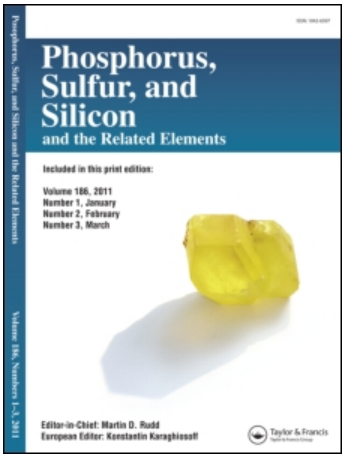

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SULFONATE ESTER-CONTAINING (IMIDAZOL-1-yl)- N-SUBSTITUTED BENZENESULFONAMIDES OF ANTICIPATED ANTINEOPLASTIC ACTIVITY

M. A. Hanna[a]; M. M. Girges[b]; M. A. Berghot[b]
[a] Dammiatta, Faculties of Science, Mansoura University, Mansoura, Egypt [b] Mansourab Faculties of Science, Mansoura University, Mansoura, Egypt

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SULFONATE ESTER-CONTAINING (IMIDAZOL-1-yl)-N-SUBSTITUTED BENZENESULFONAMIDES OF ANTICIPATED ANTINEOPLASTIC ACTIVITY

M. A. HANNA,[a,†] M. M. GIRGES[b] and M. A. BERGHOT[b]
Dammiatta[a] and Mansoura[b] Faculties of Science, Mansoura University, 35516 Mansoura, Egypt

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The stereospecific synthesis for a series of (Z)-4-{2-Aryl-4-[4-(arylsulfonyloxy)phenylmethinyl]-4,5-dihydro-5-oxo-1H-imidazol-1-yl}-N-substituted benzenesulfonamide derivatives (**VIa–o**) was investigated with a view to prepare new pharmacologically active products of extended and/or improved antineoplastic activity. Owing to the weak nucleophilicity of the nitrogen nucleophiles under investigation, acetic acid mediated cyclizations were followed for preparation of the required products. Additionally, the antimicrobial activity was screened for the compounds reported.

Key words: Sulfonamide derivatives; stereospecific synthesis; antimicrobial activity.

Numerous imidazoline derivatives were evaluated for different biological properties.[1–3] The most impressive characteristics of these compounds were their contraceptive, abortifacient[4,5] and antineoplastic activity.[6]

In continuation of our previous investigation pertaining to synthesis of sulfonate ester-containing imidazolylpyridine, imidazo(4,5-b)pyridine and imidazo(5′,1′:2,3)-imidazo(4,5-b)pyridine derivatives with predicted contraceptive activity,[7] we report here the stereospecific synthesis for a series of (Z)-4-{2-aryl-4-[4-(arylsulfonyloxy)phenylmethinyl]-4,5-dihydro-5-oxo-1H-imidazol-1-yl}-N-substituted benzenesulfonamides (**VIa–o**) for probable antineoplastic activity.

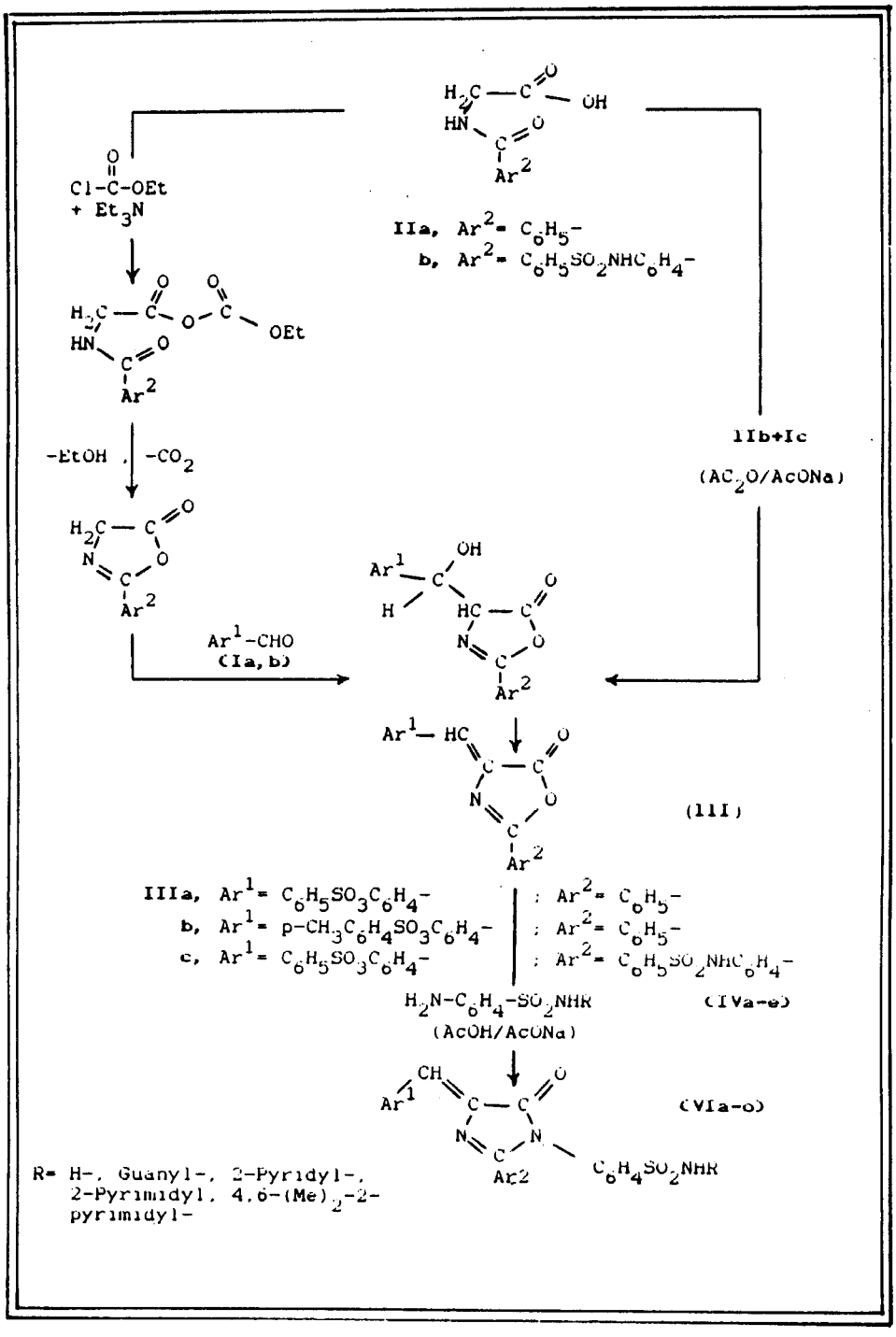
The incentive in this direction was based upon recorded potencies of the imidazole nucleus[8–10] and the N-substituted benzenesulfonamide derivatives.[11,12]

Smissman[13] also emphasized that the replacement of the basic N^4-amino group in sulfonamides by such groups as acylamino, azo or hydrazo still leads to similar pharmacological activity due to in vivo release of the parent sulfonamide by metabolic processes.

The required 2-aryl-4-[4-(arylsulfonyloxy)phenylmethinyl]-4,5-dihydro-5-oxo-1,3-oxazoles (**IIIa–c**), were prepared adopting the method of Mukerjee *et al.*[14] for stereospecific synthesis of unsaturated oxazolone derivatives. This was accomplished by allowing acylglycines to react with ethyl chloroformate in the presence of triethylamine, followed by reaction of the 4-hydroxybenzaldehyde arenesulfonate esters (**Ia,b**) as illustrated in (Scheme 1).

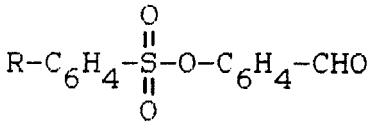
The prepared 2-aryl-4-[4-(arylsulfonyloxy)phenylmethinyl]-4,5-dihydro-5-oxo-1,3-oxazoles (**IIIa–c**) were assigned the (Z)-configuration on the bases of models constructed by us and in agreement with the fact that (E)-arylidene derivatives of azlactones are thermolabile and isomerize to the corresponding (Z)-isomer in the

† To whom all correspondence should be addressed.



SCHEME 1

presence of a tertiary base.[15] Although cyclization of acylglycines using acetic anhydride may afford a mixture of (E)- and (Z)-isomers,[16] prolonged heating—even during recrystallization—will produce only the thermodynamically stable isomer with (Z)-configuration.[14]



Ia, R=H
b, R=CH_3

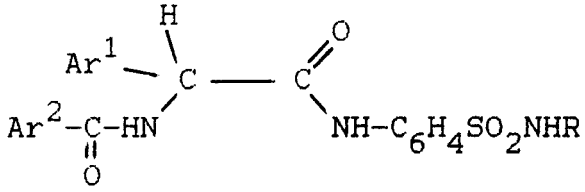
Thus, refluxing a mixture of the appropriate acylglycine with 4-hydroxybenzaldehyde benzenesulfonate ester (**Ia**) in the presence of acetic anhydride and a catalytic amount of sodium acetate, according to Erlenmeyer,[17] afforded an unequivocal procedure for the synthesis of (**IIIc**).

The IR spectra of these products were characterized by the presence of strong bands at 1775–1770, 1630–1625, 1345 and 1220 cm^{-1} that could be attributed to the lactone, (C=N) and sulfonate ester moieties respectively.

When (Z)-2-aryl-4-[4-(arylsulfonyloxy)phenylmethinyl]-4,5-dihydro-5-oxo-1,3-oxazoles (**IIIa–c**) were allowed to react with different sulfonamide derivatives (**IVa–c**) in the presence of glacial acetic acid and a catalytic amount of freshly fused sodium acetate, the corresponding (Z)-4-{2-aryl-4-[4-(arylsulfonyloxy)phenylmethinyl]-4,5-dihydro-5-oxo-1H-imidazol-1-yl}-N-substituted benzenesulfonamides (**VIa–o**) were obtained in good yield. The (Z)-configuration was assigned to these products depending on the fact that cleavage of the 1,5-bond in unsaturated azlactones does not affect the stereochemistry of the olefinic center during aminolysis.[15]

In addition to absorption bands that are characteristic for imidazolone and sulfonate ester moieties (Experimental part) the IR spectra of these products revealed the presence of characteristic absorption bands for the differently N-substituted benzenesulfonamide moieties. Thus, while the sulfanilamide derivatives (**VIa,f,k**) showed absorption bands at 1165 and 840 cm^{-1}, both the pyridyl and pyrimidylsulfamoyl derivatives (**VIc–e**), (**VIh–j**) and (**VIm–o**) exhibited absorption bands at 1165 and 680 cm^{-1}. Similarly, guanylsulfamoyl derivatives (**VIb,g,l**) revealed characteristic absorption bands at 3470, 1150, 690 and 630 cm^{-1}. These results are in agreement with the reported findings of Bossche and Leenheer.[18]

Apparently, the conversion of **III** to the final product **VI**, was initiated by aminolysis of the 1,5-bond in **III** through attack of the nucleophilic amino nitrogen atom in the sulfonamide derivatives (**IVa–c**) on the carbonyl lactone giving rise to the corresponding anilides (**V**).



V

The latter intermediate loses rapidly one molecule of water to give the final product (**VI**) (Scheme 1).

Contrary to the earlier observations[14] that the interaction of an oxazolone moiety with aromatic amines in ethanol usually affords the corresponding anilides, it is expected that the weakly nucleophilic sulfonamide derivatives (**IVa–e**) – (σ_p = 0.62 for —SO_2NH_2 group)[19]—will not react under the same condition.

In presence of acetic acid, as a solvent, the latter would probably protonate the ring-oxygen atom leading to ring opening and consequently increase the positive charge at the positive end of the $\left(\rangle C^{\delta+}=O^{\delta-}\right)$ dipole. This, in turn, will facilitate the nucleophilic attack even by the weak nucleophiles (**IVa–e**) leading to the required products (**VIa–o**).

The prepared compounds are expected to possess antineoplastic activity and are under investigation for their antitumor activity *in vivo* against *Ehrlich ascites carcinoma*.

The acute toxicity of these new compounds in tumour-bearing mice showed that compounds (**VIa–0**) have a relatively high value of maximum tolerance dose (MTD = 75–90 mg/kg body weight).‡

The newly synthesized products were also tested *in vitro* for their antimicrobial activity: the microorganisms and the minimum inhibitory concentrations (MIC) in $\mu g\ ml^{-1}$ are given unless they exceed 100 $\mu g\ ml^{-1}$: *Escherichia coli*, **VIa** 6.25, **VId** 12.5, **VIe** 12.5, **VIh** 12.5, **VIo** 6.25; *Staphylococcus aureus*, **VIe** 50, **VIg** 50, **VIh** 100, **VII** 100; *Staphylococcus albus*, **IIIc** 25, **VIb** 100, **VIc** 50, **VId** 100, **VIe** 25, **VIj** 50, **VIm** 50; *diplococcal Nesseria catarrhalis*, **VIa** 12.5, **VId** 100, **VIe** 12.5, **VIn** 12.5; *Saccharomyces cerevisiae*, **IIIc** 12.5, **VId** 50, **VIj** 25.

The low values of (MIC) in the case of gram negative bacteria are of high significance from the chemotherapeutic point of view, since many synthetic products exhibiting activities against gram negative bacteria are recorded to have antitumor activity.[20] These findings substantiate the potential antineoplastic activity of the prepared compounds.

EXPERIMENTAL

The purities of the prepared compounds were checked by thin layer chromatography. Melting points were determined using Fisher-Johns apparatus and are not corrected. Infra-red spectra (KBr) were recorded on an SP 2000 Pye-Unicam spectrophotometer. ^1H NMR spectra ($CDCl_3$) were recorded on a Varian EM 360 spectrophotometer at 60 MHz using TMS as an internal standard. Mass spectra were performed on a Varian 111 spectrometer (70 eV). The nomenclature of the prepared compounds is in line with IUPAC rules of organic nomenclature.

4-Aminobenzenesulfonamide derivatives (**IVa–e**). These derivatives were extracted from commercial sulfa drugs according to literature.[21]

(Z)-2-Aryl-4-[4-(arylsulfonyloxy)phenylmethinyl]-4,5-dihydro-5-oxo-1,3-oxazole (**IIIa–c**). *Method (A) for* (**IIIa–c**). To a suspension of N-acylglycine (**IIa,b**), (0.01 mol in each case) in dry benzene (30 ml/g of **II**) containing triethylamine (0.015 mol), ethyl chloroformate (0.012 mol) was added and the

‡ Details of study of antineoplastic activity and chronic toxicological study together with LD_{50} values for the prepared compounds will be published separately.

TABLE I

Characterization data for compounds (**IIIa–c**)

No.	M.p. °C % (Yield)	Colour	Formula (Mol. Wt.)	Analysis Calculated/Found %C	%H	%N	%S
IIIa	142*	Yellow	$C_{22}H_{15}NO_5S$	65.17	3.73	3.46	7.91
	(69)		(405.41)	65.23	3.69	3.52	8.04
IIIb	176**	Yellow	$C_{23}H_{17}NO_5S$	65.86	4.09	3.34	7.64
	(73)		(419.44)	66.01	4.29	3.51	7.74
IIIc	225	Yellow	$C_{28}H_{20}N_2O_7S_2$	59.99	3.60	5.00	11.44
	(78)		(560.59)	60.12	3.45	5.11	11.83

* Literature[1] m.p. 140 °C

** Literature[1] m.p. 175 °C

mixture was shaken at room temperature until the acid crystals disappeared and triethylamine hydrochloride separated out. 4-Hydroxybenzaldehyde arenesulfonate esters (**Ia,b**), (0.01 mol in each case) dissolved in dry benzene (5 ml/g) were added and the mixture was refluxed for 30 min and cooled. Triethylamine hydrochloride was removed by filtration and washed twice with dry benzene. The benzene solution and washings were combined and concentrated to dryness under reduced pressure. Trituration with ethanol afforded a solid which was filtered off, washed with ethanol and recrystallized from acetic acid to give the products (Table I). IR spectrum of **IIIc**: 3300 cm^{-1} (NH), 1775 cm^{-1} (lactone moiety), 1630 cm^{-1} (C=N), 1345, 1220 cm^{-1} (sulfonate ester moiety) and at 1145 cm^{-1} (sulfonamide group). ^{1}H-NMR spectrum δ: 9.15 ppm (*s*, 1H, $SO_2N\underline{H}$), 7.85–7.05 ppm (*m*, 18H, Ar) and at 6.85 ppm (*s*, 1H, ylidene proton).

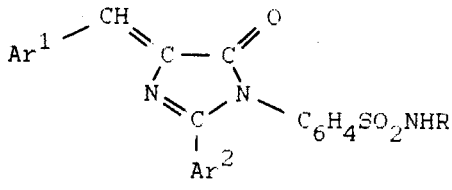
Method (B) for (**IIIc**). A mixture of 4-hydroxybenzaldehyde benzenesulfonate ester (**Ia**), (0.012 mol), 4-benzenesulfonamidohippuric acid (**IIb**)[22] (0.01 mol) and freshly fused sodium acetate (0.1 g) in acetic anhydride (10 ml) was refluxed on steam bath for two hours, cooled, diluted with ethanol (10 ml) and left overnight. The crystalline solid that separated was filtered off and recrystallized twice from ethanol to give **IIIc** in 60% yield (no depression in m.p. on admixing with authentic sample prepared by method A).

(Z)-4-{2-Aryl-4-[4-(arylsulfonyloxy)phenylmethinyl]-4,5-dihydro-5-oxo-1H-imidazol-1-yl}-N-substituted benzenesulfonamide (**VIa–o**). A mixture of (**IIIa–c**), (0.003 mol in each case) and the corresponding sulfonamide derivative (**IVa–e**), (0.0032 mol in each case) was refluxed in acetic acid (25 ml) containing freshly fused sodium acetate (0.1 g) for three hours and cooled. The solid that separated was filtered off, washed twice with water, dried and recrystallized from ethanol to give the required products (**VIa–o**) as yellow to orange colored crystals. IR spectra for these compounds revealed absorption bands at: 3335–3290 cm^{-1} (NH), 1720–1715 cm^{-1} (imidazolone moiety), 1635–1620 cm^{-1} (C=N), 1345–1340, 1220–1215 cm^{-1} (sulfonate ester group), and at 1165–630 cm^{-1} (for differently N-substituted sulfonamide moieties); ^{1}H NMR spectra δ: 9.5–9.1 ppm (—$SO_2N\underline{H}$—) and 7.10–6.80 ppm (ylidene proton). The MS spectrum of (**VIo**) revealed a molecular ion peak at $\overline{M}^+$ = 821, leading to a molecular formula of the compound as $C_{40}H_{32}N_6O_8S_3$. Three prominent peaks appeared at m/e 589 (70.80%), 588 (100%) and 559 (62.2%) indicating the loss of $C_{12}H_{10}NO_2S$ (232 mass unit), $C_{12}H_9O_3S$ (233 mass unit) and $C_{12}H_{12}N_3O_2S$ (262 mass unit) respectively, and establishing the structure of the compound. The relevant data of these products are listed in (Table II).

Biological screening for the prepared compounds was carried out according to the previously reported method.[23] The minimum inhibitory concentration (MIC) was determined by dilution assay technique.[24]

TABLE II

Characterization data for compounds (**VIa–o**)



No.	R	M.p. °C % (Yield)	Formula (Mol. Wt.)	Analysis Calculated/Found %C	%H	%N	%S
Ar^1 = $C_6H_5SO_3C_6H_4$- ; Ar^2 = C_6H_5-							
VIa	H	232 (81)	$C_{28}H_{21}N_3O_6S_2$ (559.60)	60.09 59.82	3.78 3.57	7.51 7.38	11.46 11.31
VIb	Guanyl	105 (69)	$C_{29}H_{23}N_5O_6S_2$ (601.64)	57.89 57.94	3.85 3.80	11.64 11.69	10.66 10.51
VIc	2-Pyridyl	236 (74)	$C_{33}H_{24}N_4O_6S_2$ (636.68)	62.25 62.49	3.80 3.97	8.80 8.71	10.07 10.34
VId	2-Pyrimidyl	>300 (77)	$C_{32}H_{23}N_5O_6S_2$ (637.67)	60.27 60.12	3.64 3.39	10.98 10.81	10.06 10.28
VIe	4,6-$(Me)_2$-2-pyrimidyl	104 (79)	$C_{34}H_{27}N_5)_6S_2$ (665.73)	61.34 61.56	4.09 4.13	10.52 10.41	9.63 9.90
Ar^1 = p-CH_3.$C_6H_4SO_3C_6H_4$- ; Ar^2 = C_6H_5-							
VIf	H	250 (70)	$C_{29}H_{23}N_3O_6S_2$ (573.62)	60.72 60.94	4.04 4.12	7.33 7.22	11.18 11.00
VIg	Guanyl	150 (66)	$C_{30}H_{25}N_5O_6S_2$ (615.67)	58.52 58.64	4.09 4.17	11.38 11.49	10.42 10.65
VIh	2-Pyridyl	110 (79)	$C_{34}H_{26}N_4O_6S_2$ (650.71)	62.75 62.95	4.03 4.28	8.61 8.78	9.86 9.60
VIi	2-Pyrimidyl	245 (68)	$C_{33}H_{25}N_5O_6S_2$ (651.70)	60.81 60.72	3.87 3.69	10.75 10.98	9.84 9.91
VIj	4,6-$(Me)_2$-2-pyrimidyl	90 (61)	$C_{35}H_{29}N_5O_6S_2$ (679.75)	61.84 61.69	4.30 4.26	10.30 10.58	9.43 9.73

TABLE II *(continued)*

No.	R	M.p. °C % (Yield)	Formula (Mol. Wt.)	Analysis Calculated/Found %C	%H	%N	%S
$Ar^1 = C_6H_5SO_3C_6H_4-$; $Ar^2 = C_6H_5SO_2NHC_6H_4-$							
VIk	H	145 (59)	$C_{34}H_{26}N_4O_8S_3$ (714.78)	57.13 57.32	3.67 3.72	7.84 7.61	13.46 13.41
VIl	Guanyl	205 (61)	$C_{35}H_{28}N_6O_8S_3$ (756.82)	55.54 55.79	3.73 3.52	11.11 11.33	12.71 12.50
VIm	2-Pyridyl	200 (64)	$C_{39}H_{29}N_5O_8S_3$ (791.86)	59.15 59.43	3.69 3.48	8.84 8.75	12.15 12.00
VIn	2-Pyrimidyl	185 (63)	$C_{38}H_{28}N_6O_8S_3$ (792.85)	57.56 57.50	3.56 3.39	10.60 10.38	12.13 12.29
VIo	4,6-$(Me)_2$-2-pyrimidyl	120 (60)	$C_{40}H_{32}N_6O_8S_3$ (820.91)	58.52 58.41	3.93 3.78	10.24 10.56	11.72 11.54

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