SYNTHESES OF VARIOUS IMIDAZO[5,1-*c*][1,2,4]-TRIAZOLE DERIVATIVES HAVING POTENTIAL BIOLOGICAL ACTIVITIES

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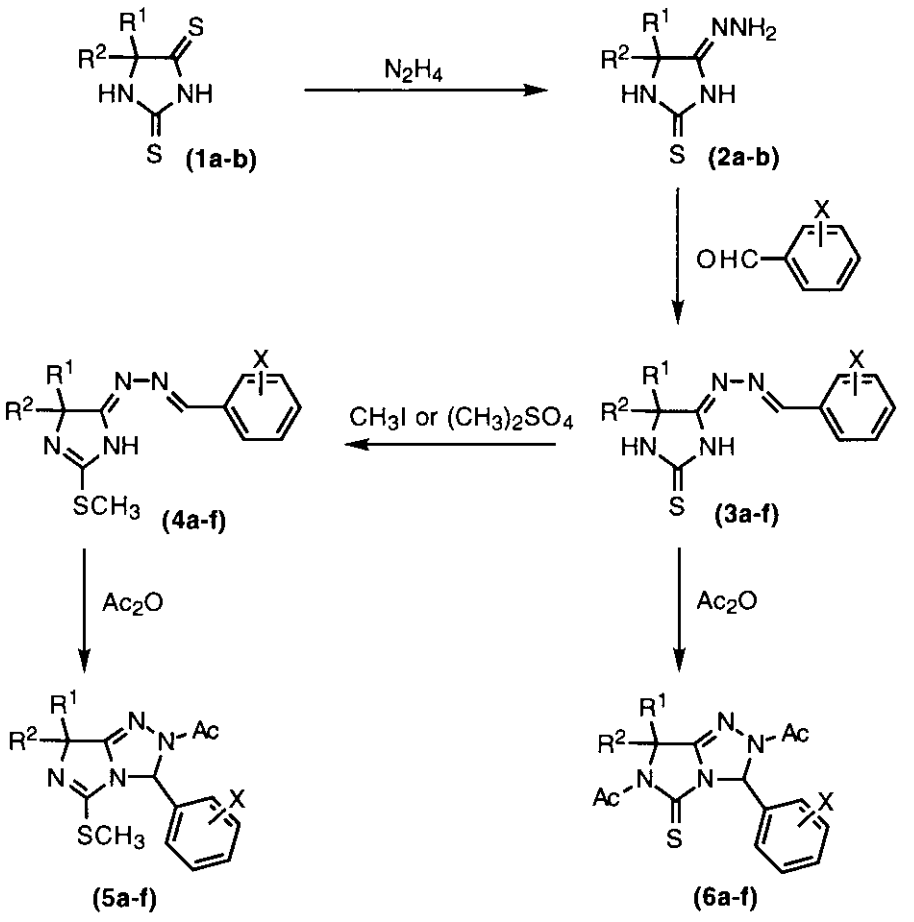
Abstract- The title compounds (**5a-f**) and (**6a-f**) were synthesized from the corresponding 4-arylidene-hydrazonoimidazolidines (**3a-f**) and (**4a-f**) on treatment with acetic anhydride. The intermediates (**3a-f**) were obtained by reacting 4-hydrazono-2-thioxoimidazolidines (**2a-b**) with various aldehydes. The later (**2a-b**) were resulted by reacting 2,4-dithiohydantoins (**1a**-b) with N_2H_4. Methylation of **3a-f** gave **4a-f**.

During the last few years, a considerable attention has been devoted to construct new antihypertensive drugs with more selective mode of actions.[1] In this connection, different series of imidazo[1,2-*b*]triazoles were found to have a selective angiotensin II antagonistic activity and as a consequence inducing hypotension.[1,2] This means that a generation of nonpeptide angiotensin II antagonistic agents having imidazole ring could be introduced in the clinical field.[2] Moreover, recent publications[3-7] showed high progress in determing two imidazoline receptors (I_1&I_2) linking the brain and the cardiovascular system. Selective agonists of these receptors may have a superior antihypertensive activity. A group of clinically useful antihypertensive agents including clonidine and moxonidine, which have imidazole nucleus, are highly bounded to these receptors leading to a pronounced and long lasting blood pressure reduction in different animal models of hypertension.[8,9]

In a continuation of a previous researches[10,11] on imidazole ring system; this investigation would involve the syntheses of various compounds of imidazo[5,1-*c*]triazoles which have very rare attention in the literatures[12] and are isosteres to the above mentioned biologically active compounds in the hope that they might possess high antihypertensive activity. The sequence of the reactions followed in syntheses of the designed compounds is illustrated in Scheme 1.

Scheme 1:



	R^1	,	R^2
1, 2 : **a** =	CH_3	,	CH_3
b =	$(-CH_2-)_5$		

	R^1	,	R^2	;	X
3, 4, 5, 6 : **a** =	CH_3	,	CH_3	;	2-Cl
b =	CH_3	,	CH_3	;	4-Cl
c =	CH_3	,	CH_3	;	3-Br
d =	$(-CH_2-)_5$			;	2-Cl
e =	$(-CH_2-)_5$			;	4-Cl
f =	$(-CH_2-)_5$			;	3-Br

2,4-Dithiohydantoins (**1a-b**) and 5,5-dimethyl-4-hydrazono-2-thiohydantoins (**2**a) were prepared according to a reported procedure.[13]

Hydrazinolysis of **1a-b** by one equivalent N_2H_4, followed by a condensation of the products (**2a-b**) with different aldehydes, gave the key intermediates (**3a-b**) in nearly quantitative yields. The ^{1}H-NMR spectra of **3a-f** showed the characteristic azamethine (CH=N) singlet signals at δ 8.6-9.5 ppm. Methylation of **3a-f** with equivalent methyl iodide or dimethyl sulfate, in mild basic medium afforded the

S-methylated products (**4a-f**). The results are consonant with similar researches[14,15] and with the spectral data of the products. The ^{1}H-NMR spectra of **4a-f** showed the singlet signals of CH_3S groups at δ 2.6-2.8 ppm. Acetylation of **4a-f** and **3a-f** by heating with acetic anhydride under reflux successfully produced the corresponding imidazo[5,1-*c*][1,2,4]triazoles (**5a-f**) and (**6a-f**) in nearly quantitative yields. Meanswhile, it was reported[16] that acylation of imidazolidines occurs mainly at both N-1 and N-3 atoms. But in this investigation, the N-3 atom of compounds (**4a-f**) and (**3a-f**) could not undergo acylation, due to the steric hindrance induced by the arylidenehydrazono side chain at the position 2. Consequently, the nitrogen atom of the azamethine (CH=N) group of this side chain would be more easily acylated into a quaternary nitrogen and the facile attack of the N-3 atom to the azamethine carbon would produce **5a–f** and **6a–f** (Figure 1). This reaction proceeded in a similar way as reported[17] for constructing triazoles ring system by reacting hydrazones and amines with acetic anhydride.

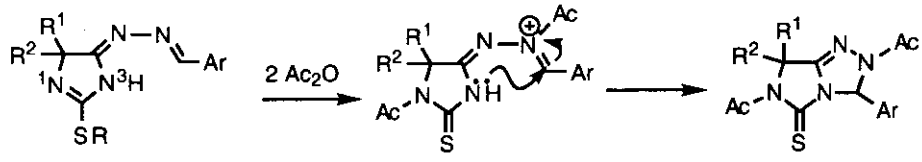


Figure 1

The ^{1}H-NMR spectra of **5a-f** and **6a-f** showed the disappearance of the azamethine (CH=N) singlet signals and instead new singlet signal appeared at δ 7.0-7.3 ppm, indicating the formation of the saturated methine (CH) moieties. Additionally, ^{13}C-NMR of **6b** confirmed the existence of this methine carbon at δ 75.05 ppm. Worthwhile the cyclized *p*-chloro derivatives (**5b,e**) and (**6b,e**) showed aromatic hydrogens having the same chemical shift without *ortho*-coupling in their ^{1}H -NMR spectra (90 MHz) and the two doublets due to the *p*-chlorophenhyl hydrogens coalesced in one signal. But 300 MHz ^{1}H-NMR spectrum of **6b** showed two closed signals at δ 7.381 and 7.378. This may be attributed to the existence of different rotamers around the C3-Ar bond which is consistent with similar findings.[18]

EXPERIMENTAL

All melting points were obtained using recrystallized products and are uncorrected. IR spectra were recorded as cm^{-1} on a Shimadzu 435

spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectral data were measured in δ scale on a JEOL Fxo 90 MHz and 300 MHz spectrometers. EIMS spectra were fulfilled on a Shimadzu, GC-MSOP 1000-Ex mass spectrometer. HRMS for elemental composition was determined on JEOL-JMS-AX-500 spectrometer. Progress of the reaction was monitored by TLC till completion. Physical and analytical data are given in Tables 1 and 2.

General Experimental Procedures for Scheme 1:
5,5-Dimethyl-4-hydrazono-2-thioxoimidazolidine (2a): To a solution of 5,5-dimethyl-2,4-dithiohydantoin (**1a**) (16 g, 0.1 mol) in ethanol (100 mL), a hydrazine hydrate (98%, 6 mL, 0.15 mmol) was added and the mixture was warmed at 60 °C for 30 min and evaporated under reduced pressure and the obtained solid (**2a**) was recrystallized from ethanol. Yield 15.0 g, 95%. mp 189-190 °C (lit.,[12] mp 189-190 °C).

4-Hydrazono-2-thioxo-1,3-diazaspiro[5.4]decane (2b): 5,5-Cyclopentamethylene-2,4-dithiohydantoin (**1b**) (20 g, 0.1 mol) was treated with hydrazine hydrate (98%, 6 mL, 0.15 mmol) following the same procedure of preparation of **2a** Yield: 18 g, 90 %, mp 192-193 °C. IR: ν 3400, 3350, 3150, 3080, 1700. ^{1}H-NMR (90 MHz): 1.58-2.01 (br s, 10H), 10.40 (s, 1H), 10.70 (s, 1H), 11.05 (s, 1H), 11.90 (s, 1H).

5,5-Dimethyl-4-(arylidenehydrazono)-2-thioxoimidazolidines (3a-c) and 4-Arylidenehydrazono-2-thioxo-1,3-diazaspiro[5.4]decanes (3d-f): A mixture of the hydrazono derivatives (**2a-f**), (0.01 mol), acetic acid (0.05 mL, 1 mmol) and the appropriate aldehyde (viz: 2-chlorobenzaldehyde, 4-chlorobenzaldehyde and 3-bromobenzaldehyde) (0.01 mol) was refluxed in ethanol (20 mL) for 3 h. The reaction mixture was evaporated under vacuum and the formed solid of **3a-f** was recrystallized from the appropriate solvent.

5,5-Dimethyl-4-arylidenehydrazono-2-methylthio-1-imidazo-lidines (4a-c) and 4-Arylidenehydrazono-2-methylthio-1,3-diaz aspiro-[5.4]dec-1-enes (4d-f): Methyl iodide (1.5 g, 0.01 mol) was added to a solution of **3a-b** (0.01 mol) in acetone (25 mL) containing K_2CO_3 (1.3 g, 0.011 mol) and KI (0.02 g, 0.001 mol). The reaction mixture was stirred overnight at rt, filtered and the filtrate was evaporated under vacuum. The residue was recrystallized from the appropriate solvent. Dimethyl sulfate (0.65 g, 0.005 mol) may be used.

2-Acetyl-3-aryl-5-methylthio-7,7-dimethyl-2,3-dihydro-7*H*-imidazo-[5,1-*c*]triazoles (5a-c) and 2-Acetyl-3-aryl-5-methylthio-7,7-pentamehylene-2,3-dihydro-7H-imidazo[5,1-*c*]triazoles (5e-f): The intermediates (**4a-f**) (0.01 mol) were refluxed with acetic anhydride (3 mL, 30 mmol) for 3 h. The reaction mixture were poured onto ice, and the formed solid of **5a-f** was recrystallized from the appropriate solvent.

Table 1: Physical and analytical data of 3–6

compound	formula	mp °C (solvent)	yield(%)	found(%) (requires) C	H	N	IR ν max (cm^{-1})
3a	$C_{12}H_{13}N_4ClS$	150-151 (M–H)	96	51.40 (51.33)	4.50 (4.63)	19.60 (19.96)	3350, 3100, 1660, 1650
3b	$C_{12}H_{13}N_4ClS$	255-256 (M–H)	98	51.60 (51.33)	4.90 (4.63)	19.40 (19.96)	3350, 3000, 1660, 1650
3c	$C_{12}H_{13}N_4BrS$	170-171 (M–E)	91	44.20 (44.30)	4.10 (4.00)	17.10 (17.23)	3300, 3010, 1660, 1640
3d	$C_{15}H_{17}N_4ClS$	235-236 (M–H)	92	56.00 (56.16)	5.60 (5.30)	11.30 (11.07)	3250, 3150, 1670, 1650
3e	$C_{15}H_{17}N_4ClS$	258-259 (M–E)	94	57.50 (56.16)	4.90 (5.30)	11.10 (11.07)	3180, 3100, 1660, 1650
3f	$C_{15}H_{17}N_4BrS$	220-221 (M)	94	49.40 (49.31)	4.40 (4.65)	15.60 (15.34)	3200, 3000, 1650, 1640
4a	$C_{13}H_{15}N_4ClS$	146-147 (Pet-E)	60	53.10 (52.97)	5.10 (5.09)	19.30 (19.01)	3420, 3210, 1650, 1640
4b	$C_{13}H_{15}N_4ClS$	91-92 (Pet-E)	52	52.50 (52.97)	5.20 (5.09)	18.90 (19.01)	3400, 3200, 1650, 1640
4c	$C_{13}H_{15}N_4BrS$	170-171 (Pet-E)	59	46.30 (46.01)	4.30 (4.42)	16.70 (16.51)	3410, 3180, 1650, 1635
4d	$C_{16}H_{19}N_4ClS$	143-144 (Pet-E)	65	57.40 (57.39)	6.00 (5.68)	17.00 (16.71)	3150, 1640, 1630
4e	$C_{16}H_{19}N_4ClS$	110-111 (Pet-E–H)	65	57.40 (57.39)	5.50 (5.68)	16.90 (16.71)	3160, 3150, 1635, 1625
4f	$C_{16}H_{19}N_4BrS$	108-110 (Pet-E–H)	57	51.40 (50.65))	4.80 (5.01)	14.90 (14.77)	3200, 1650, 1630
5a	$C_{15}H_{17}N_4OClS$	161-162 (M–H)	95	53.10 (53.49)	4.90 (5.05)	16.20 (16.64)	1660, 1650, 1630
5b	$C_{15}H_{17}N_4OClS$	120-121 (M–H)	92	52.90 (53.49)	5.00 (5.05)	16.90 (16.64)	1665, 1640, 1630
5c	$C_{15}H_{17}N_4OBrS$	179-180 (M–E)	96	46.90 (47.29)	4.70 (4.46)	14.30 (14.69)	1660, 1630
5d	$C_{18}H_{21}N_4OClS$	162-163 (M–H)	89	57.00 (57.37)	5.90 (5.57)	14.50 (14.87)	1685, 1640, 1625
5e	$C_{18}H_{21}N_4OClS$	136-137 (M–H)	85	57.60 (57.37)	5.80 (5.57)	14.60 (14.87)	1660, 1640, 1620
5f	$C_{18}H_{21}N_4OBrS$	134-135 (M–E)	84	51.60 (51.30)	4.60 (4.98)	12.90 (13.30)	1655, 1635, 1620
6a	$C_{16}H_{17}N_4O_2ClS$	126-128 (H)	95	52.30 (52.67)	4.30 (4.66)	15.50 (15.36)	1705, 1670, 1630, 1580
*6b	$C_{16}H_{17}N_4O_2ClS$	196-198 (M–A)	98	52.20 (52.67)	4.70 (4.66)	15.70 (15.36)	1700, 1678, 1640, 1580
6c	$C_{16}H_{17}N_4O_2BrS$	139-141 (H–A)	95	47.20 (46.94)	4.50 (4.15)	14.00 (13.69)	1600, 1670, 1640, 1570

Table 1 (cont.):

6d	$C_{19}H_{21}N_4O_2ClS$	232-234 (M–H)	95	56.80 (56.36)	5.10 (4.67)	13.40 (13.84)	1697, 1687, 1590
*6e	$C_{19}H_{21}N_4O_2ClS$	155-156 (M)	90	56.50 (56.36)	5.00 (4.67)	14.00 (13.84)	1700, 1687, 1650, 1585
*6f	$C_{19}H_{21}N_4O_2BrS$	137-139 (M)	90	51.10 (50.77)	4.90 (4.67)	12.70 (12.47)	1695, 1685, 1640, 1570

M = methanol, H = hexane, E = ether, Pet-E = pet. ether, A = erthyl acetate,

*MS, m/z of M^+, (M^++2) and base peak of the following compound

6b: 364.0757 (45.30%), 366.0741 (19.05%) (HRMS)

6e: 404 (27%), 406 (9.6%), 150 (LRMS)

6 f: 448 (11.1%), 450 (11.7%), 150 (LRMS)

TabIe 2 : ^{1}H-NMR data of 3–6

3a	1.4-1.8 (br s, 6H), 7.7-8.4 (m, 4H), 9.5 (s, 1H), 10.05 (s, 1H), 11.8 (s, 1H).
3b	1.6-1.8 (br s, 6H), 8.0 (d, J=12.6 Hz, 2H), 8.3 (d, J=12.6 Hz, 2H), 8.8 (s, 1H), 10.1 (s, 1H), 11.8 (s, 1H).
3c	1.55-1.6 (s, 6H), 7.6-8.6 (m, 4H), 8.6 (s, 1H), 10.4 (s,1H), 12.4 (s, 1H).
3d	1.6-2.0 (br s, 10H), 7.6-8.9 (m, 4H), 9.2 (s, 1H), 10.4 (s, 1H), 12.4 (s, 1H).
3e	1.5-2.0 (br s, 10H), 7.9 (d, J=11.7 Hz, 2H), 8.5 (d, J=11.7 Hz, 2H), 8.6 (s, 1H), 10.5 (br s, 1H), 12.1 (br s, 1H).
3f	1.8-2.0 (br s, 10H), 7.6-8.6 (m, 4H), 10.6 (s, 1H), 12.1 (s, 1H).
4a	1.6 (s, 3H), 1.6 (s, 3H), 2.7 (s, 3H), 7.8-8.6 (m, 4H), 8.9 (s, 1H), 10.4 (br s, 1H).
4b	1.5 (s, 3H), 1.6 (s, 3H), 2.7 (s, 3H), 7.7 (d, J=10.8 Hz , 2H), 8.9 (d, 1 J=0.8 Hz , 2H), 9.0 (s,1H), 10.6 (br s, 1H).
4c	1.7-2.1 (br s, 10H), 2.6 (s, 3H), 7.6-8.8 (m, 4H), 9.0 (s, 1H), 11.8 (br s, 1H).
4d	1.5 (s, 3H), 1.6 (s, 3H), 2.7 (s, 3H), 7.7-8.7 (m, 4H), 8.8 (s, 1H), 10.2 (br s, 1H).
4e	1.7-2.1 (br s, 10H), 2.6 (s, 3H), 7.7 (d, J=9.9 Hz, 2H), 8.9 (d, J=9.9 Hz, 2H).
4f	1.5-2.0 (br s, 10H), 2.8 (s, 3H), 7.6-8.6 (m, 4H), 8.8 (s, 1H), 11.4 (s, 1H).
5a	1.5 (s, 3H), 1.5 (s, 3H), 2.2 (s, 3H), 2.8 (s, 3H), 7.0 (s, 1H), 7.7-8.4 (m, 4H).
5b	1.5 (s, 3H), 1.6 (s, 3H), 2.3 (s, 3H), 2.9 (s, 3H), 7.0 (s, 1H), 7.8-8.5 (br s, 4H).
5c	1.8 (s, 3H), 1.9 (s, 3H), 2.3 (s, 3H), 2.5 (s, 3H), 7.0 (s, 1H), 7.6-8.6 (m, 4H).
5d	1.4-2.0 (br s, 10H), 2.4 (s, 3H), 2.6 (s, 3H), 7.0 (s,1H), 7.6-7.9 (m, 4H).
5e	1.4-2.0 (br s, 10H), 2.5 (s, 3H), 2.7 (s, 3H), 7.0 (s, 1H), 7.7-7.8 (br s, 4H).
5f	1.5-2.0 (br s, 10H), 2.4 (s, 3H), 2.6 (s, 3H), 7.05 (s, 1H), 7.7-8.0 (m, 4H).
6a	1.9-2.0 (br s, 6H), 2.3 (s, 3H), 2.8 (s, 3H), 7.3 (s, 1H), 7.8-7.9 (m, 4H).
6b* (300 MHz)	1.9 (s, 3H), 1.9 (s, 3H), 2.3 (s, 3H), 2.7 (s, 3H), 6.8 (s, 1H), 7.4 (s, 2H), 7.5 (s, 2H).
6c	1.9-2.1 (br s, 6H), 2.2 (s, 3H), 2.8 (s, 3H), 7.1 (s, 1H), 7.8-8.1 (m, 4H).
6d	1.7-2.2 (br s, 10H), 2.3 (s, 3H), 2.8 (s, 3H), 7.4 (s, 1H), 7.7-7.9 (m, 4H).
6e	1.7-2.1 (br s, 10H), 2.4 (s, 3H), 2.9 (s, 3H), 7.1 (s, 1H), 7.7 -7.8 (br s , 4H), 7.8 (d, J=1.5 Hz, 2H).
6f	1.6-2.0 (br s,10H), 2.2 (s, 3H), 2.8 (s, 3H), 7.1 (s, 1H), 7.5-7.9 (m, 4H).

*^{13}C-NMR of compound (6b): 21.17, 24.81, 24.97, 28.50, 64.36, 75.65, 128.99, 129.17, 133.30, 135.92, 155.23, 168.07, 171.58.

3-Aryl-2,6-diacetyl-7,7-dimethyl-5-thioxo-2,3,6,7-tetrahydroimidazo[5,1-*c*][1,2,4]triazoles (6a-c) and 3-Aryl-2,6-diacetyl-7,7-pentamethylene-5-thioxo-2,3,6,7-tetra-hydroimidazo[5,1-*c*][1,2,4]triazoles (6c-f): The arylidene hydrazono derivatives (**3a-f**) (0.01 mol) were refluxed with acetic anhydride (3 mL, 30 mmol) for 3 h. The reaction mixture was worked up as the previous to provide **6a-f**.

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