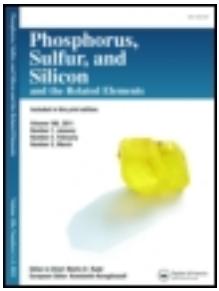


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthesis of Thiazolidine and Thiophene Derivatives for Evaluation as Anticancer Agents

M. S. A. El-Gaby [a] , Z. H. Ismail [a] , S. M. Abdel-Gawad [b] , H. M. Aly [b] & M. M. Ghorab [c]

[a] Department of Chemistry, Faculty of Science, Al-Azhar University at Assiut, Assiut, Egypt

[b] Department of Chemistry, Faculty of Science (Girls), Al-Azhar University, Cairo, Egypt

[c] Department of Drug Radiation Research, National Center for Radiation Research and Technology, Nasr City, Cairo, Egypt

Published online: 21 Sep 2009.

To cite this article: M. S. A. El-Gaby , Z. H. Ismail , S. M. Abdel-Gawad , H. M. Aly & M. M. Ghorab (2009): Synthesis of Thiazolidine and Thiophene Derivatives for Evaluation as Anticancer Agents, Phosphorus, Sulfur, and Silicon and the Related Elements, 184:10, 2645-2654

To link to this article: http://dx.doi.org/10.1080/10426500802561096

Phosphorus, Sulfur, and Silicon, 184:2645–2654, 2009

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802561096

Taylor & Francis
Taylor & Francis Group

Synthesis of Thiazolidine and Thiophene Derivatives for Evaluation as Anticancer Agents

M. S. A. El-Gaby,[1] Z. H. Ismail,[1] S. M. Abdel-Gawad,[2] H. M. Aly,[2] and M. M. Ghorab[3]
[1]Department of Chemistry, Faculty of Science, Al-Azhar University at Assiut, Assiut, Egypt
[2]Department of Chemistry, Faculty of Science (Girls), Al-Azhar University, Cairo, Egypt
[3]Department of Drug Radiation Research, National Center for Radiation Research and Technology, Nasr City, Cairo, Egypt

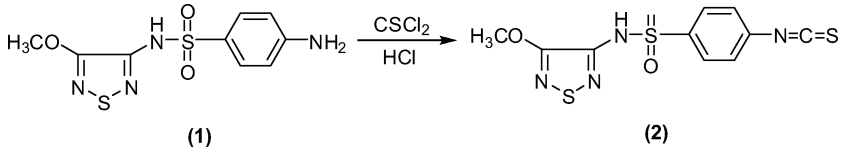
*The non-isolated adducts **(3a,b)** were used as key intermediates to synthesize some novel thiazolidine and thiophene derivatives. Compound **(4)** exhibited a remarkable antitumor activity against EAC cells compared with the Doxorubicin as a positive control.*

Keywords 1,2,5-Thiadiazole; thiazolidine and thiophene derivatives

INTRODUCTION

1,2,5-Thiadiazole derivatives are known to exhibit a wide spectrum of biological activity.[1,2] In addition to pronounced herbicide activity, 1,2,5-thiadiazole derivatives were found to be efficient muscarine receptor agonists,[3] as well as inhibitors of HIV-1 replication.[4] For example, 1-(1,1-dimethylethylamino)-3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)-2-propanol (Timolol) is one of the most important medicines for the treatment of glaucoma.[5,6] Furthermore, antibacterial,[7] antifungal,[8] insulin releasing,[9] carbonic anhydrase inhibitory,[10] anti-inflammatory,[11] and antitumor[12] properties of the sulfamoyl moiety have been described. In view of the above observations and as a continuation of our research program on the synthesis of heterocyclic compounds from readily available starting materials,[13–16] we report here on the synthesis and antitumor activity of some novel thiazolidine and thiophene derivatives bearing a 1,2,5-thiadiazole moiety.

Received 14 July 2008; accepted 16 October 2008.
Address correspondence to M. S. A. El-Gaby, Department of Chemistry, Faculty of Science, Al-Azhar University at Assiut, Assiut 71524, Egypt. E-mail: m_elgaby@hotmail.com



(1) (2)

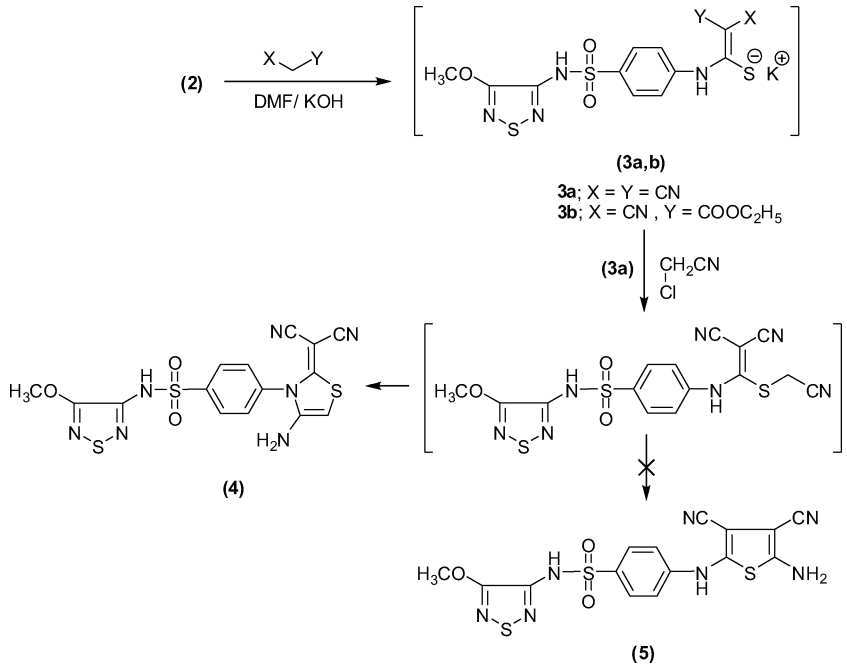
SCHEME 1

RESULTS AND DISCUSSION

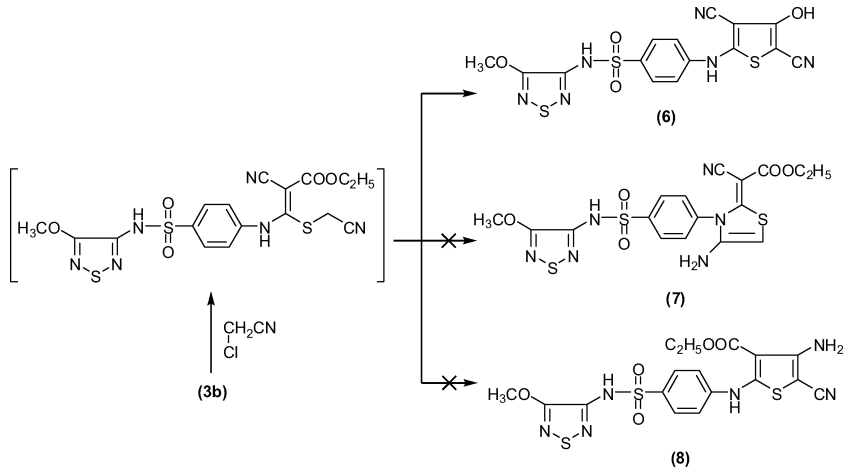
The starting material 4-isothiocyanato-N-(4-methoxy-1,2,5-thiadiazol-2-yl) benzene sulfonamide (2) was synthesized via the reaction of sulfonamide derivative (1) with thiophosgene at room temperature in the presence of hydrochloric acid (Scheme 1). The mass spectrum of isothiocyanate (2) revealed a molecular ion peak at m/z = 328 (2.27%), and the base peak was found in the spectrum at m/z = 134, which is characteristic for phenyl isothiocyanate minus hydrogen.

The reactivity of isothiocyanate derivative **(2)** towards active methylene compounds in the presence of potassium hydroxide followed by in situ cyclization with halo compounds was studied. Thus, the non-isolated adducts **(3a,b)** were prepared by the treatment of isothiocyanate derivative **(2)** with malononitrile and ethyl cyanoacetate. Treatment of the non-isolated adduct **(3a)** with chloroacetonitrile at room temperature furnished 4-amino-thiazole derivative **(4)**. The other possible structure **(5)** was discarded on the basis of spectral data. The infrared spectrum revealed the following absorption bands: 3487, 3197 (NH_2), 3085 (CH-arom.), 2931 (CH-aliph.), 2202 (C≡N), and 1589 cm^{-1} (C=C). The ^{1}HNMR spectrum (DMSO-d_6) exhibited the following signals: 4.06 (s, 3H, OCH_3), 4.21 (hump, 2H, NH_2), 6.60 (s, 1H, thiazole-H), 7.25–8.09 (m, 4H, Ar-H), and 9.52 ppm (s, 1H, NH). The formation of compound **(4)** is assumed to proceed through the initial alkylation followed by in situ heterocyclization[17] via a nucleophilic addition of the secondary amino group to the cyano group and tautomerization, as shown in Scheme 2.

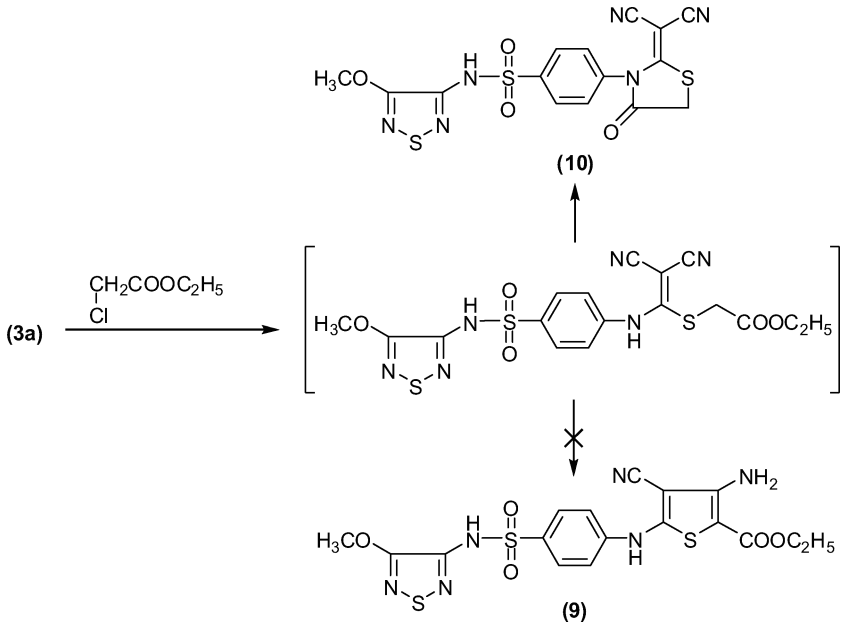
Cyclization of the non-isolated adduct **(3b)** at room temperature with chloroacetonitrile yielded hydroxythiophene derivative **(6)** rather than the expected products **(7)** and **(8)**, on the basis of analytical and spectral data shown in Scheme 3. Its infrared spectrum showed the following absorption bands at: 3201 (OH; broad) and 2210 cm^{-1} (C≡N). Also, its ^{1}H NMR (DMSO-d_6) exhibited the absence of the ethoxycarbonyl moiety and revealed the presence of the following signals: 3.80 (s, 3H, OCH_3), 7.4–7.9 (m, 6H, Ar-H + 2NH), and 10.8 ppm (s, 1H, OH). The formation of **(6)** is assumed to proceed via initial alkylation by loss of potassium chloride followed by elimination of ethanol.



SCHEME 2



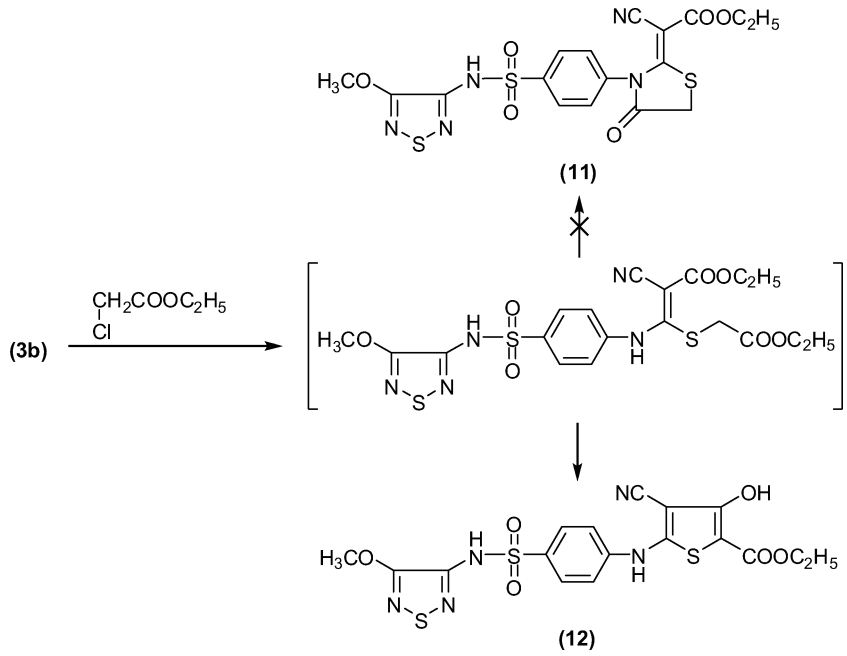
SCHEME 3



SCHEME 4

The reaction of the non-isolated adduct **(3a)** with ethyl chloroacetate at room temperature produced the novel 4-thiazoli-dinone derivative **(10)**, and the other possible structure **(9)** was ruled out on the basis of analytical and spectral data (Scheme 4).The infrared spectrum of compound **(10)** showed the following absorption bands: 3197, 3116 (2NH), 2954 (CH-aliph.), 2214 (C≡N), and 1735 cm^{-1}(C=O). Also, its ^{1}H NMR (DMSO-d_6) revealed the following signals: 3.91 (s, 3H, OCH_3), 4.6 (s, 2H, CH_2), 7.8–8.2 (m, 4H, Ar-H), and 11.60 ppm (s, 1H, NH). The formation of **(10)** was assumed to proceed through initial alkylation followed by elimination of ethanol.

Alternatively, treatment of the non-isolated adduct **(3b)** with ethyl chloroacetate gave the thiophene derivative **(12)**, and the other possible structure **(11)** was excluded on the basis of analytical and spectral data (Scheme 5). The infrared spectrum of compound **(12)** showed the following absorption bands: 3494, 3105 (OH/NH), 2985 (CH-aliph.), 2210 (C≡N), and 1739 cm^{-1} (C=O). The ^{1}H NMR spectrum of compound (**12**; DMSO-d_6) revealed the following signals: 1.30 (t,3H, CH_3), 4.10 (s, 3H, OCH_3),4.2 (q, 2H, CH_2), 7.2–8.1 (m, 6H, Ar-H + 2NH), and 11.8 ppm (br, 1H, OH). The formation of **(12)** is assumed to proceed via an initial alkylation followed by the elimination of ethanol.

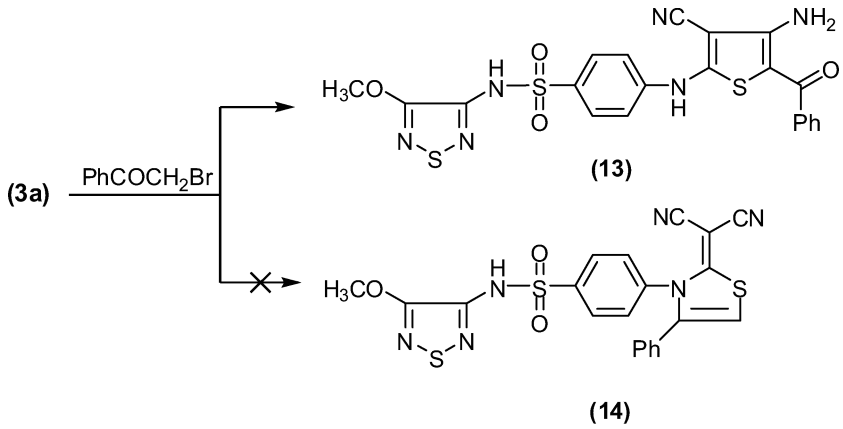


SCHEME 5

Treatment of the non-isolated adduct **(3a)** with phenacyl bromide at room temperature afforded the corresponding thio-phene derivative **(13)** and not thiazolidine derivative **(14)** on the basis of analytical and spectral data (Scheme 6). Its infrared spectrum showed the following absorption bands: 3373, 3277, 3129 (NH, NH_2), 2937 (CH-aliph.), 2208 (C≡N), and 1690 cm^{-1} (C=O). Also, its mass spectrum revealed a molecular ion peak at m/z 512 (35%) together with a base peak at m/z 77.

EXPERIMENTAL

All melting points are uncorrected and were determined on a Stuart melting point apparatus. IR spectra were recorded on a Shimadzu-440 IR spectrophotometer using the KBr technique (Shimadzu, Japan). ^{1}H NMR spectra were recorded on a Bruker proton NMR-Avance 300 (300MHz), in DMSO-d_6 as a solvent, using tetramethylsilane (TMS) as an internal standard. The mass spectra were performed by HP Model MS-5988. Elemental analyses were carried out by the Microanalytical Research Centre, Faculty of Science, Cairo University. Characteristics of the prepared compounds are given in Table I; analytical results for C, H, N were within ±0.4% of the calculated values.



SCHEME 6

4-Isothiocyanato-N-(4-methoxy-1,2,5-thiadiazol-3-yl)benzenesulfonamide (2)

A mixture of sulfanilamide derivative **1** (0.01 mol), thiophosgene (0.01 mol), and dilute HCl (50 mL) was stirred at room temperature for 1 h. The solid residue was collected by filtration, washed with cold water, and recrystallized from acetone to give **(2)**. The IR spectrum of **(2)** revealed absorption bands at 3226 (NH), 3099 (CH arom.), 2100 (NCS), 1332, 1162 cm^{-1} (SO_2). The mass spectrum of **(2)** revealed a molecular ion peak m/z at 328 (M^+, 2.77%), with a base peak at 134 (100%), and other significant peaks appeared at 264 (43.98%), 231 (4.88%), 198 (61.96%), 167 (7.97%), 97 (37.02%), 57 (41.79%).

4-(4-Amino-2-(dicyanomethylene)thiazol-3-(2H)-yl)-*N*-(4-methoxy-1,2,5-thiadiazol-3-yl)benzenesulfonamide (4), 4-(3,5-Dicyano-4-hydroxythiophen-2-ylamino)-*N*-(4-methoxy-1,2,5-thiadiazol-3-yl)benzenesulfonamide (6), 4-(2-(Dicyanomethylene)-4-oxothiazolidin-3-yl)-*N*-(4-methoxy-1,2,5-thiadiazol-3-yl)benzenesulfonamide (10), Ethyl 4-Cyano-3-hydroxy-5-(4-(*N*-(4-methoxy-1,2,5-thiadiazol-3-yl)sulfamoyl)phenylamino)thiophene-2-carboxylate (12), and 4-(4-Amino-5-benzoyl-3-cyanothiophen-2-ylamino)-*N*-(4-methoxy-1,2,5-thiadiazol-3-yl)benzenesulfonamide (13): General Procedure

To a solution of finely powdered potassium hydroxide (0.01 mole) in dry DMF (10 mL) at room temperature, the malononitrile or ethyl

TABLE I Characterization Data for Newly Synthesized Compounds

Compd. No.	Mp (°C)	Yield (%)	Solvent	Mol. Formula (Mol.Wt)	Elemental Analyses Calculated/(Found)		
					C%	H%	N%
2	148–150	95	DMF-EtOH	$C_{10}H_8N_4O_3S_3$ (328)	36.57 (36.80)	2.46 (2.20)	17.06 (17.40)
4	88–90	70	Dioxane	$C_{15}H_{11}N_7O_3S_3$ (433)	41.56 (41.90)	2.56 (2.20)	22.62 (22.30)
6	110–112	59	EtOH	$C_{15}H_{10}N_6O_4S_3$ (434)	41.47 (41.17)	2.32 (2.08)	19.34 (19.04)
10	118–120	63	Dioxane	$C_{15}H_{10}N_6O_4S_3$ (434)	41.47 (41.50)	2.32 (2.20)	19.34 (19.60)
12	125–127	76	Dioxane	$C_{17}H_{15}N_5O_6S_3$ (481)	42.40 (42.20)	3.14 (3.40)	14.54 (14.20)
13	190–192	81	DMF-EtOH	$C_{21}H_{16}N_6O_4S_3$ (512)	49.21 (49.50)	3.15 (3.40)	16.40 (16.70)

cyanoacetate and then the isothiocyanate derivative **2** (0.01 mol) were added in portions. The reaction mixture was stirred at room temperature for 3 h, then with the appropriate halo compounds (0.01 mol), and left at room temperature for 24 h. The reaction mixture was cooled and poured into ice water (60 mL) and acidified with 0.1*N* HCl. The resulting precipitate was filtered off, dried, and recrystallized from the proper solvent.

Antitumor Activity (In Vitro Study)

Reagents

1. RPMI 1640 medium (sigma).
2. Ehrlich Ascites Carcinoma cells (EAC) suspension (2.5×10^6/mL).
3. Trypan blue dye; A stock solution was prepared by dissolving one gram of the dye in distilled water (100 mL). The working solution was then prepared by diluting (1 mL) of the stock solution with (9 mL) of distilled water. The stain was used then for staining the dead EAC cells.
4. The compounds tested were (**4**, **6**, **10**, **12**, and **13**).

Procedure

1. EAC cells were obtained by needle aspiration of the ascetic fluid from preinoculated mice under aseptic conditions.[18]
2. The cells were tested for viability and contamination by staining certain cell volume of this fluid by an equal volume of the working solution of trypan blue dye.[19,20]
3. The ascetic fluid was diluted with saline (1:10) to contain 2.5×10^6 cells on a hemocytometer.
4. In a set of sterile test tubes, 0.1 mL of tumor cells suspension, 0.8 mL RPMI 1640 media, and 0.1 mL of each tested compound (corresponding to 100, 50, and 25 μg/mL) were mixed. The test tubes were incubated at 37°C for 2 h. The trypan blue exclusion test[19,20] was carried out to calculate the percentage of nonviable cells. Compounds producing more than 70% nonviable cells are considered active.[21]
5. Doxorubicin (Adriablastina®) is taken as a reference.

$$\%\,\text{of non}--\text{viable cells} = \frac{\text{No. of non} - \text{viable}}{\text{Total No. of cells}} \times 100$$

The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of EAC cell. The response parameter calculated was the IC_{50} value, which corresponds to the

TABLE II In Vitro Cytotoxic Activity of Some Selected Synthesized Compounds

	Non-viable cells (%) Concentration(μg/ml)			
Compd. No.	100	50	25	IC_{50} (μg/mL)
4	100	50	25	42.8
6	50	40	20	91
10	50	40	20	91
12	0	0	0	$>100^a$
13	0	0	0	$>100^a$
Doxorubicin (reference)	100	55	20	43.6

[a] $IC_{50} > 100$ (μg/mL) is considered to be inactive.

compound concentration causing 50% mortality in net cells (Table II). The results obtained from this study showed that 1,2,5-thiadiazole benzenesulfonamide having thiazole moiety **(4)** is nearly as active as the positive control (Doxorubicin) with IC_{50} of 42.8 μg/mL.

REFERENCES

[1] S. Yoon, J. Cho, and K. Kim, *J. Chem. Soc. Perkin Trans* **1,** 109 (1998).

[2] E. I. Strunskaya, Z. A. Bredikhina, N. M. Azancheev, and A. A. Bredikhina, *Russ. J. Org. Chem.*, **37**(9), 1330 (2001).

[3] Y. Cao, M. Zhang, C. Wu, S. Lee, M. E. Worblewsk, T. Whipple, P. I. Nagy, K. Takacs-Novak, A. Balazs, S. Toros, and W. S. Messer, *J. Med. Chem.*, **46,** 4273 (2003).

[4] Y. Hanasaki, H. Watanabe, K. Katsuura, H. Takayama, S. Shirakawa, K. Yamaguchi, S. Sakai, K. Ijichi, M. Fujiwara, K. Konno, T. Yokota, S. Shigeta, and M. Baba, *J. Med. Chem.*, **38**(12), 2038 (1995).

[5] S. J. Sorensen and S. R. Abel, *Ann. Pharmacother.*, **30,** 43 (1996); *Chem. Abstr.*, **124,** 219106b.

[6] L. M. Weinstock, D. M. Mulvey, and R. Tull, *J. Org. Chem.*, **41**(19), 3121 (1976).

[7] M. S. A. El-Gaby, A. A. Atalla, A. M. Gaber, and K. A. Abd Al-Wahaby, *IL Farmaco*, **55,** 596 (2000).

[8] M. S. A. El-Gaby, A. M. Gaber, A. A. Atalla, and K. A. Abd Al-Wahaby, *IL Farmaco*, **57,** 613 (2002).

[9] T. H. Maren, *Ann. Rev. Pharmacol. Toxicol.*, **16,** 309 (1976).

[10] C. T. Supuran, A. Scozzafava, B. C. Jurca, and M. A. Iies, *Eur. J. Med. Chem.*, **33,** 83 (1998).

[11] J. J. Li, D. Anderson, E. G. Burton, J. N. Cogburn, J. T. Collins, D. J. Garland, S. A. H. Huang, P. C. Isokson, C. M. Koboldt, E. W. Logusch, M. B. Morton, W. Perkins, E. J. Reinhard K. Seibert, A. W. Veenhuizen, Y. Zhang, and D. B. Reitz, *J. Med. Chem.*, **38,** 4570 (1995).

[12] S. M. Sondhi, M. Johar, N. Singhal, S. G. Dastidar, R. Shukla, and R. Raghubir, *Monatsh. Chem.*, **131,** 511 (2000).

[13] S. M. Abdel-Gawad, M. S. A. El-Gaby, H. I. Heiba, H. M. Aly, and M. M. Ghorab, *J. Chin. Chem. Soc.*, **52,** 1227 (2005).
[14] S. M. Abdel-Gawad, M. S. A. El-Gaby, and M. M. Ghorab, *IL Farmaco*, **55,** 287 (2000).
[15] M. M. Ghorab, S. M. Abdel-Gawad, and M. S. A. El-Gaby, *IL Farmaco*, **55,** 249 (2000).
[16] M. S. A. El-Gaby, S. M. Abdel-Gawad, M. M. Ghorab, H. I. Heiba, and H. M. Aly, *Phosphorus, Sulfur, and Silicon*, **181,** 279 (2006).
[17] S. M. Sherif, *Monatsh. Fur Chemie*, **127,** 557 (1996).
[18] M. M. El-Merzabani, A. A. El-Aaser, A. K. El-Dueini, and A. M. EL-Masry, *Planta Medica*, **36,** 87 (1979).
[19] D. Raffa, G. Daidone, B. Maggio, S. Cascioferro, F. Plescig, and D. Schillaci, *IL Farmaco*, **59,** 215 (2004).
[20] D. J. Takemoto, C. Dunford, and M. M. McMurray, *Toxicon*, **20,** 593 (1982).
[21] M. M. El-Merzabani, A. A. El-Aaser, M. A. Attia, A. K. El-Dueini, and A. M. Ghazal, *Planta Medica*, **36,** 150 (1979).