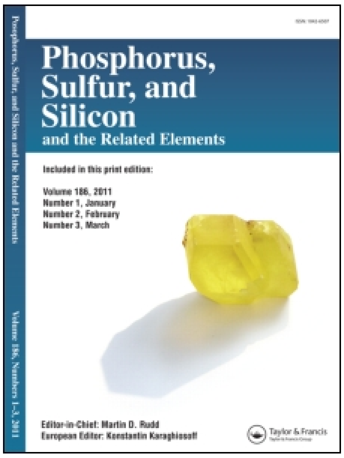

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The Syntheses of New Cyclopenta[d][1,3]thiazine Derivatives and Their Use as Antimicrobial Agents

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The Syntheses of New Cyclopenta[*d*][1,3]thiazine Derivatives and Their Use as Antimicrobial Agents

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*Cyclopentanone (**1**) was exploited as a starting material for the syntheses of hitherto unknown cyclopenta[d][1,3]thiazine derivatives.*

Keywords Cyclopentanone; thiazine and cyclopenta[d][1,3]thiazine derivatives

INTRODUCTION

1,3-thiazine derivatives are reported to show antibacterial,[1] antimycobacterial,[2] antiviral,[3] and pesticide[4] agents. In addition, 4,6,6-trimethyl-2-mercaptothiazine (**A**) is slightly active in producing hyperplasia of the thyroid and an impairment of the ability to fix administered I in rats.[5] Further, 2-aminothiazines increase the survival time in mice irradiated with X-rays.[6] Also, arylthiazines have bactericidal, fungicidal, and algicidal properties that are useful in agriculture, spinning mixtures, and manufacturing papers and paints.[7] Cephalosporins (**B**) have a 3,6-dihydro-2H-1,3-thiazine nucleus (Scheme 1).[8] In continuation with our work on the synthesis of some novel heterocyclic compounds from readily available starting materials,[9–13] we report herein on the synthesis of novel cyclopenta[d][1,3]thiazine derivatives from cyclopentanones.

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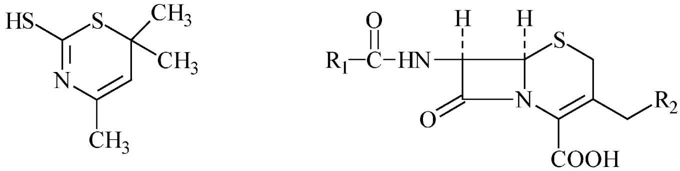


(A) (B)

SCHEME 1

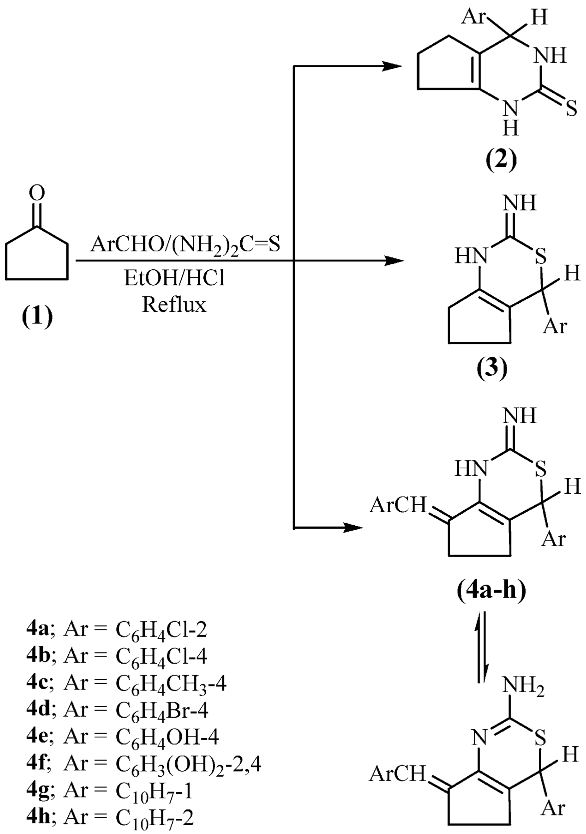
RESULTS AND DISCUSSION

The 2-oxo-1,3-thiazine derivative was prepared by the acid-catalyzed reaction of chalcone with thiourea.[14] Lorand and Szabo[15,16] investigated the reaction of 2-arylidene cyclohexanones and 2-arylidene-1-tetralones with thiourea under acidic conditions and synthesized 1,3-thiazines and 3,1-benzothiazines. The reaction of 2-arylidenecycloalkanones, 2-arylidene-1-tetralones, and 2-arylidene-1-benzosuberones with thiourea in the presence of sodium ethoxide or sodium hydroxide gave pyrimidines.[17,18] In the present article, the reaction of cyclopentanone with aromatic aldehyde in the presence of thiourea or urea under acidic and alkaline reaction conditions was investigated. Thus, three possible structures can be formulated, (**2**), (**3**), and (**4**), when cyclopentanone (**1**) was condensed with aromatic aldehyde and thiourea in ethanol in the presence of concentrated hydrochloric acid at a reflux temperature (Scheme 2). The cyclopenta[d][1,3]thiazines (**4a–h**) were confirmed as the only product on the basis of analytical and spectroscopic data. The ^{1}H NMR spectrum of compound (**4a**) in DMSO-d_6 revealed a signal at $\delta = 5.8$ ppm for an thiazine-H in addition to two methylene, methylidene aromatic, and two NH protons. Also, the mass spectrum of compound (**4g**; $C_{28}H_{22}N_2S$) showed a molecular ion peak at m/z = 418, which is the base peak in the spectrum. Also, the following fragments were found in the mass spectrum of (**4g**) at m/z: 419 (M+1; 29.2%), 420 (M+2; 10.5%), 386 (M-sulphur; 4.3%), 359 (M-HNCS; 5.3%), 291 (M-naphthyl group; 63.1%), 232 (7.9%), 164 (14.5%), 141 ($C_{10}H_7CH_2$; 96%), 127 (naphthyl; 32%), 217 (23.8%), 105 (1.5%), 92 (2.6%), and 77 (11.8%).

The formation of thiazine derivatives (**4a–h**) was assumed to proceed according to the following mechanism (Scheme 3):

The structure of thiazine derivatives (**4a–h**) was established via the following synthetic routes:

1. by ternary condensation of cyclopentanone (**1**), aromatic aldehyde, and thiourea (1:2:1 molar ratio) in refluxing ethanol in the presence of potassium hydroxide; and

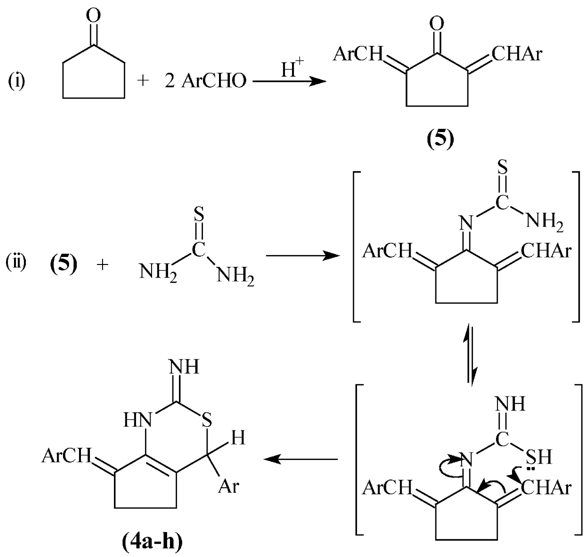


4a; Ar = C_6H_4Cl-2
4b; Ar = C_6H_4Cl-4
4c; Ar = $C_6H_4CH_3$-4
4d; Ar = C_6H_4Br-4
4e; Ar = C_6H_4OH-4
4f; Ar = $C_6H_3(OH)_2$-2,4
4g; Ar = $C_{10}H_7$-1
4h; Ar = $C_{10}H_7$-2

SCHEME 2

2. through the cyclocondensation of 2,5-diarylidene cyclopentanones (**5**)[19] with thiourea in an ethanolic solution in the presence of concentrated hydrochloric acid at a reflux temperature (Scheme 4).

The treatment of compound (**4c**) with chloroacetyl chloride in dimethyl-formamide in the presence of anhydrous potassium carbonate gave the corresponding 2-(dichloroacetyl)amino-4-(4-methylphenyl)-7-(4-methyl-phenyl)methylidene-4,5,6,7-tetrahydrocyclopenta[d][1,3]thiazine (**7**). Condensed imidazole (**6**) was discarded on the basis of analytical and spectral data. The infrared spectrum of compound (**7**) exhibited $\nu_{C=O}$ at 1725 cm^{-1} in addition to CH-aliph. The ^1H NMR spectrum in DMSO-d_6 was characterized by the presence of a $N(COCH_2Cl)_2$ moiety in addition to two methylenes, methylidene, thiazine, and aromatic protons. In a similar manner, diacetylamino

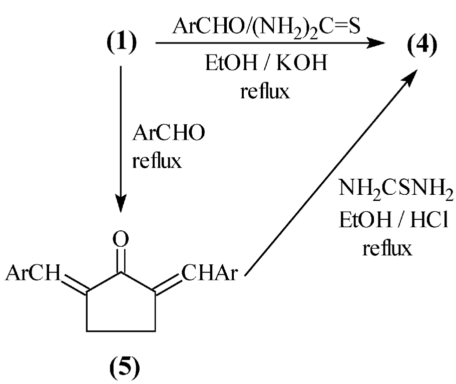


SCHEME 3

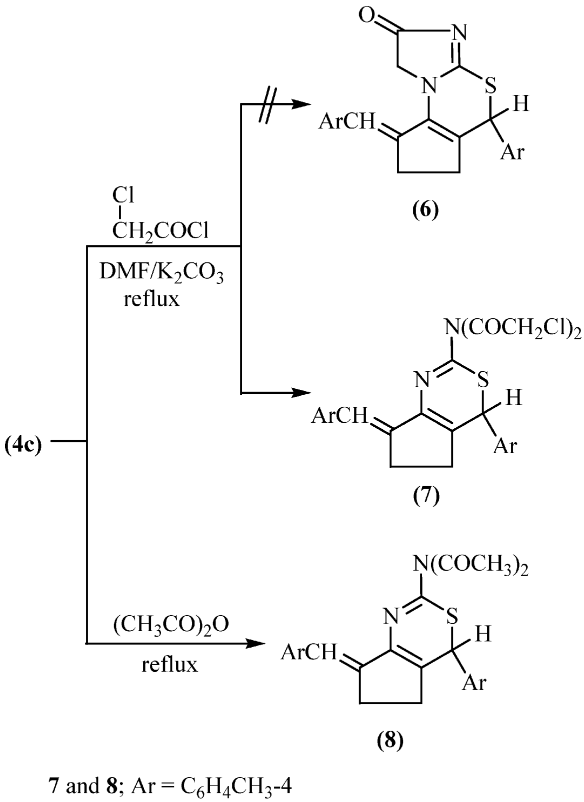
derivatives (**8**) were achieved by heating compound (**4c**) in acetic anhydride (Scheme 5).

Antimicrobial Activity

All synthesized compounds were screened in vitro for their antimicrobial activities against two strains of bacteria, *Staphylococcus aureus* and *Bacillus cereus*, and two strains of fungi, *Aspergillus funigatus* and *Candida albicans*, by agar diffusion techniques.[20] The tested



SCHEME 4



SCHEME 5

compounds were dissolved in *N*,*N*-dimethylformamide (DMF) to get a solution of 1000 μg mL^{-1} concentration. The bacteria and fungi cultures were maintained on nutrient agar and Czapek's Dox agar media, respectively. The agar media were incubated with different microorganisms that were culture tested. After 24 h of incubation at 30°C for bacteria and 48 h of incubation at 28°C for fungi, the diameter of the inhibition zone (mm) was measured. Chloramphenicol and fungicide Terbinafin were used as references.

The results indicated that most of the tested compounds exhibit mild to strong activities. However, none of the tested compounds showed superior activity over the reference (Table I).

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded (KBr) on a Perkin Elmer 1650 spectrophotometer. ^{1}H NMR spectra were recorded

TABLE I Antimicrobial Activity of the Synthesized Compounds and Inhibition Zones

Compound no.	*Staphylococcus aureus*	*Bacillus cereus*	*Aspergillus funigatus*	*Candida albicans*
4a	++	++	+	+
4b	++	+	+	+
4c	+ + +	+	++	+
4d	+	++	+	+
4e	++	+	+	++
4f	+ + +	+	+	+
4g	+	++	+	+
4h	++	+	+	+
7	++	+ + +	+	+
8	+ + +	+	+	+
Reference	+ + ++	+ + ++	+ + ++	+ + ++

+: Less active (2–5 mm), ++: Moderately active (6–14 mm), + + +: Highly active (15–20 mm).

on a Varian Gemini spectrometer 200 (200 MHz), using DMSO-d_6 as a solvent and TMS as internal standard. Chemical shifts are expressed as δ ppm units. Mass spectra were recorded on a gas chromatographic GC-MS gp 1000 Ex Shimadzu instrument at 70 eV. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University, Egypt. Physical data for synthesized compounds are given in Table II. Also, the infrared spectral data are collected in Table III.

2-Amino-4-aryl-7-arylmethylidene-4,5,6,7-tetrahydrocyclopenta-[d][1,3]thiazines (4a–h): General Procedure

Method A

A mixture of cyclopentanone **1** (0.01 mole), thiourea (0.01 mole), aromatic aldehyde (0.02 mole) in ethanol (30 mL), and concentrated hydrochloric acid (37%; 3 mL) was refluxed for 3 h. The solid product, which separated on heating, was collected and recrystallized to give **4**.

Method B

A mixture of 2,5-diarylidenecyclopentanone **5** (0.01 mole), thiourea (0.01 mole) in ethanol (30 mL), and concentrated hydrochloric acid (37%; 3 mL) was refluxed for 3 h. The solid product, which separated on heating, was collected to give **4**.

TABLE II Physical Data for the Synthesized Compounds

Compound no.	M.P. (°C)	Yield (%) (Color)	Solvent	Molecular formula (Mol. Wt.)	Elemental analyses C%	H%	N%
4a	140–141	88	Dioxane	$C_{20}H_{16}Cl_2N_2S$	62.00	4.16	7.23
		(Brown)		(387.40)	62.10	4.20	7.20
4b	168–169	83	Dioxane	$C_{20}H_{16}Cl_2N_2S$	62.00	4.16	7.23
		(Red)		(387.40)	62.30	4.20	7.20
4c	170–172	89	Dioxane	$C_{22}H_{22}N_2S$	76.26	6.40	8.08
		(Orange)		(346.49)	76.30	6.30	8.10
4d	230–233	86	Dioxane	$C_{20}H_{18}Br_2N_2S$	50.21	3.79	5.85
		(Brown)		(478.44)	50.20	3.80	5.90
4e	306–308	79	Dioxane	$C_{20}H_{18}N_2O_2S$	68.55	5.18	7.99
		(Brown)		(350.44)	68.50	5.20	8.00
4f	246–248	85	Dioxane	$C_{20}H_{18}N_2O_4S$	62.81	4.74	7.32
		(Red)		(382.44)	62.80	4.70	7.30
4g	240–243	80	Dioxane	$C_{28}H_{22}N_2S$	80.34	5.29	6.69
		(Yellow)		(418.56)	80.30	5.30	6.70
4h	258–259	84	Dioxane	$C_{28}H_{22}N_2S$	80.34	5.29	6.69
		(Orange)		(418.56)	80.30	5.30	6.80
7	138–139	79	Benzene	$C_{26}H_{24}Cl_2N_2O_2S$	62.51	4.84	5.61
		(Brown)		(499.53)	62.50	4.90	5.60
8	166–168	70	Benzene	$C_{26}H_{26}N_2O_2S$	72.53	6.87	6.50
		(Brown)		(430.57)	72.60	6.90	6.51

Method C

A mixture of cyclopentanone **1** (0.01 mole), thiourea (0.01 mole), aromatic aldehyde (0.02 mole), and potassium hydroxide (0.12 mole) in ethanol (30 mL) was refluxed for 3 h. The solid product, which separated on heating, was collected to give **4**.

TABLE III Infrared Spectra of the Synthesized Compounds

Compound no.	ν_{max}/cm^{-1}
4a	3398, 3171 (2NH), 3062 (CH-arom.), 2949 (CH-aliph.), 1545 (C=C)
4b	3394, 3201 (2NH), 3085 (CH-arom.), 2923 (CH-aliph.), 1558 (C=C)
4c	3384, 3173 (2NH), 3019 (CH-arom.), 2920 (CH-aliph.), 1544 (C=C)
4d	3386, 3189 (2NH), 3085 (CH-arom.), 2916 (CH-aliph.), 1555 (C=C)
4e	3307, 3200 (NH/OH), 3079 (CH-arom.), 3950 (CH-aliph.), 1559 (C=C)
4f	3243 (broad; NH/OH), 3030 (CH-arom.), 1560 (C=C)
4g	3388, 3195 (2NH), 3062 (CH-arom.), 2922 (CH-aliph.), 1542 (C=C)
4h	3419, 3180 (2NH), 3092 (CH-arom.), 2993, 2914 (CH-aliph.), 1561 (C=C)
7	3021 (CH-arom.), 2921 (CH-aliph.), 1725 (C=O)
8	3021 (CH-arom.), 2922 (CH-aliph.), 1716 (C=O)

^{1}H NMR spectrum (**4a**; DMSO-d_6) (δ/ppm): 2.14, 2.91 (2s, 4H, $2CH_2$), 5.80 (s, 1H, thiazine-H), 6.72 (s, 1H, methylidene-H), 6.93–7.59 (m, 8H, Ar-H), 9.39, 10.50 (2s, 2H, 2NH; exchangeable with D_2O).

^{1}H NMR spectrum (**4b**; DMSO-d_6) (δ/ppm): 2.16, 2.85 (2s, 4H, $2CH_2$), 5.29 (s, 1H, thiazine-H), 6.96 (s, 1H, methylidene-H), 7.29–7.54 (m, 8H, Ar-H), 9.08. 10.17 (2s, 2H, 2NH; exchangeable with D_2O).

Compounds (**4c–h**) insoluble in DMSO-d_6.

In the mass spectrum of compound (**4h**), a molecular ion peak was observed at m/z = 418, which is the base peak in the spectrum.

2-(Dichloroacetyl)amino-4-(4-methylphenyl)-7-(4-methylphenyl)-methylidene-4,5,6,7-tetrahydrocyclopenta[d][1,3]thiazine (7)

To a solution of compound **4c** (0.01 mole) and chloroacetyl chloride (0.02 mole) in N,N-dimethylformamide (10 mL), anhydrous potassium carbonate (2 g) was added and refluxed for 1 h. It then was allowed to cool and was poured into cold water (50 mL). The solid product was collected and recrystallized to give **7**.

^{1}H NMR spectrum (**7**; DMSO-d_6) (δ/ppm): 1.25, 1.40 (2s, 6H, $2CH_3$), 2.27–2.34 (m, 4H, $2CH_2$), 3.99 (s, 4H, $2CH_2CO$), 4.28 (s, 1H, thiazine-H), 7.08–7.36 (m, 9H, Ar-H + methylidene-H).

2-(Diacetyl)amino-4-(4-methylphenyl)-7-(4-methylphenyl)methyl-idene-4,5,6,7-tetrahydrocyclopenta[d][1,3]thiazine (8)

A sample of compound **4c** (0.01 mole) in acetic anhydride (10 mL) was refluxed for 30 min and then allowed to cool. The solid product was collected and recrystallized to give **8**.

^{1}H NMR spectrum (**8**; DMSO-d_6) (δ/ppm): 1.92 (s, 6H, $2CH_3$), 2.22–2.28 (m, 4H, $2CH_2$), 2.34 (s, 6H, $2COCH_3$), 5.20 (s, 1H, thiazine-H), 6.60–7.84 (m, 9H, Ar-H + methylidene-H).

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