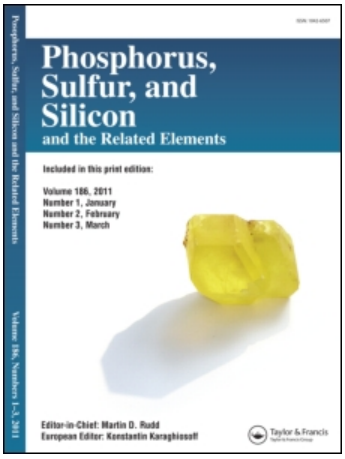

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Poly Fused/Isolated/Spiro Sulphur Compounds of Quinone and Their Biological Activity

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Poly Fused/Isolated/Spiro Sulphur Compounds of Quinone and Their Biological Activity

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A series of some fused and spiro heterocyclic compounds such as pyrazolines, Isoxazolines, pyrimidines, β-lactams, and thiazolidinone derivatives ***3***, ***6a–d***, ***7a–d***, ***9a–c***, ***10a–c***, ***11a–c***, ***12a–c***, ***13a–c*** *have been synthesised by cycloaddition and cycloconden-sation reaction of monochloroacetyl chloride, mercaptoacetic acid, hydrazines, hydroxylamine, urea, and thiourea incorporating the prepared compounds* ***5a–d***, ***8a–c***. *The synthesized compounds were tested for antibacterial and fungicidal activity. Gram-negative Bacillus cereus, Gram-negative serratia sp, as well as the fungus were used for this purpose. The biological assay was determined according to the filter paper disc method. Assay plates were incubated at 30°C one day for the bacteria and three dayes for the fungus (British Pharmacopoeia commisson, 1102m, London 1963). The test results show that the components have a strong and satisfactory effect.*

Keywords Isoxazoline; pyrazolone; pyrimidine; pyrimidine thione; spiro β-Lactam; spiro thiazolidinone; thiophene quinone compounds

INTRODUCTION

The activated β-lactam unit was a salient feature of these antibacterials, but the nature and sterical arrangement of the substituents also play a major role in the antibacterial activity and pharmacokinetics,[1] monocyclic β-lactams exhibiting in vitro antibacterial activity versus anaerodes and Gram-positive aerobes.[2–4] Thiazole derivatives such as pencillins which have fused thiazolidine and β-lactam rings were known and used as potent antibiotics.[5] Thiazolidinones derivatives are used in biological activities such as bactericidal, pesticidal, fungicidals, insecticidal.[6,7]

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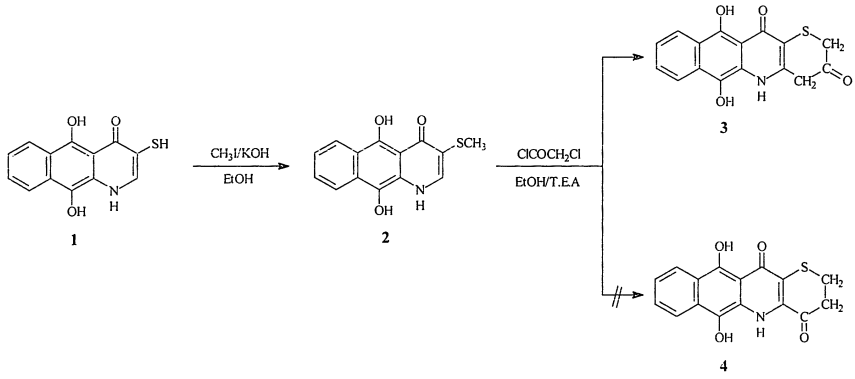
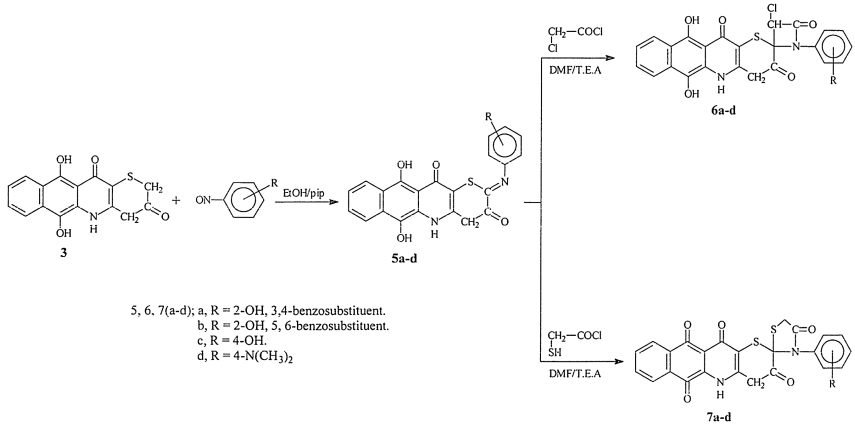
In our research project, we aimed to investigate and develop newer approaches for the synthesis of new heterocyclic quinone incorporating sulphur—some or all of which may be associated with biological activities or other applications of certain interest.[8–14]

RESULTS AND DISCUSSION

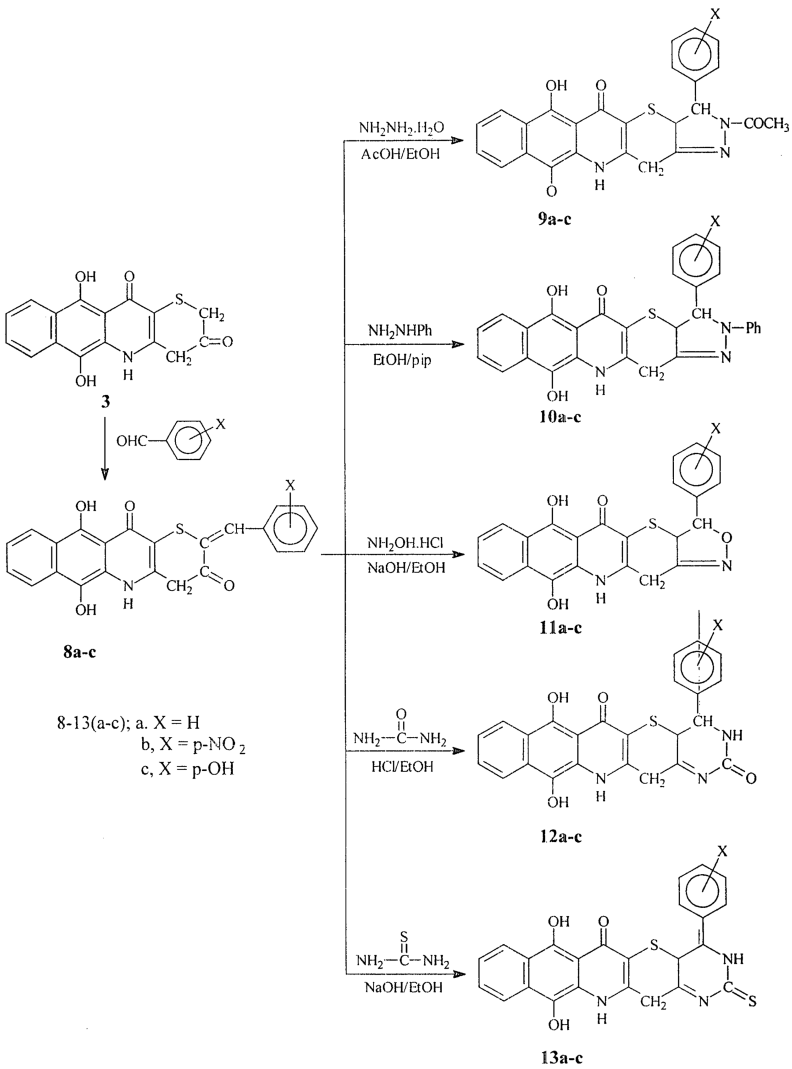
It is interesting to mention that along with an efficient strategy for synthesis of new heterocyclic by cyclocondensation, reaction of compound **2** with chloroacetyl chloride produced the new compound **3** or **4** which is used for the synthesis of β-lactam, thiazolidinone; pyrazolines, isoxazolines, and pyrimidines **6a–d**, **7a–d**, **9a–c**, **10a–c**, **11a–c**, **12a–c**, **13a–c** (Schemes 1, 2, 3).



SCHEME 1



SCHEME 2



SCHEME 3

The new compound **2** was synthesized by the reaction of compound **1**[15] with equimolar ratios of methyl iodide in ethanol containing potassium hydroxide catalyst.

The structure of compound **2** was confirmed by IR spectra, which revealed the present of peak at υ 3400–3100 cm^{-1} for NH group, peak at υ 1650 cm^{-1} for (C=O), also ^1H NMR spectra revealed the presence of signglet peak for CH group at δ 1.25, singlet peak for CH_3 at δ 1.27,

TABLE I Characterization of Compounds 2–13

No.	Yield %	m.p.	Crystal solvent	Molecular formula	Molecular weight	MS
2	63	270	DMF	$C_{14}H_{11}O_3NS$	(273.36)	273
3	78	> 300	DMF	$C_{16}H_{11}O_4NS$	(313.39)	313
5a	68	> 300	DMF	$C_{26}H_{16}O_5N_2S$	(468.60)	465
5b	69	> 300	DMF	$C_{26}H_{16}O_5N_2S$	(468.60)	468
5c	70	> 300	DMF	$C_{22}H_{14}O_5N_2S$	(418.54)	418
5d	73	> 300	DMF	$C_{24}H_{19}O_4N_3S$	(455.81)	455
6a	75	> 300	DMF	$C_{28}H_{17}O_6N_2SCl$	(545.09)	545
6b	73	> 300	DMF	$C_{28}H_{17}O_6N_2SCl$	(545.09)	545
6c	70	> 300	DMF	$C_{24}H_{15}O_6N_2SCl$	(495.03)	495
6d	68	> 300	DMF	$C_{26}H_{20}O_5N_3SCl$	(522.16)	522
7a	67	> 300	DMF	$C_{28}H_{18}O_6N_2S_2$	(542.69)	542
7b	65	> 300	DMF	$C_{28}H_{18}O_6N_2S_2$	(542.69)	542
7c	67	> 300	DMF	$C_{28}H_{16}O_6N_2S_2$	(492.64)	492
7d	69	> 300	DMF	$C_{26}H_{21}O_5N_3S_2$	(519.78)	519
8a	65	> 300	DMF	$C_{23}H_{15}O_4NS$	(446.56)	446
8b	69	> 300	DMF	$C_{23}H_{14}O_6N_2S$	(446.43)	446
8c	68	> 300	DMF	$C_{23}H_{15}O_5NS$	(417.49)	417
9a	70	> 300	DMF	$C_{25}H_{19}O_4N_3S$	(457.68)	457
9b	73	> 300	DMF	$C_{25}H_{18}O_6N_4S$	(502.74)	502
9c	75	> 300	DMF	$C_{25}H_{19}O_5N_3S$	(473.68)	473
10a	69	> 300	DMF	$C_{29}H_{21}O_3N_3S$	(491.74)	491
10b	68	> 300	DMF	$C_{29}H_{20}O_7N_5S$	(582.87)	582
10c	65	> 300	DMF	$C_{29}H_{21}O_5N_3S$	(523.74)	523
11a	67	> 300	DMF	$C_{23}H_{16}O_4N_2S$	(416.57)	416
11b	65	> 300	DMF	$C_{23}H_{15}O_6N_3S$	(416.63)	461
11c	69	> 300	DMF	$C_{23}H_{16}O_5N_2S$	(432.57)	432
12a	66	> 300	DMF	$C_{24}H_{17}O_4N_3S$	(443.66)	443
12b	68	> 300	DMF	$C_{24}H_{16}O_6N_4S$	(498.79)	498
12c	69	> 300	DMF	$C_{24}H_{16}O_5N_3S$	(458.65)	458
13a	65	> 300	DMF	$C_{24}H_{16}O_3N_3S_2$	(458.71)	458
13b	67	> 300	DMF	$C_{24}H_{15}O_5N_4S_2$	(503.77)	503
13c	68	> 300	DMF	$C_{24}H_{16}O_4N_3S_2$	(474.71)	474

singlet peak for NH group at δ 10.25, and broad singlet for two OH group at δ 10.50. The mass spectra showed the molecular ion peak at m/z M^+ 273 (c. f., Tables I–III).

Reaction of compound **2** with chloroacetyl chloride in the presence of triethylamine catalyst is considered chloroketene chemistry.[16] Reaction of the more likely tautomeric structure of compound, **3** or **4** with chloroketene gives the appor-tunity for a [3 + 2] cycloaddition because triethylamine is really only strong enough to deprotonate the thiol; it is barely strong enough to deprotonate the NH (Scheme 1).

TABLE II ^{1}H NMR Spectral Data of Compounds (2–13)

Comp. no.	^{1}H-NMR (DMSO) δ ppm
2	1.25 (s, 1H), 1.27 (s, 3H), 7.3-8.1 (m, 4H), 10.25 (s, NH), 10.5 (brs, 2OH)
3	2.3 (s, 2H), 2.7 (s, 2H), 7.01–8.1 (m, 4H), 10.2 (s, NH), 10.56 (brs, 2OH)
5a	2.23 (s, 2H), 8.02–8.03 (m, 10H), 10.26 (s, NH), 10.57 (brs, 3OH)
5b	2.24 (s, 2H), 7.01–8.02 (m, 10H), 10.25 (s, NH), 10.56 (brs, 3OH)
5c	2.22 (s, 2H), 7,01–8.02 (m, 8H), 10.24 (s, NH), 10.55 (brs, 3OH)
5d	1.25 (ds, 2CH_3), 2.25 (s, 2H), 7.02–8.01 (m, 8H), 10.25 (s, NH), 10.57 (brs, 2OH)
6a	2.22 (s, 2H), 7.02, 8.1 (m, 11H), 10.25 (s, NH), 10.56 (brs, 3OH)
6b	2.23 (s, 2H), 7.02–8.1 (m, 11H), 10.23 (s, NH), 10.66 (brs, 3OH)
6c	2.24 (s, 2H), 7.01–8.02 (m, 9H), 10.25 (s, NH), 10.57 (brs, 3OH)
6d	1.26 (ds, 2CH_3), 2.24 (s, 2H), 7.02–8.0 1 (m, 9H), 10.26 (s, NH), 10.55 (brs,2OH)
7a	1.22 (s, 2H), 2.25 (s, CH_2 of thiazolidinone), 7.01–8.02 (m, 10H), 10.24 (s, NH), 10.55 (brs, 3OH)
7b	1.23 (s, 2H), 2.25 (s, CH_2 of thiazolidinone), 7.01–8.02 (m, 10H), 10.26 (s, NH), 10.57 (brs, 3OH)
7c	2.31 (s, 2H), 2.25 (s, CH2 of thiazolidinone), 7.01–8.02 (m, 9H), 10.24 (s, NH), 10.56 (brs, 3OH)
7d	1.25 (ds, 2CH_3), 2.21 (s, 2H), 2.25 (s, CH2 of thiazolidinone), 7.02–8.01 (m, 9H), 10.25 (s, NH), 10.26 (brs, 2OH)
8a	2.2 (s, 2H), 7.01–8.02 (m, 10H), 10.23 (s, NH), 10.58 (brs, 2OH)
8b	2.23 (s, 2H), 7.01–8.01 (m, 9H), 10.25 (s, NH), 10.57 (brs, 2OH)
8c	2.22 (s, 2H), 7.01–8.03 (m, 9H), 10.26 (s, NH), 10.55 (brs, 3OH)
9a	1.9 (s, 3H), 7.01–8.01 (m, 13H), 10.24 (s, NH), 10.55 (brs, 2OH)
9b	1.92 (s, 3H), 7.01–8.02 (m, 12H), 10.26 (s, NH), 10.58 (brs, 2OH)
9c	2.1 (s, 3H), 7.0'l–8.03 (m, 12H), 10.27 (s, NH), 10.56 (brs, 3OH)
10a	7.01–8.02 (m, 18H), 10.26 (s, NH), 10.6 (brs, 2OH)
10b	7.02–8.01 (m, 17H), 10.25 (s, NH), 10.65 (brs, 2OH)
10c	7.03–8.01 (m, 17H), 10.27 (s,NH), 10.64 (brs, 3OH)
11a	7.01–8.02 (m, 13H), 10.29 (s, NH), 10.92 (brs, 2OH)
11b	7.01–8.02 (m, 12H), 10.28 (s,NH), 10.89 (brs, 2OH)
11c	7.02–8.01 (m, 12H), 10.3 (s,NH), 10.86 (brs, 3OH)
12a	7.01–8.02 (m, 13H), 10.89 (s, 2NH), 11.3 (brs, 2OH)
12b	7.02–8.03 (m, 12H), 10.88 (s, 2NH), 11.34 (brs, 2OH)
12c	7.01–8.02 (m, 11H), 10.9 (s, 2NH), 11.5 (brs, 3OH)
13a	7.01–8.02 (m, 12H), 10.75 (s, 2NH), 11.55 (brs, 2OH)
13b	7.02–8.01 (m, 11H), 10.8 (s, 2NH), 11.59 (brs, 2OH)
13c	7.01–8.01 (m, 11H), 10.85 (s, 2NH), 11.6 (brs, 3OH)

Structure (3) was preferred over possible (4) based on elemental analysis, IR, ^{1}H NMR spectrum of the product in DMSO showed singlet at δ 2.7 for 2H and singlet at δ 2.3 for 2H supporting the structure of compound **3** and mass spectral data showed the molecular ion peak at m/z (313).

TABLE III IR and Elemental Analysis Data of Compounds (2–13)

Comp. no.	IR n_{max}/cm^{-1}	(Calcd.)/Found C	H	N	S	Cl
2	3400–3100 (NH), 1650 (C═O)	(61.51)	(4.06)	(5.15)	(11.73)	—
		61.50	4.07	5.13	11.72	
3	3400–3f150 (NH, OH), 1650 (C═O)	(61.32)	(3.54)	(4.49)	(10.23)	—
		61.31	3.52	4.48	10.22	
5a	3400–3100 (NH, OH), 1691 (OO),	(66.64)	(3.44)	(6.00)	(6.84)	—
	1617 (C═N)	66.63	3.42	6.00	6.81	
5b	3400–3100 (NH, OH), 1687 (C═O),	(66.64)	(3.44)	(6.00)	(6.84)	—
	1619 (C═N)	66.63	3.43	6.00	6.82	
5c	3400–3100 (NH, OH), 1690 (OO),	(63.13)	(3.37)	(6.72)	(7.66)	—
	1622 (C═N)	63.12	3.35	6.71	7.65	
5d	3400–3100 (NH, OH), 1689 (C═O),	(63.24)	(4.20)	(9.26)	(7.03)	—
	1618 (C═N)	63.23	4.19	9.25	7.02	
6a	3400–3100 (NH, OH), 1697 (C═O)	(61.69)	(3.14)	(5.16)	(5.88)	(6.51)
		61.68	3.12	5.15	5.87	6.50
6b	3450–3100 (NH, OH), 1699 (C═O)	(61.69)	(3.14)	(5.16)	(5.88)	(6.51)
		61.67	3.13	5.14	5.86	6.49
6c	3400–3100 (NH, OH), 1690 (C═O)	(58.23)	(3.05)	(5.68)	(6.48)	(7.16)
		58.21	3.04	5.67	6.47	7.15
6d	3400–3100 (NH), 1695 (C═O)	(59.81)	(3.86)	(8.08)	(6.14)	(6.79)
		59.80	3.85	8.06	6.13	6.77
7a	3400–3100 (NH, OH), 1692 (C═O)	(61.97)	(3.34)	(5.18)	(11.82)	—
		61.96	3.33	5.16	11.80	
7b	3400–3100 (NH, OH), 1687 (C═O)	(61.97)	(3.34)	(5.18)	(11.82)	—
		61.95	3.32	5.17	11.81	
7c	3400–3150 (NH, OH), 1690 (C═O)	(58.51)	(3.27)	(5.71)	(13.02)	—
		58.50	3.26	5.70	13.01	
7d	3400–3100 (NH, OH), 1692 (C═O)	(60.08)	(4.07)	(8.11)	(12.34)	—
		60.07	4.06	8.10	12.33	
8a	3450–3150 (NH,OH),	(68.81)	(3.77)	(3.50)	(7.99)	—
	1675,1610–1580 (C═C)	68.80	3.75	3.49	7.98	
8b	3400–3100 (NH, OH), 1665 (C═O),	(61.86)	(3.16)	(6.30)	(7.18)	—
	1610–1580 (C═C)	61.85	3.15	6.29	7.17	
8c	3450–3100 (NH, OH), 1675 (C═O),	(66.17)	(3.62)	(3.37)	(7.68)	—
	1610–1580 (C═C)	66.16	3.60	3.36	7.67	
9a	3400–3100 (NH, OH), 1680 (C═O),	(65.61)	(4.18)	(9.22)	(7.01)	—
	1616 (C═N)	65.60	4.17	9.20	7.00	
9b	3400–3100 (NH, OH), 1680 (C═O),	(59.73)	(3.61)	(11.19)	(6.38)	—
	1620 (C═N)	59.72	3.60	11.18	6.36	
9c	3450–3150 (NH, OH), 1685 (C═O),	(63.39)	(4.04)	(8.91)	(6.77)	—
	1625 (ON)	63.38	4.03	8.90	6.75	
10a	3400–3100 (NH,OH), 1695 (C═O),	(70.83)	(4.30)	(8.58)	(6.52)	—
	1618 (C═N)	70.82	4.29	8.57	6.51	
10b	3400–3100 (NH, OH), 1667 (C═O),	(59.76)	(3.46)	(12.07)	(5.50)	—
	1617 (C═N)	59.75	3.54	12.06	5.49	
10c	3450–3150 (NH, OH), 1675 (C═O),	(66.51)	(4.04)	(8.06)	(6.12)	—
	1618 (C═N)	66.50	4.03	8.05	6.11	
11a	3400–3100 (NH, OH), 1617 (C═N),	(66.32)	(3.87)	(6.75)	(7.69)	—
	1587 (C═O)	66.31	3.86	6.73	7.68	

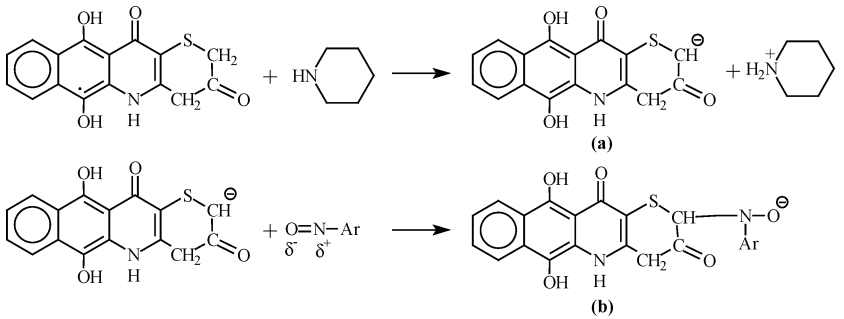
TABLE III IR and Elemental Analysis Data of Compounds (2–13) ***(Continued)***

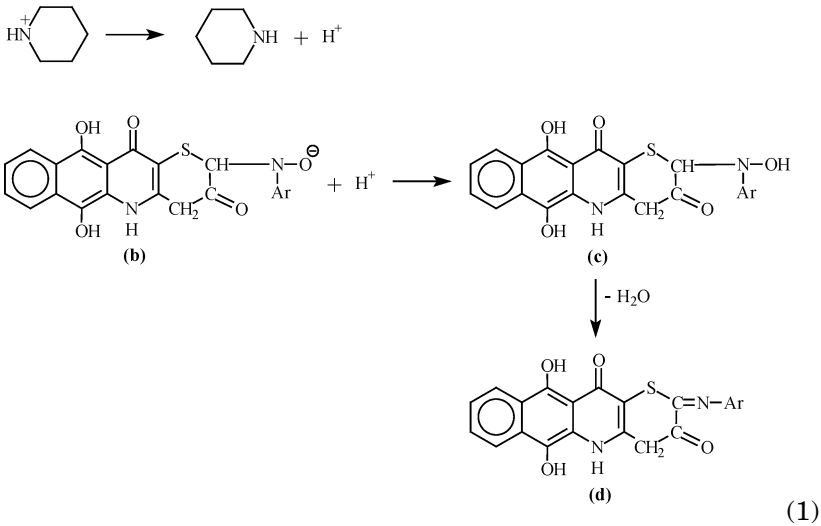
Comp. no.	IR n_{max}/cm-1	(Calcd.)/Found C	H	N	S	Cl
11b	3400–3100 (NH, OH), 1615 (C=N), 1590 (C=O)	(59.84) 59.83	(3.28) 3.27	(9.14) 9.13	(6.95) 6.94	—
11c	3450–3150 (NH, OH), 1612 (C=N), 1588 (C=O)	(63.86) 63.85	(3.73) 3.72	(6.50) 6.49	(7.41) 7.40	—
12a	3400–3100 (NH, OH), 1680 (C=O), 1619 (C=N)	(64.98) 64.97	(3.86) 3.84	(9.51) 9.50	(7.39) 7.37	—
12b	3400–3100 (NH, OH), 1686 (C=O), 1625 (ON)	(57.79) 57.78	(3.23) 3.22	(13.09) 13.08	(6.43) 6.42	—
12c	3450–3150 (NH, OH), 1.693 (C=O), 1622 (C=N)	(62.85) 62.84	(3.52) 3.50	(9.20) 9.19	(6.99) 6.98	—
13a	3400–3100 (NH, OH), 1694 (C=O), 1620 (C=N)	(62.84) 62.83	(3.52) 3.51	(9.19) 9.17	(13.98) 13.97	—
13b	3400—3100 (NH, OH), 1685 (C=O), 1615 (C=N)	(57.22) 57.21	(3.00) 3.00	(11.17) 11.15	(12.73) 12.72	—
13c	3400–3100 (NH, OH), 1688 (C=O), 1620 (C=N)	(60.73) 60.72	(3.39) 3.37	(8.89) 8.87	(13.51) 13.50	—

Our approach to the synthesis of the desired spiro compounds started with the 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 compound **3** in ethanol using piperidine catalyst afforded the new Schiff bases compounds (Scheme 2).

The structure of these newly synthesised Schiff bases compounds **5a–d** was confirmed by elemental analysis, infrared spectra, which showed absorption bands at υ 1620–1580 cm^{-1} attributed to (C=N), characteristic band attributed to (C=O), at υ **1700–1696** cm^{-1}, and at υ 3310 cm^{-1} attributed to (NH).[17]

Formation of Schiff bases **5a–d** is expected to owing suggested mechanism Eq. (1)

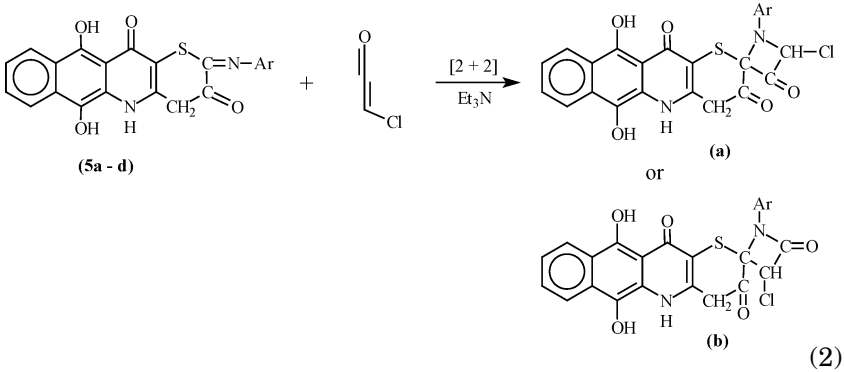




(1)

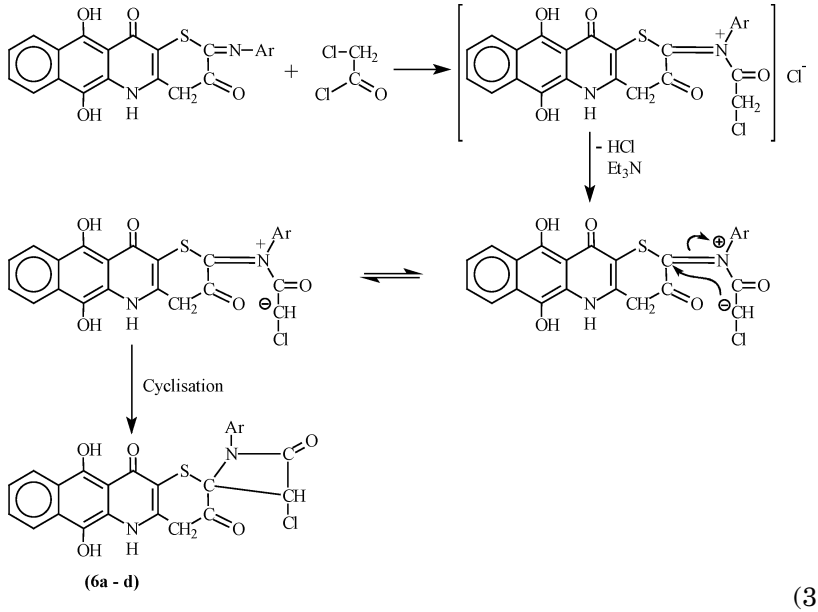
The first step in the previous mechanism involves formation of carbanion (a) using piperidine as catalyst, which abstracts a proton from the active hydrogen center; accordingly, it attached to the polarized aromatic nitroso compounds forming the intermediate compound (b) uptake a proton from the piperidinium ion forming compound (c). The latter compound (c) loses a mole of water to produce the Schiff base compounds **5a–d**.

Compound **5a–d** underwent cycloaddition reaction with chloroketene to give spiro lactam **6a–d**. The cycloaddition proceeded smoothly in dimethylformamide in the presence of triethyl amine catalyst[18–20] to afford **6a–d**. The reaction of compound **5a–d** with chloroketene proceeded through [2+2] cycloaddition, the reaction are presented as follows: Eq. (2). The structure (a) was preferred over possible (b) based on ^{1}H NMR spectrum.



(2)

The more stable product formed according to the following mechanisms Eq. (3):



(3)

Thus, we would fully expect a further rearrangement to a more product and the structure of spiro Lactams **6a–d** confirmed by analytical data and infrared spectra, which showed the disappearance of the absorption band of (C=N) at υ 1580 cm^{-1}, also shown C-N absorption band at υ 1222 cm^{-1} and (C=O) of β-Lactam ring at υ1760 cm^{-1}, and ^{1}H NMR showed singlet signals at δ1.9 support that the further rearrangement structure is more stable compound.

Spiro thiazolidinone **7a–d** were prepared by the cycloaddition of thioglycolic acid (1:1 molar ratios) in boiling benzene using a water separator system for five days[21] and afforded the corresponding compounds **7a–d** (Scheme 2).

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

The activity of 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 piperidine catalyst and reflux for 19–20 hr to give **8a–c**. The structure of compounds **8a–c** were confirmed by elemental analysis, IR which revealed the presence of

peak NH at υ 3400–3100 cm^{-1}, C=O at υ 1730–1660 cm^{-1}, and C=C at υ 1610–1580 cm^{-1}. Also, ^1H NMR spectra for **8a**, as an example, showed singlet peak for CH_2 at δ 2.20, singlet peak for NH group at δ 10.23, and broad singlet for two OH group at δ 10.58. The mass spectra showed the molecular ion peak at m/z 466 (M^+, 466), (c.f., Tables I–III).

The activity of exocyclic group C=C in compound **8a–c** in conjugation with carbonyl group was demonstrated by reaction with hydrazines, hydroxylamine hydrochloride, urea, and thiourea. The nature of the structure of the products for the abovementioned 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 condensation addition reaction through α,β-unsaturated ketonic system. Thus, the chemical work covers the implementation of the following fused heterocyclic compounds; the details are as follows :

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 piperidine as catalyst respectively[21] (Scheme 3).

The structures of **9a–c** were confirmed by IR Spectra for **9a**, as an example, which revealed the presence of peak at υ 3400—3100 cm^{-1} for NH, OH, peak at υ 1680 cm^{-1} for(C=O), peak at υ 1616 cm^{-1} for (C=N). ^1H NMR spectra, which revealed the presence of singlet peak for CH_3 at δ 1.90, singlet peak for NH group at δ 10.24, and broad singlet for two OH groups at δ 10.55. Also, the mass spectra showed the molecular ion peak at m/z 457, (M^+, 457), (c.f., Tables I–III). The structure of compounds **10a–c** were confirmed by IR spectra of **10a** for example, which revealed the presence of peaks at υ 34000–3100 cm^{-1} for NH, OH groups, peaks for C=O at υ 1690 cm^{-1}, and peak for C=N at υ 1618 cm^{-1} . Also, ^1H NMR spectra revealed the presence of singlet peaks at δ 10.26 for NH group and broad singlet at 10.60 for two OH groups. The mass spectra showed the molecular ion peak at m/z 491 (M^+, 491), (c.f., Tables I–III).

Compounds **9a–c** and **10a–c** proved to be stable on boiling with mixture of acetic acid and dilute sulphuric acid or on heating above their melting points which are the condition that bring out the cyclisation of hydrazine hydrate or phenyl hydrazine to pyrazolines. The prepared pyrazolines gave violet colored tests, characteristic for aryl pyrazolines.[22,23]

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. The structure of compounds **11a–c** were confirmed by IR spectra of compound **11a** for example, which revealed the presence of peaks at υ 3400–3100 cm^{-1} for NH,

OH group, peak at 1617 cm^{-1} for (C=N), and peak at υ 1587 cm^{-1} for (C=O). Also, ^1H NMR spectra revealed the presence of singlet peak at 10.29 for two NH groups and broad singlet at 10.92 for two OH groups. The mass spectra showed the molecular ion peak at m/z 416 (M^+, 416), (c.f., Tables I–III).

Pyrimidino and pyrimidine thiono derivatives of compounds **12a–c** and **13a–c** were synthesised by the reaction of **8a–c** with equimolecular ratio of urea and/or thiourea in ethanol containing 5 ml hydrochloric acid, and/or in the presence of sodium hydroxide, respectively. The structures of compounds **12a–c** were confirmed by IR spectra of compound **12a**, as an example that revealed the presence of peaks at υ 3400 3100 cm^{-1} for NH and OH groups, peak at 1680 cm^{-1} for (C=O), and peak at υ 1619 cm^{-1} for (C=N). Also, ^1H NMR spectra revealed the presence of singlet peak at δ 10.89 for two NH groups and broad singlet at δ 11.30 for two OH groups. Also, the mass spectra showed the molecular ion peak at m/z 443, (M^+, 443), (c.f., Tables I–III). The structure of compounds **13a–c** were confirmed by IR spectra of compound **13a** as an example, which revealed the presence of peaks at υ 3400–3100 cm^{-1} for NH, OH groups, peak at υ 1694 cm^{-1} for (C=O), peak at υ 1620 cm^{-1} for (C=O). Also, ^1H NMR spectra revealed the presence of singlet peak at δ 10.75 for NH group and broad singlet at δ 11.55 for two OH groups. The mass spectra showed the molecular ion peak at m/z 458 (M^+, 458), (c.f., Tables I–III).

Many antimicrobial agents have been introduced into the therapy,[24,25] thus we selected and tested the biological activity of some of the prepared compounds. The biological activity of some selected prepared compounds were determined using the filter paper disk method.[26] The data of the disc susceptibility tests for the used **2**, **3**, **5a**, **6a**, and **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's were also tested against fungi. The results are shown in Tables IV.

EXPERIMENTAL SECTION

Melting points were obtained uncorrected. IR spectra were obtained as KBr pellets on a Pye-unican Sp 1000 spectrophotometer. ^1H NMR spectra were recorded in DMSO-d6 MHz on a varian Gemini NMR spectrometer using TMS as initial reference. Mass spectra were obtained on a Shimadzu GCMS QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

TABLE IV Biological Activity of Some Compounds

Test organism	Name	Compound						
		2	3	5a	6a	7a	Ampicillin	Nys-tatin
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(313)	−	−	−	−	−	−	+

Synthesis of Compound 2

A solution of compound **2** (0.01 mol, 2.59 g) in ethanol (20 ml) was treated with methyl Iodide (0.01 mol) in the presence of potassium hydroxide as catalyst the reaction mixture was heated under reflux for 13–15 h. The solvent was then evaporated under reduced pressure poured onto ice/water acidified by HC1, the solid product so formed was collected by filtration and crystallized from ethanol.

Synthesis of Compound 3

A solution of compound **3** (0.01 mol, 2.73 g) in ethanol (30 ml) was treated with chloroacetylchloride (0.01 mol, 1.13 g) and 5 ml of triethylamine as catalyst. The reaction mixture was heated under reflux for 20 h. The solvent was then evaporated under reduced pressure. The solid

product was collected by filtration and crystallized from the proper solvent to give compound **3**.

Synthesis of New Schiff Bases 5a–d

A solution of 4 (0.01 mol, 3.13 g) in ethanol (30 ml) was treated with aromatic nitroso compounds (0.01 mol) in the presence of a catalytic amount of piperidine (0.5 ml). The reaction mixture was heated under reflux for 13–14 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.

Synthesis of Spiro Lactam 6a–d

A solution of **5a–d** (0.01 mol) was treated with chloro acetyl 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 23 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.

Synthesis of Spiro Thiazolidinone 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 water bath for about 5 days. The mixture was then separated using a separator funnel. The solid product was collected and crystallized from dimethylformamide.

Synthesis of Arilideno Compound 8a–c

A solution of compound **3** (0.01 mol, 3.13 g) in absolute ethanol (30 ml) and DMF was treated with different aromatic aldehydes (0.01 mol) in the presence of (0.1 ml) 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.

Reaction of Compound 8a–c with Hydrazine Hydrate to Give 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 catalyst. The reaction mixture was heated under reflux for 19 h (monitored by TLC). The reaction mixture was filtered hot, the solvent was then evaporated under reduced pressure, and the remaining resin boiled with petroleum ether (60–80°C). The residue was treated with ice/water, and the solid obtained was collected and crystallized from dimethylformamide.

Reaction of Compound 8a–c with Phenylhydrazine to Give 10a–c

A solution of **9a–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 20 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.

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

A solution of **8a–c** (0.01 mol) in absolute ethanol (30 ml) was treated with hydroxylamine hydrochloride (0.01 mol, 0.69 g) in the presence of sodium hydroxide (0.2 g) as catalyst. The reaction mixture was heated under reflux for 20–22 h (monitored by TLC). The reaction mixture was filtered hot. The solvent was then evaporated under reduced pressure, and the remaining resin boiled with petroleum ether (60–80°C). The solid product was collected and crystallized from dimethylformamide.

Reaction of Compound 9a–c with Urea to Give 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 23–25 h (monitored by TLC). It was then filtered hot, allowed to cool, solvent evaporated under reduced pressure, and the residue treated with crushed ice and neutralized with 5N NaOH. The solid product was collected and crystallized from dimethylformamide.

Reaction of Compound 8a–c with Thiourea to Give 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 catalyst. The reaction mixture was heated under reflux for 20–22 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°C).

The excess of petroleum ether was removed and the residue treated with cold water. The solid product was collected and crystallized from dimethylformamide.

REFERENCES

[1] W. Durckheimer, J. Blumbach, R. Lattrell, and H. Scheunemannk, *Angew. Chem.*, **97,** 183 (1985).
[2] J. Brickners, J. J. Gaikema, L. J. Greenfield, G. E. Zurenko, and P. R. Manninen, *Bioorg. Med. Chem. Lett*., **3,** 2241 (1993).
[3] J. Brickners, J. Gaikema, G. Zurenko, L. Greenfield, P. Manninen, and J. Ulanowicz, *Antibiot*., **45,** 213 (1992).
[4] S. J. Brickners, *Eur. Pat.*, 232017 (1987); (b) *Chem. Abstr.*, **107,** 236366 (1987).
[5] W. O. Foye, Principles of Medicinal Chemistry, (Lea and Febiger, Philadelphia, 1981), 2nd ed.
[6] A. K. Khalafallah, A. I. M. Koraiem, M. A. El-Maghraby, and H. A. Shindy, *Egypt J. Chem.*, **36**(3), 159–166, 1, 1993.
[7] A. K. Khalafallah, F. M. Abdlatif, M. A. Salim, and M. A. El-Maghraby, Asian, *Journal of Mem.*, **5**(4) (1993).
[8] El-M. A. Maghraby, A. K. Khalafallah, M. E. Hassan, and H. A. Soleiman, *J. Chin. Chem. Soc*., **35,** 278 (1988).
[9] El.-M. A. Maghraby, A. K. Khalafallah, M. E. Hassan, and H. A. Soleiman, *J. Indian Chem. Soc.*, **LxIII,** 910 (1986).
[10] H. A. Soleiman, A. K. Khalafallah, and H. M. Abdelzaher, *J. Chin. Chem. Soc.*, **47,** 1267 (2000).
[11] H. A. Soleiman, F. M. Abdel-Latif, M. A. Khalil, and I. H. Elazab, *Phosphorus, Sulfur and Silicon*, **177,** 1001 (2002).
[12] H. A. Soleiman, A. K. Khalafallah, and H. A. Shindy, *Indian J. Chem*., **42B,** 1159 (2003).
[13] H. A. Soleiman, A. I. M. Koraiem, and N. Y. Mahmoud, *J. Chin. Chem. Soc.*, **51**(3), 553 (2004).
[14] H. A. Soleiman, A. I. M. Koraiem, and N. Y. Mahmoud, *J. Chin. Chem. Soc.*, **52**(1) (2005).
[15] A. K. Khalafallah, N. A. A. El-Kanzi, H. A. Soleiman, and Younis, M., *Phosphorus, Sulfur and Silicon*, **181**(11), 2483–2503 (2006).
[16] D . Ferando and G. Geon, *Tetrahedron Letters*, **3**, 245 (1970).
[17] L. J. Bellamy, The Infrared Spectra of Complex Molecules, (Methuen and Co. Lt., London, 1958, Reprinted 1964), 2nd Ed..
[18] B. B. Harinath and R. N. Y. Subba, *Proc. Indian Acad. Sci,* **67A,** 31 (1968).
[19] M. A. Abdel Mawgoud, MS.C. Thesis, Assiut Univ., Assuit, Egypt, 105, 1976.
[20] A. K. Khalafallah, A. I. M. Koraiem, M. A. Elmaghraby, and H. A. Shindy, *Egypt, J. Chem.* **36**(3), 159–166 (1993).
[21] A. K. Khalafallah, F. M. Abd Latif, and M. A. Salim, *Asian Journal of Chem.*, **5**(4) (1993).
[22] B. H. Nicolet, *J. Am. Chem. Soc.*, **57,** 1098 (1935).
[23] L. Knorr, *Ann.* 200–238 (1887).
[24] L. Z. Yan, A. C. Gibbs, M. E. Stiles, D. S. Wishart, and J. C. Vederas, *J. Med. Chem.*, **43,** 4579 (2000).
[25] K. C. Fang, Y. L. Chen, J. Y. Sheu, T. C. Wang, and C. C. Tzeng, *J. Med. Chem.*, **43,** 3809 (2000).
[26] Y. H. Loo and J. C. Sylvester, *J. Bact.*, **50,** 701 (1945).