Synthesis and Anti-*Helicobacter pylori* Activity of 4-(Coumarin-3-yl)thiazol-2-ylhydrazone Derivatives

Franco Chimenti,[a] Bruna Bizzarri,[a]* Adriana Bolasco,[a] Daniela Secci,[a] Paola Chimenti,[a] Arianna Granese,[a] Simone Carradori,[a] Melissa D'Ascenzio,[a] M. Maddalena Scaltrito,[b] and Francesca Sisto[b]

[a]Dipartimento di Chimica e Tecnologie del Farmaco, University "La Sapienza," P.le A. Moro 5, 00185 Rome, Italy
[b]Dipartimento di Sanità Pubblica-Microbiologia-Virologia, Università degli Studi di Milano, via Pascal 36, 20133 Milan, Italy
*E-mail: bruna.bizzarri@uniroma1.it

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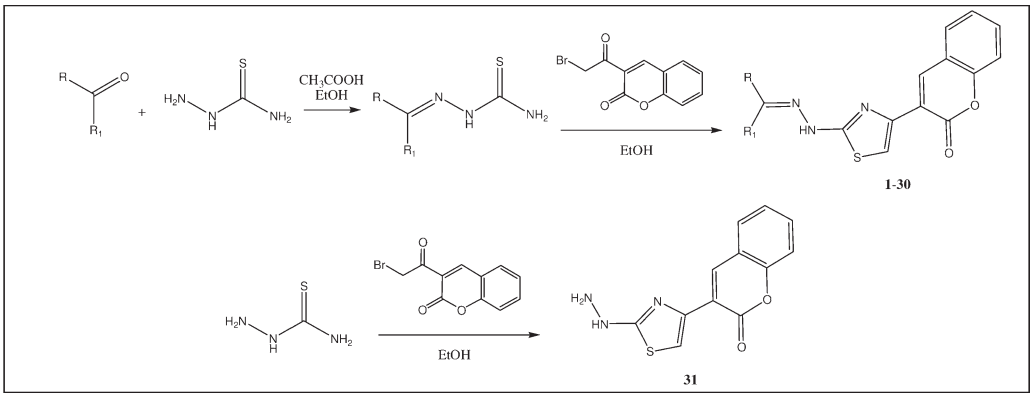

A novel class of coumarin-thiazole conjugated systems (**1–31**) were synthesized by Hantzsch condensation between α-bromo-3-acetyl coumarin and several thiosemicarbazone intermediates. This scaffold was also evaluated for selective antibacterial activity against 20 isolates of *H. pylori* clinical strains, including four metronidazole resistant ones.

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INTRODUCTION

Helicobacter pylori are spiral-shaped Gram-negative bacteria with polar flagella that live near the surface of the human gastric mucosa. They have evolved specific mechanisms to avoid the bactericidal acid environment in the gastric lumen to survive near, to attach to, and to communicate with the human gastric epithelium and host immune system. This interaction sometimes results in severe gastric pathology. In fact, *H. pylori* infection is indeed the most known risk factor for the development of gastroduodenal ulcers, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma.

H. pylori infections are difficult to cure and successful treatment generally requires the simultaneous somministration of several antibacterial agents. Antibiotic resistance has resulted in unsatisfactory eradication with dual and now triple therapy in many countries. Newer antibiotics and changes in dosing and duration of therapy may overcome resistant strains but may only provide limited improvement in eradication rates [1–3].

In our previous works [4,5] and from the analysis of the structure of natural coumarins reported as potent anti-*H. pylori* agents [6], we have pointed out that the coumarin ring might play an important role in determining activity and seemed to be crucial for the selective antimicrobial activity of such compounds. Recently, we have synthesized and chemically and biologically characterized some new conjugated coumarin-thiazole systems, which were endowed with interesting industrial properties and especially antimicrobial activity on *H. pylori* clinical strains [7].

Furthermore, interest in these structures has renewed due to the recent discovery of their promising antibacterial, antifungal, and antimycobacterial activity [8–11].

Moving from these indications, in this report we described the synthesis and selective antimicrobial evaluation of a new series of 4-(coumarin-3-yl)thiazol-2-ylhydrazone derivatives which differ for the electronic and steric characteristics on the hydrazone nitrogen (aliphatic chains, cycloaliphatic moiety, and heterocyclic rings).

RESULTS AND DISCUSSION

The coumarin-thiazole derivatives (**1–30**) were prepared in high yields (69–99%) according to a protocol

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Table 1

Structure of derivatives **1–31**.

Comp	R	R_1
1 [ref. 12]	CH_3	CH_3
2	CH_2CH_3	CH_3
3	$CH(CH_3)_2$	CH_3
4	$(CH_2)_2CH_3$	CH_3
5	CH_2CH_3	CH_2CH_3
6	$(CH_2)_2CH{=}CH_2$	CH_3
7	$(CH_2)_4CH_3$	CH_3
8	$(CH_2)_3CH_3$	CH_2CH_3
9	$(CH_2)_5CH_3$	CH_3
10	2-CH_3-Cyclopentyliden	
11	3-CH_3-Cyclopentyliden	
12	Cyclooctyliden	
13	Cyclohexyl	CH_3
14[ref. 11]	Fur-2-yl	H
15	Fur-2-yl	CH_3
16	Tiophen-2-yl	H
17	Tiophen-2-yl	CH_3
18[ref. 13]	Phenyl	CH_3
19	Pyridin-2-yl	CH_3
20	Pyridin-3-yl	H
21	Pyridin-3-yl	CH_3
22	Pyridin-4-yl	H
23	Pyridin-4-yl	CH_3
24	1*H*-indol-3-yl	H
25[ref. 14]	3,4-Methylendioxophenyl	H
26	Naphtalen-1-yl	H
27	Naphtalen-2-yl	CH_3
28[ref. 15]	Coumarin-3-yl	CH_3
29	2-COOH-9*H*-fluoren-5-yliden	
30	Thiazol-2-yl	CH_3
31[ref. 16]	H	H

used in our laboratory (Table 1). Different carbonyl compounds reacted directly with thiosemicarbazide in ethanol with catalytic amounts of acetic acid, and the obtained thiosemicarbazones were subsequently converted into 4-(coumarin-3-yl)-2-thiazolylhydrazones by reaction with α-bromo-3-acetyl coumarin in the same solvent at room temperature (Hantzsch condensation). α-Bromo-3-acetyl coumarin has been synthesized by direct halogenation of 3-acetyl coumarin with bromine in chloroform. Moreover, knowing that all reported structures possess an imine bond, which could be hydrolyzed in the acidic environment of the stomach (reproduced in the biological assay), we also synthesized and assayed their common intermediate (**31**) by direct reaction between thiosemicabazide and α-bromo-3-acetyl coumarin in ethanol at room temperature.

All synthesized products were purified with petroleum ether and diethyl ether and, if requested, by chromatography before characterization by spectroscopic methods (IR and ^{1}H NMR) and elemental analysis. The compounds, correctly analyzed for their molecular formula, showed in the IR spectrum strong bands at 1710 and 1600 cm^{-1} due to the presence of a δ-lactone C=O and C=N group, respectively.

Moreover, the presence of a C=N double bond can give rise to isomeric geometry E/Z. The ^{1}H NMR (in $CDCl_3$) spectra analysis revealed that the E isomer was more favored and stable than the Z-configuration. The amounts of both conformers were measured by area integration of the signal relative to the CH_3 (R^1) protons (area ratio of proton signals E:Z was generally 6:1). The low-field signal was assigned to the E isomer, as it is widely accepted in thiosemicarbazone derivatives [17]. Our choice, as reaction medium, of a polar alcoholic solvent appeared to be preferred to obtain the E-configuration and limit the interconversion according to the results of our previous theoretical and chromatographic study for similar compounds [18].

Then, all compounds were evaluated, as mixture of E/Z conformers, against 20 clinical strains of *H. pylori*, which are more resistant to conventional therapy. Metronidazole was used as standard antibacterial drug (Table 2).

Most of the assayed compounds showed no anti-*H. pylori* activity or comparable activity with respect to Metronidazole (MIC $\geq$ 16 μg/mL). Only some compounds (**14**, **21**, and **26**), bearing a specific heterocyclic ring (furan, pyridine, and naphthalene) on the hydrazone nitrogen, possessed MIC values slightly inferior to the reference drug (MIC = 8 μg/mL) against some clinical *H. pylori* strains. Unfortunately, it was not possible to correlate this biological activity with lipophilicity (Clog*P*).

EXPERIMENTAL

The chemicals, solvents for synthesis and spectral grade solvents were purchased from Aldrich (Italy) and used without further purification. Melting points are uncorrected and were determined automatically on an FP62 apparatus (Mettler-Toledo). ^{1}H NMR spectra were recorded at 400 MHz on a Bruker spectrometer. Chemical shifts are expressed as δ units (parts per millions) relative to the solvent peak. Coupling constants *J* are valued in Hertz (Hz). IR spectra were registered on a Perkin Elmer FTIR Spectrometer Spectrum 1000 in KBr. Elemental analysis for C, H, and N were recorded on a Perkin-Elmer 240 B microanalyzer and the analytical results were within ±0.4% of the theoretical values for all compounds. All reactions were monitored by TLC performed on 0.2-mm-thick silica gel plates (60 F_{254} Merck). Lipophilicity parameter, Clog*P*, has been calculated for each molecule by using ChemDraw ultra 8.0. The synthesis of some compounds has been described in previous references (Table 1) and was performed with slight changes. Their analytical and spectral data were in full agreement with those reported in the literature.

Typical procedure for the thiosemicarbazones synthesis. The appropriate carbonylic compound (50 mmol) was dissolved in 100 mL of ethanol and stirred vigorously at

Table 2

MIC values (μg/mL) of derivatives **1–31** and **M** (metronidazole) against 20 *H. pylori* strains.

Compound	Metronidazole sensitive strains (16 strains)	Metronidazole resistant strains (4 strains)
1	≥16	>16
2	≥16	>16
3	≥16	>16
4	≥16	>16
5	≥16	>16
6	≥16	≥16
7	≥16	≥16
8	≥16	≥16
9	≥16	≥16
10	≥16	≥16
11	≥16	≥16
12	≥16	≥16
13	≥16	>16
14	8–≥16	8–≥16
15	≥16	≥16
16	>16	≥16
17	≥16	≥16
18	≥16	>16
19	≥16	≥16
20	≥16	≥16
21	8–≥16	≥16
22	≥16	≥16
23	≥16	≥16
24	>16	≥16
25	≥16	≥16
26	8–≥16	≥16
27	≥16	≥16
28	>16	>16
29	≥16	>16
30	>16	>16
31	≥16	>16
M	0.5–16	>16

room temperature with an equimolar amount of thiosemicarbazide for 24 h with catalytic amount of acetic acid. The desired thiosemicarbazone precipitated from reaction mixture was filtered and crystallized from suitable solvent and dried.

Typical procedure for the Hantzsch protocol for the preparation of derivatives 1–30. Equimolar amounts of the prepared thiosemicarbazones (50 mmol) and freshly synthesized 3-α-bromo-acetyl coumarin (50 mmol), both dissolved in ethanol, were reacted at room temperature under magnetic stirring for 4 h. The precipitate was filtered and dried to give compounds **1–30** in 69–99% yield.

3-(2-(2-Butylidenehydrazynyl)thiazol-4-yl)-2H-chromen-2-one (2). Light brown crystals, 96% yield, mp 205–210°C; ^{1}H NMR ($CDCl_3$): δ 1.15–1.18 (t, 3H, J = 7.2, CH_3), 2.20 (s, 3H, CH_3), 2.42–2.47 (q, 2H, J = 7.2, CH_2), 7.35–7.39 (m, 1H, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.8 Hz, $J_{7\text{-}5}$ = 2.3 Hz, C_7H-chrom), 7.41–7.43 (dd, 1H, $J_{5\text{-}6}$ =7.9, $J_{5\text{-}7}$ = 2.4 Hz, C_5H-chrom), 7.62–7.65 (m, 1H, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.8 Hz, $J_{6\text{-}8}$ = 2.3 Hz, C_6H-chrom), 7.68 (s, 1H, C_5H-thiaz.), 7.77–7.83 (dd, 1H, $J_{8\text{-}7}$ = 7.8 Hz, $J_{8\text{-}6}$ = 2.2 Hz, C_8H-chrom.), 10.75 (bs, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04. Found: C, 60.13; H, 4.37; N, 14.06.

3-(2-(2-(3-Methyl-2-butylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (3). Yellow crystals, 99% yield, mp 170–173°C; ^{1}H NMR ($CDCl_3$): δ 0.95–0.97 (d, J = 6.6 Hz, 6H, 2 × CH_3), 1.98–2.11 (m, J = 6.6 Hz, 1H, CH), 2.17 (s, 3H, CH_3), 7.35–7.38 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.3 Hz, $J_{7\text{-}5}$ = 1.8 Hz, 1H, C_7H-chrom.), 7.39–7.41 (dd, $J_{5\text{-}6}$ = 7.3 Hz, $J_{5\text{-}7}$ = 1.8 Hz, 1H, C_5H-chrom.), 7.61–7.65 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.3 Hz, $J_{6\text{-}8}$ = 1.8 Hz, 1H, C_6H-chrom.), 7.79–7.82 (dd, $J_{8\text{-}7}$ = 7.3 Hz, $J_{8\text{-}6}$ = 1.9 Hz, 1H, C_8H-chrom.), 7.84 (s, 1H, C_5H-thiaz.), 8.54 (s, 1H, C_4H-chrom.), 12.00 (br s, 1H, NH, D_2O exch.); *Anal*. Calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83. Found: C, 62.41; H, 5.24; N, 12.82.

3-(2-(2-(2-Pentanylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (4). Orange crystals, 82% yield, mp 186–187°C; ^{1}H NMR ($CDCl_3$): δ 0.97–1.03 (t, J = 7.4 Hz, 3H, CH_3), 1.59–1.65 (m, J = 7.4 Hz, J = 5.6 Hz, 2H, CH_2), 2.18 (s, 3H, CH_3), 2.33–2.38 (t, J = 5.6 Hz, 2H, CH_2), 7.34–7.37 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.6 Hz, $J_{7\text{-}5}$ = 2.1 Hz, 1H, C_7H-chrom.), 7.62–7.65 (dd, $J_{5\text{-}6}$ = 7.6 Hz, $J_{5\text{-}7}$ = 2.2 Hz, 1H, C_5H-chrom.), 7.68–7.75 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.7 Hz, $J_{6\text{-}8}$ = 2.1 Hz, 1H, C_6H-chrom.), 7.77–7.81 (dd, $J_{8\text{-}7}$ = 7.8 Hz, $J_{8\text{-}6}$ = 2.1 Hz, 1H, C_8H-chrom.), 7.85 (s, 1H, C_5H-thiaz.), 8.62 (s, 1H, C_4H-chrom.), 11.90 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83. Found: C, 62.39; H, 5.22; N, 12.83.

3-(2-(2-(3-Pentanylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (5). Yellow crystals, 82% yield, mp 180–183°C; ^{1}H NMR ($CDCl_3$): δ 1.16–1.19 (t, J = 7.3 Hz, 6H, 2 × CH_3), 2.40–2.46 (m, 4H, 2 × CH_2), 7.35–7.37 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 6.8 Hz, $J_{7\text{-}5}$ = 1.4 Hz, 1H, C_7H-chrom.), 7.38–7.41 (dd, $J_{5\text{-}6}$ = 6.8 Hz, $J_{5\text{-}7}$ = 1.4 Hz, 1H, C_5H-chrom.), 7.59–7.63 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$= 6.8 Hz, $J_{6\text{-}8}$ = 1.4 Hz, 1H, C_6H-chrom.), 7.78–7.80 (dd, $J_{8\text{-}7}$ = 6.8 Hz, $J_{8\text{-}6}$ = 1.4 Hz, 1H, C_8H-chrom.), 7.84 (s, 1H, C_5H-thiaz.), 8.61 (s, 1H, C_4H-chrom.), 12.01 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83. Found: C, 62.38; H, 5.24; N, 12.82.

3-(2-(2-(5-Hexen-2-ylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (6). Light yellow crystals, 73% yield, mp 195–197°C; ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H, CH_3), 2.38–2.45 (t, J = 6.5 Hz, 2H, CH_2), 2.48–2.53 (m, J = 6.5 Hz, J = 7.2 Hz, 2H, CH_2), 5.05–5.08 (dd, J_{cis} = 8.8 Hz, J_{gem} = 1.7 Hz, 1H, CH=), 5.09–5.13 (dd, J_{trans} = 17.7 Hz, J_{gem} = 1.7 Hz, 1H, CH=), 5.78–5.85 (m, J_{cis} = 8.8 Hz, J_{trans} = 17.8 Hz, J = 7.2 Hz 1H, CH=), 7.36–7.40 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.5, $J_{7\text{-}5}$ = 1.5, 1H, C_7H-chrom.), 7.41–7.43 (dd, $J_{5\text{-}6}$ = 7.5, $J_{5\text{-}7}$ = 1.5, 1H, C_5H-chrom.), 7.62–7.64 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.5, $J_{6\text{-}8}$ = 1.4, 1H, C_6H-chrom.), 7.79–7.81 (dd, $J_{8\text{-}7}$ = 7.6, $J_{8\text{-}6}$ = 1.4, 1H, C_8H-chrom.), 7.86 (s, 1H, C_5H-thiaz.), 8.61 (s, 1H, C_4H-chrom.), 12.00 (br s, 1H, NH, D_2O exch.); *Anal*. Calcd. for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.75; H, 5.04; N, 12.38.

3-(2-(2-(2-Heptanylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (7). Yellow crystals, 99% yield, mp 198–201°C; ^{1}H NMR (DMSO-d_6): δ 0.93–0.95 (m, 3H, CH_3), 1.22–1.30 (m, 2H, CH_2), 1.32–1.38 (m, 2H, CH_2), 1.55–1.61 (m, 2H, CH_2), 2.18 (s, 3H, CH_3), 2.36–2.40 (m, 2H, CH_2), 7.37–7.39 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.1 Hz, $J_{7\text{-}5}$ = 3.7 Hz, 1H, C_7H-chrom.), 7.40–7.42 (dd, $J_{5\text{-}6}$ = 7.16, $J_{5\text{-}7}$ = 3.8, 1H, C_5H-chrom.), 7.61–7.66 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.2 Hz, $J_{6\text{-}8}$ = 3.8 Hz, 1H, C_6H-chrom.), 7.79–7.81 (dd, $J_{8\text{-}7}$ = 7.1, $J_{8\text{-}6}$ = 3.7, 1H, C_8H-chrom.), 7.84 (s, 1H, C_5H-thiaz.), 8.61 (s, 1H, C_4H-chrom.), 12.06 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{19}H_{21}N_3O_2S$: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.15; H, 5.93; N, 11.84.

3-(2-(2-(3-Heptanylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (8). Yellow crystals, 77% yield, mp 175–180°C; ^{1}H NMR ($CDCl_3$): δ 0.95–0.98 (m, 3H, CH_3), 1.13–1.19 (m, 2H, CH_2), 1.34–1.40 (m, 2H, CH_2), 1.55–1.62 (m, 3H, CH_3), 2.39–2.42 (m, 2H, CH_2), 2.45–2.51 (m, 2H, CH_2), 7.36–7.38 (m, 1H, C_7H-chrom.), 7.39–7.41 (m, 1H, C_5H-chrom.), 7.60–7.64 (m, 1H, C_6H-chrom.), 7.79–7.82 (m, 1H, C_8H-chrom.), 7.83 (s, 1H, C_5H-thiaz.), 8.61 (s, 1H, C_4H-chrom.), 12.14 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{19}H_{21}N_3O_2S$: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.25; H, 5.95; N, 11.81.

3-(2-(2-(2-Octanylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (9). Yellow crystals, 74% yield, mp 149–150°C; ^{1}H NMR (DMSO-d_6): δ 0.84–0.88 (m, 3H, CH_3), 1.25–1.32 (m, 6H, 3 × CH_2), 1.47–1.51 (m, 2H, CH_2), 1.88–1.91 (m, 3H, CH_3), 2.19–2.23 (m, 2H, CH_2), 7.37–7.39 (m, 1H, C_7H-chrom.), 7.42–7.44 (m 1H, C_5H-chrom.), 7.60–7.64 (m, C_6H-chrom.), 7.68 (s, 1H, C_5H-thiaz.), 7.77–7.80 (m, 1H, C_8H-chrom.), 8.53 (s, 1H, C_4H-chrom.), 10.71 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{20}H_{23}N_3O_2S$: C, 65.01; H, 6.27; N, 11.37. Found: C, 65.06; H, 6.28; N, 11.35.

3-(2-(2-(2-Methylcyclopentylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (10). Yellow crystals, 79% yield, mp 143–145°C; ^{1}H NMR ($CDCl_3$): δ 1.21–1.23 (m, 3H, CH_3), 1.31–1.39 (m, 1H, cyclopentyl), 1.71–1.77 (m, 1H, cyclopentyl), 1.95–2.02 (m, 1H, cyclopentyl), 2.05–2.12 (m, 1H, cyclopentyl), 2.25–2.33 (m, 1H, cyclopentyl), 2.37–2.46 (m, 1H, cyclopentyl), 2.58–2.64 (m, 1H, cyclopentyl), 7.27–7.33 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.7 Hz, $J_{7\text{-}5}$ = 3.63 Hz, 1H, C_7H-chrom.), 7.34–7.37 (dd, $J_{5\text{-}6}$ = 7.8, $J_{5\text{-}7}$ = 3.6, 1H, C_5H-chrom.), 7.50–7.54 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.7 Hz, $J_{6\text{-}8}$ = 3.7 Hz, 1H, C_6H-chrom.), 7.57–7.60 (dd, $J_{8\text{-}7}$ = 7.7, $J_{8\text{-}6}$ = 3.6, 1H, C_8H-chrom.), 7.88 (s, 1H, C_5H-thiaz.), 8.49 (s, 1H, C_4H-chrom.), 12.00 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.75; H, 5.04; N, 12.39.

3-(2-(2-(3-Methylcyclopentylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (11). Light yellow crystals, 99% yield, mp 214–216°C; ^{1}H NMR ($CDCl_3$): δ 1.10–1.12 (m, 3H, CH_3), 1.49–1.56 (m, 1H, cyclopentyl), 2.10–2.12 (m, 1H, cyclopentyl), 2.14–2.17 (m, 1H, cyclopentyl), 2.19–2.22 (m, 1H, cyclopentyl), 2.54–2.62 (m, 1H, cyclopentyl), 2.64–2.73 (m, 1H, cyclopentyl), 2.75–2.81 (m, 1H, cyclopentyl), 7.35–7.38 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.9 Hz, $J_{7\text{-}5}$ = 3.3 Hz, 1H, C_7H-chrom.), 7.38–7.40 (dd, $J_{5\text{-}6}$ = 8.0, $J_{5\text{-}7}$ = 3.2, 1H, C_5H-chrom.), 7.63–7.67 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.9 Hz, $J_{6\text{-}8}$ = 3.3 Hz, 1H, C_6H-chrom.), 7.77–7.79 (dd, $J_{8\text{-}7}$ = 7.9, $J_{8\text{-}6}$ = 3.4, 1H, C_8H-chrom.), 7.84 (s, 1H, C_5H-thiaz.), 8.59 (s, 1H, C_4H-chrom.), 11.80 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.65; H, 5.06; N, 12.38.

3-(2-(2-(Cyclooctylidene)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (12). Yellow crystals, 69% yield, mp 143–145°C; ^{1}H NMR ($CDCl_3$): δ 1.47–1.50 (m, 2H, cyclooctyl), 1.52–1.58 (m, 4H, cyclooctyl), 1.79–1.84 (m, 4H, cyclooctyl), 2.43–2.46 (m, 4H, cyclooctyl), 7.27–7.30 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.5 Hz, $J_{7\text{-}5}$ = 1.6 Hz, 1H, C_7H-chrom.), 7.38–7.40 (dd, $J_{5\text{-}6}$ = 7.4, $J_{5\text{-}7}$ = 1.7, 1H, C_5H-chrom.), 7.50–7.54 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.4 Hz, $J_{6\text{-}8}$ = 1.7 Hz, 1H, C_6H-chrom.), 7.69–7.71 (dd, $J_{8\text{-}7}$ = 7.4, $J_{8\text{-}6}$= 1.7, 1H, C_8H-chrom.), 7.87 (s, 1H, C_5H-thiaz.), 8.51 (s, 1H, C_4H-chrom.), 11.97 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{20}H_{21}N_3O_2S$: C, 65.37; H, 5.76; N, 11.44. Found: C, 65.33; H, 5.76; N, 11.45.

3-(2-(2-(1-(Cyclohexyl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (13). Yellow crystals, 69% yield, mp 195–200°C; ^{1}H NMR (DMSO-d_6): δ 1.48–1.52 (m, 2H, cyclohexyl), 1.75–1.79 (m, 4H, cyclohexyl), 2.41–2.45 (m, 4H, cyclohexyl), 7.37–7.41 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.5 Hz, $J_{7\text{-}5}$ = 1.8 Hz, 1H, C_7H-chrom.), 7.41–7.43 (dd, $J_{5\text{-}6}$ = 7.6, $J_{5\text{-}7}$ = 1.9, 1H, C_5H-chrom.), 7.53–7.57 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.5 Hz, $J_{6\text{-}8}$ = 1.8 Hz, 1H, C_6H-chrom.), 7.68–7.70 (dd, $J_{8\text{-}7}$ = 7.9, $J_{8\text{-}6}$ = 1.7, 1H, C_8H-chrom.), 7.85 (s, 1H, C_5H-thiaz.), 8.54 (s, 1H, C_4H-chrom.), 11.75 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{20}H_{21}N_3O_2S$: C, 65.37; H, 5.76; N, 11.44. Found: C, 65.33; H, 5.77; N, 11.45.

3-(2-(2-(1-(Furan-2-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (15). Light green crystals, 77% yield, mp 218–220°C; ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, CH_3), 6.57–6.58 (d, $J_{3\text{-}4}$ = 1.7 Hz, 1H, C_3H-furan), 6.84–6.86 (dd, $J_{4\text{-}5}$ = 3.3 Hz, $J_{4\text{-}3}$ = 1.7 Hz, 1H, C_4H-furan), 7.37–7.41 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 7.6 Hz, $J_{7\text{-}5}$ = 2.9 Hz, 1H, C_7H-chrom.), 7.44–7.47 (dd, $J_{5\text{-}6}$ = 7.6 Hz, $J_{5\text{-}7}$ = 2.6 Hz, 1H, C_5H-chrom.), 7.61–7.63 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.2 Hz, $J_{6\text{-}8}$ = 2.9 Hz, 1H, C_6H-chrom.), 7.73–7.75 (d, $J_{5\text{-}4}$ = 3.3 Hz, 1H, C_5H-furan), 7.76 (s, 1H, C_5H-thiaz.), 7.80–7.83 (dd, $J_{8\text{-}7}$ = 7.6 Hz, $J_{8\text{-}6}$ = 2.9 Hz, 1H, C_8H-chrom.), 8.56 (s, 1H, C_4H-chrom.), 11.25 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{18}H_{13}N_3O_3S$: C, 61.53; H, 3.73; N, 11.96. Found: C, 61.56; H, 3.72; N, 11.98.

3-(2-(2-(Thiophen-2-ylmethylen)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (16). Yellow crystals, 99% yield, mp 230–235°C; ^{1}H NMR (DMSO-d_6): δ 7.08–7.12 (m, 1H, thiophene), 7.37–7.40 (m, 1H, thiophene), 7.41 (s, 1H, C_5H-thiaz.), 7.43–7.48 (m, $J_{7\text{-}6}$ = $J_{7\text{-}8}$ = 6.8 Hz, $J_{7\text{-}5}$ = 3.4 Hz, 1H, C_7H-chrom.), 7.58–7.62 (dd, $J_{5\text{-}6}$ = 6.3 Hz, $J_{5\text{-}7}$ = 3.3 Hz, 1H, C_5H-chrom.), 7.63–7.68 (m, 1H, thiophene), 7.75–7.78 (m, 1H, C_8H-chrom.), 7.82–7.87 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 6.3 Hz, $J_{6\text{-}8}$ = 3.4 Hz, 1H, C_6H-chrom.), 8.24 (s, 1H, CH=N), 8.53 (s, 1H, C_4H-chrom.), 12.10 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{17}H_{11}N_3O_2S_2$: C, 57.77; H, 3.14; N, 11.89. Found: C, 57.72; H, 3.15; N, 11.90.

3-(2-(2-(1-(Thiophen-2-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (17). Yellow crystals, 92% yield, mp 221–223°C; ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 3H, CH_3), 7.03–7.06 (m, 1H, thiophene), 7.37–7.40 (m, 1H, C_7H-chrom.), 7.45–7.47 (dd, $J_{5\text{-}6}$ = 7.4 Hz, $J_{5\text{-}7}$ = 2.1 Hz, 1H, C_5H-chrom.), 7.52–7.55 (m, 1H, thiophene), 7.57–7.60 (m, 1H, thiophene), 7.61–7.64 (m, 1H, C_6H-chrom.), 7.77 (s, 1H, C_5H-thiaz.), 7.81–7.84 (dd, $J_{8\text{-}7}$ = 7.4, $J_{8\text{-}6}$ = 2.5, 1H, C_8H-chrom.), 8.57 (s, 1H, C_4H-chrom.), 11.20 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{17}H_{11}N_3O_2S_2$: C, 57.61; H, 3.41; N, 11.86. Found: C, 57.60; H, 3.42; N, 11.86.

3-(2-(2-(1-(Pyridin-2-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (19). Orange crystals, 99% yield, mp 258–262°C; ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 7.37–7.40 (m, 1H, C_7H-chrom.), 7.42–7.47 (dd, $J_{5\text{-}6}$ = 7.5 Hz, $J_{5\text{-}7}$ = 1.9 Hz, 1H, C_5H-chrom.), 7.50–7.54 (m, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.3 Hz, $J_{6\text{-}8}$ = 1.2 Hz, 1H, C_6H-chrom.), 7.55–7.61 (m, 1H, C_5H-pyridine), 7.81 (s, 1H, C_5H-thiaz.), 7.82–7.84 (dd, $J_{8\text{-}7}$ = 7.3 Hz, $J_{8\text{-}6}$ = 1.3 Hz, 1H, C_8H-chrom.), 8.05–8.10 (m, 1H, C_4H-pyridine), 8.11–8.13 (m, 1H, C_3H-pyridine), 8.58 (s, 1H, C_4H-chrom.), 8.63–8.65 (m, 1H, C_6H-pyridine), 11.77 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{19}H_{14}N_4O_2S$: C, 62.97; H, 3.89; N, 15.46. Found: C, 62.95; H, 3.88; N, 15.45.

3-(2-(2-(1-(Pyridin-3-yl)methylen)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (20). Yellow crystals, 99% yield, mp 257–258°C; ^{1}H NMR (DMSO-d_6): 7.32–7.35 (m, 1H, C_7H-chrom.), 7.38–7.41 (dd, $J_{5\text{-}6}$ = 7.5 Hz, $J_{5\text{-}7}$ = 1.3 Hz, 1H, C_5H-chrom.), 7.60–7.64 (m, 1H, C_6H-chrom.), 7.80–7.83 (dd, $J_{8\text{-}7}$ = 7.6 Hz, $J_{8\text{-}6}$ = 1.4 Hz, 1H, C_8H-chrom.), 7.84 (s, 1H, C_5H-thiaz.), 7.85–7.88 (m, 1H, C_5H-pyridine), 8.17 (s, 1H, CH=N), 8.48–8.52 (m, 1H, C_4H-pyridine), 8.56 (s, 1H, C_4H-chrom.), 8.73–8.75 (m, 1H, C_6H-pyridine), 9.01 (s, 1H, C_2H-pyridine), 12.75 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{18}H_{12}N_4O_2S$: C, 62.06; H, 3.47; N, 16.08. Found: C, 62.07; H, 3.48; N, 16.10.

3-(2-(2-(1-(Pyridin-3-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (21). Yellow crystals, 99% yield, mp 269–270°C; ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 7.40–7.44 (m, 1H, C_7H-chrom.), 7.48–7.50 (dd, $J_{5\text{-}6}$ = 7.8 Hz, $J_{5\text{-}7}$ = 1.7 Hz, 1H, C_5H-chrom.), 7.58–7.62 (m, 1H, C_6H-chrom.), 7.80–7.83 (dd, $J_{8\text{-}7}$ = 7.7 Hz, $J_{8\text{-}6}$ = 1.7 Hz, 1H, C_8H-chrom.), 7.84 (s, 1H, C_5H-thiaz.), 7.87–7.90 (m, 1H, C_5H-pyridine), 8.52 (s, 1H, C_4H-chrom.), 8.55–8.58 (m, 1H, C_4H-pyridine), 8.72–8.74 (m, 1H, C_6H-pyridine), 9.07 (s, 1H, C_2H-pyridine), 11.75 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{19}H_{14}N_4O_2S$: C, 62.97; H, 3.89; N, 15.46. Found: C, 62.98; H, 3.90; N, 15.46.

3-(2-(2-(1-(Pyridin-4-yl)methylen)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (22). Orange crystals, 99% yield, mp > 300°C; ^{1}H NMR (DMSO-d_6): 7.40–7.43 (m, 1H, C_7H-chrom.), 7.48–7.50 (dd, $J_{5\text{-}6}$ = 7.9 Hz, $J_{5\text{-}7}$ = 1.4 Hz, 1H, C_5H-chrom.), 7.59–7.63 (m, 1H, C_6H-chrom.), 7.85–7.88 (dd, $J_{8\text{-}7}$ = 7.6 Hz, $J_{8\text{-}6}$ = 1.5 Hz, 1H, C_8H-chrom.), 7.91 (s, 1H, C_5H-thiaz.), 8.07–8.10 (d, J = 4.1 Hz, 2H, pyridine), 8.16 (s, 1H, CH=N), 8.55 (s, 1H, C_4H-chrom.), 8.81–8.83 (d, J = 4.5 Hz, 2H, pyridine), 13.00 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{18}H_{12}N_4O_2S$: C, 62.06; H, 3.47; N, 16.08. Found: C, 62.05; H, 3.46; N, 16.08.

3-(2-(2-(1-(Pyridin-4-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (23). Yellow crystals, 98% yield, mp 215–220°C; ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 7.42–7.46 (m, 1H, C_7H-chrom.), 7.48–7.50 (dd, $J_{5\text{-}6}$ = 7.4 Hz, $J_{5\text{-}7}$ = 1.6 Hz, 1H, C_5H-chrom.), 7.64–7.68 (m, 1H, C_6H-chrom.), 7.76–7.78 (dd, $J_{8\text{-}7}$ = 7.5 Hz, $J_{8\text{-}6}$ = 1.9 Hz, 1H, C_8H-chrom.), 7.85 (s, 1H, C_5H-thiaz.), 8.45–8.48 (d, J = 5.8 Hz, 2H, pyridine), 8.67 (s, 1H, C_4H-chrom.), 8.78–8.81 (d, J = 5.8 Hz, 2H, pyridine), 10.75 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{19}H_{14}N_4O_2S$: C, 62.97; H, 3.89; N, 15.46. Found: C, 62.95; H, 3.98; N, 15.45.

3-(2-(2-(1-(1H-indol-4-yl)methylen)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (24). Yellow crystals, 90% yield, mp 248–250°C; ^{1}H NMR (DMSO-d_6): 6.95–6.98 (t, J = 3.5, 1H, C_5H-indole), 7.12–7.15 (t, J = 3.7, 1H, C_6H-indole), 7.32 (s, 1H, C_2H-indole), 7.39–7.43 (m, $J_{7\text{-}6} = J_{7\text{-}8}$ = 7.3 Hz, $J_{7\text{-}5}$ = 1.7 Hz, 1H, C_7H-chrom.), 7.44–7.46 (d, J = 3.7, 1H, C_7H-indole), 7.48–7.50 (dd, $J_{5\text{-}6}$ = 7.3 Hz, $J_{5\text{-}7}$ = 1.7 Hz, 1H, C_5H-chrom.), 7.49–7.53 (m, 1H, C_6H-chrom.), 7.55 (s, 1H, C_5H-thiaz.), 7.58–7.60 (dd, $J_{8\text{-}7}$ = 7.3 Hz, $J_{8\text{-}6}$ = 1.3 Hz, 1H, C_8H-chrom.), 7.62–7.64 (d, J = 3.5, 1H, C_4H-indole), 8.16 (s, 1H, CH=N), 8.57 (s, 1H, C_4H-chrom.), 10.79 (br s, 1H, NH, D_2O exch.), 11.51 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{21}H_{14}N_4O_2S$: C, 65.27; H, 3.65; N, 14.50. Found: C, 65.25; H, 3.64; N, 14.51.

3-(2-(2-(1-(Naphthalen-1-yl)methylen)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (26). Yellow crystals, 70% yield, mp 240–242°C; ^{1}H NMR (DMSO-d_6): 7.40–7.44 (m, 1H, C_7H-chrom.), 7.49–7.51 (dd, $J_{5\text{-}6}$ = 7.8 Hz, $J_{5\text{-}7}$ = 1.5 Hz, 1H, C_5H-chrom.), 7.53–7.55 (m, 1H, C_6H-chrom.), 7.56 (s, 1H, C_5H-thiaz.), 7.57–7.60 (dd, $J_{8\text{-}7}$ = 7.8 Hz, $J_{8\text{-}6}$ = 1.3 Hz, 1H, C_8H-chrom.), 7.77–7.81 (m, 2H, naphtalene), 7.82–7.85 (m, 1H, naphtalene), 7.97–8.02 (m, 2H, naphtalene), 8.08–8.10 (m, 1H, naphtalene), 8.12 (s, 1H, CH=N), 8.22–8.24 (m, 1H, naphtalene), 8.60 (s, 1H, C_4H-chrom.), 11.54 (br s, 1H, NH, D_2O exch.); *Anal*. Calcd. for $C_{24}H_{17}N_3O_2S$: C, 70.05; H, 4.16; N, 10.21. Found: C, 70.00; H, 4.15; N, 10.22.

3-(2-(2-(1-(Naphthalen-2-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (27). Yellow crystals, 91% yield, mp 244–245°C; ^{1}H NMR (DMSO-d_6): 7.38–7.42 (m, 1H, C_7H-chrom.), 7.46–7.48 (dd, $J_{5\text{-}6}$ = 7.4 Hz, $J_{5\text{-}7}$ = 1.8 Hz, 1H, C_5H-chrom.), 7.49–7.53 (m, 1H, C_6H-chrom.), 7.54 (s, 1H, C_5H-thiaz.), 7.58–7.60 (dd, $J_{8\text{-}7}$ = 7.3 Hz, $J_{8\text{-}6}$ = 1.4 Hz, 1H, C_8H-chrom.), 7.77–7.82 (m, 2H, naphtalene), 7.90–7.94 (m, 2H, naphtalene), 7.98–8.01 (m, 1H, naphtalene), 8.08–8.10 (m, 1H, naphtalene), 8.21–8.23 (m, 1H, naphtalene), 8.59 (s, 1H, C_4H-chrom.), 11.50 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{24}H_{17}N_3O_2S$: C, 70.05; H, 4.16; N, 10.21. Found: C, 70.00; H, 4.15; N, 10.22.

9-(2-(4-(2H-2-oxo-chromen-3-yl)thiazol-2-yl)hydrazono)-9H-fluorene-2-carboxylic acid (29). Yellow crystals, 99% yield, mp 190–192°C; ^{1}H NMR (DMSO-d_6): 7.28–7.30 (m, 1H, fluorene), 7.38–7.42 (m, 1H, C_7H-chrom.), 7.45–7.47 (dd, $J_{5\text{-}6}$ = 7.7 Hz, $J_{5\text{-}7}$ = 1.3 Hz, 1H, C_5H-chrom.), 7.49–7.53 (m, 1H, C_6H-chrom.), 7.56 (s, 1H, C_5H-thiaz.), 7.57–7.61 (m, 2H, fluorene), 7.62–7.64 (dd, $J_{8\text{-}7}$ = 7.4 Hz, $J_{8\text{-}6}$ = 1.4 Hz, 1H, C_8H-chrom.), 7.78–7.82 (m, 2H, fluorene), 8.33–8.38 (m, 2H, fluorene), 8.57 (s, 1H, C_4H-chrom.), 11.77 (br s, 1H, COOH, D_2O exch.), 12.50 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{26}H_{15}N_3O_4S$: C, 67.09; H, 3.25; N, 9.03. Found: C, 67.13; H, 3.25; N, 9.04.

3-(2-(2-(1-(Thiazol-2-yl)ethyliden)hydrazynyl)thiazol-4-yl)-2H-chromen-2-one (30). Light brown crystals, 99% yield, mp 256–260°C; ^{1}H NMR (DMSO-d_6): δ 2.43 (s, 3H, CH_3), 7.39–7.43 (m, 1H, C_7H-chrom.), 7.46–7.48 (dd, $J_{5\text{-}6}$ = 8.0 Hz, $J_{5\text{-}7}$ = 1.6 Hz, 1H, C_5H-chrom.), 7.63–7.67 (m, 1H, C_6H-chrom.), 7.79 (s, 1H, C_5H-thiaz.), 7.83–7.85 (dd, $J_{8\text{-}7}$ = 7.9 Hz, $J_{8\text{-}6}$ = 1.8 Hz, 1H, C_8H-chrom.), 7.86–7.89 (m, 2H, thiazole), 8.72 (s, 1H, C_4H-chrom.), 11.75 (br s, 1H, NH, D_2O exch.); Anal. Calcd. for $C_{17}H_{12}N_4O_2S_2$: C, 55.42; H, 3.28; N, 15.21. Found: C, 55.47; H, 3.28; N, 15.24.

Procedure for the synthesis of derivative 31. 3-α-Bromoacetyl coumarin (50 mmol) was dissolved in 2-propanol and reacted with an equimolar amount of thiosemicarbazide at room temperature under magnetic stirring for 4 h. The precipitate was filtered and dried to give intermediate **31**.

***H. pylori* culture.** The *H. pylori* strains used in this study were maintained at −80°C in Wilkins Chalgren broth with 10% (v/v) horse serum (Seromed) and 20% (v/v) glycerol (Merck) until required for the experiments. Before being used the bacteria were subcultured twice on Columbia agar base (Difco Laboratories) supplemented with 10% horse serum and 0.25% Bacto yeast extract (Difco). Plates were incubated for 72 h at 37°C in an atmosphere of 10% CO_2 in a gas incubator.

Anti-*Helicobacter pylori* activity. Antimicrobial activity against *H. pylori* was determined by the agar dilution standard method [19]. The strains were inoculated onto Columbia agar base (Difco) supplemented with 10% horse serum and 0.25%

bacto yeast extract (Difco) and were incubated for 72 h at 37°C in an atmosphere of 10% CO_2 in a gas incubator. Colonies were suspended in Wilkins Chalgren broth to achieve a turbidity equivalent to 0.5 Mc Farland. Columbia agar plates with 10% horse serum were prepared by using twofold dilutions of the antimicrobial agents (128–0.0039 μg/mL). The inoculum was delivered to the surface of the agar plates with a Steer's replicator to obtain $\sim 5 \times 10^5$ CFU per spot. Growth control plates without antibiotics were inoculated in each series of tests. All plates were incubated at 37°C for 72 h under conditions (10% CO_2 in a gas incubator). The minimal inhibitory concentration was defined as the lowest concentration of drug inhibiting visible bacterial growth.

REFERENCES AND NOTES

[1] Hunt, R. H. Scand J Gastroenterol 1996, 220, 3.

[2] Bardhan, P. K. Clin Infect Dis 1997, 25, 973.

[3] IARC. IARC monographs on the evaluation of carcinogenic risks to humans, Vol. 61; IARC: Lyon, 1994; pp 177–240.

[4] Chimenti, F.; Bizzarri, B.; Bolasco, A.; Secci, D.; Chimenti, P.; Carradori, S.; Granese, A.; Rivanera, D.; Lilli, D.; Scaltrito, M. M.; Brenciaglia, M. I. Eur J Med Chem 2006, 41, 208.

[5] Chimenti, F.; Bizzarri, B.; Bolasco, A.; Secci, D.; Chimenti, P.; Carradori, S.; Granese, A.; Rivanera, D.; Lilli, D.; Zicari, A.; Scaltrito, M. M.; Sisto, F. Bioorg Med Chem Lett 2007, 17, 3065.

[6] Kawase, M.; Motohashi, N. Curr Med Chem Anti-Infect Agents 2004, 3, 89.

[7] Chimenti, F.; Carradori, S.; Secci, D.; Bolasco, A.; Chimenti, P.; Granese, A.; Bizzarri, B. J Heterocycl Chem 2009, 46, 575.

[8] Raghu, M.; Nagaraj, A.; Reddy, Ch. S. J Heterocycl Chem 2009, 46, 261.

[9] Rao, V. R.; Reddy, M. M. M. Indian J Heterocycl Chem 2003, 13, 69.

[10] Kalluraya, B.; Isloor, A. M.; Shenoy, S. Indian J Heterocycl Chem 2001, 11, 159.

[11] Kalluraya, B.; Vishwanatha, P.; Isloor, A. M.; Rai, G.; Kotian, M. Bollettino Chimico Farmaceutico 2000, 139, 263.

[12] Rao, V. R.; Kumar, V. R.; Vardhan, V. A. Phosphorus Sulfur 1999, 152, 257.

[13] Srimanth, K.; Rao, V. R. Indian J Chem B 1999, 38B, 473.

[14] Gursoy, A. J Fac Pharm Istanbul U 1974, 10, 57.

[15] Gursoy, A.; Eczacilik F. J Fac Pharm Istanbul U 1973, 9, 51.

[16] Rao, V. R.; Srimanth, K. J Chem Res S 2002, 9, 420.

[17] Benassi, R.; Benedetti, A.; Taddei, F.; Cappelletti, R.; Nardi, D.; Tajana, A. Org Magn Reson 1982, 20, 26.

[18] Cirilli, R.; Ferretti, R.; La Torre, F.; Secci, D.; Bolasco, A.; Carradori, S.; Pierini, M. J Chromatogr A 2007, 1172, 160.

[19] National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic bacteria. Approved standard M11-A6, 6th ed.; National Committee for Clinical Laboratory Standards: Villanova, PA, 2004.