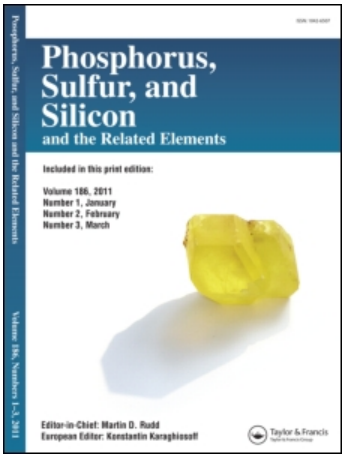

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Elgazwy, Abdel-Sattar S. Hamad and Azab, Mohamed E.(2001) 'SYNTHESIS AND BIOLOGICAL ACTIVITY OF2-THIOXO-[1*H*]-5-SPIROCYCLOHEXYLIMIDAZO[4,3-*b*] QUINAZOLONE AND 8-AZAQUINAZOLONE DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 173: 1, 105 — 113
To link to this Article: DOI: 10.1080/10426500108045263
URL: http://dx.doi.org/10.1080/10426500108045263

Phosphorus, Sulfur and Silicon, 2001, Vol. 173, pp. 105-113
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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-THIOXO-[1*H*]-5-SPIROCYCLOHEXYLIMIDAZO[4,3-*b*] QUINAZOLONE AND 8-AZAQUINAZOLONE DERIVATIVES

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(Received October 13, 1999; In final form December 16, 2000)

The reaction of 5-spirocyclohexylimidazole-2,4-dithion with one and two mole equivalent of β-aminocarboxylic acid derivatives (**2a-b** and **5**) to give new heterocyclic systems of synthetic and potential biological interest viz. compounds (**3a-b, 4a-b, 6** and **7**). The structures of the products have established by chemical and spectroscopic evidence. The antimicrobial activity of the synthesized compounds was tested against 10 bacterial and yeast strains.

Keywords: 5-Spirocyclohexylimidazole-2,4-dithion; β-aminocarboxylic acid; Quinazolone; 8-azaquinazolone; Thiohydantoin

INTRODUCTION

To our knowledge there are few reports concerning the biological activity and chemistry of 2-thiohydantoins.[1–6] 2-Thiohydantoin derivatives are present in many compounds having functions to explore their biological properties of vasodilator, antispasmodic, blood platelet aggregation inhibitors,[7] antiarrhythmics[8] and anticholesterolesmic activities.[9] It was recently reported that mitomycin[10] and streptocin[11] are known antineoplastics containing an amide function. Most of the aforementioned drugs have a thiazolecarboxamide moiety as a common structural feature.

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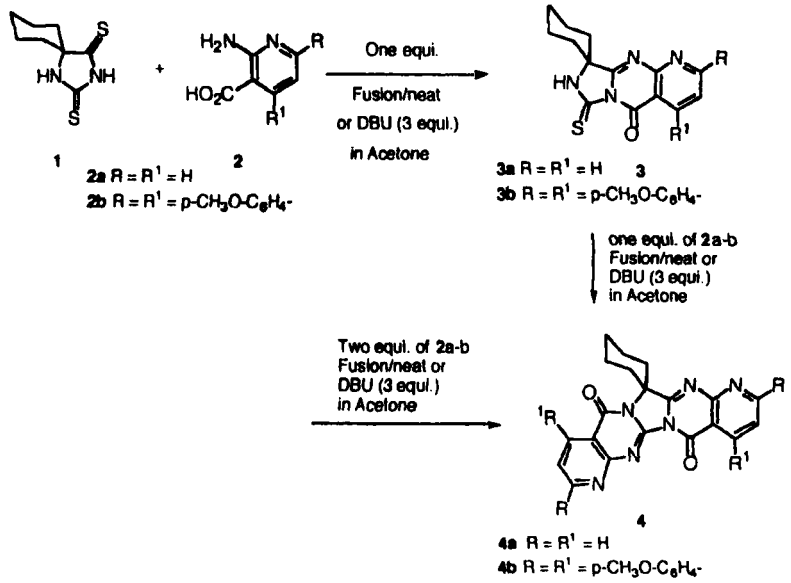
Mercaptotriazoles,[12–15] semicarbazides[16] and thiosemicarbazides[17,18] have long been reported to possess an antimicrobial activity.

These observations prompted us to continue the earlier investigations carried out in our laboratory, with the hope to discover an active, less toxic compound, We would like to report here an efficient and easily reproducible synthesis of certain thiohydantoin (**3a-b** and **6**) derivatives, bearing the functional groups believed to be responsible for antitumor antibiotic activity. The synthetic challenges of dithiohydantoin[19] **1** was reacted with one or two mole equivalent of 2-aminopyridine-3-carboxylic acid derivatives **2a-b** and anthranilic acid **5** to provide imidazole[4,3-b]quinazolone (**3a-b, 4a-b, 6** and **7**) derivatives respectively. Firstly the compound **2b** was prepared in 75 % yield following the literature reports[20] by condensation reaction of chalcone with one equivalent ethyl cyanoacetate in the presence of ammonium acetate (4 equi.) to provide ester in 80 % yield. Hydrolysis of the ester with 10% KOH in alcohol gave 4,6-(4″-methoxyphenyl)-2-aminopyridine-3-carboxylic acid **2b** in 70 % yield.

This reported biological importance of thiohydantoins allowed us to prepare 5-spirocyclohexylimidazole-2,4-dithion **1** following the literature reports.[19] The ^{1}H NMR spectrum of thiohydantoin **1** exhibited signals for 6 non-equivalent protons in the cyclohexyl ring corresponding to 10 H-atoms. The up field signals are assigned to the 2H protons for -CH_2-which appear as triplets at δ 1.21 (t, 2H, J = 4.5 Hz, -CH_2-) and show signals multiplets for 8H protons at δ 1.47–1.75 (m, 8H) and down field two single signals for two NH at δ 11.65 and 13.13 respectively. Moreover, in the ^{13}C-NMR spectrum, signals for three (-CH_2-) at δ = 21.75, 25.28, 37.59, with the carbon (C^i) at δ = 76.99. The expected chemical shifts of the C^i-atoms in the ^{13}C NMR for two C=S groups exhibited at δ 179.91 and 211.78 ppm in the position (2 and 4) respectively.

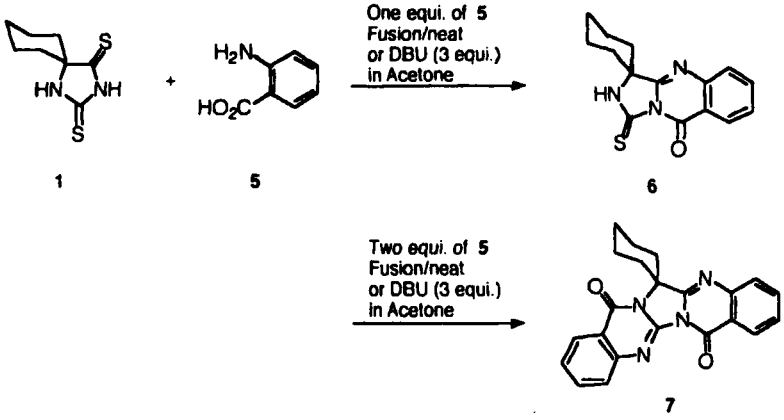
Thiohydantoin **1** reacted with one mole equivalent of 2-aminopyridine-3-carboxylic acid derivatives **2a-b** in the presence (3 equi.) of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in acetone provided compound **3a-b** in 75% yield. But when allowed the thiohydantoin **1** to react with two mole equivalent of 2-aminopyridine-3-carboxylic acid derivatives **2a-b** following the same previous procedure method (A), afforded compounds **4a-b** in low yield 36% respectively. In the light of these results, the compounds **4a-b** were prepared as authentic sample by another route when we allowed to react the compounds **3a-b** with one mole equivalent of 2-ami-

nopyridine-3-carboxylic acid derivatives **2a** in the presence (3 equiv.) of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) following the same procedure described in Method (A). Spectral data characteristics were identical with those of the authentic sample in all aspects, which was previously reported.



SCHEME I

Thiohydantoin **1** reacted also with one mole equivalent of anthranilic acid **5** in the presence (3 equi) of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in acetone to provide compound **6** in 75% yield. But when allowed the thiohydantoin **1** to react with two mole equivalent of anthranilic acid **5** following the same previous procedure described in (method A), compounds **7** was obtained in low yield 36%. The compound **7** which was prepared as an authentic sample by another route when we allowed to react the compound **6** with one mole equivalent of anthranilic acid **5** in the presence (3 equiv.) of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). Spectral data characteristics were identical with those of the authentic sample in all aspects, which was previously reported.



1 5 6 7

SCHEME 2

This reaction was achieved also via fusion (neat) to provide the compounds **3a-b, 4a-b, 6** and **7** in low yield (35–45%) respectively. Both the reaction conditions failed to provide any products from similar compounds such as highly hundred aromatic compounds of 2-phenyl-5-spirocyclohexylimidazole-2,5-dithion as detected by GC/MS analysis, and considerable amount of both starting materials remained. We do believe this due to the steric hindrance of highly aromatic substitution to inhibit the condensation reaction.

BIOLOGICAL ACTIVITY

The biological activity of the different products synthesized was tested against 10 bacterial and yeast strains (*candida albicans*), one. We found there are only one yeast strains (*candida albicans*, one gram-negative (*escherichia coli*), and three gram-positive strains (*staphylococcus aureus*, *staphylococcus epidermidio* and *bacillus subtilis*) which were sensitive against the tested compounds (cf. Table I). It was observed that the 5-spirocyclohexyldithiohydantoin **1**, [1*H*]-5-spirocyclohexylimidazo[4,3-*b*]8-azaquinazoline-4-one **3a-b** and [1*H*]-5-spirocyclohexyl imidazo[4,3-*b*] quinazolone **6** derivatives showed a great effect in inhibiting the yeast

strain (*candida albicans*), three gram-positive (*staphylococcus aureus, staphylococcus epidermidio* and *bacillus subtilis*) and one gram-negative (*escherichia coli*) strains. While the diazaquinazolone compounds **4a-b** and **7** showed also a great effect in inhibiting the yeast strains (*candida albicans*), one gram negative (*escherichia coli*) and one gram positive (*bacillus subtilis*). None of these diazaquinazolone compounds **4a-b** and **7** were showed to us the activity against *staphylococcus aureus, staphylococcus epidermidio or proteus vulgaris.*

TABLE I Antimicrobial activity of the tested compounds (mean diameter of inhibition zone, mm)

Compounds	*(staphylococcus aureus)*	*(staphylococcus epidermidio)*	*(bacillus subtilis)*	*(escherichia coli)*	*(candida albicans)*
1	27	29	22	26	25
3a	18	21	16	21	13
3b	23	24	17	19	15
4a	–	–	31	35	34
4b	–	–	30	32	29
6	19	22	18	20	17
7	–	–	15	28	29

Experimental Section

^{1}H NMR spectra were recorded on Varian Plus 300 (300 MHz) or Bruker XL 300 (300 MHz) instruments, the ^{13}C NMR spectra (with DEPT 135) on a Bruker WP80 or XL 300 instrument. Infrared Red spectra listed as recorded `"neat" refer to a thin film of material on NaCl disks, and were taken on a Perkin Elmer 1600 FT-IR spectrometer. Mass points were recorded on a Kratos concept instrument. Melting points were measured on an electrothermal digital melting point apparatus and are uncorrected The R_f value reported for TLC analysis was determined on Macherey-Nagel 0.25 mm layer fluorescent UV_{254} plates with the indicated solvent system. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ) at University of Minho, Braga, Portugal and Central Lab. of Ain Shams University, Cairo, Egypt. Biological activity measurements

were carried out in the Departamento de Química, Universidade do Minho, 4710 Braga, Portugal.

General Procedure

Method (A)

A mixture of 5-spirocyclohexylimidazole-2,4-dithion 1 (1 mole equiv.) and one mole equivalent or two mole equivalent of 2-aminopyridine-3-carboxylic acid **2a-b** or antheranilic acid **5** were suspension in (25 mL) of acetone then added (3 equiv.) of DBU(1,8-diazabicyclo[5.4.0]undec-7-ene). The reaction mixture was refluxed for 3 days. The solvent was removed using rotatory evaporator to provide the products in 35–75 % yields. Recrystalisation the residue by using acetone or dioxan.

1,3-Diaza-spiro[4.5]decane-2,4-dithione (1)

2,4-Dithiohydantoin **1** was prepared following the literature reports.[19] IR (Nujol): $\upsilon = 1116\ cm^{-1}$ (C=S), 1630 (C=N), 1536 (2,4-dithiohydantoin), 928.4, 709.8, 3176.00 (NH); m.p 274–276 °C (acetone); ^1H NMR (300 MHz, DMSO): $\delta = 13.13$ [s, 1H, NH (3)], 11.06 [s, 1H, NH (1)], 1.19(t, 2H, J = 4.5 Hz, -C<u>H</u>$_2$), 1.41–1.75 (m, 8H, cyclohexyl) ppm.; ^{13}C NMR (75 MHz, DMSO): $\delta = 211.78, 179.91, 76.99, 37.57, 25.25, 21.72$.; Anal. Calcd for $C_8H_{12}N_2S_2$ (200): C, 48.00; H, 6.00. N, 14.00, S, 32.00 Found: C, 48.06; H, 5.97. N, 13.86, S, 32.16;

2-Thioxo-[1H]-5-spirocyclohexylimidazo[4,3-b]-8-azaquinazoline-4-one (3a)

IR (Nujol): $\upsilon = 1760\ cm^{-1}$ (C=O), 1610 (C=N), 1520 (thiohydantoin), 1200–1300 (C=S), 3050–3290 (-NH); m.p = >350 °C (dioxan); ^1H NMR (300 MHz, DMSO): $\delta = 11.06$ [s, 1H, NH (1)], 1.43–1.76 (m, 10H, cyclohexyl), 7.27 (dd, 1H, J = 8.5, 4.3 Hz, Hb) 8.01 (dd, J = 8.3, 1.8 Hz, Ha), 8.81 (dd, J = 4.3, 1.8 Hz, Hc) ppm.; Anal. Calcd for $C_{14}H_{14}N_4SO$ (286): C, 58.74, H, 4.98, N, 19.58, S, 11.18 Found: C, 58.46; H, 5.07. N, 19.46, S, 11.16; HRMS (EI) Calcd for $C_{14}H_{14}N_4SO$ (286), found 286.1;

2-Thioxo-[1H]-5-spirocyclohexylimidazo[4,3-b]-8-azaquinazoline-4-one (3b)

IR (Nujol): $\upsilon = 1780\ cm^{-1}$ (C=O), 1625 (C=N), 1518(thiohydantoin), 1200–1300 (C=S), 3170–3300 (-NH).; m.p = >300 °C (dioxan); ^1H NMR (300 MHz, DMSO); $\delta = 11.06$ [s, 1H, NH(1)], 1.43–1.76 (m, 10H, cyclohexyl), 6.89 (dd, J = 8.7 Hz, ArH), 7.20 (s, 1H, Hb), 8.00 (dd, J = 8.7 Hz, ArH) ppm.; Anal. Calcd for $C_{28}H_{26}N_4SO_3$ (498): C, 67.46; H, 5.22. N, 11.24, S, 6.42 Found: C, 67.52; H, 5.17. N, 11.26, S, 6.36; HRMS (EI) Calcd for $C_{28}H_{26}N_4SO_3$ (498), found 498.33;

5-Spirocyclohexylimidazo[(2,1-a), (4,3-b)]bis(8-azaquinazoline-4-one) (4a)

IR (Nujol): $\upsilon = 1760\ cm^{-1}$ (C=O), 1620 (C=N); m.p = >300°C (dioxan); ^1H NMR (300 MHz, DMSO): $\delta = 1.43–1.76$ (m, 10H, cyclohexyl), 7.30 (dd, 1H, J = 8.5, 4.3 Hz, Hb) 8.16 (dd, J = 8.3, 1.8 Hz, Ha), 8.78 (dd, J = 4.3, 1.8 Hz, Hc) ppm.; Anal. Calcd for $C_{20}H_{16}N_6O_2$(372): C, 64.51; H, 4.30. N, 22.58, Found: C, 64.61; H, 4.70, N, 23.19; HRMS (EI) Calcd for $C_{20}H_{16}N_6O_2$(372), found 372.2;

5-Spirocyclohexylimidazo[(2,1-a)-(4,3-b)]bis(8-azaquinazoline-4-one (4b)

IR (Nujol): $\upsilon = 1780\ cm^{-1}$ (C=O), 1640 (C=N); m.p = >350 °C (acetone); ^1H NMR (300 MHz, DMSO): $\delta = 1.43–1.76$ (m, 10H, cyclohexyl), 6.90 (d, J = 8.7 Hz, ArH), 7.27 (s, 1H, Hb), 8.90 (d, J = 8.7 Hz, ArH) ppm.; Anal. Calcd for $C_{34}H_{28}N_6O_4$ (584): C, 69.86; H, 4.79. N, 14.38, Found: C, 69.30; H, 5.19. N, 13.99; HRMS (EI) Calcd for $C_{28}H_{26}N_4SO_3$(498), found 498.33;

2-Thioxo-[1H]-5-Spirocyclohexylimidazo[4,3-b]quinazoline-4-one (6)

IR (Nujol): $\upsilon = 1760\ cm^{-1}$ (C=O), 1620 (C=N), 1515(thiohydantoin), 1200–1300(C=S), 3050–3290(-NH).; m.p = 298–300°C (acetone); ^1H NMR (300 MHz, DMSO): $\delta = 11.06$ [s, 1H, NH(1)], 1.43–1.76 (m, 10H, cyclohexyl), 7.58 (dd, 1H, J = 7.8, 1.3 Hz, ArH_7) 7.83 (dd, J = 8.5, 1.2 Hz, ArH_6), 7.84 (dd, J = 7.8., 1.2 Hz, ArH_8), 8.01(dd, J = 8.5, 1.2 Hz, ArH_5)

ppm.; Anal. Calcd for $C_{15}H_{15}N_3SO$ (285): C, 63.15; H, 5.26. N, 14.73, S, 11.22 Found C, 63.45; H, 5.53. N, 15.03, S, 11.23; HRMS (EI) Calcd for $C_{15}H_{15}N_3SO$(285), found 285.3;

[1H]-5-Spirocyclohexylimidazo[(2,1-a)-(4,3-b)]bis(qninazoline-4-one) (7)

IR (Nujol): υ = 1770 cm^{-1} (C=O), 1635 (C=N), m.p = 310–312 °C (acetone); ^1H NMR (300 MHz, DMSO): δ = 1.43–1.76 (m, 10H, cyclohexyl), 7.59 (dd, 1H, J = 7.8, 1.3 Hz, ArH_7) 7.78 (dd, J = 8.5, 1.2 Hz, ArH_6), 7.82 (dd, J = 7.8., 1.2 Hz, ArH_8), 7.91(dd, J = 8.5, 1.2 Hz, ArH_5) ppm; Anal. Calcd for $C_{22}H_{18}N_4O_2$ (370): C, 71.35; H, 4.86. N, 15.13, Found: C, 71.51; H, 5.16. N, 15.26; HRMS (EI) Calcd for $C_{22}H_{18}N_4O_2$ (370), found 370.1;

BIOLOGICAL ACTIVITY

The bacterial strains were 5 gram-positive (*staphylococcus aureus, bacillus megatherium, bacillus subtilis, bacillus cereus and staphylococcus epidermidio*), 3 gram-negative (*escherichia coli, klebsiella aerogens and pseudomonas aeruginosa*). Two strains of yeast (*saccharomyces cervisia and candida albicans*) were also used. The tested organisms were inoculated on nutrient agar medium.[21] The assaying test was carried out according to the diffusion method.[22,13] Four holes 10-mm diameter was made in each plate, 0.2 mL of each of the tested compounds 10 mg/l ML DMF) were inserted in each hole. The plates were incubated at 37 °C for 24 hrs for bacteria and at 28 °C for 48 hrs in case of yeast. The average of inhibition clear zone diameters was calculated for each compound and recorded (Table I).

Acknowledgements

The authors thanks gratefully Departamento de Química, Universidade do Minho, 4710 Braga, Portugal for facilities.

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