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Structural studies of 4-aminoantipyrine derivatives

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Abstract

Reaction of 4-aminoantipyrine with acetylacetone, ethyl acetoacetate, benzoyl isothiocyanate, phenyl isothiocyanate, maleic anhydride and methoxymethylene Meldrum's acid afforded a series of new antipyrine derivatives. The antibacterial activity of the synthesized compounds against *Micrococcus luteus* ATCC 9341, *Staphilococcus aureus* ATCC 29737, and *Escherichia coli* ATCC 8739 was evaluated and the minimal inhibitory concentration determined. Modest activity was found only to the maleamic acid obtained from the reaction of 4-aminoantipyrine and maleic anhydride. ^{1}H NMR investigation of this maleamic acid showed that it is slowly converted to the corresponding toxic maleimide. The structures of three derivatives were determined by X-ray diffraction analysis.

Keywords: Enaminones; Thioureas; Meleimide

1. Introduction

The syntheses of 4-aminoantipyrine derivatives have attracted the attention of several research groups due to their potential biological activities [1]. In this context, broad spectra of bioactive 4-aminoantipyrine derivatives and their metal complexes have been investigated and diversities of bioactivities such as analgesic [2,3], antiinflammatory [3], antimicrobial [4,5], and anticancer activity [6] have been reported. The antibacterial activity caught our attention because antimicrobial resistance developed by important pathogens has increased in the last decade [7]. Besides, emerging and re-emerging bacterial infectious diseases still causes death and disability worldwide [8].

As part of our continuing interest on the syntheses of potential bioactive compounds [9], including enaminone [10], we undertook the syntheses of 4-aminoantipyrine derivatives in search for antibacterial agents. In this work, we describe our results concerning the syntheses, X-ray structural analysis, and the antimicrobial activity of these substances.

2. Experimental

2.1. Reagents and techniques

Melting points were determined on a Microquímica MQAPF 301 hot plate apparatus and are uncorrected. Infrared spectra were recorded as KBr discs on a FT-IR BOMEM MB100 instrument. NMR spectra were obtained for ^{1}H at 300 MHz and for ^{13}C at 75 MHz using a Varian Gemini 300 spectrometer. Chemical shifts are reported in ppm units downfield from reference (internal TMS). EIMS spectra were measured on a HP MSD 5973 apparatus with direct probe insertion at 70 eV. Elemental analyses were performed on a 2400 CHN Perkin Elmer. Meldrum's acid and methoxymethylene Meldrum's acid were prepared according to known procedures [11]. The single crystal X-ray data collections of compounds **7** and **14** were carried

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out on a Nonius CAD-4 diffractometer at Instituto de Física/UFG. Compound **11** was collected at the University of Pittsburgh during ACA 2003 Summer Course at Kappa CCD at low temperature.

2.2. Synthetic procedures

2.2.1. (Z)-4-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-4-pyrazolylamino)-3-penten-2-one (*3*)

A net solution of 4-aminoantipyrine (1.05 g, 0.51 mmol) and acetylacetone (1 mL, 1.0 mmol) was left at room temperature with stirring for 20 min. The yellow solid that formed was decanted and triturated with ethyl ether, affording **3** (1.61 g, 80%, m.p. 127.3–129.0 °C). IR (KBr): ν_{max} (cm^{-1}) 1674, 1617, 1561, 1270. ^1H NMR ($CDCl_3$): $\delta = 1.95$ (s, 3H); 2.05 (3H, s); 2.21 (3H, s); 3.06 (3H, s); 5.20 (1H, s); 7.25–7.47 (5H, m); 11.52 (1H, s). ^{13}C NMR ($CDCl_3$): 10.6 (CH_3); 19.3 (CH_3); 29.1 (CH_3); 36.1 (CH_3); 97.4 (CH); 110.6 (C); 124.1 (CH); 126.9 (CH); 129.2 (CH); 134.8 (C); 150.8 (C); 162.0 (C); 163.3 (C); 196.4 (C). MS, m/z (%): 287 (0.9) [$M^+ + 2$], 286 (8) [$M^+ + 1$], 285 (42) [M^+], 195 (48%). Anal. calcd for $C_{16}H_{19}N_3O_2$: C, 67.35%; H, 6.71%; N, 14.73%. Found: C, 67.42%; H, 6.72%; N, 14.61%.

2.2.2. Ethyl (Z)-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-4-pyrazolylamino)-2-butenoate (*5*)

A net solution of 4-aminoantipyrine (0.80 g, 3.92 mmol) and ethyl acetoacetate (1 mL, 7.85 mmol) was left at room temperature with stirring for 20 min. The yellow solid that formed was decanted and triturated with ethyl ether, affording 1.64 g. To the ethyl ether solution petroleum ether was added and allowed to cool in the freezer (−25 °C) and more 0.09 g of the yellow solid precipitated, affording **5a** (1.73 g, 95%, m.p. 128–130 °C). IR (KBr): ν_{max} (cm^{-1}) 3245, 1679, 1661, 1605, 1540, 1135. ^1H NMR ($CDCl_3$): 1.26 (3H, t, *J* 7.2 Hz); 1.92 (3H, s); 2.22 (3H, s); 3.06 (3H, s); 4.12 (2H, q, *J* 7.2 Hz); 4.71 (1H, s); 7.29–7.48 (5H, m); 9.39 (1H, s). ^{13}C NMR ($CDCl_3$): 10.5 (CH_3); 14.6 (CH_3); 19.5 (CH_3); 36.2 (CH_3); 58.6 (CH_2); 85.8 (CH); 111.2 (C); 123.9 (CH); 126.7 (CH); 129.2 (CH); 134.9 (C); 151.5 (C); 161.7 (C); 162.6 (C); 170.4 (C). Anal. calcd for $C_{17}H_{21}N_3O_3$: C, 64.75%; H, 6.71%; N, 13.32%. Found: C, 64.72%; H, 6.68%; N, 13.41%.

2.2.3. 1,5-Dimethyl-3-oxo-2-phenyl-4-phenylcarboxamido(thioxo)methylamino-2,3-dihydro-1H-pyrazole (*7*)

To a solution of 4-aminoantipyrine (1.97 g, 9.7 mmol) in benzene (10 mL) benzoyl isothiocyanate (1.4 mL, 10.4 mmol) was added dropwise under stirring and ice-bath cooling. The reaction mixture was left for 3 h at room temperature after which time the solvent was evaporated and crude solid was triturated with petroleum ether. Recrystallization with CH_2Cl_2/petroleum (4:1) ether afforded **7** (3.16 g, 89%, m.p. 210 °C) as yellow needles. IR (KBr): ν_{max} (cm^{-1}) 3420, 3127, 1677, 1648, 1625, 1590, 1528, 1490, 1157. ^1H NMR ($CDCl_3$): 2.27 (3H, s); 3.13 (3H, s); 7.25–7.63 (8H, m); 7.86 (2H, d, *J* 7.7 Hz); 9.36 (1H, s); 11.53 (1H, s). ^{13}C NMR ($CDCl_3$): 12.1 (CH_3); 35.8 (CH_3); 109.4 (C); 124.4 (CH); 126.9 (CH); 127.6 (CH); 129.0 (CH); 129.2 (CH); 131.7 (C); 133.5 (CH); 134.7 (C); 151.8 (C); 161.3 (C); 166.7 (C); 181.5 (C). Anal. calcd for $C_{19}H_{18}SN_4O_2$: C, 62.28%; H, 4.95%; N, 15.29%. Found: C, 62.02%; H, 5.02%; N, 15.21%.

2.2.4. 4-Anilino(thioxo)methylamino-1,5-dimethyl-2-phenyl-2,3-dihydro-1H-3-pyrazolone (*9*)

To a solution of 4-aminoantipyrine (1.04 g, 5.1 mmol) in benzene (10 mL) phenyl isothiocyanate (0.65 mL, 5.4 mmol) was added dropwise under stirring and ice-bath cooling. The reaction mixture was left for 3 h at room temperature after which time the solvent was evaporated and crude solid was triturated with petroleum ether. Recrystallization with CH_2Cl_2/petroleum (4:1) ether afforded **9** (1.57 g, 91%, m.p. 198–200 °C) as yellow needles. IR (KBr): ν_{max} (cm^{-1}) 3420, 3277, 1632, 1567, 1532, 1294. ^1H NMR ($CDCl_3$ + DMSO-D6): 2.24 (3H, s); 3.12 (3H, s); 7.11 (1H, t, *J* 7.2 Hz); 7.26–7.33 (3H, m); 7.38 (2H, d, *J* 7.2 Hz); 7.46–7.51 (4H, m); 8.85 (1H, br s); 9.82 (1H, s). ^{13}C NMR ($CDCl_3$ + DMSO-D6): 11.0 (CH_3); 35.6 (CH_3); 108.8 (C); 123.9 (CH); 124.5 (CH); 126.4 (CH); 128.1 (CH); 128.9 (CH); 134.8 (C); 139.7 (CH); 161.7 (C); 181.4 (C). Anal. calcd for $C_{18}H_{18}SN_4O$: C, 63.88%; H, 5.36%; N, 16.56%. Found: C, 63.72%; H, 5.20%; N, 16.33%.

2.2.5. (Z)-3-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-4-pyrazolylcarbamoyl)-2-propenoic acid (*11*)

A solution of 4-aminoantipyrine (0.10 g, 0.5 mmol) and maleic anhydride (0.05 g, 0.5 mmol) in ethyl acetate (10.0 mL) was left at room temperature with stirring for 30 min (the solution turned yellow and a precipitate began to form after 15 min), after which time the solid that formed was separated from the solvent and was recrystallized from $CHCl_3$ affording **11** (0.15 mg, 99.6%, m.p. 177.6–179.9 °C) as a pale yellow solid. IR (KBr): ν_{max} (cm^{-1}) 3349, 1676, 1646. ^1H NMR ($CDCl_3$): 2.27 (s, 3H), 3.27 (s, 3H), 5.95 (1H, d, *J* 12.9 Hz), 6.40 (1H, d, *J* 12.9 Hz), 7.36 (2H, d, *J* 7.2 Hz), 7.50–7.60 (3H, m); 10.82 (1H, s).

2.2.6. 1-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-4-pyrazolyl)-2,5-dihydro-1H-2,5-azoledione (*12*)

To a solution of 4-aminoantipyrine (2.01 g, 10.0 mmol) in $CHCl_3$ (8.0 mL) a solution of maleic anhydride (1.01 g, 10.0 mmol) in $CHCl_3$ (3.0 mL) was added dropwise with stirring and ice-bath cooling for 15 min., after which time the solvent was evaporated. To the solid that formed acetic anhydride (5.0 mL) and sodium acetate (0.51 g, 6.2 mmol) was added and the reaction mixture was heated at reflux for 30 min, and then it was cooled to room temperature and 10 mL of water was added and extracted with CH_2Cl_2 (2× 10 mL). The organic phase was dried with $MgSO_4$, filtered

and the solvent evaporated under reduced pressure. The residual maroon oleo was treated with CH_2Cl_2/petroleum ether (4:1) affording a pale maroon oil. The solvent was decanted from the oleo and the residue was dried under reduced pressure, yielding **12** (1.89 g, 62%, m.p. 29.4–32.0 °C) as a hygroscope bright yellow solid. IR (KBr): ν_{max} (cm^{-1}) 1716, 1655, 1567, 1488, 1297. ^1H NMR ($CDCl_3$): 2.18 (3H, s); 3.20 (3H, s); 6.86 (s, 2H); 7.30–7.53 (m, 5H). ^{13}C NMR ($CDCl_3$): 10.9 (CH_3); 35.4 (CH_3); 124.8 (CH); 124.4 (CH); 127.3 (CH); 129 (CH); 129.2 (CH); 134.3 (C); 133.8 (CH); 152.8 (C); 160.9 (C); 163.3 (C); 169.1 (C).

2.2.7. 5-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-4-pyrazolylaminomethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (*14*)

A solution of Meldrum's acid (0.15 g, 1.1 mmol) in trimethyl orthoformate (1.5 mL,19.6 mmol) was heated at reflux for 3 h after which time the solvent was evaporated. The solid that formed was dissolved in CH_3OH (2 mL) and 4-aminoantipyrine (0.21 g, 1.0 mmol) in CH_3OH (3 mL) was added and the solution was allowed to stand at room temperature with stirring for 15 min (a precipitate began to form after a few minutes). The solvent was evaporated and the crude solid was recrystallized from CH_2Cl_2/petroleum ether (4:1) affording **14** (0.28 g, 78%, m.p. 211–212 °C) as yellow needles. IR (KBr): ν_{max} (cm^{-1}) 3206, 1717, 1674, 1585. ^1H NMR ($CDCl_3$): 1.72 (6H, s); 2.34 (3H, s); 3.13 (3H, s); 7.31–7.37 (3H, m); 7.45–7.50 (2H, m); 9.07 (1H, d, *J* 13.8 Hz); 10.99 (1H, d, *J* 14.1 Hz). ^{13}C NMR ($CDCl_3$): 10.2 (CH_3); 26.8 (CH_3); 35.8 (CH_3); 86.4 (C); 104.7 (C); 109.8 (C); 124.4 (CH); 127.5 (CH); 129.3 (CH); 133.7 (C); 144.1 (C); 155.5 (CH); 158.8 (C); 162.8 (C); 165.9 (C). Anal. calcd for $C_{18}H_{19}N_3O_5$: C, 60.50%; H, 5.36%; N, 11.76%. Found: C, 60.62%; H, 5.26%; N, 11.77%.

2.3. Crystal structure determination of compounds *7*, *11* and *14*

Single crystal X-ray diffraction data of **7** and **14** were collected using a CAD-4 diffractometer [12] while data for **11** was collected using Kappa CCD diffractometer [13]. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 for all data using SHELXL97 [14]. The hydrogen atoms were added at calculated positions and refined using a riding model, except for those involved in H-bonds, whose coordinates were refined isotropically. Anisotropic displacement parameters were used for all non-H atoms.

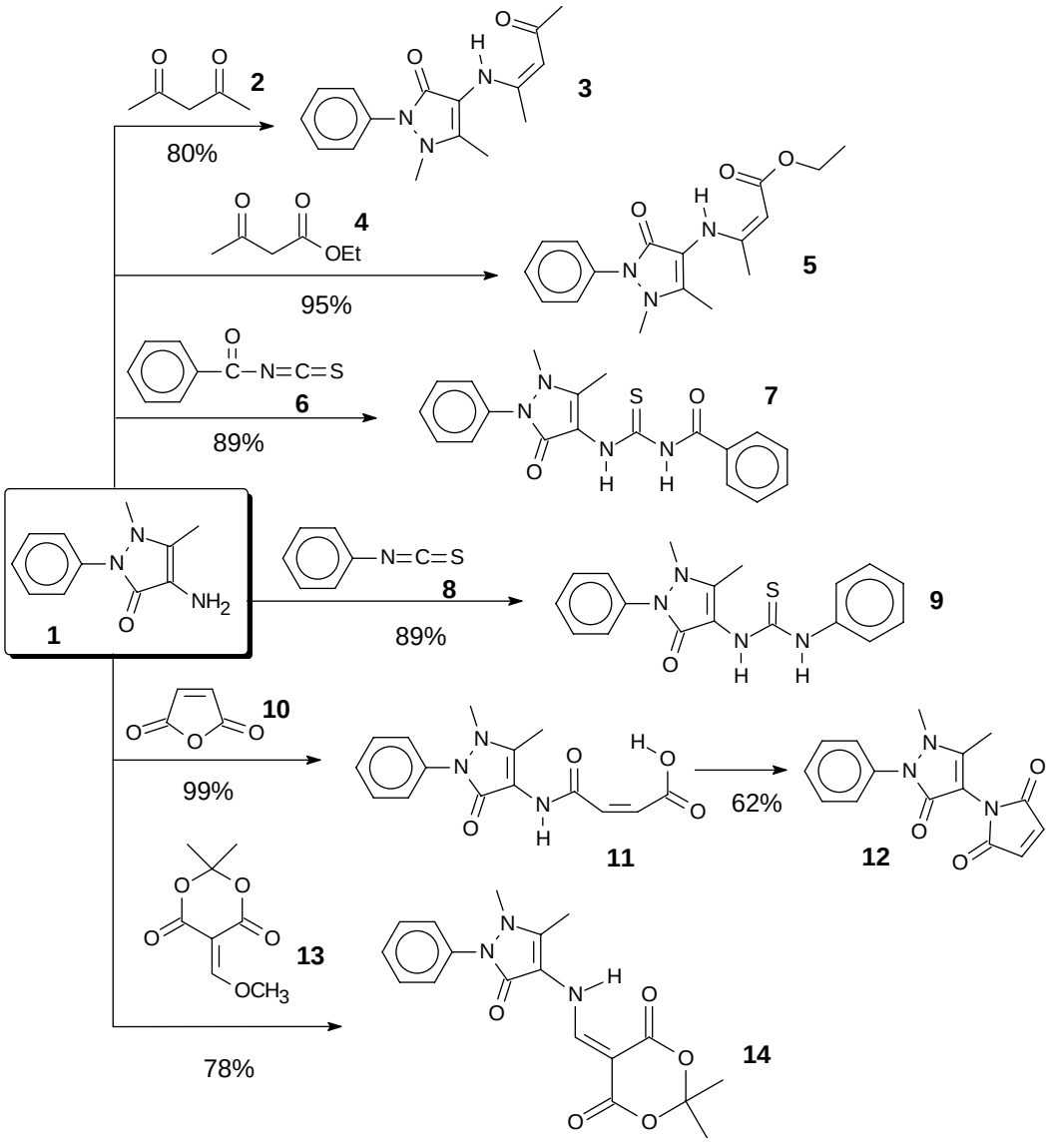
The crystallographic data for structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 252825 for **7** and CCDC 252826 for **14**. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Fax: +44 1223 336033; e-mail: deposit@ccdc.camac.uk.).

2.4. Antibacterial assay

The bacteria used in this experiment were *Micrococcus luteus* ATCC 9341, *Staphilococcus aureus* ATCC 29737, and *Escherichia coli* ATCC 8739. For the bioautography bioassay [15], pure compounds were applied to Silica gel TLC plates at concentrations of 1–3 mg in EtOH or $CHCl_3$. TLC plates were dried until complete removal of solvents. The inoculum was prepared by culturing each organism in sterile Miller–Hinton broth at 37 °C to a turbidity equivalent to McFarland 0.5 standard (10^8 CFU/mL). One microliter of each diluted inoculum ($10^4 - 10^6$ CFU/mL) was added in 10 mL of Mueller-Hinton agar medium (MHA-DIFCO), and distributed over TLC plates. After the solidification, the TLC plates were incubated at 36 °C for 24 h. Plates were sprayed with a 2 mg/mL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, thiazolyl blue) and the clear zones on the chromatogram indicated inhibition of growth. The minimal inhibitory concentration was determined by serial dilution using 96-well microplates [16]. The compounds were solubilized in 0.5 mL of the dimethyl sulfoxide (DMSO) and diluted in a sterile 0.85% saline solution containing Tween 80. This solution was added into the first column of the wells on the microplates and serially diluted in Miller–Hinton broth to obtain a concentration range of 15.6–1000 μg/mL. The wells in the dilution series were inoculated with the cultures prepared as described above. Finally, microplates were incubated overnight at 37 °C and the results were marked by observing the change of color when *p*-iodonitrotetrazolium violet (INT, Sigma) was added. Negative control (DMSO and Miller–Hinton broth) as well as positive control (chlorophenicol) were included in each assay. All data represent two replicated experiments per microorganism.

3. Results and discussions

To synthesize the derivatives of 4-aminoantipyrine (**1**), a group of ambident eletrophiles was selected which could be converted into test compounds. In this way, enaminone derivatives of **1** were prepared by the procedure described earlier [17]. Thus, 4-aminoantipyrine and acetylacetone (**2**) were refluxed in toluene with azeotropic removal of water, but poor yield was obtained after tedious purification. To overcome this, the reaction was performed without solvent, and a solution of 4-aminoantipyrine in an excess of acetylacetone afforded enaminone **3** with improved yield (80%). Using this modification of the reported protocol [17] of enaminone's synthesis, amine **1** was reacted with ethyl acetoacetate (4) affording enaminone **5** in 95% yield. In addition to the above ambident eletrophiles, we extended the reaction of **1** to benzoyl isothiocyanate (**6**), phenyl isothiocyanate (**8**), maleic anhydride (**10**) and Meldrum's acid derivative **13**, whereby thioureas **7** and **9**, maleamic acid **11** and enaminone **14** were obtained in excellent yields



Scheme 1.

(Scheme 1). All derivatives but **11** and **12** [2] are substances not previously described.

The structure of **11** was unambiguously assigned through its crystal structure determination, in agreement with a previous X-ray study of the same compound, leading us to use the previously obtained for comparison throughout the paper [18]. Besides, compounds **7** and **14** had their structures assigned by X-ray crystallography. The ORTEP-3 [19] representations of compounds **7**, **11**, and **14** are shown in Fig. 1. Regarding the crystal structure of **7** (Fig. 2 and Table 1), there is one intramolecular N14–H14···O20 H-bond forming a pseudo planar six-membered ring. The dihedral angle between rings (N1–C5) and (C6–C11) is 55.54(5)°. The crystal data and structure refinement parameters of **7** and **14** are given in Table 2.

In the molecular structure of **11** (Fig. 2 and Table 1) there is one strong intramolecular O21–H21···O20 H-bond involving the group COOH forming a quasi-planar pseudo seven-membered ring. One intermolecular N14–H14···O15^{i} ($i = 1-x, 2-y, 1-z$) H-bond between the amide groups of two neighboring molecules link them in a centrosymmetric dimeric form about the B-face.

The crystal structure of **14** (Fig. 2 and Table 1) shows one intramolecular N14–H14···O24 H-bond forming a pseudo planar six-membered ring together with a non-classical bifurcate intramolecular H-bond involving C16–H16···O15 and C16–H16···O23 that support two quasi-planar pseudo five-membered rings, resulting in an almost flattened molecule. The dihedral angle between rings (N1–C5) and (C6–C11) is 47.53(6)°.

When maleamic acid **11** was left in $CDCl_3$ in the NMR tube it was slowly converted into maleimide **12** (Fig. 3). After 1 day, the proportion **11:12** was 1:1 (Fig. 3b), based on the integral of methyl groups between 2 and 4 ppm in the ^{1}H

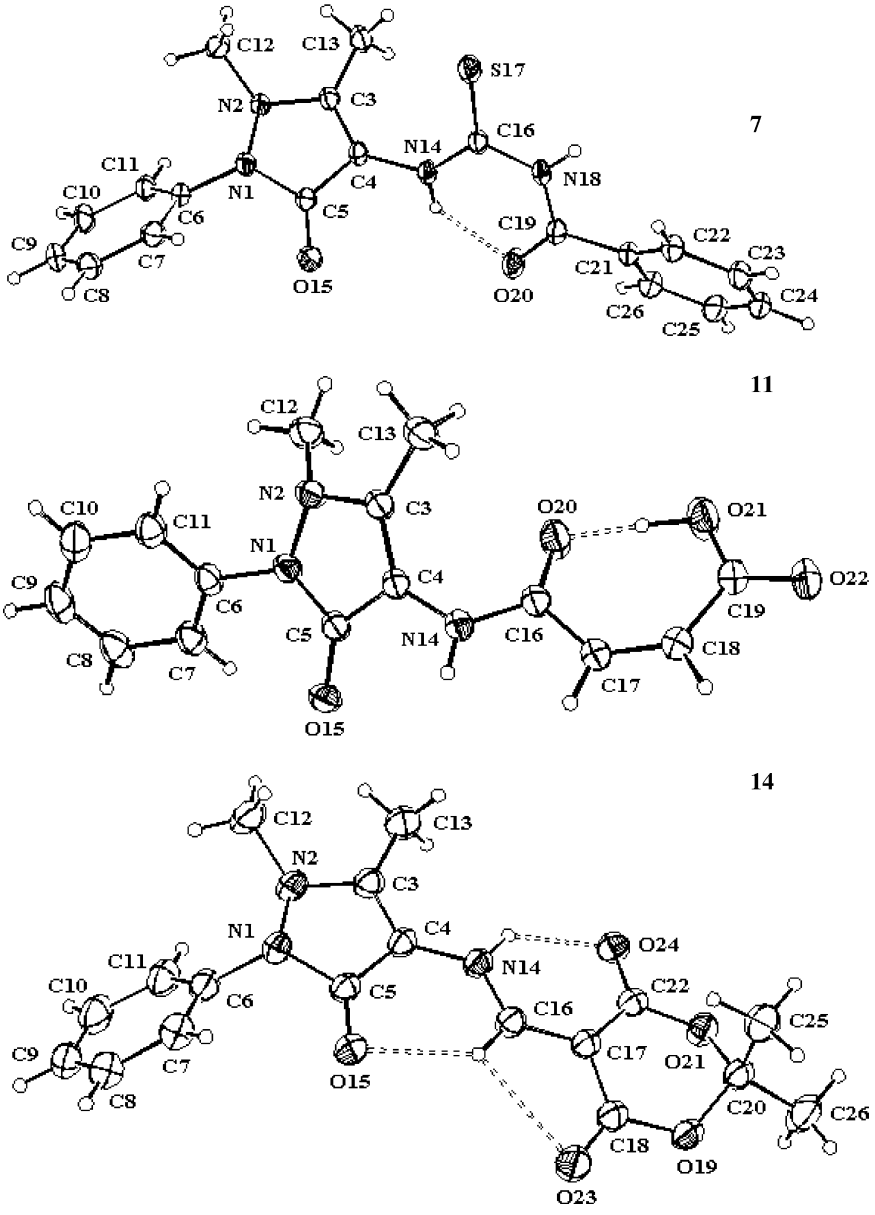


Fig. 1. ORTEP-3 [19] drawings of the molecules **7**, **11**, and **14**, with the atom-numbering schemes. The displacement ellipsoids are drawn at the 30% probability levels.

NMR spectrum (it is important to point out that the spectrum of **11**, Fig. 3a, should be recorded immediately after sample preparation). This proportion changed to 1:1.8, 1:3.2 and 1:4.6 after 4, 7, and 15 days, respectively, and only signals of compound **12** were detected after 22 days of sample preparation. Other structural features corroborated the conversion of maleamic acid **11** into maleimide **12**. The acid hydrogen at 10.82 ppm was not observed after 15 days (Fig. 3a–e), and, moreover, the doublets referent to the chemically non-equivalent olefinic hydrogens of **11** became one singlet integrated to two hydrogens (Fig. 3a–f), in agreement to structure **12**. In addition, the formation of **12** was alternatively accomplished by the treatment of maleamic acid **11** with sodium acetate in $CHCl_3$ (maleimide **12** was described as an oil [2], but we found it as hygroscopic solid, see Section 2), and the ^1H NMR data were identical to the obtained by the slow conversion. The transformation of **11** into **12** in the $CDCl_3$ solution can be attributed to trace of acid in this deuterated solvent. A literature search reveals that spontaneous conversion of maleamic acid into maleimide is not a common feature [20]. Maleimide **12** was described as an analgesic compound more active than aspirin and paracetamol, but with high toxic effect also [2].

The antibacterial activity of the 4-aminoantipyrine and its derivatives was evaluated by means of direct

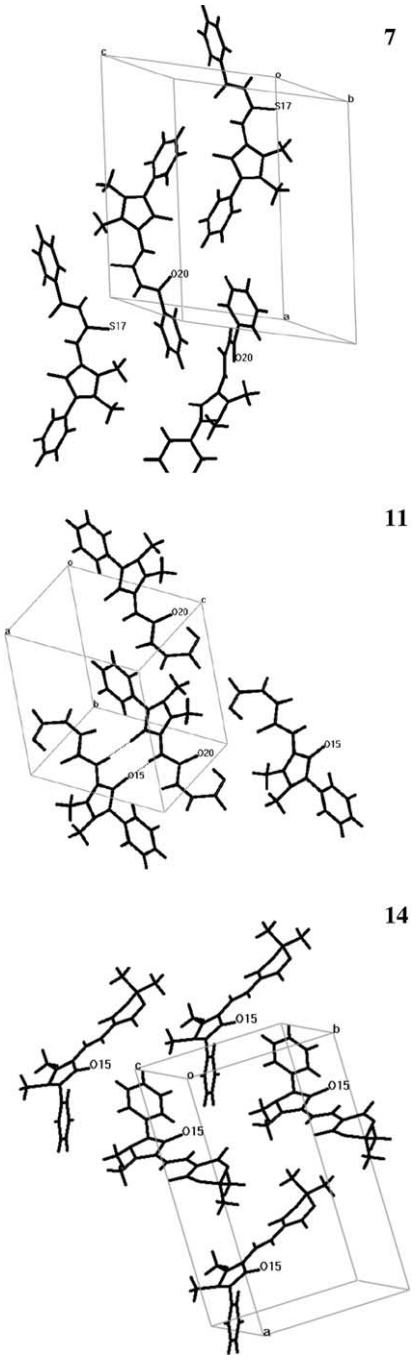


Fig. 2. The packing diagrams of molecules **7**, **11**, and **14**. Dashed lines indicate hydrogen bonds. H atoms not involved in hydrogen bonds have been omitted.

bioautography in a TLC bioassay against *M. luteus* ATCC 9341, *S. aureus* ATCC 29737, and *E. coli* ATCC 8739. Among them, the derivatives **7**, **9**, **11** and **14** exhibited mild to good antibacterial activity in the preliminary screening at 1 and 3 mg concentrations. All compounds were then tested for minimal inhibitory concentration (MIC) by serial microdilution technique. Their MIC (μg/mL) are shown in Table 3. Derivative **11** was the unique active compound showing a modest growth inhibition at concentrations ranging between 125 and 250 μg/mL against all the bacteria tested. The others were less potent with MIC ≥ 1000 μg/mL. However, compound **11** is slowly converted to the highly toxic [2] compound **12** in solution phase, as indicated by the NMR study.

Table 1
H-bonding for compounds **7**, **11**, and **14**

D–H (Å)	H···A (Å)	D···A (Å)	<(DHA) (degrees)	
Compound ***7***				
0.81(3)	1.96(3)	2.617(2)	138(2)	N14–H14···O20
Compound ***11***				
1.03(2)	1.46(2)	2.483(2)	175(2)	O21–H21···O20
0.92(2)	1.91(2)	2.821(2)	171(2)	N14–H14···O15^{i}
Compound ***14***				
0.91(3)	2.00(3)	2.700(2)	133(3)	N14–H14···O24
1.00(3)	2.20(3)	2.930(2)	128(2)	C16–H16···O15
1.00(3)	2.50(3)	2.815(2)	98(2)	C16–H16···O23

Symmetry operation: (*i*) $1-x, 2-y, 1-z$

Table 2
Crystal data and structure refinement for compounds **7** and **14**

Identification code	**7**	**14**
Molecular formula	$C_{19}H_{18}N_4O_2S$	$C_{18}H_{19}N_3O_5$
Formula weight	366.43	357.36
Temperature (K)	293(2)	293(2)
Space group	$P2_1/c$	$P2_1/c$
a (Å)	16.134(4)	17.813(1)
b (Å)	8.3286(8)	10.664(1)
c (Å)	13.853(2)	9.388(1)
α (degrees)	90	90
β (degrees)	106.08(1)	96.316(9)
γ (degrees)	90	90
V (Å^3)	1788.6(5)	1772.5(3)
Z	4	4
D_{cal} (g cm^{-3})	1.361	1.339
μ (mm^{-1})	1.787	0.828
Absorption corr.: T_{max}, T_{min}	0.633, 0.574	none
Ranges of *h,k, l*	−1/19, 9/0, −16/16	−1/21, −12/0, −11/11
No. of measured ref.	3489	3472
No. of independent ref., R_{int}	3134, 0.027	3150, 0.0124
Data/restraints/parameters	3134/0/248	3150/0/254
R_{obs}	0.0504	0.0470
R_{all}	0.0531	0.0608
R_w (all data)	0.1349	0.1359
S	1.139	1.034

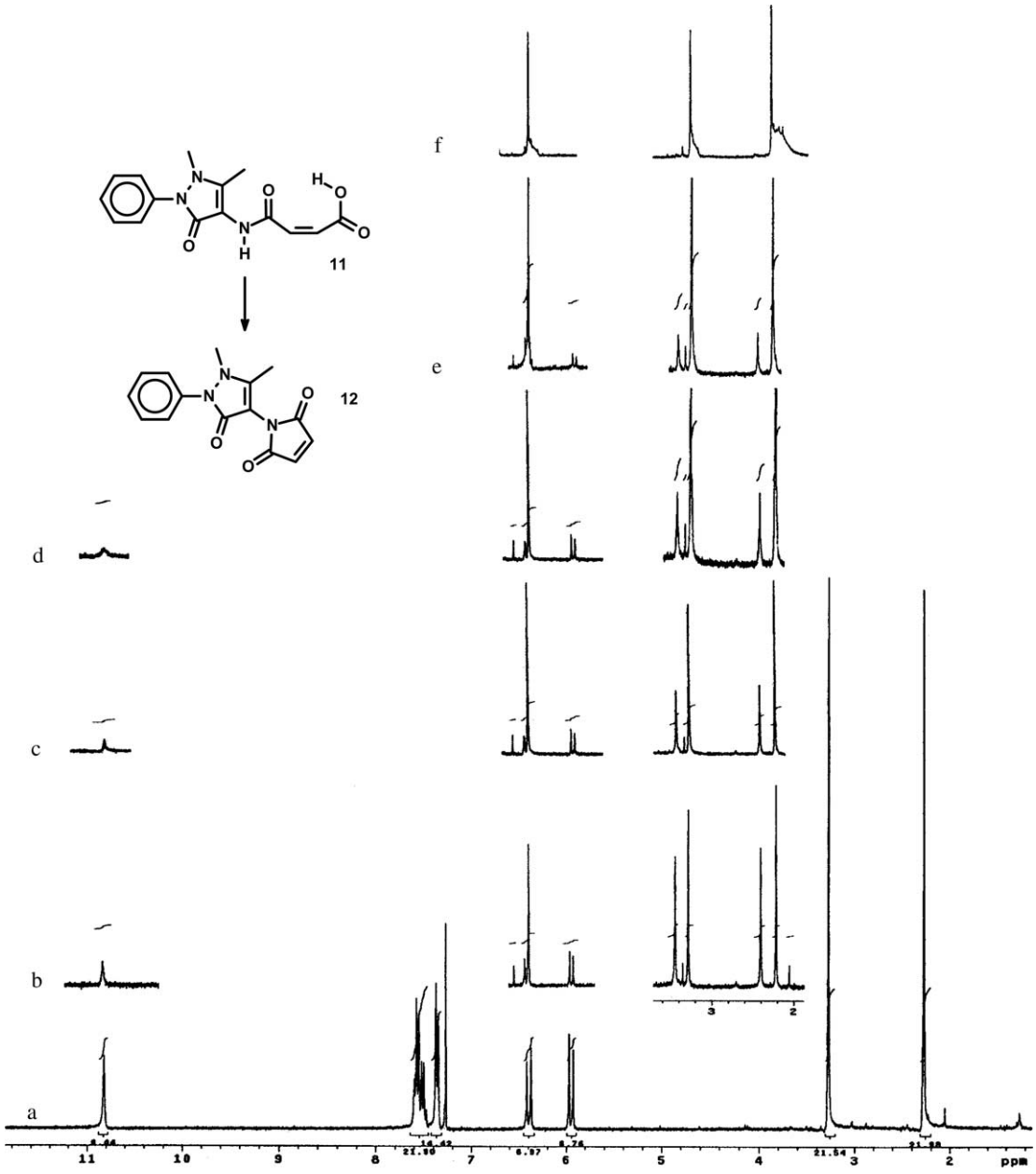


Fig. 3. ^{1}H NMR spectra of maleamic acid **11** in $CDCl_3$ solution, showing its conversion into maleimide **12**. The captions a, b, c, d, e, and f correspond to the spectrum of the same sample recorded after 0, 1, 4, 7, 15, and 22 days of preparation, respectively.

Table 3
Antimicrobial activity of aminoantipyrine derivatives

Compound	MIC (μg/mL)[a]		
	M. luteus	*S. aureus*	*E. coli*
7	1000	1000	1000
9	>1000	>1000	500
11	125	250	250
14	1000	1000	1000
PC[b]	<3.9	<3.9	<3.9

[a] Minimal inhibitory concentration.
[b] PC (positive control—chloranphenicol).

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