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Synthesis of 2-Substituted 4*H*-Thieno[2,3-*b*][1]benzothiopyran-4-ones as Potential Chemotherapeutic Agents

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Abstract□A convenient route is reported for the synthesis of certain series of 4*H*-thieno[2,3-*b*][1]benzothiopyran-4-ones, carrying various substituents at position 2 such as arylazomethines (**7,8**), thiazolidin-4-ones (**9-13**), α,β-unsaturated ketones (**16,17**), 2-pyridones (**19-23**), tetrahydrothiophen-4-ones (**24,28**), and nitroalkenes (**29,30**), as potential schistosomicidal or antihistaminic agents.

Keywords□Synthesis,4*H*-Thieno[2,3-*b*][1]benzothiopyran-4-ones.

A number of xanthone and thioxanthone-like structures have been reported to exert several biological activities. 4H-Thieno[2,3-b][1]benzothiopyran-4-ones appeared to be the most interesting structures of these series as they were reported to exhibit marked antihistaminic[1-3] and antipsychotic[4] activities. In addition, 4H-thieno[2,3-b][1] benzopyrane-4-ones may be considered, from the chemical point of view, as the thiophenic isosteres of thioxanthones which were early reported as potent schistosomicides[5-7] and recently proved to possess antitumour activities[8,9]. The present work describes the synthesis and characterization of a new series of 2-substituted 4H-thieno[2,3-b][1]benzothiopyran-4-ones as potential chemotherapeutic agents.

Our synthetic approach is outlined in Scheme 1. The title compound, 2-formyl-4H-thieno[2,3-b][1]-benzothiopyran-4-one (**3**), was recently prepared in our laboratory by the reaction of 5-bromo-2-thenaldehyde (**1**) with thiosalicylic acid (**2**) in presence of anhydrous potassium carbonate, followed by cyclization with 70% polyphosphoric acid ethyl ester in chloroform.[10] Reaction of **3** with a variety of aromatic amines afforded the corresponding Schiff's bases, **4-8** which were then cyclocondensed with mercaptoacetic acid in dry toluene to afford the thiazolidin-4-ones, **9-13** in reasonable yields. The ,m-unsaturated ketones, **14-18** were prepared *via* the reaction of compound, **3** with the appropriate arylmethyl ketone in ethanolic sodium hydroxide solution at room temperature. Compounds, **14-18** were condensed with cyanoacetamide in presence of catalytic amounts of piperidine or with mercaptoacetic acid to yield the 2-pyridones, **19-23** and the tetrahydrothiophen-4-ones, **24-28** respectively. Reaction of nitroethane or nitropropane with compound, **3** afforded the corresponding nitroalkenes, **29,30**. Structural assignment of the newly synthesized compounds was based on the correct elemental analyses data, IR, and ^{1}H-NMR spectroscopy.

EXPERIMENTAL METHODS

Melting points were recorded on a Fisher-Johns apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian EM 360 90 MHz, NMR spectrometer using TMS as an internal standard (Chemical shift in , ppm). IR spectra were recorded in KBr using a Pye Unicam SP 1000 apparatus (v in cm^{-1}). Compounds (**4,6,14,15 & 18**) were reported in lit.[10]. Melting points, yield percentages and molecular formulae of the newly synthesized compounds are listed in Table I.

2-Arylazomethine-4H-thieno[2,3-b][1]benzothiopyran-4-ones (7,8)

Compound **3** (0.25 g, 1.0 mmol) was added to a solution of the appropriate aromatic amine (1.0 mmol), in acetic acid (20 m*l*) and the mixture was heated under reflux for one hour. On cooling, the separated solid was filtered, dried and recrystallized

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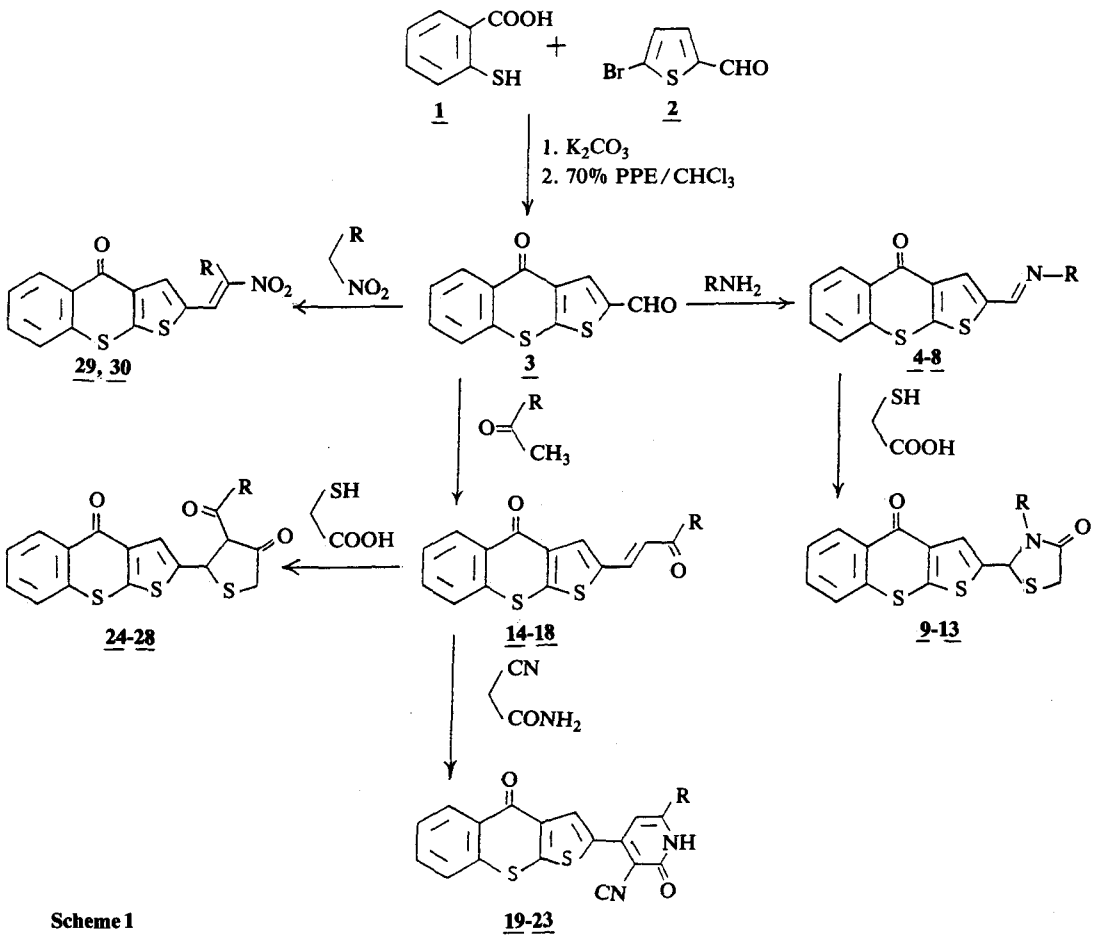

Scheme 1

from dimethylformamide.

2-(3-Aryl-4H-4-thiazolidinon-2-yl)-4H-thieno[2,3-b][1]benzothiopyran-4-ones (9-13).

A mixture of the azomethine derivative **4-8** (10 mmol) and mercaptoacetic acid (1.0 m*l*), in dry toluene (30 m*l*), was heated under reflux for 5 h. The solvent was then distilled *in vacuo* and the obtained crude product was washed with water, dried and recrystallized from xylene. IR: **9**; 1675(C = O). **10**; 1680(C = O). ^{1}H-NMR: **9** (DMSO-d_6); 4.3(s, 2H, S-CH_2-CO), 5.9(s, 1H, N-CH-S), 7.5-8.0(m, 1H, Ar-H) and 8.4-8.6(m, 8H, Ar-H). **10** (DMSO-d_6); 4.2(s, 2H, S-CH_2-CO), 6.2(s, 1H, N-CH-S), 7.3-8.1(m, 7H, Ar-H) and 8.3-8.5(m, 1H, Ar-H).

2-(3-Aryl-3-oxo-1-propenyl)-4H-thieno[2,3-b][1]-benzothiopyran-4-ones (16,17)

Compound **3** (0.25 g, 1.0 mmol) was added portionwise to a solution of the appropriate arylmethyl ketone (1.0 mmol) in 2.5% ethanolic sodium hydroxide solution (10 m*l*). The reaction mixture was stirred at ambient temperature for 2 h. The separated solid product was filtered, dried and recrystallized from dimethylformamide.

2-(3-Cyano-6-aryl-1H-2-pyridon-4-yl)-4H-thieno[2,3-b][1]benzothiopyran-4-ones (19-23)

A mixture of the α,β-unsaturated ketone **14-18** (50 mmol), cyanoacetamide (4.2 g) and few drops of piperidine, was heated under reflux on an oil bath at 140-150 C for 3 h. On cooling, the reaction mixture was washed with water then with hot ethanol. The obtained solid was filtered, dried and crystallized from dimethylformamide. IR: **19**; 1680 (C = O), 2220 (CN) and 3380 (NH). **20**; 1640 (C = O), 1710 (C = O), 2215 (CN) and 3350 (NH). ^{1}H-NMR: **19** (CF_3COOH); 3.8(s, 3H, OCH_3), 7.1-8.2(m, 9H, Ar-H) and 8.4-8.6(m, 1H, Ar-H). **20** (CF_3COOH); 7.0-8.4(m, 9H, Ar-H) and 8.6-8.8(m,

Table I. Melting points, yield percentages and molecular formula of the newly synthesized compounds.

Compd. No.	R	mp °C	Yield %	Molecular Formula*
7	2,5-$(CH_3)_2C_6H_3$	241	85	$C_{20}H_{15}NOS_2$
8	2-CH_3,5-ClC_6H_3	290	80	$C_{19}H_{12}ClNOS_2$
9	4-BrC_6H_4	190	62	$C_{20}H_{12}BrNO_2S_3$
10	2,4-$(Cl)_2C_6H_3$	178	75	$C_{20}H_{11}Cl_2NO_2S_3$
11	2-$CH_3C_6H_4$	169	58	$C_{21}H_{15}NO_2S_2$
12	2,5-$(CH_3)_2C_6H_3$	156	50	$C_{22}H_{17}NO_2S_3$
13	2-CH_3,5-ClC_6H_3	184	80	$C_{21}H_{14}ClNO_2S_3$
16	4-$CH_3C_6H_4$	230	72	$C_{21}H_{14}O_2S_2$
17	3,4,5-$(CH_3O)_3C_6H_2$	162	64	$C_{23}H_{18}O_5S_2$
19	4-$CH_3OC_6H_4$	>300	78	$C_{24}H_{14}N_2O_3S_2$
20	4-ClC_6H_4	>300	82	$C_{23}H_{11}ClN_2O_2S_2$
21	4-$CH_3C_6H_4$	>300	87	$C_{24}H_{14}N_2O_2S_2$
22	3,4,5-$(CH_3O)_3C_6H_2$	286	64	$C_{26}H_{18}N_2O_5S_2$
23	2-Thienyl	>300	78	$C_{21}H_{10}N_2O_2S_2$
24	4-$CH_3OC_6H_4$	156	25	$C_{23}H_{16}O_4S_3$
25	4-ClC_6H_4	164	48	$C_{22}H_{12}ClO_3S_3$
26	4-$CH_3C_6H_4$	182	30	$C_{23}H_{16}O_3S_3$
27	3,4,5-$(CH_3O)_3C_6H_2$	150	40	$C_{25}H_{20}O_6S_3$
28	2-Thienyl	173	35	$C_{20}H_{12}O_3S_4$
29	H	295	48	$C_{13}H_7NO_3S_2$
30	CH_3	264	61	$C_{14}H_9NO_3S_2$

*Satisfactory elemental analyses for C, H and S within ± 0.4% of the theoretical values were obtained for all compounds.

1H, Ar-H).

2-(3-Acetyl-4-oxo-tetrahydrothiophen-2-yl)-4H-thieno[2,3-b][1]benzothiopyran-4-ones (24-28)

A mixture of the α,β-unsaturated ketone **14-18** (10 mmol) and mercaptoacetic acid (1.0 m*l*), in dry toluene (50 m*l*) was heated under reflux and continued as mentioned under compounds **9-13**. The crude product was washed with water, dried and crystallized from xylene. IR: **24**; 1690 (C=O), 1710 (C=O) and 1730 (C=O). ^{1}H-NMR: **24** (DMSO-d_6); 3.9(s, 3H, OCH_3), 4.2(s, 2H, s-CH_2-CO), 5.8-6.0(m, 2H, CH-CH of tetrahydrothiophene), 7.6-8.1(m, 8H, Ar-H) and 8.3-8.5(m, 1H, Ar-H).

2-(2-Nitroalkenyl)-4H-thieno[2,3-b][1]benzothiopyran-4-ones (29,30)

A mixture of compound **3** (1.0 mmol), ammonium acetate (1.0 mmol) and the appropriate nitropropane (1.5 mmol), in acetic acid (50 m*l*), was heated uner reflux for 3 h. The solvent was then removed *in vacuo* and the remaining solid was quenched with water, filtered, dried and recrystallized from dimethylformamide. IR: **30**; 1700 (C = O). ^{1}H-NMR: **30** (acetone-d_6); 2.3(s, 3H, CH_3) and 6.9-8.2(m, 6H, Ar-H and olefinic-H).

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