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Synthesis and Biological Study of Novel Bis-chalcones, Bis-thiazines and Bis-pyrimidines

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A series of novel bis-chalcones **3** were prepared by the reaction of 5,5'-methylene-bis-salicylaldehyde **2** with various acetophenones, subsequent treatment of **3** with thiourea or guanidine resulted to the corresponding bis-thiazines or bis-pyrimidines in good yields. All the new compounds have been characterized by IR, ^{1}H NMR, MS and elemental analysis. The antibacterial, antifungal and anti-inflammatory activities of the compounds have also been evaluated.

Keywords: Bis-chalcones, Bis-thiazines, Bis-pyrimidines, 5,5'-Methylene-bis-salicylaldehyde

INTRODUCTION

Heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics etc. [1]. Hence, they have attracted considerable attention in the design of biologically active molecules [2]. A practical method for the synthesis of such compounds is of great interest in synthetic organic chemistry. Among the heterocycles, 1,3-thiazines are a class of compounds with biological activity, such as antimicrobial [3], antitumor [4], antioxidant [5], calcium channel modulators [6] and antipyretic [7]. On the other hand, the classes of pyrimidines possess a broad spectrum of biological effectiveness such as antitubercular [8], calcium channel blockers [9], and many classes of chemotherapeutic agents containing pyrimidine nucleus are in clinical use. Apart from these, chalcones have been reported to possess various biological activities such as antibacterial [10], antitumor [11] anticancer [12], and prostaglandin binding [13] properties.

In view of these observations and in continuation of our work on biologically active heterocycles [14] and their increasing importance in pharmaceutical and biological field, it was considered of interest to synthesize some new chemical entities incorporating the two active pharmacophores in a single molecular frame work and to evaluate their biological activities. In this regard, bis-chalcone **3** would be suited for preparing both bis-thiazines **4** and bis-pyrimidines **5**.

EXPERIMENTAL

Apparatus and Chemicals

Melting points were determined on a Fisher-Johns melting point apparatus and were uncorrected. The purity of the compounds was checked using precoated TLC plates (Merck, 60_F-254). The IR spectra were obtained on a Perkin-Elmer BX series FTIR 5000 spectrophotometer, using KBr. The ^{1}H NMR spectra were obtained with a Varian Gemini 300 MHz spectrometer and the chemical shifts were reported as parts per million (δ ppm) using TMS as an internal standard. The mass spectra were obtained on a VG micromass 7070H spectrometer operating at 70 eV. The UV spectra were obtained on a UV-2401 spectrophotometer. Elemental

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analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. All solvents and chemicals were purchased from Sigma-Aldrich chemical company and used without further purification.

Synthesis of Bis[3-[(E)-3(4-bromophenyl)-3-oxo-1-prop enyl]-4-hydroxyphenyl]methane (3e)

A solution of **2** (2.56 g, 0.01 mol) and 4-bromoacetophenone (0.02 mol) in 20 ml of ethanol was treated with 20 ml of 60% KOH solution at 5-10 ºC. The reaction mixture was stirred at room temperature for 4 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 and dried. The crude product was purified by crystallization from benzene: MeOH (3:2). Yellow solid, yield 91%, m.p.: 160-161 ºC; IR (KBr): υ_{max} (cm^{-1}) 3440, 3056, 1571, 1640, 1482, 1224. UV: λ_{max} (nm) (EtOH) 370.5, 304.9, 268.1. ^{1}H NMR (DMSO-d_6): 9.21 (s, 2H), 8.05 (d, J = 9.0 Hz, 4H), 7.82-8.18 (m, 6H), 7.70 (d, J = 16.2 Hz, 2H), 7.18 (d, J = 9.0 Hz, 4H), 6.84 (d, J = 16.2 Hz, 2H), 3.84 (s, 2H). MS: m/z 616 (M^+). Anal. Calcd. for $C_{31}H_{22}Br_2O_4$: C, 60.22; H, 3.59; Br, 25.85. Found: C, 60.12; H, 3.50; Br, 25.61. The other chalcones 3 were prepared by the similar procedure.

General Procedure for the Synthesis of Bis-thiazines (4a-f)

A solution of **3** (0.01 mol) and thiourea (0.03 mol) in 20 ml ethanol was added 5 ml alcoholic KOH (0.02 mol). The reaction mixture was refluxed. TLC (EtOAc: Pet-ether, 2:1) showed that the reaction was completed in 5 h. The reaction mixture was poured in 50 ml of 10% HCl solution (cold) and the precipitate was filtered, washed with water until free from acid and recrystallized from benzene-ethanol gave **4**.

2-(2-Amino-4-phenyl-6H-1,3-thiazin-6-yl)-4-[3-(2-amin o-4-phenyl-6H-1,3-thiazin-6-yl)-4-hydroxybenzyl] phenol (4a). Yellow solid, yield 97%, m.p.: 148-150 ºC; IR (KBr): υ_{max} (cm^{-1}) 3266, 3326, 3040, 1630, 1590, 1471. ^{1}H NMR (DMSO-d_6): 7.65-7.34 (m, 10H), 7.26-7.01 (m, 6H), 5.92 (d, J = 6.07 Hz, 2H), 5.27 (d, J = 6.07 Hz, 2H), 4.10 (s, 2H), 3.92 (s, 2H), 3.81 (bs, 4H). MS: m/z 576 (M^+). Anal. Calcd. for $C_{33}H_{28}N_4O_2S_2$: C, 68.72; H, 4.89; N, 9.71. Found: C, 68.66; H, 4.82; N, 9.66.

2-[2-Amino-4-(4-methoxyphenyl)-6H-1,3-thiazin-6-yl]-4 -{3-[2-amino-4-(4-methoxyphenyl)-6H-1,3-thiazin-6-yl]-4-hydroxybenzyl}phenol (4b). Orange solid, yield 96%, m.p.: 102-103 ºC; IR (KBr): υ_{max} (cm^{-1}) 3274, 3320, 3040, 1626, 1594, 1480, 1122. ^{1}H NMR (DMSO-d_6): 7.54 (d, J = 8.5 Hz, 4H), 7.26-7.00 (m, 6H), 7.10 (d, J = 8.5 Hz, 4H), 5.92 (d, J = 6.07 Hz, 2H), 5.34 (d, J = 6.07 Hz, 2H), 4.10 (s, 2H), 3.92 (s, 2H), 3.81 (bs, 4H), 3.72 (s, 6H). MS: m/z 636 (M^+). Anal. Calcd. for $C_{35}H_{32}N_4O_4S_2$: C, 66.02; H, 5.07; N, 8.80. Found: C, 65.91; H, 5.0; N, 8.52.

2-[2-Amino-4-(4-chlorophenyl)-6H-1,3-thiazin-6-yl]-4-{ 3-[2-amino-4-(4-chlorophenyl)-6H-1,3-thiazin-6-yl]-4-hyd roxybenzyl}phenol (4c). Yellow solid, yield 90%, m.p.: 150-151 ºC; IR (KBr): υ_{max} (cm^{-1}) 3260, 3320, 3035, 1626, 1596, 1486. ^{1}H NMR (DMSO-d_6): 7.62 (d, J = 8.4 Hz, 4H), 7.37 (d, J = 8.4 Hz, 4H), 7.26-7.00 (m, 6H), 5.92 (d, J = 6.07 Hz, 2H), 5.34 (d, J = 6.07 Hz, 2H), 4.10 (s, 2H), 3.92 (s, 2H), 3.81 (bs, 4H). MS: m/z 644 (M^+). Anal. Calcd. for $C_{33}H_{26}Cl_2N_4O_2S_2$: C, 61.39; H, 4.06; N, 8.68. Found: C, 61.21; H, 4.0; N, 8.39.

2-[2-Amino-4-(4-nitrophenyl)-6H-1,3-thiazin-6-yl]-4-{3-[2-amino-4-(4-nitrophenyl)-6H-1,3-thiazin-6-yl]-4-hydrox ybenzyl}phenol (4d). Red solid, yield 97%, m.p.: 142-144 ºC; IR (KBr): υ_{max} (cm^{-1}) 3247, 3327, 3042, 1626, 1592, 1482, 1347, 853. ^{1}H NMR (DMSO-d_6): 8.10 (d, J = 8.5 Hz, 4H), 7.90 (d, J = 8.5 Hz, 4H), 7.26-7.00 (m, 6H), 5.92 (d, J = 6.07 Hz, 2H), 5.34 (d, J = 6.07 Hz, 2H), 4.10 (s, 2H), 3.92 (s, 2H), 3.81 (bs, 4H). MS: m/z 666 (M^+). Anal. Calcd. for $C_{33}H_{26}N_6O_6S_2$: C, 59.45; H, 3.93; N, 12.60. Found: C, 58.92; H, 3.69; N, 12.33.

2-[2-Amino-4-(4-bromophenyl)-6H-1,3-thiazin-6-yl]-4-{ 3-[2-amino-4-(4-bromophenyl)-6H-1,3-thiazin-6-yl]-4-hyd roxybenzyl}phenol (4e). Yellow solid, yield 96%, m.p.: 122-123 ºC; IR (KBr): υ_{max} (cm^{-1}) 3260, 3320, 3038, 1626, 1596, 1480. ^{1}H NMR (DMSO-d_6): 7.52 (d, J = 8.3 Hz, 4H), 7.33 (d, J = 8.3 Hz, 4H), 7.26-7.00 (m, 6H), 5.91 (d, J = 6.07 Hz, 2H), 5.37 (d, J = 6.07 Hz, 2H), 4.10 (s, 2H), 3.87 (s, 2H), 3.80 (bs, 4H). MS: m/z 732 (M^+). Anal. Calcd. for $C_{33}H_{26}Br_2N_4O_2S_2$: C, 53.96; H, 3.57; N, 7.63. Found: C, 53.56; H, 3.52; N, 7.47.

2-[2-Amino-4-(2-chlorophenyl)-6H-1,3-thiazin-6-yl]-4-{ 3-[2-amino-4-(2-chlorophenyl)-6H-1,3-thiazin-6-yl]-4-hyd roxybenzyl}phenol (4f). Yellow solid, yield 90%, m.p.: 128-129 ºC; IR (KBr): υ_{max} (cm^{-1}) 3261, 3326, 3035, 1621, 1592, 1482. ^{1}H NMR (DMSO-d_6): 7.61-7.00 (m, 14H), 5.82 (d, J =

6.07 Hz, 2H), 5.32 (d, J = 6.07 Hz, 2H), 3.90 (s, 2H), 3.87 (s, 2H), 3.79 (bs, 4H). MS: m/z 644 (M^+). Anal. Calcd. for $C_{33}H_{26}Cl_2N_4O_2S_2$: C, 61.39; H, 4.06; N, 8.68. Found: C, 61.22; H, 3.98; N, 8.48.

General Procedure for the Synthesis of Bis-pyrimidines (5a-f)

A solution of **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: Pet-ether, 2:1) showed that the reaction was complete after 6 h. The reaction mixture was poured in 50 ml of 10% HCl solution (cold) and the precipitate was filtered, washed with water until free from acid and recrystallized from benzene-ethanol gave **5**.

4-[3-(2-Amino-4-phenylpyrimidine-6-yl)-4-hydroxybenzyl]-2-(2-amino-4-phynylpyrimidine-6-yl)phenol (5a). Brown solid, yield 81%, m.p.: 117-119 ºC; IR (KBr): υ_{max} (cm^{-1}) 3390, 3027, 2580, 1620, 1470. ^{1}H NMR (DMSO-d_6): 7.81-6.92 (m, 18H), 7.10 (s, 2H), 7.03 (s, 4H), 4.06 (s, 2H). MS: m/z 538 (M^+). Anal. Calcd. for $C_{33}H_{26}N_6O_2$: C, 73.59; H, 4.87; N, 15.60. Found: C, 72.98; H, 4.72; N, 15.34.

4-[3-(2-Amino-4-(4-methoxyphenyl)pyrimidine-6-yl)-4-hydroxybenzyl]-2-(2-amino-4-(4-methoxyphynyl)pyrimidine-6-yl)phenol (5b). Brown solid, yield 86%, m.p.: 162-163 ºC; IR (KBr): υ_{max} (cm^{-1}) 3396, 3045, 2583, 1640, 1470. ^{1}H NMR (DMSO-d_6): 7.96 (d, J = 8.4 Hz, 4H), 7.59-6.87 (m, 8H), 7.10 (s, 2H), 7.03 (s, 4H), 7.00 (d, J = 8.4, 4H), 4.06 (s, 2H). MS: m/z 598 (M^+). Anal. Calcd. for $C_{35}H_{30}N_6O_4$: C, 70.22; H, 5.05; N, 14.04. Found: C, 70.01; H, 4.96; N, 14.01.

4-[3-(2-Amino-4-(4-chlorophenyl)pyrimidine-6-yl)-4-hydroxybenzyl]-2-(2-amino-4-(4-chlorophynyl)pyrimidine-6-yl)phenol (5c). Brown solid, yield 79%, m.p.: 134-136 ºC; IR (KBr): υ_{max} (cm^{-1}) 3395, 3032, 2579, 1640, 1216. ^{1}H NMR (DMSO-d_6): 7.91 (d, J = 8.3 Hz, 4H), 7.59-6.87 (m, 8H), 7.15 (d, J = 8.3 Hz, 4H), 7.10 (s, 2H), 7.03 (s, 4H), 4.06 (s, 2H). MS: m/z 606 (M^+). Anal. Calcd. for $C_{33}H_{24}Cl_2N_6O_2$: C, 65.25; H, 3.98; N, 13.83. Found: C, 65.19; H, 3.88; N, 13.77.

4-[3-(2-Amino-4-(4-nitrophenyl)pyrimidine-6-yl)-4-hydroxybenzyl]-2-(2-amino-4-(4-nitrophynyl)pyrimidine-6-yl)phenol (5d). Red solid, yield 91%, m.p.: 135-136 ºC; IR (KBr): υ_{max} (cm^{-1}) 3389, 30402, 2592, 1637, 1220. ^{1}H NMR (DMSO-d_6): 8.26 (d, J = 8.6 Hz, 4H), 8.12 (d, J = 8.6 Hz, 4H), 7.59-6.89 (m, 8H), 7.10 (s, 2H), 7.03 (s, 4H), 4.06 (s, 2H). MS: m/z 628 (M^+). Anal. Calcd. for $C_{33}H_{24}N_8O_6$: C, 63.05; H, 3.85; N, 17.83. Found: C, 62.96; H, 3.81; N, 17.80.

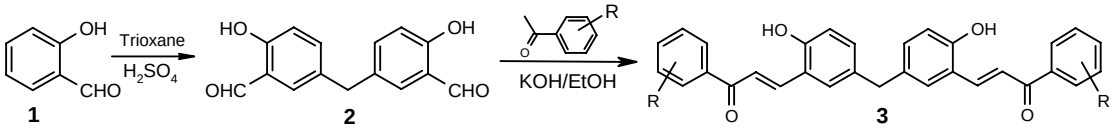
4-[3-(2-Amino-4-(4-bromophenyl)pyrimidine-6-yl)-4-hydroxybenzyl]-2-(2-amino-4-(4-bromophynyl)pyrimidine-6-yl)phenol (5e). Brown solid, yield 83%, m.p.:123-124 ºC; IR (KBr): υ_{max} (cm^{-1}) 3392, 3047, 2587, 1627, 1471. ^{1}H NMR (DMSO-d_6): 7.72 (d, J = 8.1, 4H), 7.69 (d, J = 8.1, 4H), 7.59-6.89 (m, 8H), 7.10 (s, 2H), 7.03 (s, 4H), 4.06 (s, 2H). MS: m/z 694 (M^+). Anal. Calcd. for $C_{33}H_{24}Br_2N_6O_2$: C, 56.92; H, 3.47; N, 12.07. Found: C, 56.83; H, 3.41; N, 12.01.

4-[3-(2-Amino-4-(2-chlorophenyl)pyrimidine-6-yl)-4-hydroxybenzyl]-2-(2-amino-4-(2-chlorophynyl)pyrimidine-6-yl)phenol (5f). Red solid, yield 86%, m.p.: 132-133 ºC; IR (KBr): υ_{max} (cm^{-1}) 3396, 3042, 2595, 1637, 1472. ^{1}H NMR (DMSO-d_6): 7.73-6.9 (m, 16H), 7.10 (s, 2H), 7.03 (s, 4H), 4.06 (s, 2H). MS: m/z 606 (M^+). Anal. Calcd. for $C_{33}H_{24}Cl_2N_6O_2$: C, 65.25; H, 3.98; N, 13.83. Found: C, 65.17; H, 3.87; N, 13.62.

RESULTS AND DISCUSSION

Synthesis of Compounds 2-5

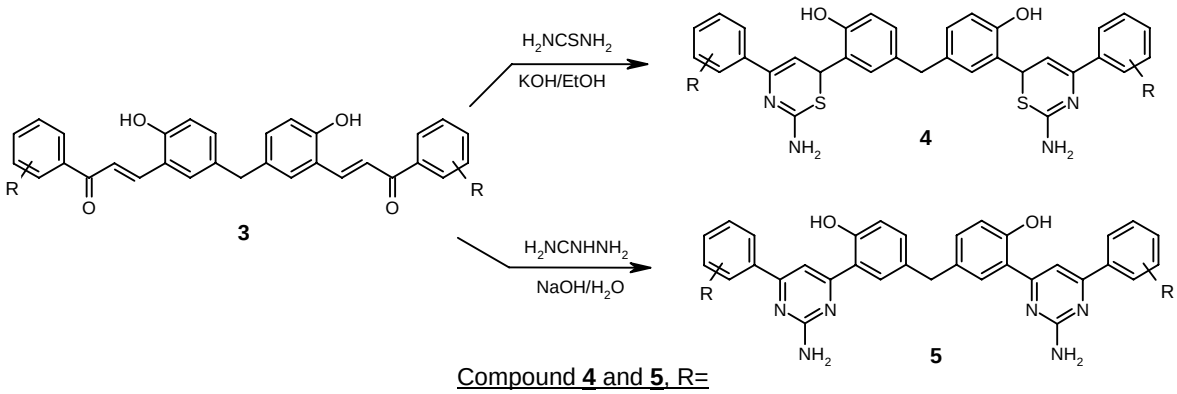
The 5,5'-methylene-bis-salicylaldehyde **2** was prepared by the reaction of salicylaldehyde **1** with trioxane [15]. The bis-chalcone **3** was synthesized by Claisen condensation of acetophenones with 5,5'-methylene-bis-salicylaldehyde **2** in ethanol in the presence of aqueous KOH at room temperature (Scheme 1). The reaction time as well as the yield varies depending on the corresponding reagents. The crude product was contaminated with some starting materials which could easily be removed by extracting with ether. Compound **3** reacted with thiourea in the presence of alcoholic KOH to get the corresponding bis-thiazine **4** in excellent yields and with guanidine hydrochloride in the presence of aqueous NaOH to get the corresponding bis-pyrimidine **5** (Scheme 2). The compounds have low solubility in most common solvents. They were purified in small quantities by crystallizing the solid products in appropriate amounts of ethyl alcohol/ benzene. The structures of the synthesized compounds were confirmed by IR, ^{1}H NMR, MS and elemental analyses and further screened for their antibacterial, antifungal and anti-inflammatory activities.



Compound **3**, R=

a) H d) 4-NO_2
b) 4-OMe e) 4-Br
c) 4-Cl f) 2-Cl

Scheme 1



Compound **4** and **5**, R=

a) H d) 4 -NO_2
b) 4-OMe e) 4-Br
c) 4-Cl f) 2-Cl

Scheme 2

Antimicrobial Activity

The compounds **4a-f** and **5a-f** were screened for their antibacterial activity against human pathogenic bacteria *Escherichia coli, Staphylococcus aureus* and *Bacillus subtilis*. The minimum inhibition concentration (MIC) was determined using the tube dilution method [16]. DMF was used as a blank and streptomycin/neomycin was used as antibacterial standard. The antibacterial activity was compared with the known antibiotic streptomycin/neomycin and the results are given in Table 1.

An examination of the data reveals that all the compounds showed antibacterial activity ranging from 25 to 100 μg ml^{-1}. The compounds **4b**, **5b** were highly active against all the three organisms employed. Compounds **4e**, **5e**, and **5f** were highly active against *E. coli, S. aureus* and compound **4f** is highly active against *E. coli*, *B. subtilis* and compound **5c** is highly active against *S. aureus* and *B. subtilis*. The compound **4a** is almost inactive against all the three organisms employed. From the screened results, it is observed that the presence of methoxy/chloro group at the phenyl ring increases the antibacterial activity. The activity is maximum in a compound with methoxy group at 4^{th} position.

Antifungal Activity

The compounds **4a-f** and **5a-f** were also screened for their antifungal activity against *Candida albicans* at 160, 320, 480 and 640 μg ml^{-1} concentration using Agar plate technique [17]. The antifungal activity was compared with the known antibiotic fluconazole and the results are presented in Table 2. The compounds **4e** and **5b** are highly active against *C.*

Table 1. Antibacterial Activity of **4** (**a-f**) and **5** (**a-f**) (Minimum Inhibitory Concentration)

Compound	Antibacterial activity (MIC; μg ml^{-1})		
	E. coli	*S.aureus*	*B.subtilis*
4a	100	-	-
4b	25	25	25
4c	25	75	50
4d	50	100	100
4e	25	25	50
4f	25	50	25
5a	75	100	-
5b	25	25	25
5c	50	25	25
5d	75	50	-
5e	25	25	50
5f	25	25	75
Streptomycin	10	10	10
Neomycin	30	30	30

Table 2. Antifungal Activity of **4** (**a-f**) and **5** (**a-f**) Spore Germination Inhibition (%) at Different Concentrations Against *Candida Albicans*

Compound	Concentration (μg ml^{-1})			
	160	320	480	640
4a	23.4	26.2	28.0	29.0
4b	45.4	79.1	89.5	91.0
4c	42.0	49.4	83.1	90.0
4d	19.6	27.0	29.0	31.2
4e	79.0	84.0	87.0	88.4
4f	77.1	79.3	81.0	86.5
5a	68.2	74.1	82.1	86.4
5b	82.4	86.4	87.6	92.3
5c	71.3	78.2	79.4	87.6
5d	59.7	65.2	69.9	72.1
5e	77.3	78.0	81.0	84.0
5f	75.1	78.7	80.3	83.2
Fluconazole	84.0	87.0	95.0	98.0

albicans. Remaining compounds showed moderate activity.

Acute Anti-inflammatory Activity

The compounds were tested for acute toxicity in Albino mice and observed for gross behavioral changes. The behavior of all the animals was normal, neither any gross behavioral changes nor nay serious toxicity could be recorded even up to a dose of 600 mg/kg. Compounds (**4b**, **5b**, **4c**, **5c**) were screened for their anti-inflammatory activity using rat paw edema method as described by Winter *et al*. [18]. Ibuprofen was used as standard anti-inflammatory drug. These compounds showed 22.01, 25.2, 42.02, 32.1% of inhibition respectively, whereas standard ibuprofen showed 44% of inhibition.

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