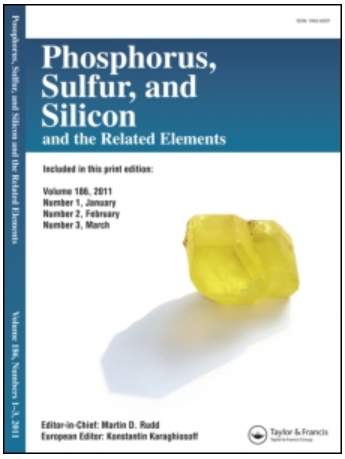

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A Facile One-Pot Synthesis of Some New Spiro-thiazolidin-4-ones and Benzimidazoles of Biological Interest

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A Facile One-Pot Synthesis of Some New Spiro-thiazolidin-4-ones and Benzimidazoles of Biological Interest

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*In a one-pot procedure, aromatic amines **1a–c**, 9-fluorenone (**2**) and 2-mercaptoacetic acid (**3**) were converted into fluorenespiro-thiazolidinone derivatives **4a–c**, which undergo condensation, oxidation and thiation to afford **6a–i**, **7a–c**, and 4-thioxo **8a–c**, respectively. A new fluorenespiro-thiazolo-benzimidazole **10** was also obtained in one step via cyclocondensation of 1,2-phenylenediamine, 9-fluorenone and 2-mercaptoacetic acid. The obtained products seem to be interesting from the biological point of view.*

Keywords 2-Mercaptoacetic acid; 9-fluorenone; fluorenespiro[9.2′]-thiazolo[3′,4′-*a*]benzimidazole; fluorenespiro[9.2′]-3′-aryl-thiazolidin-4-one derivatives

INTRODUCTION

2-Substituted-thiazolidin-4-one derivatives exhibit unusual high activity in vitro against Mycobacterium Tuberculosis (TB), as drugs for anti-HIV and anticancer activity.[1–4] Recently, a number of 4-thiazolidinones having an 2-aryl substituted have been synthesized and found to exhibit potent selective anti-plateret activating factor both in vitro and in vivo.[5] Thiazolo[3,4-*a*]benzimidazoles and their analogues were reported to be potent anti-HIV agents.[6,7] Spiroheterocyclic compounds including thiazolidine moiety have also been shown to exhibit a variety of interesting biological activities.[8–11] In continuation to our search of new compounds with anticipated biological activity from accessible starting materials,[12–17] we report here a simple one-pot synthesis of some new fluorenespiro-thiazolidin-4-one and fluorenespiro-thiazolo-benzimidazole derivatives.

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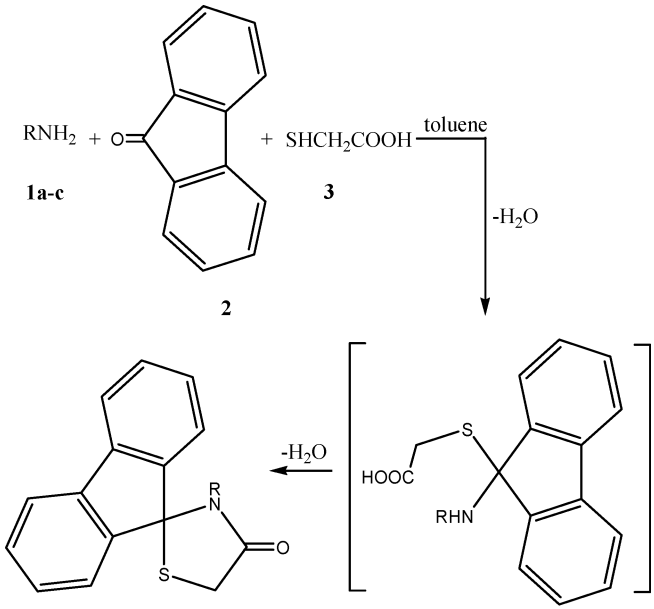
RESULTS AND DISCUSSION

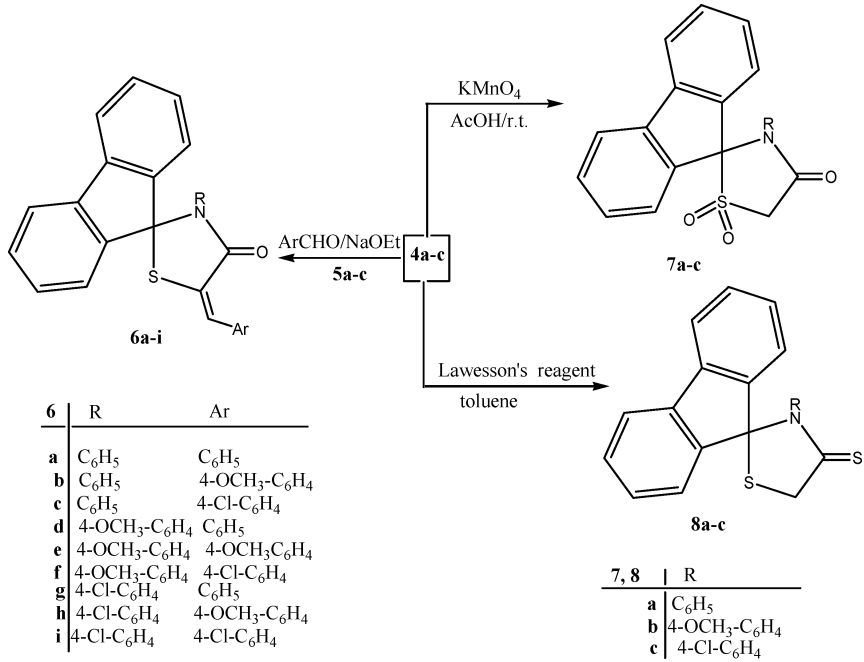
Aromatic amines **1a–c**, 9-fluorenone (**2**) and 2-mercaptocetic acid (**3**) react as a one pot reaction to afford white solids. The structures assigned for these solid compounds were proved based on elemental and spectral analysis and structures **4a–c** were assigned for them. For example, the IR spectrum of the isolated product **4a** showed absorption band near 1684 cm^{-1} corresponding to (CO) group. The ^1H NMR spectrum of **4a** revealed a singlet signal at $\delta = 4.36$ ppm attributed to methylene protons and a multiplet at $\delta = 6.60$–7.93 ppm corresponding to aromatic protons. Furthermore, the ^{13}C NMR spectrum of **4a** revealed signals at $\delta =$ 32.45, 75.13, and 171.39 ppm attributable to the methylene carbon, C-2‘ and thiazolidine carbonyl carbon, besides the signals corresponding to aromatic carbons (cf. Experimental Section and Scheme 1). Elemental analysis and mass spectral data agree with the proposed structures **4a–c**.



4	R
a	C_6H_5
b	4-OCH_3-C_6H_4
c	4-Cl-C_6H_4

SCHEME 1

The methylene group in position-5 of thiazolidin-4ones was reported to be active.[18,19] Thus, compounds **4a–c** undergo condensation with the aldehydes **5a–c** in refluxing ethanol under basic catalysis to yield the 5-arylidene derivatives **6a–i**. The IR spectra of the isolated products showed absorption bands near 1684 cm^{-1} due to CO group. The ^1H NMR spectra of these products revealed the disappearance of methylene signals at $\delta = 4.36$ ppm, and showed a multiplet at $\delta = \sim 6.65$ ppm attributable to olefinic and aromatic protons (cf. Experimental Section and Scheme 2).



6	R	Ar
a	C_6H_5	C_6H_5
b	C_6H_5	4-OCH_3-C_6H_4
c	C_6H_5	4-Cl-C_6H_4
d	4-OCH_3-C_6H_4	C_6H_5
e	4-OCH_3-C_6H_4	4-$OCH_3C_6H_4$
f	4-OCH_3-C_6H_4	4-Cl-C_6H_4
g	4-Cl-C_6H_4	C_6H_5
h	4-Cl-C_6H_4	4-OCH_3-C_6H_4
i	4-Cl-C_6H_4	4-Cl-C_6H_4

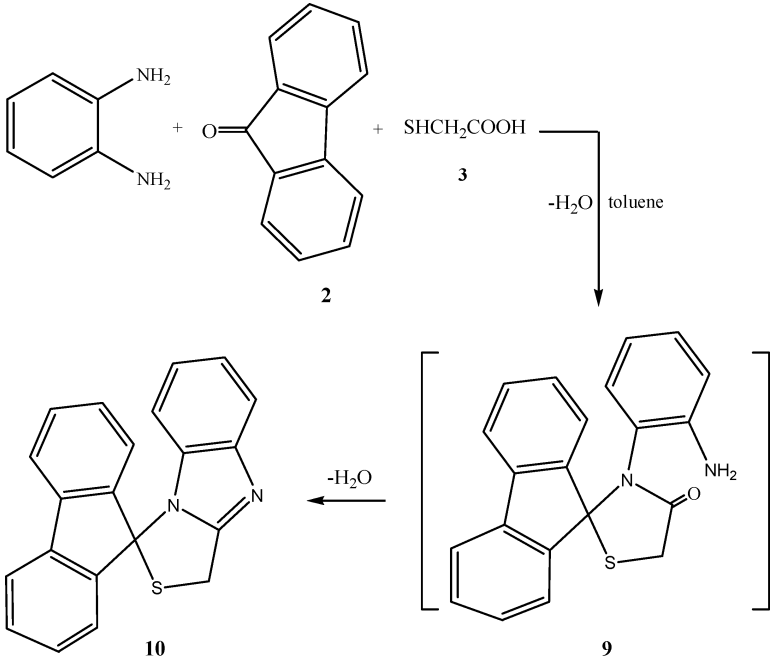
7, 8	R
a	C_6H_5
b	4-OCH_3-C_6H_4
c	4-Cl-C_6H_4

SCHEME 2

Oxidation of compounds **4a–c** with a solution of $KMnO_4$ under acidic conditions at room temperature furnished the products **7a–c**. The IR of these products showed absorption bands near 1695 cm^{-1} corresponding to CO group; 1341 and 1070 cm^{-1} corresponding to SO_2 (asymmetrical and symmetrical str.) group. The ^1H NMR spectra of these isolated products revealed a singlet at $\sim\delta = 5.0$ ppm attributed to the active methylene protons. Elemental analysis and mass spectra are in agreement with the sulfone structures **7a–c** (cf. Experimental Section and Scheme 2).

It has been reported that the biological activity thiazolidinone derivatives was much improved upon transformed to the thioxo-analogues.[10,20] Therefore, we have converted compounds **4a–c** into the corresponding thioxo-derivatives **8a–c** upon reaction with Lawesson's reagent under reflux in dry toluene for two hours (cf. Experimental Section and Scheme 2).

It is also interesting to extend our work to synthesize a novel spiro-thiazolo-benzimidazole via one-pot reaction of a mixture of 1,2-phenylenediamine, 9-fluorenone and 2-mercaptoacetic acid in refluxing toluene. From this reaction we could obtain a product of m.p. 168°C. Mass spectrum of this product showed *m/e* 326. The IR spectrum showed the disappearance of band at ~1684 cm^{-1} corresponding to the carbonyl group. The ^1H NMR spectrum revealed a singlet (2H) at $\delta = 4.99$ ppm attributed to methylene protons, beside the expected signals of aromatic protons. Furthermore, the ^{13}C NMR showed a signal at $\delta = 45.28$ ppm corresponding to methylene carbon and no signal that can be attributed to a carbonyl carbon was shown at $\sim\delta =$ 170 ppm and appearance of signal at $\delta = 143.90$ ppm corresponding to imine carbon (C=N), besides the signals corresponding to aromatic carbons (cf. Experimental Section and Scheme 3). Elemental analysis



SCHEME 3

and mass spectra agree with the IR, ^{1}H NMR and ^{13}C NMR spectra data. Based on these collective data the fluorenespiro[9.2′]thiazolo[3′,4′-*a*]benzimidazole structure **10** was assigned to this product. It is assumed that the reaction proceeds through the formation of non-isolable Schiff's base, followed by addition of the thiol to the C=N bond to afford the non-isolable **9**, which in role, undergoes ring closure in situ with the elimination of water to afford **10** (cf. Experimental Section and Scheme 3).

EXPERIMENTAL

Melting points were determined on an electrothermal (9100) apparatus and are uncorrected. The IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in deuterated dimethylsulfoxide at 300 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane as internal reference, and results are expressed as δ values. Mass spectra were taken on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalysis Center of Cairo University, Giza, Egypt.

Fluorenespiro[9.2′]-3′-aryl-thiazolidin-4-ones 3a–c—General Procedure

A mixture of the appropriate amines **1a–c** (20 mmol), 9-fluorenone (1.80 g, 10 mmol) and 2-mercaptoacetic acid (2.76 g, 30 mmol) in 25 ml dry toluene was refluxed for 8 h, and the solvent was evaporated till dryness under reduced pressure and the residue was triturated with ether. The ether layer was washed with sodium bicarbonate solution (1–2%) and finally with H_2O. The organic layer was dried over sodium sulfate and evaporated to dryness at reduced pressure. The solid so formed was collected by filtration and recrystallized from ethanol to give the title compounds, respectively (cf. Tables I and II).

5′-Arylidene-fluorenespiro[9.2′]-3′-aryl-thiazolidin-4-ones 6a–i—General Procedure

A mixture of compounds **4a–c** (10 mmol) and aldehydes **5a–c** (10 mmol) in 25 ml sodium ethoxide solution was refluxed for 1 h, left at room temperature, and the solid so formed was filtered off and recrystallized from ethyl alcohol/dioxin (cf. Tables I and II).

TABLE I Elemental Analyses of the Newly Synthesized Compounds

Compound no.	Solvent *of Cry.* yield %	Color M.P. °C	Mol. Formula Mol. wt	Analysis calcd./found %				
				C	H	N	S	Cl
4a	Ethanol	White	$C_{21}H_{15}NOS$	76.57	4.59	4.25	9.73	—
	70	228	329	76.74	4.74	4.43	9.57	
4b	Ethanol	White	$C_{22}H_{17}NO_2S$	73.51	4.77	3.90	8.92	
	74	198	359	73.68	4.58	3.72	8.78	—
4c	Ethanol	White	$C_{21}H_{14}ClNOS$	69.32	3.88	3.85	8.81	9.74
	72	208	363	69.51	4.06	4.04	8.98	9.92
6a	Ethanol/dioxane	Whitish brown	$C_{28}H_{19}NOS$	80.55	4.59	3.35	7.68	—
	86	245	417	80.37	4.78	3.55	7.50	
6b	Ethanol/dioxane	Whitish yellow	$C_{29}H_{21}NO_2S$	77.83	4.73	3.13	7.16	
	78	195	447	77.70	4.58	3.30	7.30	—
6c	Ethanol/dioxane	Yellow	$C_{28}H_{18}ClNOS$	74.41	4.01	3.10	7.09	7.84
	82	250	451	74.32	4.18	3.31	7.27	7.65
6d	Ethanol/dioxane	Yellow	$C_{29}H_{21}NO_2S$	77.83	4.73	3.13	7.16	
	72	228	447	78.0	4.58	3.32	7.0	—
6e	Ethanol/dioxane	Yellow	$C_{30}H_{23}NO_3S$	75.45	4.85	2.93	6.71	
	75	236	477	75.58	4.68	2.74	6.55	—
6f	Ethanol/dioxane	Yellow	$C_{29}H_{20}ClNO_2S$	72.26	4.18	2.91	6.65	7.36
	79	250	481	72.45	4.37	3.08	6.49	7.53
6g	Ethanol/dioxane	Yellow	$C_{28}H_{18}ClNOS$	74.41	4.01	3.10	7.09	7.84
	77	202	451	74.58	4.19	3.27	7.25	7.67

TABLE I Elemental Analyses of the Newly Synthesized Compounds

Compound no.	Solvent *of Cry.* yield %	Color M.P. °C	Mol. Formula Mol. wt	Analysis calcd./found %				
				C	H	N	S	Cl
6h	Ethanol/dioxane	Yellow	$C_{29}H_{20}ClNO_2S$	72.26	4.18	2.91	6.65	7.36
	81	248	481	72.08	4.34	3.10	6.48	7.53
6i	Ethanol/Dioxane	Yellow	$C_{28}H_{17}Cl_2NOS$	69.14	3.52	2.88	6.59	14.58
	75	297	485	69.0	3.35	3.05	6.75	14.75
7a	Ethanol	White	$C_{21}H_{15}NO_3S$	69.79	4.18	3.88	8.87	
	74	248	361	69.63	4.35	3.70	8.71	—
7b	Ethanol	White	$C_{22}H_{17}NO_4S$	67.50	4.38	3.58	8.19	
	72	238	391	67.64	4.55	3.76	8.35	—
7c	Ethanol	White	$C_{21}H_{14}ClNO_3S$	63.72	3.56	3.54	8.0	8.98
	78	252	395	63.88	3.39	3.72	7.82	9.15
8a	Ethanol	Yellow	$C_{21}H_{15}NS_2$	73.01	4.38	4.05	18.56	
	66	206	345	73.13	4.53	4.23	18.40	—
8b	Ethanol	Yellow	$C_{22}H_{17}NOS_2$	70.37	4.56	3.73	17.08	
	69	168	375	70.53	4.72	3.55	17.24	—
8c	Ethanol	Yellow	$C_{21}H_{14}ClNS_2$	66.39	3.71	3.69	16.88	9.33
	69	198	379	66.23	3.89	3.86	17.05	9.16
10	Ethanol	White	$C_{21}H_{14}N_2S$	77.27	4.32	8.58	9.82	
	75	168	326	77.11	4.48	8.40	9.98	—

TABLE II Spectral Data of the Newly Synthesized Compound

Compound No.	Spectral data, IR (cm^{-1}), ^1H NMR, and ^{13}C NMR
4a	IR: 1684 (C═O);^1H NMR: (DMSO-d_6)δ 4.36 (s, 2H, CH_2) and 6.60–9.93 (m, 13H, Ar-H);^{13}C NMR: (DMSO-d_6)δ 32.45, 75.13, 122.44, 125.33, 127.69, 128.32, 128.47, 129.87, 136.28, 138.31, 145.62, and 171.39
4b	IR: 1682 (C═O); ^1H NMR: (DMSO-d_6)δ 3.57 (s, 3H, OCH_3), 4.38 (s, 2H, CH_2), and 6.61–7.77 (m, 12H, Ar—H)
4c	IR: 1683 (C═O); ^1H NMR: (DMSO-d_6): δ 4.38 (s, 2H, CH_2) and 6.99–7.88 (m, 12H, Ar—H)
6a	IR: 1683 (CO); ^1H NMR: (DMSO-d_6)δ 7.03–7.81 (m, 19H, CH and Ar—H)
6b	IR: 1684 (C═O); ^1H NMR: (DMSO-d_6)δ 3.57 (s, 3H, OCH_3) and 6.61–7.77 (m, 18H, CH and Ar—H)
6c	IR: 1684 (C═O); ^1H NMR: (DMSO-d_6)δ 6.70–7.80 (m, 18H, CH, and Ar—H)
6d	IR: 1684 (C═O); ^1H NMR: (DMSO-d_6)δ 3.57 (s, 3H, OCH_3) and 6.75–7.86 (m, 18H, CH, and Ar—H)
6e	IR: 1685 (C═O); ^1H NMR: (DMSO-d_6)δ 3.56, 3.57 (s, 6H, OCH_3) and 6.71–7.90 (m, 17H, CH and Ar—H)
6f	IR: 1685 (C═O); ^1H NMR (DMSO-d_6)δ 3.57 (s, 3H, OCH_3) and 6.74–7.93 (m, 17H, Ar—H)
6g	IR: 1684 (C═O);^1H NMR: (DMSO-d_6)δ 7.11–7.86 (m, 18H, CH, and Ar—H)
6h	IR: 1685 (C═O); ^1H NMR: (DMSO-d_6)δ 3.57 (s, 3H, OCH_3) and 6.71–7.88 (m, 17H, CH, and Ar—H)
6i	IR: 1684 (C═O);^1H NMR: (DMSO-d_6): δ 6.71–7.91 (m, 17H, Ar—H)
7a	IR: 1695 (C═O), 1340, 1070 (SO_2); ^1H NMR: (DMSO-d_6): δ 5.07 (s, 2H, CH_2)and 7.06–7.86 (m, 13H, Ar—H)
7b	IR: 1696 (C═O), 1341, 1072 (SO_2); ^1H NMR: (DMSO-d_6)δ 3.56 (s, 3H, OCH_3), 5.10 (s, 2H, CH_2), and 6.80–7.88 (m, 12H, Ar—H)
7c	IR: 1696 (C═O), 1341, 1072 (SO_2); ^1H NMR: (DMSO-d_6)δ 5.12 (s, 2H, CH_2) and 6.95–7.90 (m, 12H, Ar—H)
8a	^1H NMR: (DMSO-d_6)δ 4.95 (s, 2H, CH_2) and 7.02–7.91 (m, 13H, Ar—H)
8b	^1H NMR: (DMSO-d_6)δ 3.56 (s, 3H, OCH_3), 4.96 (s, 2H, CH_2), and 7.10–7.85 (m, 12H, Ar—H)
8c	^1H NMR: (DMSO-d_6)δ 5.0 (s, 2H, CH_2) and 7.12–7.90 (m, 12H, Ar—H)
10	^1H NMR: (DMSO-d_6)δ 4.99 (s, 2H, CH_2) and 7.33–7.94 (m, 12H, Ar—H); ^{13}C NMR: (DMSO-d_6) 45.28, 48.40, 118.30, 124.49, 127.75, 128.50, 128.70, 130.20, 133.93, 137.18, 138.30, 143.90, and 145.70

Fluorenespiro[9.2′]-3′-aryl-thiazolidin-4-one-1′,1′-dioxides 7a–c—General Procedure

To a solution of **4a–c** (10 mmol) in 10 ml of glacial acetic acid was added a saturated solution of potassium permanganate (5 ml) in ice bath for 10 min; and, a saturated solution of sodium hydrogen sulfite was added till the solution was faded. The precipitate so formed was filtered off, washed well with water, and crystallized from the appropriate solvent (cf. Tables I and II).

Fluorenespiro[9.2′]-3′-aryl-thiazolidin-4-thiones 8a–c—General Procedure

A mixture of **4a–c** (10 mmol) and Lawesson's reagent (0.44 g, 10 mmol) in dry toluene (15 mL) was heated at reflux for 2 h. The reaction mixture was filtered off, and the solid so formed was filtered off and recrystallized from methanol (cf. Tables I and II).

Fluorenespiro[9.2′]thiazolo[3′,4′-*a*]benzimidazole (10)—General Procedure

A mixture of 1,2-phenylenediamine (2.16 g, 20 mmol), 9-fluorenone (1.80 g, 10 mmol) (**2**), and 2-mercaptoacetic acid (**3**) (2.76 g, 30 mmol) in 25 ml dry toluene was refluxed for 48 h, and then concentrated till dryness under reduced pressure and the residue was taken-up in ether. The ether layer was washed with sodium bicarbonate solution (1–2%) and finally with H_2O. The organic layer was dried over sodium sulfate and evaporated to dryness at reduced pressure to afford **10** (cf. Tables I and II).

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