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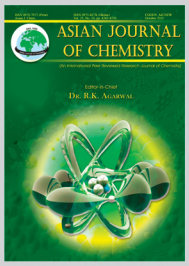

Synthesis and Biological Evaluation of Some New Thiazolo[2,3-b]quinazolines and Their Derivatives

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9-Methoxy-4-phenyl-3,4,5,6-tetrahydrobenzo[h]quinzoline-2(1H)-thione (**2**), obtained by the condensation of (E)-2-benzylidene-7-methoxy-3,4-dihydronaphthalen-1(2H)-one (**1**) with thiourea, on reaction with chloroacetic acid, α-bromopropionic acid and 1,2-dibromoethane furnishes compounds, **3**, **4** and **5** and not their other possible isomers, **7**, **8** and **9**, respectively. Arylidene thiazolidinones **6** have been obtained by two routes. Compounds **3-5** represent a novel heterocyclic system. The structural assignments of **3**, **4** and **5** are based on elemental analysis, ^{1}H NMR, IR and mass spectral data. The condensed 4-thiazolidinones (**3-5**) and their 2-arylidene derivatives (**6a-c**) were screened for antimicrobial activity and showed promising inhibition of *S. aureus*, *C. diphtheriae*, *P. aeruginosa* and *E. coli* bacteria.

Key Words: 4-Thiazolidinone, Antimicrobial activity, Arylidene derivatives.

INTRODUCTION

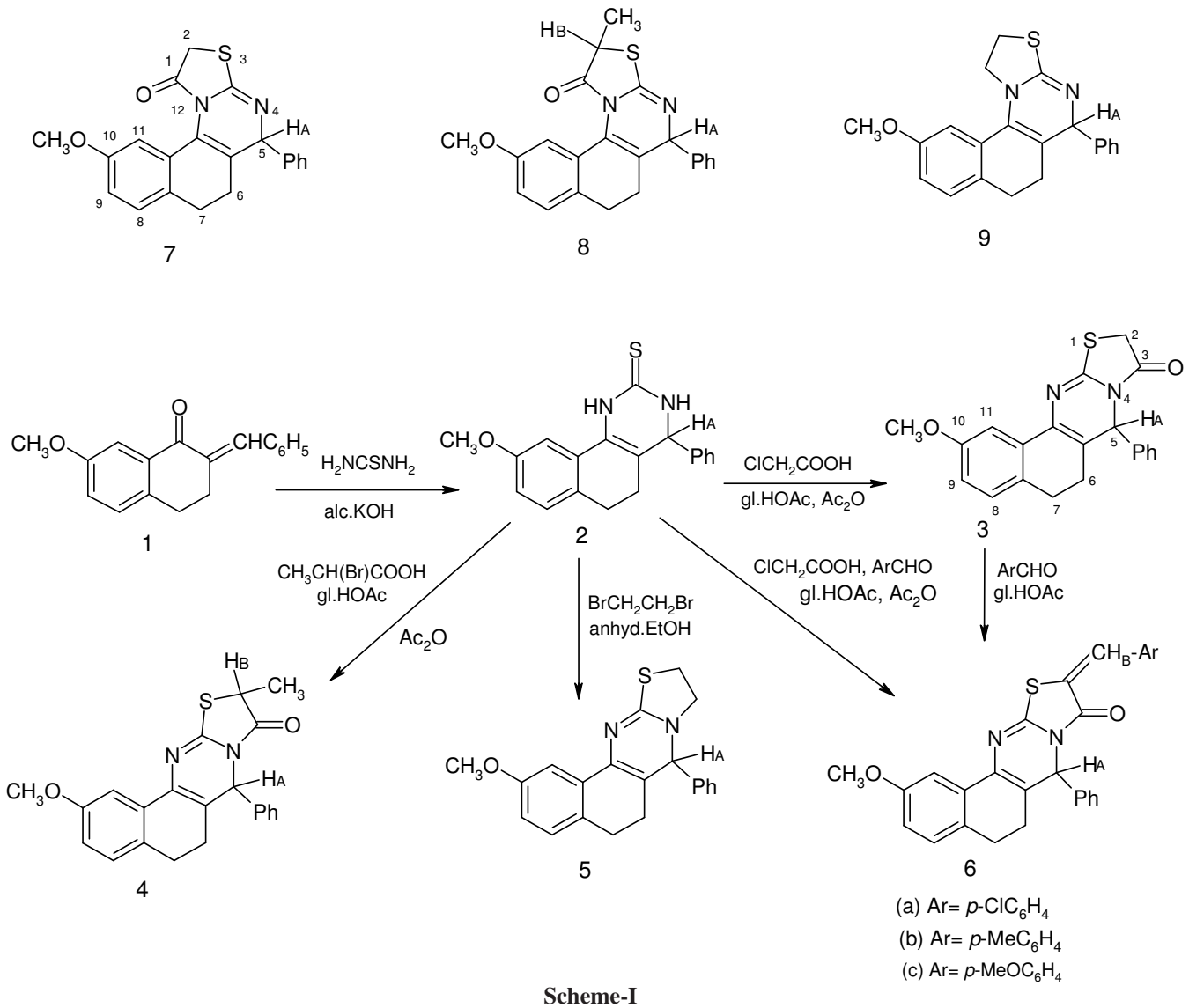
Condensed 4-thiazolidinones have received interest and attention from a large number of organic chemists, pharmacologists and biologists world over, on account of significant therapeutic and other properties associated with thiazolidinone nucleus. Applications of 4-thiazolidinones are manifold and versatile. They are widely used as anticonvulsant[1,2], antibacterial[3,4], antiinflammatory[5,6], central nervous system depressant[7], carcinostatic[8], muscle relaxant[9,10], antihypertensive[11], anti HIV[12,13], analgesic[14], cytotoxic[15], *etc*. Condensed 4-thiazolidinones have also found applications in the synthesis of cyanine and merocyanine dyes. In view of the wide spectrum activities of condensed 4-thiazolidinones it was thought worthwhile to undertake the synthesis of heterocyclic systems in which 4-thiazolidinone nucleus is fused to another biologically active heterocyclic ring *i.e*. quinazoline in this case. The product is expected to exhibit more biological activity due to synergic effect. In continuation to our work on condensed 4-thiazolidinones[16] we wish to report here the reaction of 9-methoxy-4-phenyl-3,4,5,6-tetrahydrobenzo[h]quinzoline-2-thione with halo acids and 1,2-dibromoethane furnishing benzo[h]thiazolo[2,3-b]quinazoline system (*cf.* **Scheme-I**) and biological evaluation of the cyclized compounds.

EXPERIMENTAL

Melting points were determined in sulphuric acid bath and are uncorrected. TLC was performed on silica gel G plates using benzene-ethylacetate (4:1) as irrigant and iodine vapours as visualizing agent. IR spectra were recorded in nujol mull on a Perkin-Elmer RXI FTIR spectrophotometer (ν_{max}, cm^{-1}), ^{1}H NMR in $CDCl_3$ on Bruker Advance II 400 MHz spectrometer using TMS as internal reference (chemical shift in δ, ppm) and mass spectra on Q-TOF MS/ES spectrometer. The elemental analysis (C, H, N, S) of compounds was performed on a Carlo Erba-1108 elemental analyzer.

(E)-2-benzylidene-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (1): A mixture of 7-methoxy-1-tetralone (8.8 g, 0.05 mol) and benzaldehyde (5.3 g, 0.05 mol) in aq. sodium hydroxide (2 g NaOH in 40 mL water) was heated under reflux for 5 h. The reaction mixture was cooled to room temperature and neutralized with dil. HCl. The solid, so obtained was filtered, washed with pet. ether (60-80 ºC) and finally crystallized from ethanol to give compound **1** as white needles, yield 80 %, 10 g, m.p. 108-110 ºC, IR (ν_{max}, cm^{-1}): 1667 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.92 (2H, t, CH_2, J = 6.16 Hz), 3.13 (2H, t, CH_2, J = 6.68 Hz), 3.83 (3H, s, OCH_3), 6.93-8.11 (8H, m, C_6H_5), 7.8 (1H, s, CH). Anal. calcd. (%) for $C_{18}H_{16}O_2$ (264): C, 81.8; H, 6.06. Found (%): C, 81.6; H, 6.03.

9-Methoxy-4-phenyl-3,4,5,6-tetrahydrobenzo[h] quinzoline-2(1H)-thione (2): (E)-2-benzylidene-7-methoxy-3,4-dihydronaphthalen-1(2H)-one (**1**) (5.28 g, 0.02 mol) and thiourea (1.52 g, 0.02 mol) in ethanolic potash (2.0 g KOH in 75 mL ethanol) was heated under reflux for 5 h and kept overnight. The volume was reduced to half and the concentrate



Scheme-I

poured into ice-cold water. The solid, thus obtained, was filtered, washed well with water and finally crystallized from DMF to yield white solid, yield 65 %, 4.20 g, m.p. 230-235 ºC, IR (ν_{max}, cm^{-1}): 1315 (C=S); 1558 (N=H). ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.12 (2H, t, CH_2, J = 6.16 Hz), 2.76 (2H, t, CH_2, J = 6.68 Hz), 3.82 (3H, s, OCH_3), 5.25 (1H, s, H_A), 6.77-8.16 (8H, m, C_6H_5). Anal. calcd (%) for $C_{19}H_{18}N_2OS$ (322): C, 70.8; H, 5.59; N, 8.69; S, 9.93. Found (%): C, 70.5; H, 5.56; N, 8.68; S, 9.90.

2-Methoxy-7-phenyl-7, 10-dihydro-5*H*-benzo[h]-thiazolo-[2,3-b]quinazolin-9(6*H*)-one (3): A mixture of **2** (3.22 g, 0.01 mol), chloroacetic acid (0.94 g, 0.01 mol), anhydrous sodium acetate (0.82 g), acetic acid (10 mL) and acetic anhydride (2 mL) was heated under reflux for 2 h. The reaction mixture was cooled to room temperature and then poured into water to afford a solid. Crystallization from gl. acetic acid gave brown needles, yield 61.5 %, 2.5 g, m.p. 210-214 ºC, IR (ν_{max}, cm^{-1}): 1717 (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.03-2.20 (2H, m, CH_2), 2.67-2.79 (2H, m, CH_2), 3.67-3.83 (2H, dd, SCH_2, J = 17.2 Hz), 3.77 (3H, s, OCH_3), 5.52 (1H, s, H_A), 6.83-7.95 (8H, m, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 24, 27 (CH_2-CH_2), 31 (SCH_2), 55.3 (OCH_3), 114.07, 115, 123-135 (Ar-C), 159.93 (C-OCH_3), 170 (C=O). MS, 363 $(M+1)^+$; 100 %. Anal. calcd. (%) for $C_{21}H_{18}N_2O_2S$ (362): C, 69.6; H, 4.97; N, 7.73; S, 8.83. Found (%): C, 69.30; H, 4.94; N, 7.70; S, 8.80.

2-Methoxy-10-methyl-7-phenyl-7,10-dihydro-5*H*-benzo[h]thiazolo-[2,3-b]quinazolin-9(6*H*)-one (4): Compound **4** was obtained in 40 % yield from **2** and α-bromopropionic acid following the procedure of 3 as cream coloured needles, yield 40 %, m.p. 175-177 ºC, IR (ν_{max}, cm^{-1}): 1597 (C=C, C=N) and 1729 (N-CO). ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.81 (3H, s, OCH_3), 1.17 (3H, d, CH_3, J = 6.76 Hz), 1.86 (2H, t, CH_2, J = 7.18 Hz), 2.37 (2H, t, CH_2, J = 7.16 Hz), 4.08 (1H, q, H_B, J = 7.50 Hz), 5.48 (1H, s, H_A), 6.84-7.92 (8H, m, Ar-H); MS 377 $(M+1)^+$; 54.4 (%). Anal. calcd. (%) for $C_{22}H_{20}N_2O_2S$ (376): C, 70.2; H, 5.31; N 7.44; S, 8.50. Found (%): C, 69.90; H, 5.32; N, 7.40; S, 8.10.

2-Methoxy-7-phenyl-6,7,9,10-tetrahydro-5*H*-benzo-[h]thiazolo[2, 3-b]quinazoline (5): A mixture of **2** (3.22 g, 0.01 mol) and 1,2-dibromo ethane (1.88 g, 0.01 mol) in DMF (10 mL) and anhydrous ethanol (20 mL) was refluxed for 1 h.

The reaction mixture was cooled and neutralized with sodium carbonate. The crude solid, thus separated, was purified by column chromatography to give a light yellow solid, yield 42 %, 1.25 g, m.p. 220 ºC, IR (ν_{max}, cm^{-1}): 1549 (C=N) and 1634 (C=C). ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.78 (3H, s, OCH_3), 1.94 (2H, t, CH_2, J = 6.16 Hz), 2.38-2.92 (4H, m, SCH_2 and CH_2), 3.42 (2H, t, NCH_2, J = 6.68 Hz), 4.96 (1H, s, H_A), 6.89-7.34 (8H, m, Ar-H); MS 349 $(M+1)^+$; 37.2 (%). Anal. calcd. (%) for $C_{21}H_{20}N_2OS$ (348): C, 72.4; H, 5.74; N, 8.04; S, 9.19. Found (%): C, 72.70; H, 5.76; N, 8.01; S, 9.12.

(E)-2-methoxy-10-(4-chlorobenzylidene)-7-phenyl-7,10-dihydro-5*H*-benzo[h]thiazolo[2,3-b]quinazolin-9(6*H*)-one (6a): i) A mixture of thiazolidinone **3** (0.362 g, 0.001 mol), *p*-chlorobenzaldehyde (0.14 g, 0.001 mol), anhydrous sodium acetate (0.82 g) and glacial acetic acid (10 mL) was heated under reflux for 2 h. The reaction mixture was cooled to room temperature and poured into water. The solid thus obtained was filtered and washed well with water and finally crystallized from gl. acetic acid to give brown needles, yield 61.02 %, 0.274 g, m.p. 220-23 ºC, IR (ν_{max}, cm^{-1}): 1595 (C=N) and 1704 (N-CO). ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.78 (3H, s, OCH_3), 2.17 (2H, t, CH_2, J = 6.16 Hz), 2.78 (2H, t, CH_2, J = 6.68 Hz), 5.61 (1H, s, H_A), 6.82-7.46 (12H, m, Ar-H), 7.67 (1H, s, H_B). Anal. calcd. (%) for $C_{28}H_{21}N_2O_2S$ (449): C, 74.83; H, 4.67; N, 6.23; S, 7.12. Found (%): C, 74.85; H, 4.69; N, 6.20; S, 7.09.

ii) A mixture of thione **2** (0.322 g, 0.001 mol), chloroacetic acid (0.09 g, 0.001 mol) and *p*-chloro-benzaldehyde (0.14 g, 0.001 mol) and anhydrous sodium acetate (0.082 g; 0.001 mol) in gl. acetic acid (10 mL) and acetic anhydride (2 mL) was refluxed for 2 h. A similar work up as in (i) gave **6a**, m.p. 218 ºC which remained undepressed when mixed with the compound obtained by method (i), yield 52 %, 0.32 g.

Compounds **6b-c** were similarly prepared by the first method.

Compound 6b: Light brown solid, yield 53 %, m.p. 240-46 ºC, IR (ν_{max}, cm^{-1}): 1598 (C=C), 1634 (C=N) and 1709 (N-CO). ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.82 (3H, s, OCH_3), 1.06 (3H, s, CH_3), 2.14 (2H, t, CH_2, J = 6.22 Hz), 2.74 (2H, t, CH_2, J = 6.62 Hz), 5.59 (1H, s, H_A), 6.78-7.48 (12H, m, Ar-H), 7.65 (1H, s, H_B). Anal. calcd. (%) for $C_{29}H_{24}N_2O_2S$ (464): C, 75.00; H, 5.17; N, 6.03; S, 6.89. Found (%): C, 75.02; H, 5.14; N, 6.01; S, 6.84.

Compound 6c: Cream coloured solid, yield 50 %, m.p. 190-95 ºC, IR (ν_{max}, cm^{-1}): 1494 (C-N), 1593 (C=N) and 1710 (N-CO). ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.82 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 2.12 (2H, t, CH_2, J = 6.18 Hz), 2.72 (2H, t, CH_2, J = 6.64 Hz), 5.54 (1H, s, H_A), 6.72-7.54 (12H, m, Ar-H), 7.62 (1H, s, H_B). Anal. calcd. (%) for $C_{29}H_{24}N_2O_3S$ (480): C, 72.50; H, 5.00; N, 5.83; S, 6.66. Found (%): C, 72.48; H, 4.95; N, 5.79; S, 6.62.

RESULTS AND DISCUSSION

(E)-2-benzylidene-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**1**), obtained by the reaction of 7-methoxy-1-tetralone and benzaldehyde, when condensed with thiourea gave (**2**). The unsymmetrical thione (**2**) on reaction with chloroacetic acid followed by cyclization of the intermediate *in situ* was likely to give **3** or (**7**) or both depending on the mode of cyclization. However, the thione (**2**) when reacted with chloroacetic acid gave a single product (TLC). The appearance of a band at 1717cm^{-1} (N-C=O) in the IR spectrum and exhibition of a molecular ion peak at *m/z* 362 (100 %) in the mass spectrum of the TLC- pure product suggested that the cyclization had indeed taken place. The IR and mass spectral data were of little help in deciding in favour of either structure **3** or **7**. However, the structure **3** was finally assigned to this cyclization product in preference to the structure **7** on the basis of ^1H NMR spectral data.

The reaction of **2** with 1,2-dibromoethane gave a product which was purified by column chromatography and characterized by its molecular ion peak at *m/z* 348 (37.2 %) as a compound which could be represented by either structure **5** or **9**. In either structure (**5** or **9**) the singlet at δ 4.96 in its ^1H NMR spectrum integrating for one proton was assignable to H_A. If the structure **7** is correct for the cyclization product, obtained from **2** and chloroacetic acid, then H_A will resonate in the same region as that of **5** (or **9**). On the other hand if the structure **3** is correct, H_A will be deshielded by the thiazolidinone ring and consequently, H_A will resonate downfield in comparison to H_A in **5** (or **9**). The signal at δ 5.52 (1H, s, H_A), which is downfield compared to 4.96 supported the structure **3** and ruled out the structure **7** from, which such a downfield shift would not be expected. The deshielding effect is due to the magnetic anisotropy of the >C=O group with a minor contribution from the rest of the ring.

Although the comparison of the chemical shifts of H_A in the structures **3** and **5** (or **9**) is on a better footing, on the basis that both **3** and **5** (or **9**) are tetracyclic compounds, yet the same conclusion is delivered by comparing the chemical shifts of H_A of the thione **2** with that of cyclization product **3**. The H_A proton in thione **2** resonates at δ 5.25 whereas the downfield signal at δ 5.52 (due to H_A) in the cyclized product supports the structure **3** in preference to structure **7**. Similarly, the reaction of the thione **2** with α-bromopropionic acid yielded TLC pure single product to which structure **4** was assigned and ruled out structure **8**.

Arylidene thiazolidinones (**6**) were prepared by two routes. In the first approach, the thiazolidinone **3** was condensed with aldehydes to give arylidene thiazolidinones (**6a-c**) while in the second approach **6a** was obtained directly by heating **2** with chloroacetic acid and *p*-chlorobenzaldehyde. The structures **6a-c** were established by IR and ^1H NMR spectral data. The parent thiazolidinone (**3**) exhibited an absorption band at 1717 cm^{-1} (N-C=O), but the unsaturation at the 2-position being conjugated with the carbonyl group at the 3-position as in arylidene thiazolidinones (**6a-c**) produced a bathochromic shift[17] as expected, the carbonyl absorption band appeared at 1704, 1709 and 1710 cm^{-1} in **6a-c** respectively. The structure **5** (not **9**) for the product, obtained from the reaction of **2** with 1,2-dibromoethane, was assigned on analogy with structures **3** and **4**. The compounds **3-6** were screened for their antimicrobial activities using disc diffusion method and the results reported in Table-1 shows that compound **6b** possesses maximum activity.

Antimicrobial studies: The compounds (**3-6**) were screened for their antimicrobial activity against gram-negative bacteria, *E. Coli* and *P. aeruginosa* and gram-positive bacteria, *S. aureus* and *C. diphtheriae* using disc diffusion method[18,19] (Table-1). The zone of inhibition was measured in mm and the activity was compared with standard drug.

TABLE-1
ANTIBACTERIAL ACTIVITY STUDIES
BY DRUG DIFFUSION METHOD

Compound	Zone of inhibition (mm)			
	Gram positive		Gram negative	
	S. aureus	*C. diphtheriae*	*P. aeruginosa*	*E. coli*
3	15	16	15	12
4	13	14	13	10
5	12	13	13	12
6a	16	16	18	14
6b	19	20	19	16
6c	16	17	18	13
Ampicillin trihydrate	26	28	24	21
DMSO	00	00	00	00

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