12H, N-CH_3), 3.67-3.70 (m, 4H, CH_2-S), 4.10 (s, 2H, CH_2), 5.18 (s, 2H, OH), 5.82 (s, 2H, N-CH-S), 6.70-6.80 (s, 6H, ArH), 7.20-7.35 (m, 12H, ArH), 7.55-7.60 (m, 8H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.4, 42.1, 43.8, 67.4, 110.8, 111.4, 112.0, 117.8, 126.1, 127.8, 129.1, 130.8, 131.3, 132.0, 138.7, 142.3, 142.9, 153.8, 157.3, 158.3, 162.4, 174.5; MS: *m/z* 950 (M^+).

3-4-[2-Hydroxy-5-(4-hydroxy-3-2-[2-(4-hydroxy-3-methoxyphenyl)-4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinylbenzyl)phenyl]-6-phenyl-2-pyrimidinyl-2-(4-hydroxy-3-methoxyphenyl)-1,3-thiazolan-4-one (5h): Yield: 58 %, m.p. 177-179 °C; IR (KBr, ν_{max}, cm^{-1}): 3350-3300, 2967, 1697, 1598, 1590, 1067, 716, 686; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.67-3.70 (m, 4H, CH_2-S), 3.82 (s, 6H, OCH_3), 4.11 (s, 2H, CH_2), 5.04 (s, 2H, OH), 5.19 (s, 2H, OH), 5.83 (s, 2H, N-CH-S), 6.84-6.90 (m, 4H, ArH), 7.15-7.30 (m, 12H, ArH), 7.50-7.60 (m, 8H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.4, 42.1, 56.7, 70.1, 110.1, 111.8, 112.4, 118.1, 119.0, 120.3, 126.1, 127.1, 130.8, 131.7, 132.8, 137.5, 141.9, 146.3, 148.1, 154.3, 156.9, 158.3, 161.2, 173.9; MS: *m/z* 956 (M^+).

2-(2-Furyl)-3-4-[5-(3-2-[2-(2-furyl)-4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinyl-4-hydroxybenzyl)-2-hydroxyphenyl]-6-phenyl-2-pyrimidinyl-1,3-thiazolan-4-one (5i): Yield: 60 %, m.p. 210-212 °C; IR (KBr, ν_{max}, cm^{-1}): 3400-3300, 3039, 1694, 1600, 1594, 1592, 1030, 715, 682; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.67-3.70 (m, 4H, CH_2-S), 4.10 (s, 2H, CH_2), 5.18 (s, 2H, OH), 5.98 (s, 2H, N-CH-S), 6.20-6.30 (m, 4H, ArH), 6.84 (s, 2H, ArH), 7.20-7.35 (m, 8H, ArH), 7.55-7.60 (m, 10H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.4, 42.1, 61.3, 104.5, 110.8, 111.0, 112.0, 118.1, 126.1, 127.1, 130.8, 131.0, 136.9, 141.9, 144.7, 153.9, 157.3, 158.3, 160.4, 161.0, 174.0; MS: *m/z* 842 (M^+).

2-(1,3-Benzodioxol-5-yl)-3,4-[5-(3-2-[2-(1,3-benzodioxol-5-yl)-4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinyl-4-hydroxybenzyl)-2-hydroxyphenyl]-6-phenyl-2-pyrimidinyl-1,3-thiazolan-4-one (5j): Yield: 57 %, m.p. 164-166 °C; IR (KBr, ν_{max}, cm^{-1}): 3400-3300, 3042, 1695, 1603, 1592, 1120, 717, 682; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.67-3.70 (m, 4H, CH_2-S), 4.11 (s, 2H, CH_2), 5.65-5.70 (m, 4H, O-CH_2-O), 5.85 (s, 2H, N-CH-S), 6.80-6.90 (m, 6H, ArH), 7.20-7.35 (m,

10H, ArH), 7.50-7.60 (m, 8H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.4, 42.1, 68.4, 100.6, 108.3, 110.8, 111.4, 113.1, 118.1, 121.1, 126.1, 128.1, 130.8, 131.0, 134.0, 138.7, 141.9, 145.6, 147.3, 154.3, 157.3, 158.3, 161.2, 174.7; MS: *m/z* 952 (M^+).

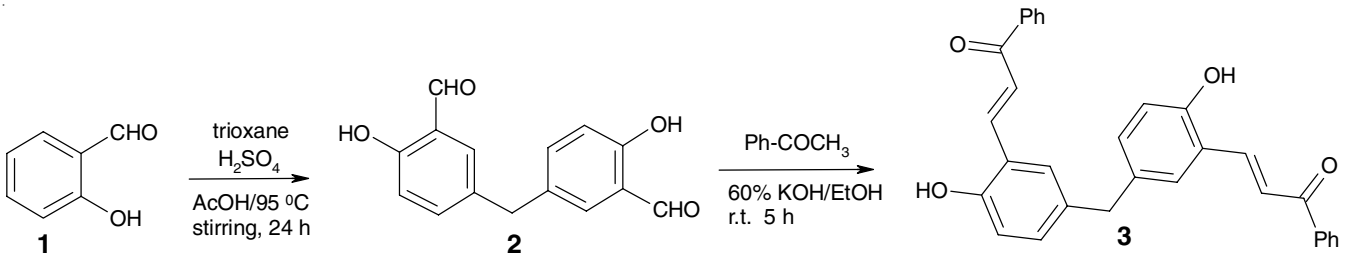
RESULTS AND DISCUSSION

The most general and widely employed synthetic route to pyrimidine involves the combination of a reagent containing the N-C-N skeleton with C-C-C unit. There are typical examples of *bis*-nucleophile with *bis*-electrophile method of constructing heterocycles. Both the nitrogens of the N-C-N reagent act as nucleophiles and both the terminal carbon atoms of C-C-C reagent are electrophiles. Urea and thiourea are the most commonly used N-C-N reagent and chalcones are typically C-C-C substrates. Method which involves the reaction of guanidine hydrochloride with chalcone has been adopted for the synthesis of pyrimidine derivatives, because, the synthesis and purification of the required starting materials *i.e*. chalcones is easy and they are stable. Further, these pyrimidine derivatives are cyclo-condensed with the thioglycolic acid and aldehydes to get the title compounds.

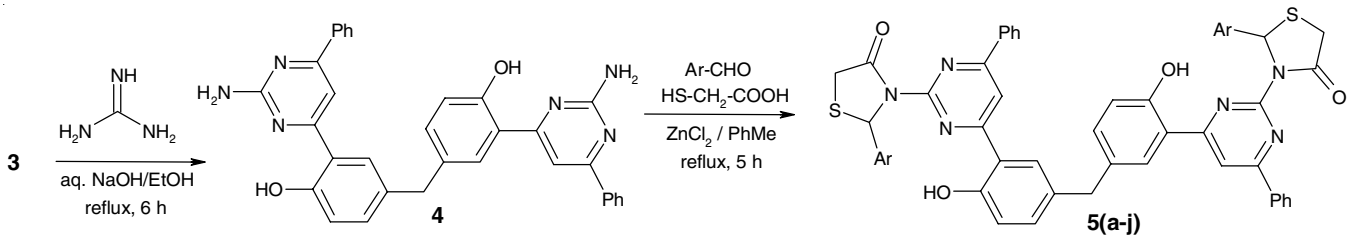
Condensation of salicylaldehyde (**1**) with trioxane in the presence of a mixture of conc. sulphuric acid and acetic acid at 95 °C with stirring for 24 h gave 5-(3-formyl-4-hydroxybenzyl)-2-hydroxybenzaldehyde (**2**) in 62 % yield [42]. The condensation of compound **2** with acetophenone in ethanol in the presence of 60 % aqueous potassium hydroxide at room temperature for 5 h to give (*E*)-3-(2-hydroxy-5-4-hydroxy-3-[(*E*)-3-oxo-3-phenyl-1-propenyl]benzylphenyl)-1-phenyl-2-propen-1-one (**3**) in 70 % yield [43] (**Scheme-I**). The crude product contaminated by some starting materials was purified by extracting with ether. When aqueous layer was neutralized with dilute hydrochloric acid, the crude product was separated out, which was purified by crystallization from benzene: methanol in 3:2 ratio. The products showed orange red colour with concentrated sulfuric acid, which is a characteristic feature of chalcones. Structures of compounds were confirmed by their EI mass, IR, ^{1}H NMR and ^{13}C NMR spectral data.

The IR spectrum of compound **2** showed the absorption band at 2736, 1665, 813 and a broad band in the 3435 cm^{-1} region. Its protons NMR spectrum showed resonances at δ 10.9 as singlet for two protons corresponding to hydroxyl protons, at δ 9.93 as singlet for two protons of carboxyl group, at δ 7.40 as doublet, 7.32 as multiplet corresponding to aromatic protons and at δ 3.99 as singlet for two protons corresponding to methylene protons. Its mass spectrum showed a signal at *m/z* 256 corresponding to molecular ion, at *m/z* 227 corresponding to the ion, which resulting by the loss of formyl radical, at *m/z* 181 corresponding the ion resulted subsequent loss of water and carbon monoxide from the molecular ion and the other signals at *m/z* 152, 135 and 77 confirming its structure. The IR spectrum of **3** exhibited a strong absorption band at 1641 cm^{-1} due the carbonyl group and at 3439 cm^{-1} due to hydroxyl group. Its proton NMR spectrum showed a signal at δ 10.18 ppm, as a singlet integrating for two protons assigned to hydroxyl protons, at δ 7.65-7.85 ppm, as a multiplet, for sixteen protons of aromatic, at δ 8.04 ppm, as a doublet with *J* value 16.4 Hz is assigned to β-H, at δ 7.15 ppm, as a doublet with *J* value 16.4 Hz, for two protons is assigned to α-H and at δ 3.84 ppm, as a singlet for two methylene protons. The mass spectrum of compound showed molecular ion peak at *m/z* 460 (77 %).

Further, the cyclocondensation of compound **3** with guanidine hydrochloride in ethanol in the presence of sodium hydroxide at reflux for 6 h, at the end of the reaction, the ethanolic solution was concentrated to half of its volume under reduced pressure and poured into cold 10 % HCl solution. The solid that separated was filtered and on purification by recrystallization from benzene-ethanol gave pure 2-(2-amino-6-phenyl-4-pyrimidinyl)-4-[3-(2-amino-6-phenyl-4-pyrimidinyl)-4-hydroxybenyl]phenol (**4**) in 69 % of yield [44]. The one-pot cyclocondensation of compound **4** with aryl/heteryl aldehyde and thioglycolic acid in the presence of $ZnCl_2$ in toluene at reflux for 5 h to gave 3-4-[2-hydroxy-5-(4-hydroxy-3-2-[2-(4-methylphenyl)-4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinylbenzyl)phenyl]-6-phenyl-2-pyrimidinyl-2-(4-methylphenyl)-1,3-thiazolan-4-one **5(a-j)** in good yields (**Scheme-II**). The



Scheme-I



5: Ar = **a**) 4-methylphenyl; **b**) 4-chlorophenyl; **c**) 4-nitrophenyl; **d**) 3-nitrophenyl; **e**) 4-hydroxyphenyl; **f**) 2-hydroxyphenyl; **g**) 4-dimethylaminophenyl; **h**) 4-hydroxy-3-methoxyphenyl; **i**) 2-furyl; **j**) 1,3-benzoxole

Scheme-II

TABLE-1
ANTIBACTERIAL ACTIVITY OF COMPOUNDS **5(a-j)**

Compounds	Minimum inhibitory concentration in µg/mL (zone of inhibition in mm)*					
	B. subtilis	*B. sphaericus*	*S. aureus*	*P. aeruginosa*	*K. aerogenes*	*C. violaceum*
5a	26 (12)	25 (11)	26 (9)	20 (17)	30 (9)	20 (16)
5b	30 (9)	27 (10)	30 (10)	20 (16)	26 (9)	20 (14)
5c	14 (18)	18 (20)	17 (22)	18 (20)	20 (16)	17 (23)
5d	13 (17)	19 (20)	18 (22)	19 (19)	19 (20)	18 (20)
5e	18 (12)	20 (17)	30 (13)	26 (12)	25 (10)	25 (11)
5f	25 (9)	30 (10)	28 (10)	28 (10)	30 (8)	28 (13)
5g	15 (14)	18 (19)	17 (24)	20 (22)	20 (20)	18 (19)
5h	27 (10)	26 (11)	28 (10)	30 (11)	28 (10)	27 (9)
5i	30 (11)	21 (12)	20 (16)	21 (15)	28 (9)	26 (10)
5j	13 (18)	15 (15)	16 (20)	20 (22)	20 (18)	16 (17)
Streptomycin	15 (15)	19 (17)	18 (20)	20 (18)	20 (16)	18 (20)

*The values in parentheses indicate the zone of inhibition.

structures of compounds were confirmed by its EI mass, IR, ^{1}H NMR and ^{13}C NMR spectral data.

The IR spectrum of compound **4** showed the absorption band corresponding to the -OH and C=N groups at 3320 and 1641 cm^{-1} respectively. Its proton NMR spectrum showed a signal at δ 7.50-7.80 ppm, as a multiplet integrating for ten protons is assigned for aromtic protons, at δ 7.30 as a doublet with *J* value 8.4 Hz, integrating for two protons is assigned for aromatic protons. A singlet signal at δ 6.98 ppm, integrating for two protons is assigned to the aromatic protons, at δ 7.00 as a doublet with *J* value 8.4 Hz, integrating for two protons is assigned for aromatic protons. A signal at δ 5.95 ppm, as a broad singlet for four protons is assigned to -NH_2 protons, at δ 4.85 as a broad singlet for two protons is assigned to -OH group. A singlet signal at δ 4.10 ppm, for two protons is assigned to methylene group. The mass spectrum of compound showed molecular ion peak at *m/z* 538.

The IR spectrum of compound **5a**, disappearance of amine (-NH_2) absorption and the absroption band at 3345 and 1675 cm^{-1} which are charcteristic of -OH and amide C=O stretching vibrations respectively. Its proton NMR spectrum showed signals at δ 7.60, 7.20-7.40 and 6.70 ppm as a singlets, for a total of twenty four aromatic protons, at δ 5.82 and 3.50-3.60 ppm as a singlet and a multiplet, integrating for two and four protons respectively, are assigned to the N-CH-S and CH_2-S groups of thiazolidin-4-one ring. The three singlet signals at δ 5.20, 3.98 and 2.18 ppm, integrating for two, two and six protons, are assigened to the -OH, CH_2 and CH_3 groups respectively. Its ^{13}C NMR spectrum exhibited the prominent signals corresponding to the carbons of thiazolidin-4-one ring observed at δ 34.3, 57.4 and 174.7 ppm and for pyrimidine ring were observed at δ 118.1, 152.7, 158.3 and 162.7 ppm respectively. In summary, all the newly synthesized compounds exhibited satisfactory elemental analyses consistent with the proposed structures.

Antibacterial activity: All the compounds **5(a-j)** were assayed for their antibacterial activity against Gram-positive bacteria *viz*. *Bacillus subtilis*, *Bacillus sphaericus* and *Staphylococcus aureus and* Gram-negative bacteria *viz*. *Pseudomonas aeruginosa*, *Klobsinella aerogenes* and *Chromobacterium violaceum* by disc diffusion method [45]. The inhibition zones and minimal inhibitory concentrations (MIC, µg/mL) were measured and compared with the standard drug streptomycin (Table-1).

The antibacterial screening data reveal that the compounds containing 4-nitrophenyl (**5c**), 3-nitrophenyl (**5d**), 4-dimethylaminophenyl (**5g**) and 1,3-benzodioxole (**5j**) moiety at 2-position of the thiazolidin-4-one ring exhibited potent inhibitory activity towards all the tested microorganism, which is higher than the standard drug streptomycin. Further, the compounds containing 4-methylphenyl (**5a**) and 4-chlorophenyl (**5b**) moiety showed good activity towards *P. aeruginosa* and *C. violaceum*. The compound **5e** containing 4-hydroxyphenyl moiety also showed potent activity towards *B. subtilis* and *B. sphaericus* and the compound **5i** containing 2-furyl moiety, showed good activity towards *B. sphaericus*, *S. aureus* and *P. aeruginosa*.

Conclusion

A series of 3-4-[2-hydroxy-5-(4-hydroxy-3-2-[2-(aryl)-4-oxo-1,3-thiazolan-3-yl]-6-phenyl-4-pyrimidinylbenzyl)-phenyl]-6-phenyl-2-pyrimidinyl-2-(aryl)-1,3-thiazolan-4-ones **5(a-j)** has been synthesized and assayed for their antibacterial activity against Gram-positive and Gram-negative bacteria. The compounds **5c**, **5d**, **5g**, **5i** and **5j** exhibited potent inhibitory activity towards all the tested organisms, higher than that of activity of the standard drug streptomycin, hence could be used as lead compounds for further studies.

ACKNOWLEDGEMENTS

The authors are thankful to the Director, Indian Institute of Chemical Technology, Hyderabad, India, for providing NMR and mass spectral data. Financial assistance from the UGC, New Delhi, India, in the form of UGC-BSR-FF (Ch. S. Reddy) is gratefully acknowledged.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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