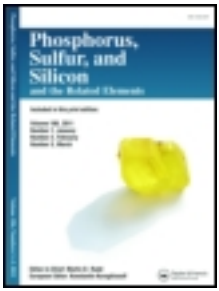

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

The Synthesis of New Spiro β-Lactam and Thiazolidinone Compounds Incorporating Quinones and Their Biological Activity

A. K. Khalafallah [a] , N. A. A. El-Kanzi [a] , H. A. Soleiman [a] & M. Younis [b]
[a] Chemistry Department, South Valley University, Aswan, Egypt
[b] Botany Department, South Valley University, Aswan, Egypt
Version of record first published: 01 Feb 2007.

To cite this article: A. K. Khalafallah, N. A. A. El-Kanzi, H. A. Soleiman & M. Younis (2006): The Synthesis of New Spiro β-Lactam and Thiazolidinone Compounds Incorporating Quinones and Their Biological Activity, Phosphorus, Sulfur, and Silicon and the Related Elements, 181:11, 2483-2503

To link to this article: http://dx.doi.org/10.1080/10426500600754760

Phosphorus, Sulfur, and Silicon, 181:2483–2503, 2006

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500600754760

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The Synthesis of New Spiro β-Lactam and Thiazolidinone Compounds Incorporating Quinones and Their Biological Activity

A. K. Khalafallah
N. A. A. El-Kanzi
H. A. Soleiman
Chemistry Department, South Valley University, Aswan, Egypt

M. Younis
Botany Department, South Valley University, Aswan, Egypt

A series of some fused and spiro heterocyclic compounds such as pyrazolines, isoxazolines, pyrimidines, β-lactams, and thiazolidinone derivatives incorporating compounds 3, 6a–d, 7a–d, 9a–c, 10a–c, 11a–c, 12a–c, and 13a–c have been synthesized by a cycloaddition and cyclocondensation reaction of monochloroacetyl chloride, mercaptoacetic acid, hydrazines, hydroxylamine, urea, and thiourea with the prepared 5a–d and 8a–c.

Keywords Spiro β-lactam; thiazolidinone

INTRODUCTION

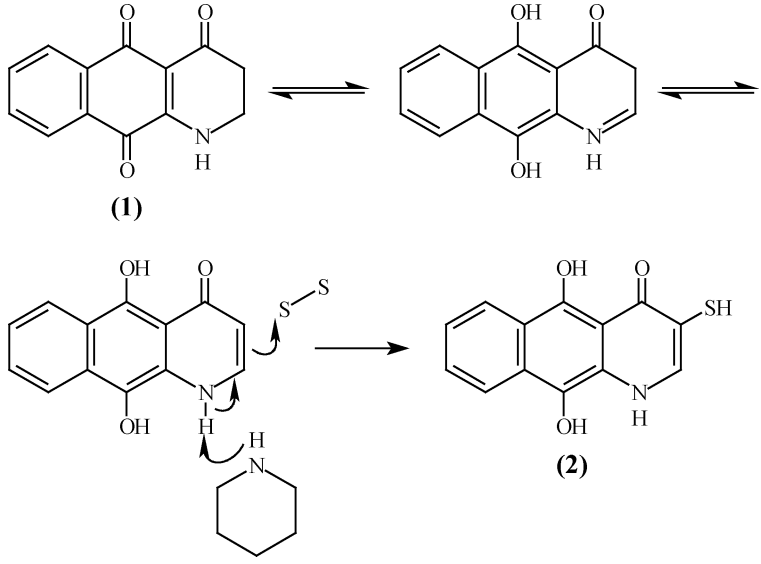
A wide range of thiazole containing metabolites have been isolated and characterized from marine organisms;[1,2] thiazole derivatives such as pencillins, which have fused thiazolidine and β-Lactam rings, are potent antibiotics.[3] The addition quinones possess widespread application in various fields, including use as fungicides,[4–9] antibacterial[10–13] drugs,[14–17] and vat dyes,[18–21] and have biological activity,[22–28] antioxidant.[29,30] The goal of this project was to investigate and develop newer approaches for the synthesis of new heterocyclic quinones incorporating sulfur. We synthesized new heterocyclic by a cyclocondensation reaction of compound **2** with chloroketene to give the new compound **3**, which was used for the synthesis of β-Lactams **6a–d**, thiazolidinones

Received October 23, 2005; accepted April 6, 2006.
Address correspondence to H. A. Soleiman, South Valley University, Chemistry Department, Faculty of Science, Aswan, Egypt. E-mail: hsoleiman2001@yahoo.com

7a–d, pyrazolines **9a–c**, **l0a–c**, Isoxazolines **lla–c**, and pyrimidines **l2a–c** and **13a–c**.

RESULTS AND DISCUSSION

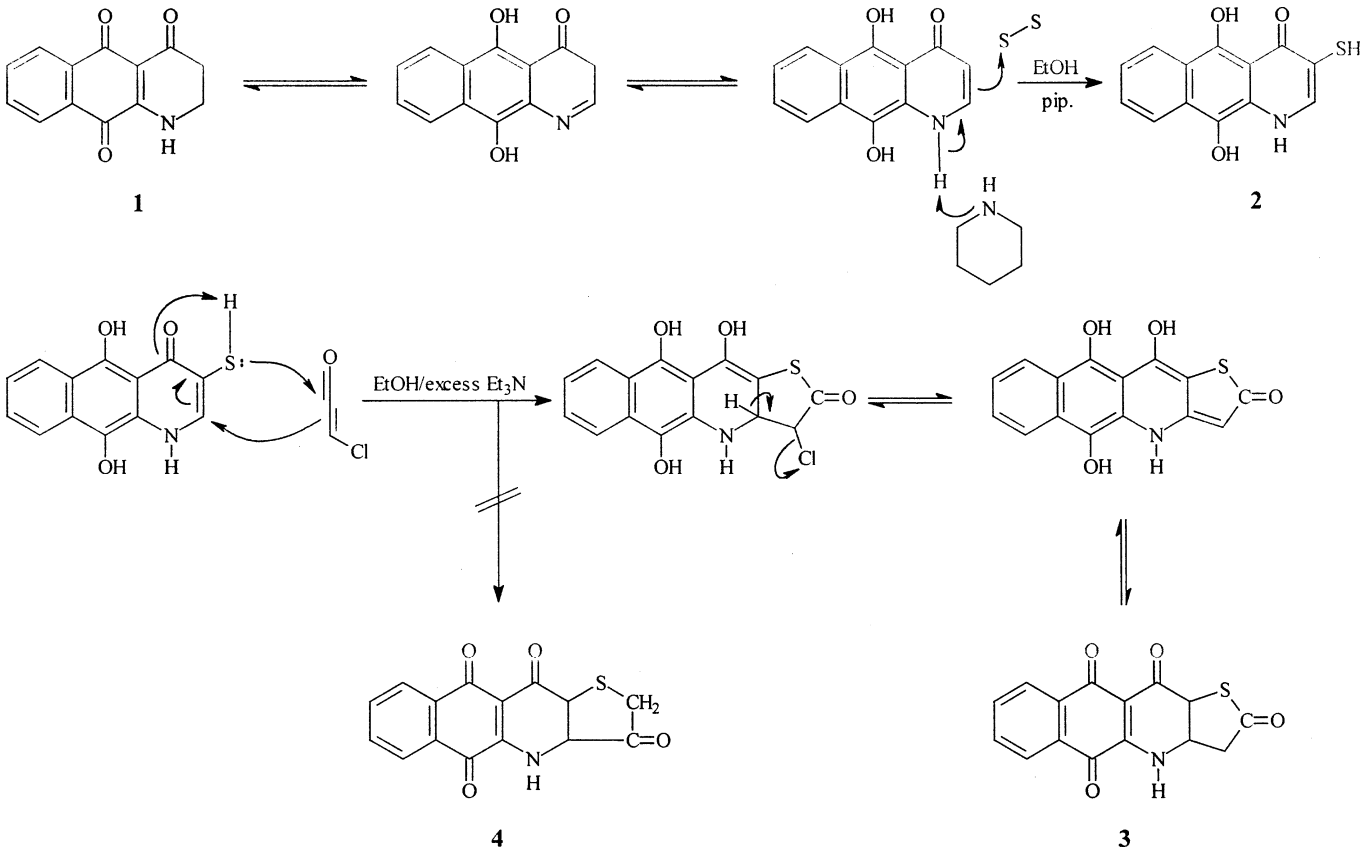
The new compound **2** was synthesised by the reaction of benz[g]-1,2,3,4-tetrahydroquinoline-4,5,10-trione **1**, which was prepared in our laboratory, as it has been reported in an earlier publication,[31] with equimolar ratios of sulfur in ethanol containing piperidine as a catalyst. In the presence of a piperidine catalyst, compound **1** transformed into a tautomeric form. The dihydroxynaphthopyrido is the more likely tautomer; thus, the reaction of the pyridone with elemental S_8 could conceivably result in the proposed product. Thus compound **2** was prepared according to Equation (1).



EQUATION 1

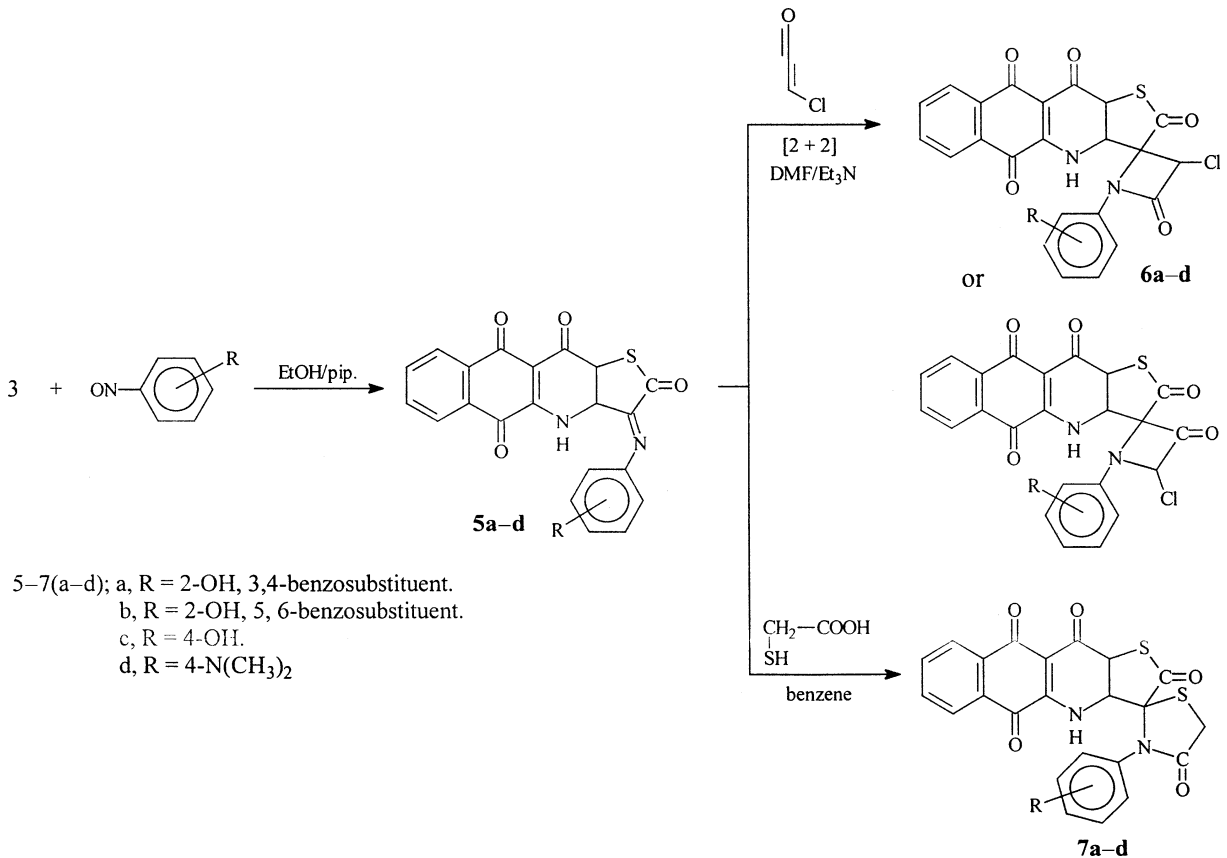
The structure of compound **2** was confirmed by elemental analysis, and an IR and ^{1}H NMR spectrum, which revealed the presence of a broad singlet signal at δ 10.2 for NH, broad signals at δ 11.8 for 2OH, and a multiplet signal at δ 8–6 for Ar H^+ at δ 5.7 (s, CH) and δ 1.8 (br, SH), and mass spectral data showed the molecular ion peak at m/z (259).

The reaction of compound **2** with chloroacetyl chloride in the presence of an excess triethylamine catalyst is considered chloroketene



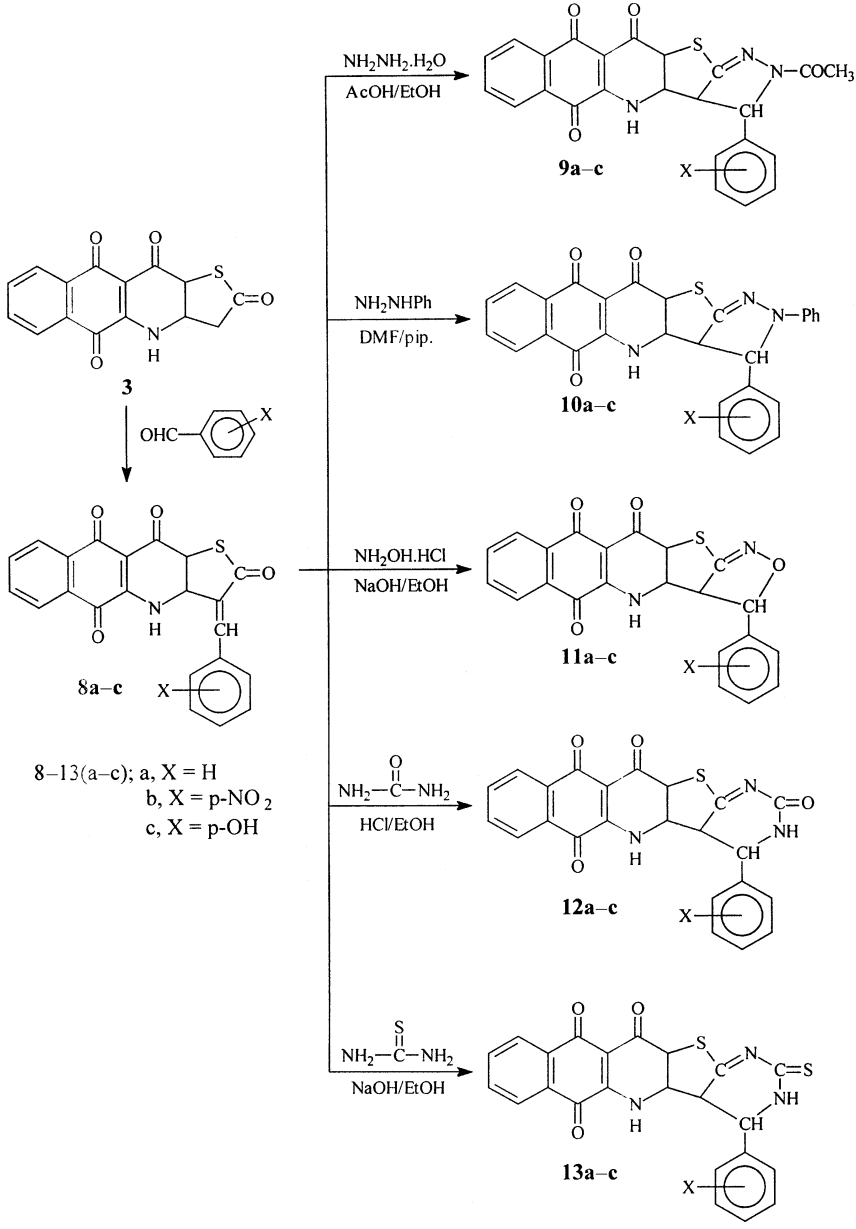
1 **2** **4** **3**

SCHEME 1



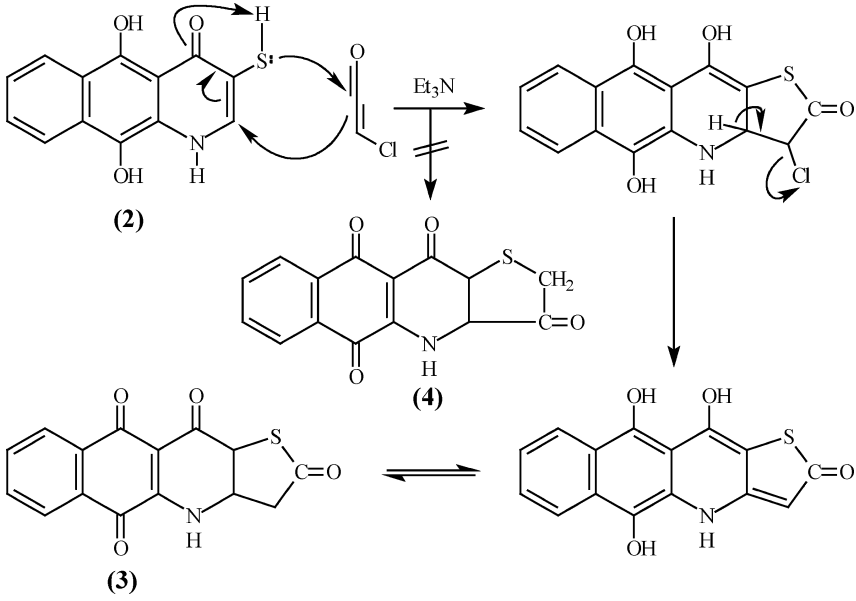
5–7(a–d); a, R = 2-OH, 3,4-benzosubstituent.
b, R = 2-OH, 5, 6-benzosubstituent.
c, R = 4-OH.
d, R = 4-$N(CH_3)_2$

SCHEME 2



SCHEME 3

chemistry.[32] The reaction of the more likely tautomeric structure of compound **2** with chloroketene gives the opportunity for a [3 + 2] cycloaddition because triethylamine is really only strong enough to deprotonate the thiolbarely strong enough to deprotonate the NH.[32] Thus compound **3** was prepared according to Equation (2).



EQUATION 2

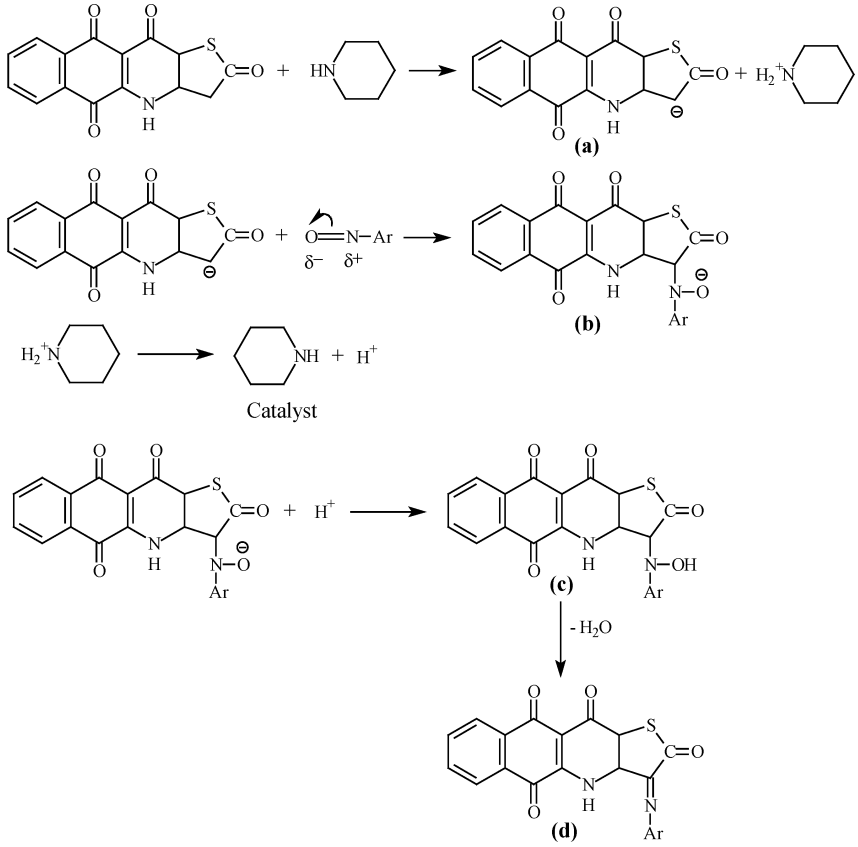
There is, of course, also the opportunity for the coupling to occur in the opposite manner with the chloroketene; this would give an intermediate that would not easily lose chlorine. Therefore, the combustion analysis rules this option out. The structure of compound **3** was confirmed by elemental analysis and an IR and ^{1}H NMR spectrum of the product in DMSO showed at δ 10.5(br, NH), δ 8–7(m, 4H), δ 2.1(d, 2H), δ 1.6(d, 1H), and at δ 1.1 (q, 1H) supporting the structure of compound **3**, and mass spectral data showed the molecular ion peak at m/z (299). According to the spectral analysis, the formation of compound **4** appears to be unlikely because there are no singlet signals assigned for the CH_2 group at δ 2.54 and singlet signals for the CH group at δ 1.65, thus, the reaction of compound 2 with chloroacetyl chloride leads to the formation of compound **3**.

Our approach to the synthesis of the desired spiro compounds started with compounds **5a–d**, which were prepared by the condensation of nitroso compounds such as α-nitroso β-naphthol, β-nitroso α-naphthol,

p-nitrosophenol, and p-nitroso-N-dimethylaniline with compounds **3** in ethanol using a piperidine catalyst, which afforded the new Schiff bases compounds.

The structure of these newly synthesised Schiff bases compounds **5a–d** were confirmed by elemental analysis and infrared spectra, which showed absorption bands at 1620–1580 cm^{-1} attributed to C=N and a characteristic band attributed to C=O at 1700–1696 cm^{-1} and 3310 attributed to NH.[33]

The formation of Schiff bases **5a–d** is expected to owing suggested mechanism, (c.f. Equation (3)).

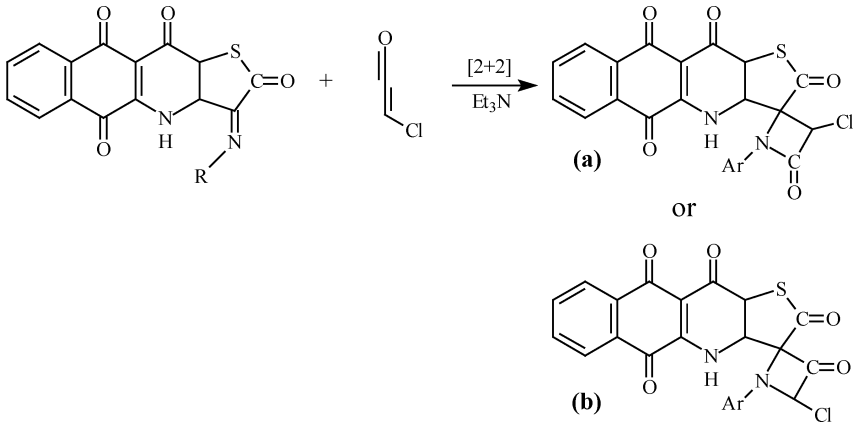


EQUATION 3

The first step in the previous mechanism involves the formation of carboanion (**a**) using piperidine as a catalyst, which abstracted a proton from the active hydrogen center; accordingly, it was added itself on

the polarized aromatic nitroso compounds forming the intermediate compound (**b**) to uptake a proton from the piperidinium ion forming compound (**c**). The latter compound (**c**) lost a mole of water to produce the Schiff base compound **5a–d**.

Compound **3** underwent cycloaddition with chloroketene to give spiro lactam **6a–d**. The cycloaddition proceeded smoothly in dimethylformamide in the presence of a triethyl amine catalyst[34,35] to afford **6a–d**. The reaction of compound 2 with chloroacetyl chloride proceeded through a [2 + 2] cycloaddition; the reaction is presented as follows (c.f. Equation (4)).

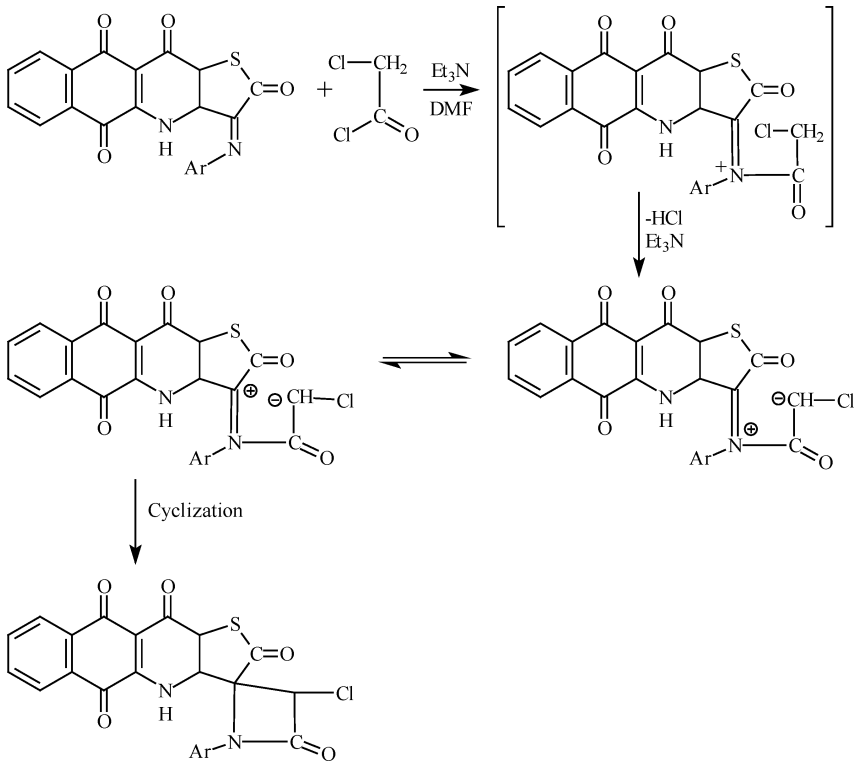


EQUATION 4

Structure (**a**) was preferred over possible (**b**) based on ^{1}H NMR, which revealed proton β-lactam nuclei that appeared at $\delta = 4$ppm. If the product of the reaction β-lactam nuclei to appear at lower field Ca = 5 ppm as it is deohielded by lone pair anisotropy.

The more stable product formed according to the following mechanisms (c.f. Equation (5)).

Thus, I would fully expect a farther rearrangement to a more stable product. The structure of spiro lactams **6a–d** confirmed by analytical data and infrared spectra, which showed the disapperance of the absorption band of C=N at 1580 cm^{-1}, also showed a C–N absorption band at 1222 cm^{-1} and C=O of a β-Lactam ring 1760 cm^{-1} and a ^{1}H NMR spectrum, which showed signals at δ 10.2(br, NH), multiplet signals at δ 8–6 for aromatic protons at δ 4, a singlet for β-lactam carbon proton at δ 1.6, a doublet singlet for a saturated carbon proton, and at δ 1.1 for another saturated carbon proton.



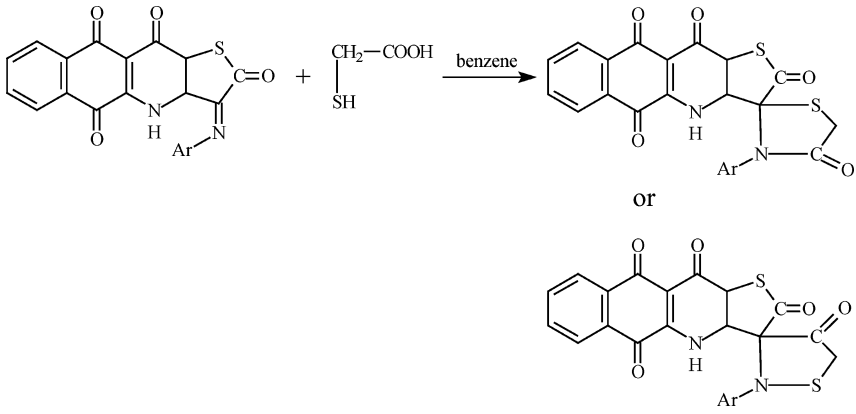
EQUATION 5

Spiro thiazolidinone **7a–d** was prepared by the cycloaddition of thioglycolic acid (1:1 molar ratios) in boiling benzene using a water separator system for five days[36,37] and afforded the corresponding compound **7a–d**, the cycloaddition proceeded as follows (c.f. Equation (6)).

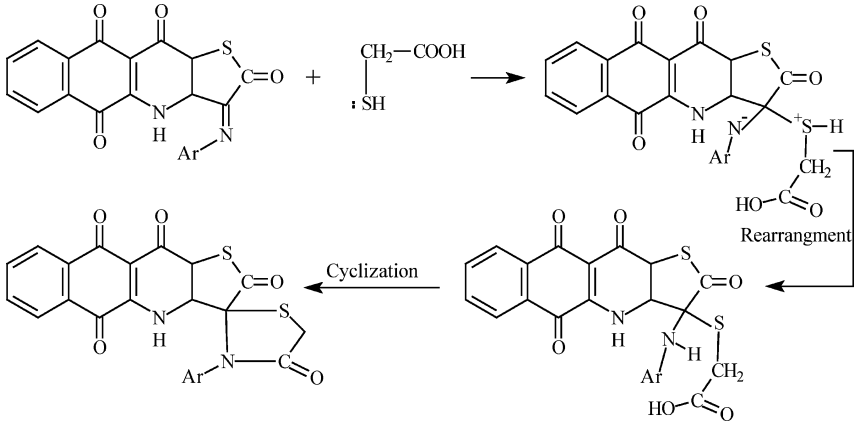
The cycloaddition reaction was assumed to go through the following suggested mechanism (c.f., Equation (7)).

The structure of thiazolidinone derivatives **7a–d** was identified from the correct elemental analysis and infrared spectra, which showed an absorption band at 1685–1645 cm^{-1} attributed to C=O group and ^1H NMR spectrum, which showed singlet a signal at 2.39 for CH_2 of the thiazolidinone ring.

The activity of the methylene group in compound **3** lead compound **3** was easily condensed with different aromatic aldehydes in ethanol and dimethyl formamide (5 mL) as a solvent using a piperidene catalyst to give **8a–c**. The structure of compound **8a–c** was confirmed by elemental analysis and IR, which revealed the presence of peak NH



EQUATION 6



EQUATION 7

at 3400–3100 cm^{-1}, C=O 1730–1660 cm^{-1}, and C=C 1610–1580 cm^{-1}; also, its structures were confirmed by ^1H NMR and mass spectral data (c.f. Tables I and II).

The activity of the exocyclic group C=C in compound 8a–c in conjugation with the carbonyl group was demonstrated by a reaction with hydrazines, hydroxylamine hydrochloride, urea, and thiourea. The nature of the structure of the products for the previously mentioned reaction, according to the different methods of analysis, elemental analysis, IR, and mass spectra, gave us the agreements that the reaction is carried out by a condensation addition reaction through the α, β-unsaturated ketonic system. Thus, the chemical work covers the implementation

TABLE I The Yield, m.p., and Elemental Analysis of Compounds (1–13)

Compound	Yield (%)	Elemental Analysis (Found)				
		C	H	N	S	Cl
1	75	68.72 (68.70)	3.99 (3.97)	6.16 (6.15)	—	—
2	65	60.22 (60.21)	3.49 (3.47)	5.43 (5.42)	12.34 (12.33)	—
3	70	60.19 (60.18)	3.03 (3.02)	4.60 (4.59)	10.69 (10.68)	—
5a	73	66.06 (66.05)	3.10 (3.05)	6.19 (6.17)	7.05 (7.03)	—
5b	69	66.06 (66.03)	3.10 (3.00)	6.19 (6.14)	7.05 (7.00)	—
5c	67	62.35 (62.34)	2.98 (2.97)	6.95 (6.94)	7.93 (7.92)	—
5d	65	64.00 (64.00)	3.97 (3.96)	9.78 (9.76)	7.43 (7.42)	—
6a	75	61.07 (61.06)	2.85 (2.84)	5.29 (5.27)	6.04 (6.03)	6.68 (6.67)
6b	68	61.07 (61.05)	2.85 (2.83)	5.29 (5.28)	6.04 (6.02)	6.68 (6.66)
6c	67	57.55 (57.54)	2.52 (2.51)	5.86 (5.85)	6.68 (6.67)	7.39 (7.38)
6d	70	59.09 (59.08)	4.57 (4.56)	8.31 (8.30)	6.31 (6.30)	6.98 (6.97)
7a	65	61.34 (61.33)	3.05 (3.04)	5.32 (5.31)	12.13 (12.12)	—
7b	67	61.34 (61.32)	3.05 (3.03)	5.32 (5.30)	12.13 (12.11)	—
7c	65	57.84 (57.83)	2.74 (2.73)	5.89 (5.87)	13.43 (13.42)	—
7d	70	59.37 (59.36)	3.79 (3.77)	8.34 (8.33)	12.68 (12.67)	—
8a	70	68.19 (68.18)	3.38 (3.37)	3.63 (3.61)	8.27 (8.26)	—
8b	68	61.09 (61.08)	2.79 (2.77)	6.50 (6.49)	7.41 (7.40)	—
8c	69	65.49 (65.48)	3.25 (3.24)	3.49 (3.48)	7.95 (7.94)	—
9a	72	64.98 (64.97)	3.86 (3.85)	9.51 (9.50)	7.39 (7.38)	—
9b	71	58.98 (58.97)	3.29 (3.27)	11.51 (11.50)	6.56 (6.55)	—
9c	73	62.71 (62.70)	3.73 (3.72)	9.18 (9.17)	6.98 (6.97)	—
10a	70	70.39 (70.38)	4.01 (4.00)	8.83 (8.82)	6.71 (6.70)	—
10b	69	64.33 (64.32)	3.47 (3.46)	12.49 (12.47)	6.31 (6.12)	—
10c	67	68.12 (68.11)	3.88 (3.86)	8.55 (8.54)	6.49 (6.47)	—
11a	65	65.64 (65.63)	3.51 (3.50)	6.99 (6.98)	7.96 (7.95)	—
11b	60	59.04 (59.03)	2.93 (2.91)	9.43 (9.42)	7.16 (7.15)	—
11c	77	63.13 (63.12)	3.37 (3.36)	6.72 (6.72)	7.66 (7.65)	—
12a	76	64.30 (64.29)	3.52 (3.51)	9.82 (9.80)	7.46 (7.45)	—
12b	77	56.30 (56.28)	2.97 (2.96)	11.86 (11.85)	6.76 (6.75)	—
12c	75	61.99 (61.98)	3.39 (3.38)	9.47 (9.45)	7.19 (7.17)	—
13a	65	67.73 (67.72)	3.55 (3.53)	9.92 (9.91)	7.53 (7.51)	—
13b	68	56.29 (56.28)	2.88 (2.87)	11.47 (11.45)	13.07 (13.06)	—
13c	69	59.84 (59.82)	3.28 (3.27)	9.14 (9.13)	13.89 (13.87)	—

All compounds were crystallized from DMF. All m.p. (except for 1, m.p., 178, 2, m.p., 280°) are above 300° and occur decomposition.

of the following fused heterocyclic compounds and the details are as follows (c.f. Equation (8)).

N-acetyl (phenyl) derivatives of compounds **9a–c** and **10a–c** were synthesised by the interaction of **8a–c** with equimolecular ratios of hydrazine hydrate or phenyl hydrazine in the presence of acetic acid (piperidine) as a catalyst, respectively.

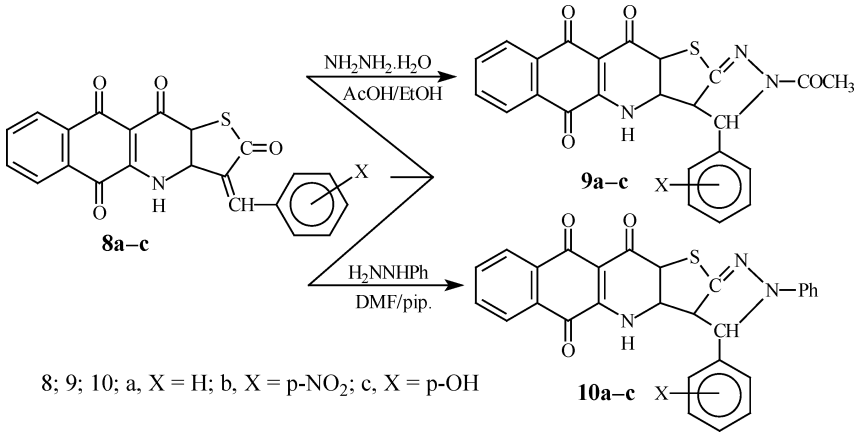
TABLE II Spectral Data of Compounds (1–13)

Compound	IR (cm^{-1})	^{1}H-NMR δ	MS (m^+)
1	3400–3150 (NH, OH), 1645 (C=O)	10.2 (br, NH), 8–7 (m, 4ArH^+), 1.4 (t, CH_2), 1.6 (t, CH_2)	227
2	3350–3200 (NH), 1640 (C=O)	11.8 (s, 2OH), 10.2 (br, NH), 8–6 (m, 4ArH^+), 5.3 (s, CH), 3.4 (br, s)	259
3	3450–3150 (NH), 1660 (C=O)	10.2 (br, NH), 8–7 (m, 4 ArH^+), 2.1 (d, 2H), 1.6 (d, 1H), 1.1 (q, 1H)	299
5a	3400–3100 (NH, OH), 1695 (C=O)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 10 ArH^+), 4 (s, CH), 1.6 (d, CH), 1.1 (d, CH)	454
5b	3400–3100 (NH, OH), 1695 (C=O), 1620 (C=N)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 10 ArH^+), 4 (s, OH), 1.6 (d, CH), 1.1 (d, CH)	454
5c	3400–3100 (NH, OH), 1680 (C=O), 1624 (C=N)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 8 ArH^+), 4 (s, CH), 1.6 (d, CH), 1.1 (d, CH)	403
5d	3400–3100 (NH), 1685 (C=O), 1625 (C=N)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 8 ArH^+), 4 (s, CH), 2.3 (s, 6H), 1.6 (d, CH), 1.1 (d, CH)	431
6a	3450–3100 (NH, OH), 1688 (C=O)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 10 ArH^+), 4 (s, CH), 1.6 (d, CH), 1.1 (d, CH)	531
6b	3400–3100 (NH, OH), 1685 (C=O)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 10 ArH^+), 4 (s, CH), 1.6 (d, CH), 1.1 (d, CH)	531
6c	3400–3100 (NH, OH), 1687 (C=O)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 8ArH^+), 4 (s, CH), 1.6 (d, CH), 1.1 (d, CH)	479
6d	3450–3150 (NH), 1689 (C=O)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 8ArH^+), 4 (s, CH), 2.3 (s, 6H), 1.6 (d, CH), 1.1 (d, CH)	508
7a	3400–3100 (NH, OH), 1697 (C=O)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 10Ar$^+$H$^+$), 2.1 (s, CH_2), 1.6 (d, CH), 1.1 (d, CH)	528
7b	3400–3100 (NH, OH), 1696 (C=O)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 10ArH^+), 2.1 (s, CH_2), 1.6 (d, CH), 1.1 (d, CH)	528
7c	3400–3100 (NH, OH), 1685 (C=O)	11.5 (s, 2OH), 10.5 (br, NH), 8–7 (m, 8ArH^+), 2.1 (s, CH_2), 1.6 (d, CH), 1.1 (d, CH)	477
7d	3400–3100 (NH), 1692 (C=O)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 8ArH^+), 2.3 (s, 6H), 2.1 (s, CH_2), 1.6 (d, CH), 1.1 (d, CH)	505
8a	3400–3100 (NH), 1647 (C=O), 1580 (C=C)	10.5 (br, NH), 8–7 (m, 9ArH^+), 6 (s, CH), 1.6 (d, CH), 1.1 (d, CH)	387
8b	3450–3100 (NH), 1665 (C=O), 1580 (C=C)	10.5 (br, NH), 8–7 (m, 8ArH^+), 6 (s, CH), 1.6 (d, CH), 1.1 (d, CH)	432

(Continued on next page)

TABLE II Spectral Data of Compounds (1–13) *(Continued)*

Compound	IR (cm^{-1})	^{1}H-NMR δ	MS (m^+)
8c	3400–3100 (NH, OH), 1668 (C═O), 1610–1580 (C═C)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 8ArH^+), 6 (s, CH), 1.6 (d, CH), 1.1 (d, CH)	403
9a	3400–3100 (NH), 1630 (C═N), 1725 (C═O)	10.5 (br, NH), 8–7 (m, 9ArH^+), 2.5 (s, CH_3) 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	443
9b	3450–3150 (NH), 1625 (C═N), 1715 (C═O)	10.5 (br, NH), 8–7 (m, 8ArH^+), 2.5 (s, CH_3) 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	488
9c	3400–3100 (NH, OH), 1620 (C═N), 1715 (C═O)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 8ArH^+), 2.5 (s, CH_3) 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	459
10a	3400–3100 (NH), 1615 (C═N), 1665 (C═O)	10.5 (br, NH), 8–7 (m, 14ArH^+), 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	477
10b	3400–3100 (NH), 1610 (C═N), 1680 (C═O)	10.5 (br, NH), 8–7 (m, 13ArH^+), 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	522
10c	3450–3150 (NH, OH), 1625 (C═N), 1680 (C═O)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 13ArH^+), 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	493
11a	3400–3100 (NH), 1636 (C═O), 1585 (C═N)	10.5 (br, NH), 8–7 (m, 9ArH^+), 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	402
11b	3400–3100 (NH), 1635 (C═O), 1590 (C═N)	10.5 (br, NH), 8–7 (m, 8ArH^+), 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	447
11c	3450–3150 (NH, OH), 1625 (C═N), 1596 (C═O)	11.5 (s, OH), 10.5 (br, NH), 8–7 (m, 8ArH^+), 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	418
12a	3400–3100 (NH), 1615 (C═O), 1590 (C═N)	10.5 (bs, 2NH), 8–7 (m, 9ArH^+), 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	429
12b	3400–3100 (NH), 1660 (C═O), 1635 (C═N)	10.5 (bs, 2NH), 8–7 (m, 8ArH^+), 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	474
12c	34500–3150 (NH, OH), 1554 (C═N), 1625 (C═O)	11.5 (s, OH), 10.5 (bs, 2NH), 8–7 (m, 8ArH^+), 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	445
13a	3400–3100 (NH), 1670 (C═O), 1619 (C═N)	10.5 (bs, 2NH), 8–7 (m, 9ArH^+), 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	425
13b	3400–3100 (NH), 1675 (C═O), 1617 (C═N)	10.5 (bs, 2NH), 8–7 (m, 8ArH^+), 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	490
13c	3400–3100 (NH, OH), 1697 (C═O), 1630 (C═N)	11.5 (s, OH), 10.5 (bs, 2NH), 8–7 (m, 8ArH^+), 2.2 (d, CH), 1.6 (d, CH), 1.4 (t, CH), 1.1 (d, CH)	461



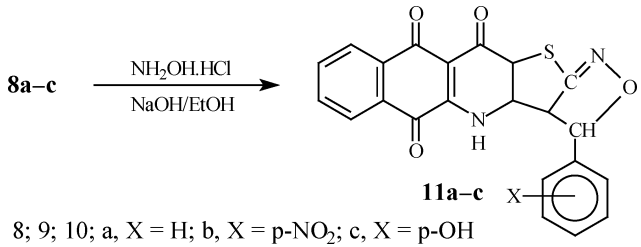
EQUATION 8

The structures of **9a–c** and **10a–c** were confirmed by elemental analysis, IR, ^{1}H NMR, and mass spectra (c.f. Tables I and II). The structure of compound 9a was confirmed by elemental analysis, IR, and an ^{1}H HNR spectrum, which revealed the presence of broad singlet signal at δ 10.5 for NH and a multiplet signal at δ 8–7 for 9 ArH^+ at δ 2.5(s, CH_3), δ 2.2(d, CH), δ 1.6(d, CH), δ 1.4(t, CH), and δ 1.1(d, CH), and mass spectral data showed the molecular ion peak at m/z(443). Also, the structure of compound 10a was confirmed by elemental anlysis, IR, and an ^{1}H NMR spectrum, which revealed the presence of a broad singlet signal at δ 10.5 for NH and a multiplet signal at δ 8–6 for 14 ArH^+ at δ 2.2(d, CH), δ 1.6(d, CH), δ 1.4(t, CH), and δ 1.1(d, CH), and mass spectral data showed the molecular ion peak at m/z(477).

Isoxazolino derivatives of compounds **11a–c** were synthesised by the reaction of **8a–c** with equimolecular ratios of hydroxylamine hydrochloride in the presence of sodium hydroxide (c.f. Equation (9)). The structures of **11a–c** were confirmed by elemental analysis, IR, ^{1}H NMR, and mass spectra (c.f. Tables I and II).

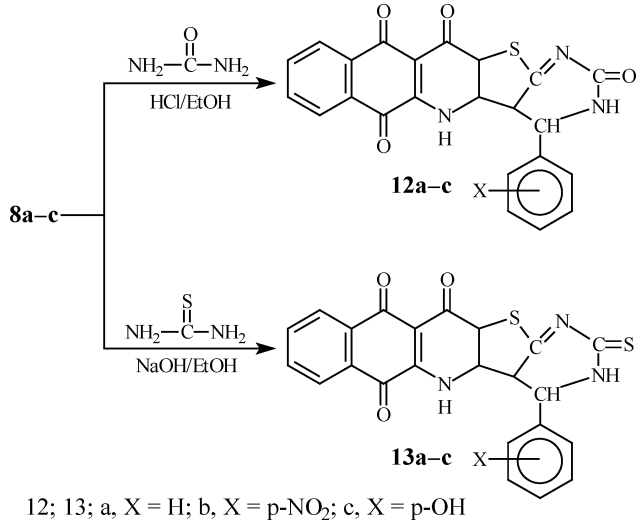
Pyrimidino and pyrimidine thiono derivatives of compounds **12a–c** and **13a–c** were synthesized by the reaction of **8a–c** with equimolecular ratios of urea and/or thiourea in ethanol containing 20 mL of hydrochloric acid and/or in the presence of sodium hydroxide, respectively (c.f. Equation (10)). The structures of compounds 12a–c and 13a–c were confirmed by analytical and spectral analysis (c.f. Tables I and II).

Many antimicrobial agents have been introduced into therapy;[37,38] thus, we selected some compounds and tested the biological activity of the prepared compounds. The biological activity of some selected



8; 9; 10; a, X = H; b, X = p-NO_2; c, X = p-OH

EQUATION 9



12; 13; a, X = H; b, X = p-NO_2; c, X = p-OH

EQUATION 10

prepared compounds determined using the filter paper disk method.[39] The data of the disc susceptibility tests for the used 2, 3, 5a, 6a, 7a compounds clearly showed significant and potent antibacterial activity (bactericidal) against all the gram positive tested bacteria; the gram negative organisms revealed weak susceptibility for most of the tested compounds. The compound also tested against fungi; the results showed as follows (see Table III).

EXPERIMENTAL SECTION

Melting points were obtained uncorrected. IR spectra were obtained as KBr pellets on a pye-unican Sp 1000 spectrophotometer. ^{1}H NMR spectra were recorded in DMSO-d6 at 200 MHz on a Varian Gemini

TABLE III

Test organism	Name	Compound						
		2	3	5a	6a	7a	Ampicillin	Nystatin
Gram positive bacteria	Bacillus subtilis NRS-744	++	+	+	++	+	+	−
	Micrococcus luteus SW-712	+++	++	++	+++	+++	+	−
	Bacillus niegaterium SW-354	++	++	+	+	++	+	−
	Staphylococcus aureus B-767	+++	+	++	++	++	+	−
	Streptomyces sp. SW-123	++	++	++	+	+	+	−
	Bacillus cereus ATCC-9634	++	+	+	++	+++	+	−
Gram negative bacteria	Serratia Mar. SW-98	+	+	−	+	+	+	−
	Pseudomonas aeruginosa ATCC-6NA 10245	−	+	−	+	+	+	−
	Escherichia coli B-3704	−	+	−	+	+	+	−
	Salmonella sp, SW-476	+	+	+	++	++	+	−
	Pseudomonas sp. SW-653	-	+	++	+	+	+	−
Fungi	Candida albicans IMRU-3669	+	+	+	+	+	−	+
	AspergiIIus flavus S-C 43 (3/3)	+	+	+	+	+	−	+

NMR spectrometer using TMS as a internal reference. Mass spectra were obtained on a Shimadzu GCMS QP 1000 EX mass spectrometer at 70 eV. Elemental analysis were carried out at the Microanalytical Center of Cairo University (Cairo, Egypt).

The Synthesis of Benz[g]1,2,3,4-tetrahydroquinoline-4,5,10-trione (1)

A solution of 1,4 naphthoquinone (0.02 mol, 2 × 1.58 g) ethanol 30 mL was treated with β-alanine (0.01 mol, 0.89 g). The reaction mixture was heated under reflux on a water bath for 8 h. The mixture was filtered hot, and the filtrate was added to ice water and stirred until red brown ppt. Separate the solid product so formed was collected by filtration and crystallized from ethanol (c.f. Tables I and II).

The Synthesis of Compound 2

A solution of compound 1 (0.01 mol, 2.27 gm) in ethanol (20 mL) containing 5 mL of piperidine was treated with sulfur (0.01 mol, 0.32 g). The reaction mixture was heated under reflux for 10–12 h. The solvent was then evaporated under reduced pressure and poured on to ice water acidified by HC1; the solid product so formed was collected by filtration and crystallized from ethanol (c.f. Tables I and II).

The Synthesis of Compound 3

A solution of 2 (0.01 mol, 2.59 g) in ethanol (30 mL) was treated with chloroacetylchloride (0.01 mol, 1.13 g) and 5 mL of triethyl amine catalyst. The reaction mixture was heated under reflux for 12 h. The solvent was then evaporated under reduced pressure. The solid product was collected by filtration and crystallized from dimethylformamide (c.f. Tables I and II).

The Synthesis of the New Schiff Bases Derivatives 5a–d

A solution of 3 (0.01 mol, 2.99 g) in ethanol (30 mL) was treated with aromatic nitroso compounds (0.01 mole) in the presence of a catalytic amount of piperidine (0.5 mL). The reaction mixture was heated under reflux for 7–6 h. The solvent was then evaporated under reduced pressure, and the residue was treated with ice water. The solid product was collected and crystallized from dimethylformamide (c.f. Tables I and II).

The Synthesis of Spiro Lactam Derivatives 6a–d

A solution of 5a–d (0.01 mole) was treated with chloroacetyl chloride (0.01 mol, 1.13 g) in dry DMF (30 mL) in the presence of a catalytic amount of triethylamine (0.01 mL); the reaction mixture was heated under reflux for l0 h. (monitored by TLC). The solvent was then evaporated under reduced pressure and the residue was treated with ice water. The solid product formed collected by filtration and crystallized from dimethylformamide (c.f. Tables I and II).

The Synthesis of Spiro Thiazolidinone Derivatives 7a–d

A solution of Schiff bases **5a–d** (0.01 mole) was treated with mercaptoacetic acid (0.01 mol, 0.92 g) in benzene (50 mL) and refluxed on a water bath for about 5 days. The mixture was then separated using a separator funnel. The solid product was collected and crystallized from dimethylformamide (c.f. Tables I and II).

The Synthesis of Arylidene Compound Derivatives 8a–c

A solution of compound **3** (0.01 mol, 2.99 g) in absolute ethanol (30 mL) and DMF was treated with different aromatic aldehydes (0.01 mol) in the presence of a piperidine catalyst. The reaction mixture was heated under reflux for 4–6 h (monitored by TLC). The solvent was then evaporated under reduced pressure, and the residue was treated with ice water acidified by HC1. The solid product was collected and crystallized from dimethylformamide (c.f. Tables I and II).

The Reaction of Compound 8a–c with Hydrazine Hydrate to Give N-Acetyl-pyrazolo Derivatives 9a–c

A solution of 8a–c (0.01 mol) in absolute ethanol (30 mL) was treated with hydrazine hydrate (0.01 mol, 0.50 g) in the presence of glacial acetic acid as a catalyst. The reaction mixture was heated under reflux for 10–12 h. (monitored by TLC). The reaction mixture was filtered hot; the solvent was then evaporated under reduced pressure, and the remaining resin was boiled with petroleum ether (60–80°C). The residue was treated with ice water, and the solid obtained was collected and crystallized from dimethylformamide (c.f. Tables I and II).

The Reaction of Compound 8a–c with Phenylhydrazine to Give N-phenyl-pyrazolo Derivatives 10a–c

A solution of 8a–c (0.01 mol) in dimethylformamide (30 mL) was treated with phenylhydrazine (0.01 mol, 1.08 g) in the presence of a catalytic amount of piperidine (0.1 mL). The reaction mixture was heated under reflux for 11 h. (monitored by TLC). The solvent was then evaporated under reduced pressure, and the residue was treated with cold water. The solid product was collected and crystallized from dimethylformamide (c.f. Tables I and II).

The Reaction of Compound 8a–c with Hydroxylamine Hydrochloride to Give Isoxazolo Derivatives 11a–c

A solution of 8a–c (0.01 mole) in absolute ethanol (30 mL) was treated with hydroxylamine hydrochloride (0.01 mol, 6.95 g) in the presence of sodium hydroxide as a catalyst. The reaction mixture was heated under reflux for 10–12 h (monitored by TLC). The reaction mixture was filtered hot. The solvent was then evaporated under reduced pressure, and the remaining resin was boiled with petroleum ether (60–80°C). The solid product was collected and crystallized from dimethylfomiamide (c.f. Tables I and II).

The Reaction of Compound 8a–c with Urea to give Pyrimidino Derivatives 12a–c

A solution of 8a–c (0.01 mol) in ethanol (20 mL) was treated with urea (0.01 mol, 0.60 g) in the presence of conc. HC1. The reaction mixture was heated under reflux for 13–15 h (monitored by TLC). It was then filtered hot and allowed to cool; the solvent evaporated under reduced pressure, and the residue was treated with crushed ice and neutralized with 5N NaOH. The solid product was collected and crystallized from dimethylformamide (c.f. Tables I and II)

The Reaction of Compound 8a–c with Thiourea to Give Thiopyrimidino Derivatives 13a–c

A solution of 8a–c (0.01 mol) in ethanol was treated with thiourea (0.01 mol, 0.76 g) in the presence of sodium hydroxide as a catalyst. The reaction mixture was heated under reflux for 10–12 h (monitored by TLC). It was then filtered hot; the solvent evaporated under reduced pressure to dryness, and the residue treated with petroleum ether (60–80°). The excess of petroleum ether was removed, and the residue was

treated with cold water. The solid product was collected and crystallized from dimethylformamide (c.f. Tables I and II).

REFERENCES

[1] M. North and G. Pattenden, *Tetrahedron*, **46,** 8269 (1990).
[2] G. Pattenden, *J. Heterocycl. Chem.*, **29,** 607 (1992).
[3] W. O. Foye, Principles of Medicinal Chemistry, 2nd ed. (Lea and Befiger, Philadelphia, 1981).
[4] J. G. Horsfall, *Chromica Botamica Co. Walthan,* 1 (1945).
[5] G. A. Gries, *Phytopathology,* **33,** 112 (1943).
[6] J. E. Little, J. J. Sporston, and M. W. Fotte, *Jour. Biol. Chem.,* **174,** 335 (1948).
[7] W. G. Lihly and H. Barnett, *Physiology of Fungi,* 1st ed., p. 257 (McGraw Hill, New York: London, Toronto, 1951).
[8] E. C. Ladd and M. P. Harvey, *Can.*, **205,** 284 (1964).
[9] M. A. Raslan, F. M. Abd El-Latif, H. H. Otto, and K. U. Sadek, *J. Chem. Soc.,* **47,** 947 (2000).
[10] S. A. Waksman and H. B. Woodroff, *J. Bactriol.,* **40,** 581 (1940).
[11] H. Brockman and H. Grone, *Chem. Ber.* **87,** 1036 (1954).
[12] W. P. Fisher, J. Charneg, and W. A. Bdnofer, *Antibiotic and Chemotherapy*, **1,** 571 (1951).
[13] B. N. Ames and B. L. Hozecker, *J. Biol. Chem.,* **220,** 113 (1956).
[14] B. S. Oppenheimer, S. Soloway, and B. E. Lowenstein, *J. Mt. Sinai Hosp.,* **11,** 23 (1994).
[15] A. K Khalafallah, M. A. Selim, R. M. Abu El-Hamed, M. A. El-Maghraby, H. A. Soleiman, and M. A. Raslan, *Ind. J. Chem.,* **34B,** 1066 (1995).
[16] V. Sunel, C. Ciugureanu, and M. Ungureanu, *Rev. Med. Chir. Soc. Med. Nat. Iasi,* **100,** 163 (1996).
[17] A. K. Khalafallah, M. E Hassan, and H. A. Soleiman, *Indian Chem. Soc.*, **69,** 318 (1992).
[18] M. F. Setori, U.S. Patent (August, 8, 1961), 2, 995, 578 (1961).
[19] M. F. Satori, French Patent (June, 16, 1959), 1, 181, 537 (1959).
[20] N. J. Buu-Hoi, *J. Chem. Soc.,* 489 (1952).
[21] U. Lohmann, K. H., and K. Hartke, *Archm Pharm.*, 313 (1984).
[22] M. A. El-Maghraby, A. K. Khalafallah, M. E. Hassan, and H. A. Soleiman, *J. Chin. Chem. Soc.*, **35,** 278 (1988).
[23] M. A. El-Maghraby, A. K. Khalafallah, M. E. Hassan, and H. A. Soleiman, *J. Indian Chem. Soc.,* **LxIII,** 910 (1986).
[24] H. A. Soleiman, A. K. Khalafallah, and H. M. Abdelzaher, *J. Chin. Chem. Soc.*, **47,** 1267 (2000).
[25] H. A. Soleiman, F. M. Abdel-Latif, M. A. Khalil, and I. H. Elazab, *Phosphorus, Sulfur, and Silicon*, **177,** 1001 (2002).
[26] H. A. Soleiman, A. K. Khalafallah, and H. A. Shindy, *Indian J. Chem.*, **42B,** 1159 (2003).
[27] H. A. Soleiman, A. I. M. Koraiem, and N. Y. Mahmoud, *J. Chin. Chem. Soc.*, **51,** 553 (2004).
[28] H. A. Soleiman, A. I. M. Koraiem, and N. Y. Mahmoud, *J. Chin. Chem. Soc.*, **52,** (2005).
[29] K. H. Gee, U.S. Patent (June, 22,1965), Appl. (June, 28, 1961), 3, 190, 843 (1961).

[30] A. K. Klialafallah, R. M. Abd El-Aal, and N. A. A. Elkanzi, *J. Chin. Chem. Soc.*, **49,** (2002).
[31] L. Loven, Brawn, and W. T. Summer Fard, *J. Chem. Eng. Data,* **11,** 264 (1966).
[32] F. Duran and L. Ghosez, *Tetrahedron Lett*., **3,** 245 (1970).
[33] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed. (Methuen and Co. Ltd., London, 1958).
[34] B. B. Harinath, and R. N. Y. Subba, *Proc. Indian Acad. Sci,* **67A,** 31 (1968).
[35] A. K. Klialafallah, A. I. M. Koraiem, M. A. Elmaghraby, and H. A. Shindy, *Egypt J. Chem.,* **36,** 1, 159 (1993).
[36] (a) *Liebiges Ann, Chem.*, 2178 (1982); (b) *Farmaco*, 435 (1993).
[37] L. Z. Yan, A. C. Gibb, M. E. Stiles, D. S. Wishart, and J. C. Vederas, *J. Med. Chem.,* **43,** 4579 (2000).
[38] K. C. Fang, Y. L. Chen, J. Y. Sheu, T. C. Wang, and C. C. Tzeng, *J. Med. Chem.,* **43,** 3809 (2000).
[39] Y. H. Loo and J. C. Sylvester, *J. Bact.*, **50,** 701 (1945).