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Article

A New Approach for the Synthesis of Bioactive Heteroaryl Thiazolidine-2,4-diones

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A condensação do 3-formilcromano (**1**) com tiazolidina-2,4-diona (**2**) produziu 5-[4-oxo-4*H*-croman-3-ila)metileno]-1,3-tiazolidina-2,4-diona (**3**). A reação de **3** com hidrato de hidrazina, fenil hidrazina e hidrocloreto de hidroxilamina produziu os derivados correspondentes pirazol e isoxazol **4**-**7**. O composto **3** reagiu com tiouréia, guanidina e cianoguanidina para produzir os derivados correspondentes de pirimidina **8**-**10**. Pirimido[1,2-*a*]pirimidina **12**, benzo[1,5]diazepina **15**, pirido[1,2-*b*][1,2,3]triazepina **16**, 1,2,4-triazolo[3,4-*b*][1,3,4]tiadiazepina **19** e 1,2,4-triazino[3,2-*b*][1,3,4]tiadiazepina **20** ligados à tiazolidina-2,4-diona foram preparados a partir da reação de **3** com nucleófilos bifuncionais *N,N*- e *N,S*-. A reatividade química de **3** frente aos nucleófilos carbonados produziu novos derivados heterocíclicos de tiazolidina-2,4-diona **22**-**25**. Os compostos sintetizados foram testados *in vitro* para verificar sua atividade antimicrobiana contra *Staphylococcus aureus, Proteus vulgaris* e *Candida albicans*.

Condensation of 3-formylchromone (**1**) with thiazolidine-2,4-dione (**2**) afforded 5-[4-oxo-4*H*-chromen-3-yl)methylene]-1,3-thiazolidine-2,4-dione (**3**). Reaction of **3** with hydrazine hydrate, phenyl hydrazine and hydroxylamine hydrochloride gave the corresponding pyrazole and isoxazole derivatives **4**-**7**. Compound **3** was subjected to react with thiourea, guanidine and cyanoguanidine to give the corresponding pyrimidine derivatives **8**-**10**. Pyrimido[1,2-*a*]pyrimidine **12**, benzo[1,5]diazepine **15**, pyrido[1,2-*b*][1,2,4]triazepine **16**, 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazepine **19** and 1,2,4-triazino[3,2-*b*][1,3,4]thiadiazepine **20** linked thiazolidine-2,4-dione were prepared from the reaction of **3** with *N,N*- and *N,S*- bifunctional nucleophiles. The chemical reactivity of **3** towards carbon nucleophiles gave new heterocyclic moieties linked thiazolidine-2,4-dione **22**-**25**. The synthesized compounds were screened *in vitro* for their antimicrobial activities against *Staphylococcus aureus, Proteus vulgaris* and *Candida albicans*.

Keywords: 2,4-thiazolidinedione, chromone, Michael addition, cyclocondensation, RORC, heterocyclic synthesis

Introduction

Thiazolidinediones were the first parent compounds in which the thiazole ring was recognized. 2,4-Thiazolidinediones (2,4-TZDs) represent a new class of antidiabetic drugs,[1] which improve glycemic control in type 2 diabetic patients by increasing insulin action in skeletal muscles, liver and adipose tissue through activation of the peroxisome proliferators-activated receptor γ.[2] 2,4-TZDs differ markedly from other antidiabetic drugs in that they are effective in normalizing glucose and lipid metabolism associated with insulin resistance and therefore are expected to be useful in treatment of type 2 diabetes mellitus and obesity.[3-5] Besides, it was reported that some 2,4-TZDs have been used as antihyperglycemic[6] and aldose reductase (AR) inhibitory agents with dual activity.[7] There is a great interest in 2,4-TZD derivatives as aldose reductase inhibitors (ARIs),[7,8] since they can be viewed as hydantoin bioisosters potentially free of the hypersensitivity reactions which are linked to the presence of the hydantoin system.

Chromones are a group of naturally occurring compounds that are ubiquitous in nature especially in fruits, vegetables, nuts, seeds, and flowers.[9,10] 3-Formyl chromone has been used as an excellent precursor to prepare a diversity of heterocyclic systems owing to the presence of an α,β-unsaturated keto-function.[11,12] In general, chromones are known as useful building blocks in organic synthesis due to the active center at position 2. This center is very reactive towards Michael addition of nucleophiles[13,14] with opening of the γ-pyrone ring followed by a new

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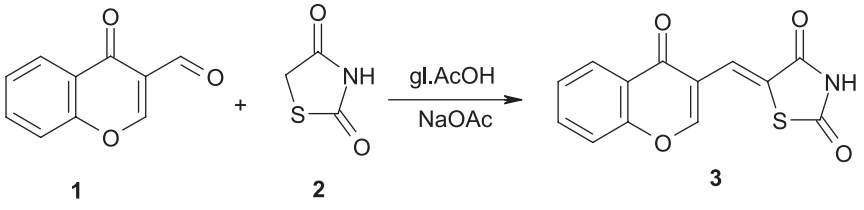
cyclization.[15] Therefore, the well-known biological activity of 2,4-TZDs systems[16-20] directed our attention to use the starting compound 5-[4-oxo-4*H*-chromen-3-yl)methylene]-1,3-thiazolidine-2,4-dione (**3**) to obtain a new thiazolidine-2,4-dione derivatives incorporated with bioactive five-, six- and seven-membered heterocyclic nuclei.

Results and Discussion

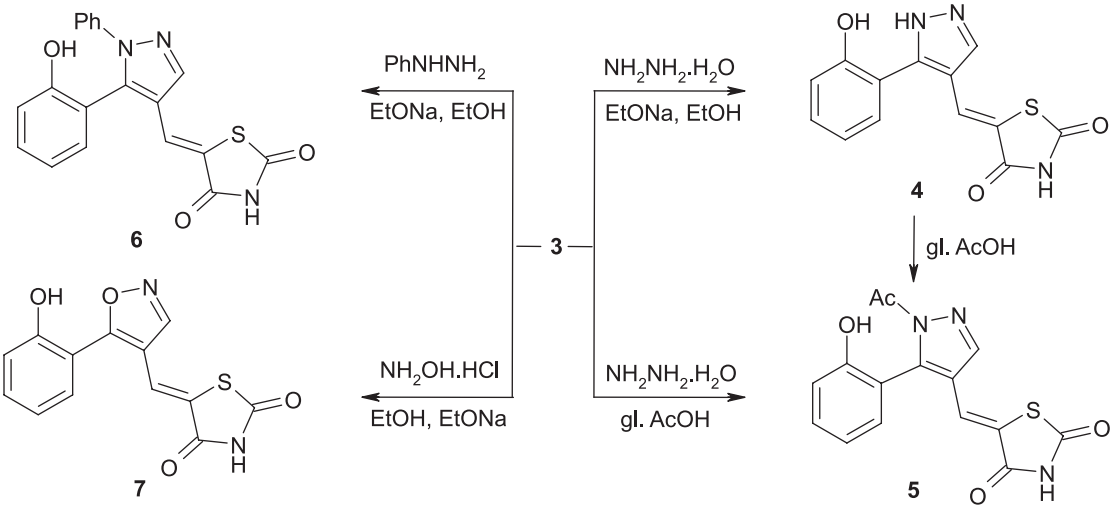
Knoevenagel condensation of 3-formylchromone (**1**) with thiazolidine-2,4-dione (**2**) in glacial acetic acid and freshly fused sodium acetate afforded the target compound, 5-[4-oxo-4*H*-chromen-3-yl)methylene]-1,3-thiazolidine-2,4-dione (**3**) (Scheme 1). The melting point of compound **3** is 319 ºC not 271 ºC as previously reported.[21] The IR spectrum of compound **3** showed characteristic absorption bands at 3145 (NH), 1728, 1681 ($2C{=}O_{thiazolidinedione}$) and 1640 cm^{-1} ($C{=}O_{\gamma\text{-pyrone}}$). Its ^1H NMR spectrum revealed characteristic singlet signals at δ 7.61 and 8.82 ppm attributed to methine proton and H-2, respectively, in addition to the NH proton which was observed as a broad signal exchangeable with D_2O at δ 12.44 ppm. The mass spectrum showed the molecular ion peak at *m/z* 273 and the base peak at *m/z* 202.

Reaction of compound **3** with an equimolar amount of hydrazine hydrate, in sodium ethoxide, led to the γ-pyrone ring opening followed by ring closure (RORC) to produce 5-[5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl]methylene-1,3-thiazolidine-2,4-dione (**4**) (Scheme 2). The pyrazole derivative **4** gave deep blue coloration with $FeCl_3$ solution indicating the presence of phenolic OH group and the ^1H NMR spectrum revealed the disappearance of the specific signal for the H-2 proton of the chromone ring which was observed in the spectrum of the parent compound **3** at δ 8.82 ppm. The spectrum showed the presence of characteristic singlet signals at δ 7.49 and 7.91 ppm attributed to the methine proton and $H\text{-}3_{pyrazole}$, respectively, in addition to three broad signals exchangeable with D_2O at δ 10.06, 12.35 and 13.49 ppm due to OH, $NH_{thiazolidinedione}$ and $NH_{pyrazole}$ protons, respectively. Moreover, the IR spectrum of compound **4** revealed the disappearance of absorption band due to C=O of the γ-pyrone ring system which appeared at 1640 cm^{-1} in the IR spectrum of the starting compound **3**.

When the reaction of compound **3** with hydrazine hydrate was carried out in molar ratio 1:1 in glacial acetic acid, an *N*-acetyl derivative of compound **4** was obtained and is formulated as 5-{[1-acetyl-5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl]methylidene}-1,3-thiazolidine-2,4-dione (**5**). Elucidative synthesis of compound **5** was achieved by boiling compound **4** in glacial acetic acid (Scheme 2). The ^1H NMR spectrum of the product **5** revealed the presence of



Scheme 1. Formation of chromenylthiazolidine-2,4-dione **3**.



Scheme 2. Reactions of compound **3** with 1,2-bifunctional nucleophiles.

the acetyl protons as a characteristic singlet at δ 1.88 ppm, in addition to the signal assigned to exocyclic enone proton at δ 7.87 ppm. The spectrum also revealed two exchangeable signals at δ 9.95 (OH), and 12.31 ppm ($NH_{thiazolidinedione}$). Also, the positive $FeCl_3$ test is a clear evidence for the γ-pyrone ring opening and indicates the presence of the OH group.

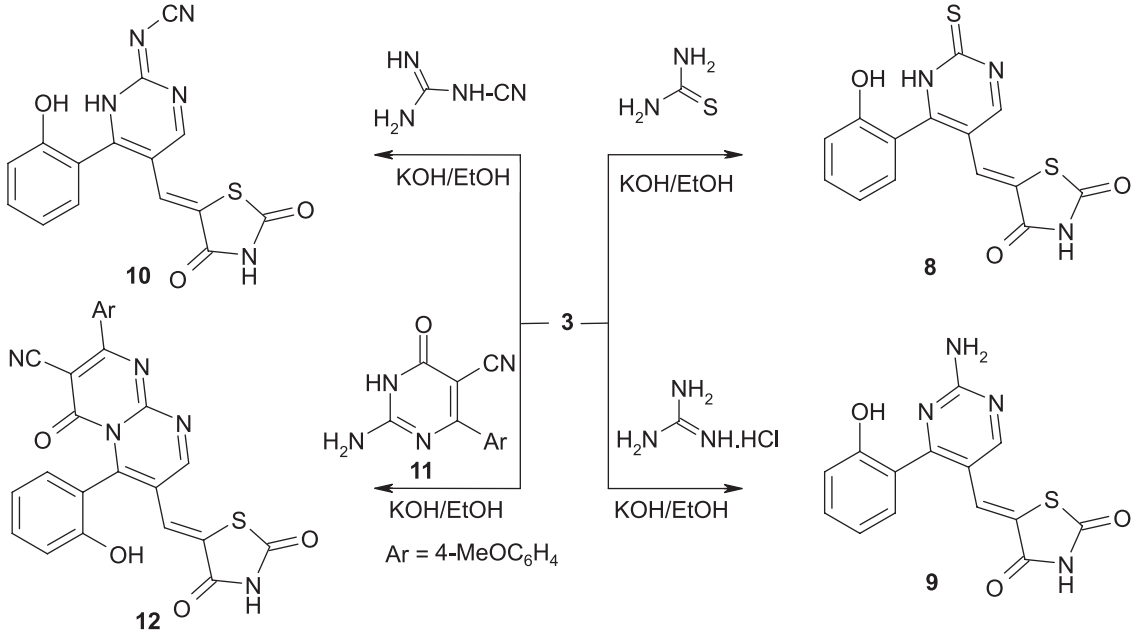
Similarly, the reaction of chromenylthiazolidine **3** with phenylhydrazine in sodium ethoxide gave 1-phenylpyrazol-4-ylmethylene-1,3-thiazolidine-2,4-dione derivative **6**. The ^{1}H NMR spectrum showed two exchangeable signals at δ 9.92 and 12.21 ppm attributed to OH and NH protons, respectively, in addition to the two characteristic singlet signals at δ 7.71 and 8.06 ppm due to the methine and H-$3_{pyrazole}$ protons, respectively.

Reaction of compound **3** with an equimolar amount of hydroxylamine hydrochloride in ethanolic sodium ethoxide solution gave 5-{[5-(2-hydroxyphenyl)isoxazol-4-yl] methylene}-1,3-thiazolidine-2,4-dione (**7**) (Scheme 2). Structure assignment of compound **7** was achieved from its spectral data in which the ^{1}H NMR spectrum presented two characteristic singlet signals at δ 7.48 and 7.87 ppm due to the exocyclic methine proton and H-$3_{isoxazole}$, respectively, along with two broad signals exchangeable with D_2O at δ 10.03 and 12.32 ppm due to OH and NH protons, respectively. The IR spectrum of compound **7** revealed the disappearance of the absorption band due to the C=O of γ-pyrone system which was seen at 1640 cm^{-1} in the IR spectrum of compound **3**.

The reaction of chromenylthiazolidine **3** with 1,3-binucleophiles was studied. Thus, treatment of **3** with thiourea and guanidine hydrochloride at molar ratio 1:1 in ethanolic potassium hydroxide solution afforded pyrimidinylmethylene-thiazolidine derivatives **8** and **9**, respectively (Scheme 3). Compounds **8** and **9** gave positive $FeCl_3$ test confirming the presence of phenolic OH groups obtained by γ.pyrone ring opening. The ^{1}H NMR spectra of **8** and **9** showed the H-4 proton of the pyrimidine moiety as a characteristic singlet at δ 8.41 and 8.40 ppm for compounds **8** and **9**, respectively. The reaction proceeds via γ-pyrone ring opening by NH_2 group followed by cyclo-condensation of the other amino group with the benzoyl carbonyl group. Moreover, the UV spectrum of compound **9** showed three absorption bands at λ_{max} 210, 320 and 440 nm assigned to π-π*, *n*-π* transition and the extended conjugation between the electron repelling amino group in the pyrimidine moiety and electron withdrawing carbonyl group in the thiazolidine moiety.

Similarly, the reaction of compound **3** with cyanoguanidine under the same reaction conditions yielded the 5-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-6-(2-hydroxyphenyl)pyrimidin-2(1*H*)-yl]cyanamide (**10**). The IR spectrum of compound **10** showed characteristic absorption band at 2190 cm^{-1} assigned to the C≡N group.

In the same manner, the reaction of chromenylthiazolidine **3** with 2-amino-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**11**)[22] in ethanolic potassium hydroxide solution afforded 2-(4-methoxyphenyl)-7-[2,4-dioxo-1,3-thiazolidin-5-ylidine)methyl]-6-(2-hydroxyphenyl)-4-oxo-4*H*-pyrimido[1,2-*a*] pyrimidine-3-carbonitrile (**12**) (Scheme 3). Compound **12** gave red color with $FeCl_3$ indicating the presence of phenolic OH group

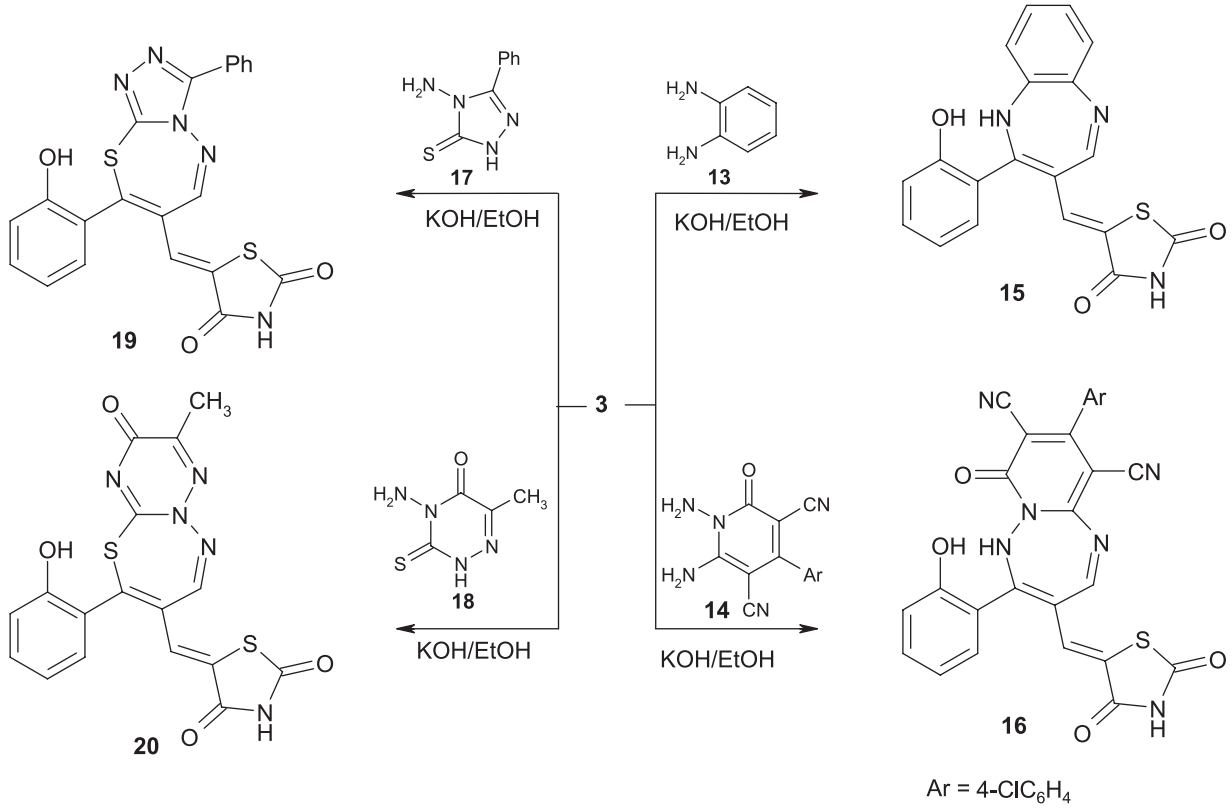


Scheme 3. Reactions of compound **3** with 1,3-bifunctional nucleophiles.

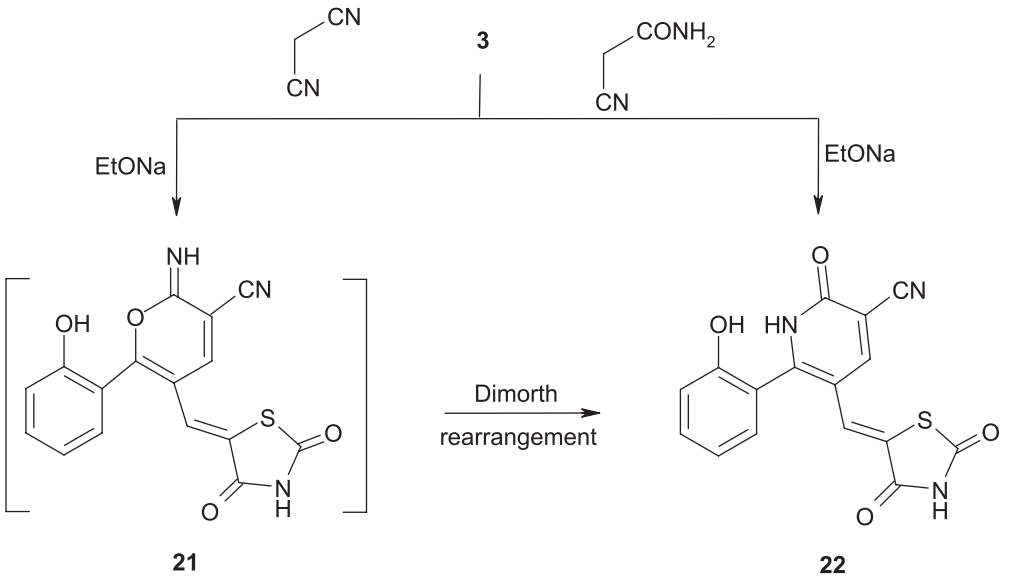
and its ^{1}H NMR showed two characteristic singlet signals due to the exocyclic methine proton and the H-4 proton of the pyrimidine system at δ 7.88 and 8.40, respectively, in addition to two exchangeable signals δ 10.40 and 12.35 ppm due to the OH and NH protons, respectively. Also, the IR spectrum showed characteristic absorption bands at 2214, 1684, 1650 and 1610 cm^{-1} assigned to C≡N, C=O$_{thiazolidinedione}$, C=O$_{pyrimidine}$ and C=N, respectively.

The RORC reactions of chromone derivative **3** with some *N,N* and *N,S* 1,4-binucleophiles were studied under basic conditions. Thus, condensation of **3** with *o*-phenylenediamine (**13**) and 4-(chlorophenyl)-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**14**)[23] gave benzo[*b*][1,4]diazepine **15** and pyrido[1,2-*b*][1,2,4] triazepine **16**, respectively. The ^{1}H NMR spectra showed the NH proton of the diazepine **15** and triazepine **16** as exchangeable signals at δ 8.21 and 8.56 ppm, respectively. The IR spectrum of compound **16** showed characteristic absorption bands due to the C≡N at 2216 cm^{-1}. Also, the mass spectrum of compound **16** revealed the molecular ion peak at *m/z* 540, which is coincident with the formula weight (540.95) and supports the identity of the structure. On the other hand, the reaction of compound **3** with 4-amino-5-phenyl-2,4-dihydro-1,2,4-triazole-3-thione (**17**)[24] and 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazein-5(2*H*)-one (**18**)[25] yielded 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazepine **19** and 1,2,4-triazino[3,2-*b*][1,3,4] thiadiazepine **20**, respectively (Scheme 4). The ^{1}H NMR spectrum of compound **20** showed three characteristic singlet signals at δ 2.07, 7.89 and 8.19 ppm attributed to CH_3, H_{enone} and H-5$_{thiadiazepine}$, respectively. The reaction of **3** with 1,4-binucleophiles proceeds via γ-pyrone ring opening followed by an intramolecular condensation reaction to effect cyclization leading to seven membered ring systems.

Moreover, the reaction of chromenylthiazolidine derivative **3** with some carbon nucleophiles was also studied under basic conditions. Thus, treatment of **3** with malononitrile and/or cyanoacetamide, in the presence of sodium ethoxide, led to the formation of the same product (the same mp and mmp and identical spectra) and was identified as 5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl]-6-(2-hydroxylphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**22**). Formation of **22** from compound **3** and malononitrile proceeds via the intermediate **21** which underwent Dimorth rearrangement under the reaction conditions to produce **22** (Scheme 5). The IR spectrum of compound **22** showed characteristic absorption band at 2202 cm^{-1} assigned to C≡N group. Its ^{1}H NMR spectrum showed two characteristic singlet signals at δ 7.89 and 8.14 ppm attributed to the exocyclic enone proton and H-4 of the pyridine ring, respectively. In addition the mass spectrum of compound **22** revealed the molecular ion peak



Scheme 4. Reactions of compound **3** with 1,4-bifunctional nucleophiles.



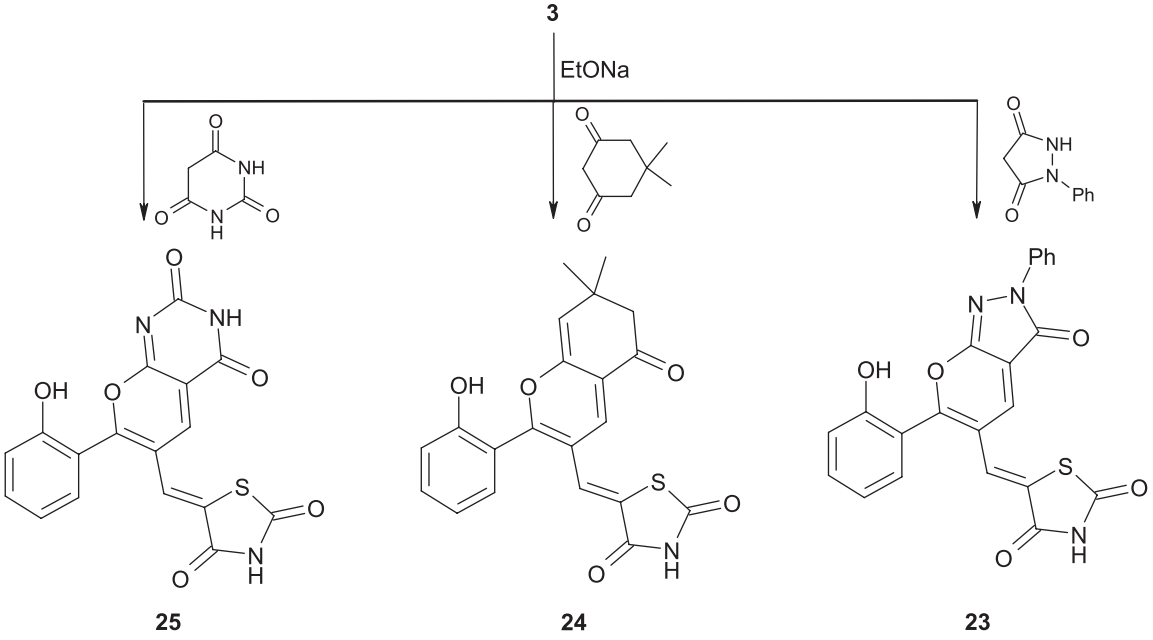
Scheme 5. Reactions of compound **3** with malononitrile and cyanoacetamide.

at *m/z* 339, which is coincident with the formula weight (339.33) and supports the identity of the structure.

Nucleophilic ring opening-ring closure (RORC) reactions of compound **3** by some cyclic active methylene compounds were studied. Therefore, the reaction of **3** with 1-phenylpyrazolidine-3,5-dione, 5,5-dimethylcyclohexane-1,3-dione, barbituric acid, in the presence of sodium ethoxide, afforded 5-{[6-(2-hydroxyphenyl)-3-oxo-2-phenyl-2,3-dihydropyrano[2,3-*c*]pyrazol-5-yl]methylidene}-1,3-thiazolidine-2,4-dione (**23**), 5-{[2-(2-hydroxyphenyl)-7,7-dimethyl-5-oxo-6,7-dihydro-5*H*-chromen-3-yl]methylidene}-1,3-thiazolidine-2,4-dione (**24**) and 6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-7-(2-hydroxyphenyl)-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (**25**), respectively. The ^{1}H NMR spectra of compounds **23-25** showed the H-4 of the pyran moiety as a characteristic singlet in the range δ 8.15-8.42 ppm.

Antimicrobial activity

The standardized disc agar diffusion method[26] was followed to determine the activity of the synthesized



Scheme 6. Formation of 1,3-thiazolidinedione derivatives **23-25**.

compounds against the sensitive organisms *Staphylococcus aureus* as Gram positive bacteria, *Proteus vulgaris* as Gram negative bacteria and *Candida albicans* as fungus starin. The antibiotics Doxymycin and Fluconazole were purchased from Egyptian markets and used in concentrations 100 μg mL^{-1} as references for antibacterial and antifungal activities.

The compounds were dissolved in DMSO which has no inhibition activity to get concentration of 100 μg mL^{-1}. The test was performed on medium potato dextrose agar (PDA) which contains infusion of 200 g potatoes, 6 g dextrose and 15 g agar.[27] Uniform size filter paper disks (3 disks *per* compound) were impregnated by equal volume (10 μL) from the specific concentration of dissolved tested compounds and carefully placed on the inoculated agar surface. After incubation for 36 h at 27 °C in the case of bacteria and for 48 h at 24 °C in the case of fungi, inhibition of the organisms was measured and used to calculate mean of inhibition zones. The results depicted in Table 1 showed different degrees of activity against all species of microorganisms which suggest that the variations in the structures affect on the growth of the microorganisms. Thus, we can conclude from these results: (*i*) the prepared thiazolidinedione derivatives showed a moderate to high antimicrobial activity towards Gram positive bacteria and the fungal stain, while showed low to moderate activity towards Gram negative bacteria (Table 1); (*ii*) compounds **22** and **23** showed the highest antimicrobial activity; the minimum inhibitory concentration (MIC) for these compounds was 6.25 μg mL^{-1}. Therefore, these compounds may be considered promising for the development of new antimicrobial agents.

Table 1. Antimicrobial activity of the newly synthesized thiazolidinedione derivatives

Compound	Diameter of inhibition zone (mm); conc. (100 μg mL^{-1})		
	S.aureus [Gram (+)]	*P. vulgaris* [Gram (–)]	*C. albicans* (Fungal strain)
3	2	-	3
4	5	2	7
5	4	-	8
6	7	3	10
7	3	-	8
8	9	4	11
9	8	2	9
10	8	3	8
12	9	2	12
15	10	4	15
16	15	4	14
19	8	3	9
20	9	5	10
22	10	4	14
23	15	5	8
24	7	-	6
25	9	-	6
Doxymycin	15	10	-
Fluconazole	-	-	16

Conclusions

The reaction of chromenylthiazolidine derivative **3** with some binucleophiles proceeds via attack of nucleophile at the C-2 position of the chromone system with concomitant opening of the γ-pyrone ring followed by cyclo-condensation to produce the desired products. The thiazoloidinedione exocyclic enone system was not involved in the course of the reaction. From these observation, it can be concluded again that the reactivity of γ-pyrone ring system is higher, compared with the exocyclic enone system, towards the nucleophilic reagents in the basic medium. Some of the compounds exhibited moderate antimicrobial activity.

Experimental

Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on a Perkin-Elmer 293 spectrophotometer (cm^{-1}), using KBr disks. UV absorption spectra (DMF) were recorded on a Jasco model (V-550) UV spectrophotometer. ^{1}H NMR spectra were measured on Gemini-200 (200 MHz) and/or Mercury-300BB (300MHz) spectrometers, using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. Mass spectra were obtained using Jeol-AMS-AX-500 and/or GC-2010 Shimadzu Gas chromatography instrument mass spectrometers (70 eV). Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer.

*5-[4-Oxo-4H-chromen-3-yl)methylene]-1,3-thiazolidine-2,4-dione (**3**)*

A mixture of chromone-3-carboxaldehyde (**1**) (1.74 g, 1 mmol) and thiazolidine-2,4-dione (**2**) (1.17 g, 1 mmol), in glacial acetic acid (25 mL) and freshly fused sodium acetate (0.2 g), was heated under reflux for 2 h. The solid obtained after cooling was filtered, washed several times with water and crystallized from DMF/EtOH to give **3** as yellow crystals, yield (2.11 g, 77%), mp 319 ºC. IR (KBr) ν_{max}/cm^{-1}: 3145 (NH), 3044 ($CH_{arom.}$), 1728, 1681 ($2C{=}O_{thiazolidinedione}$), 1640 ($C{=}O_{\gamma\text{-pyrone}}$), 1591 (C=C). ^{1}H NMR (DMSO-d_6) δ 7.54 (t,1H, H-6, *J* 8.1 Hz), 7.61 (s, 1H, H_{enone}), 7.72 (d, 1H, H-8, *J* 8.1 Hz), 7.87 (t, 1H, H-7, *J* 8.1 Hz), 8.12 (d, 1H, H-5, *J* 8.1 Hz), 8.82 (s, 1H, H-2), 12.44 (bs,

1H, NH exchangeable with D_2O). MS (*m/z*, %): 273 (40), 230 (22), 202 (100), 170 (12), 146 (12), 120 (34), 105 (15), 92 (50), 77 (13), 64 (29).

*5-{[5-(2-Hydroxyphenyl)-1H-pyrazol-4-y1]methylene-1,3-thiazolidine-2,4-dione (**4**)*

A mixture of compound **3** (0.546 g, 2 mmol) and hydrazine hydrate (0.12 mL, 2 mmol) in sodium ethoxide (prepared from 0.26 g sodium in 40 mL ethanol) was refluxed for 4 h. After cooling, the reaction mixture was poured onto ice/water and neutralized with dilute HCl. The precipitated solid was filtered, washed with water and crystallized from ethanol to give **4** as yellow crystals, yield (0.40 g, 70%), mp 278 ºC. UV λ_{max}/nm: 270, 340. IR (KBr) ν_{max}/cm^{-1}: 3269 (OH, NH), 1733 (C=O), 1698 (C=O$_{thiazolidinedione}$), 1602 (C=N). ^{1}H NMR (DMSO-d_6) δ 6.94-7.03 (m, 2H, Ar-H), 7.23-7.35 (m, 2H, Ar-H), 7.49 (s, 1H, H$_{enone}$), 7.91 (s, 1H, H-3$_{pyrazole}$), 10.06 (br, 1H, OH exchangeable with D_2O), 12.35 (br, 1H, NH exchangeable with D_2O), 13.49 (br, 1H, NH exchangeable with D_2O). Anal.Calc. for $C_{13}H_9N_3O_3S$ (287.30); C, 54.35; H, 3.16; N, 14.63; S, 11.16%. Found: C, 54.51; H, 3.38; N, 14.33; S, 11.35%.

*5-{[1-Acetyl-5-(2-hydroxyphenyl)pyrazol-4-yl]methylene}-1,3-thaizolidine-2,4-dione (**5**)*

A mixture of compound **3** (0.546 g, 2 mmol) and hydrazine hydrate (0.12 mL, 2 mmol) was refluxed in glacial acetic acid (20 mL) for 6 h. The solid obtained after cooling was filtered and recrystallized from dioxane to give **5** as yellow crystals, yield (0.68 g, 88%), mp 282 °C. UV λ_{max}/nm: 260, 335. IR (KBr) ν_{max}/cm^{-1}: 3320 (OH), 3199 (NH), 1754 (C=O$_{acetyl}$), 1691 (2C=O$_{thiazolidinedione}$), 1615 (C=N). ^{1}H NMR (DMSO-d_6) δ 1.88 (s, 3H, CH$_3$), 6.91-7.03 (m, 2H, Ar-H), 7.20-7.35 (m, 2H, Ar-H), 7.50 (s, 1H, H-3$_{pyrazole}$), 7.87 (s, 1H, H$_{enone}$), 9.95 (br, 1H, OH exchangeable with D_2O), 12.31 (br, 1H, NH exchangeable with D_2O). Anal. Calc. for $C_{15}H_{11}N_3O_4S$ (329.34): C, 54.71; H, 3.37; N, 12.76; S, 9.74%. Found: C, 54.89; H, 3.47; N, 12.55; S, 9.75%.

*5-{[5-(2-Hydroxyphenyl)-1-phenylpyrazol-4-y1]methylene}-1,3-thiazolidine-2,4-dione (**6**)*

A mixture of compound **3** (0.546 g, 2 mmol) and phenyl hydrazine (0.41 mL, 2 mmol), in DMF (10 mL) containing few drops of piperidine, was refluxed for 4 h. After cooling, the precipitate so formed was filtered and recrystallized from dioxane to give **6** as pale yellow crystals, yield (0.46 g, 63%), mp 179 °C. UV λ_{max}/nm: 255, 330. IR (KBr) ν_{max}/cm^{-1}: 3250 (OH), 3185 (NH), 3051 (CH$_{arom.}$), 1695 (C=O$_{thiazolidinedione}$), 1598 (C=N). ^{1}H NMR (DMSO-d_6) δ 6.70-7.47 (m, 9H, Ar-H), 7.71 (s, 1H, H$_{enone}$), 8.06 (s, 1H, H-3$_{pyrazole}$), 9.92 (br, 1H, OH exchangeable with D_2O), 12.21 (br, 1H, NH exchangeable with D_2O). Anal. Calc. for $C_{19}H_{13}N_3O_3S$ (363.40); C, 62.80; H, 3.61; N, 11.56; S, 8.82%. Found: C, 62.67; H, 3.50; N, 11.57; S, 8.74%.

*5-{[5-(2-Hydroxyphenyl)isoxazol-4-yl]methylene}-1,3-thiazolidine-2,4-dione (**7**)*

A mixture of compound **3** (0.546 g, 2 mmol) and hydroxylamine hydrochloride (0.14 g, 2 mmol) in sodium ethoxide (prepared from 0.26 g sodium in 40 mL ethanol) was refluxed 4 h. After cooling, the reaction mixture was poured onto ice/water and neutralized with dilute HCl. The formed solid was filtered, washed with water and crystallized from benzene to give **7** as yellowish-white crystals, yield (0.31 g, 54%), mp 191°C. UV λ_{max}/nm: 270, 345. IR (KBr) ν_{max}/cm^{-1}: 3425 (OH), 3229 (NH), 3078 (CH$_{arom.}$), 1708 (C=O$_{thiazolodinedione}$), 1609 (C=N). ^{1}H NMR (DMSO-d_6) δ 6.91-7.03 (m, 2H, Ar-H), 7.20-7.34 (m, 2H, Ar-H), 7.48 (s, 1H, H$_{enone}$), 7.87 (s, 1H, H-3$_{isoxazole}$), 10.03 (br, 1H, OH exchangeable with D_2O), 12.32 (br, 1H, NH exchangeable with D_2O). Anal. Calc. for $C_{13}H_8N_2O_4S$ (288.28): C, 54.16; H, 2.80; N, 9.72; S, 11.12%. Found: C, 54.01; H, 2.74; N, 9.54; S, 11.08%.

*5-{[4-(2-Hydroxyphenyl)-2-thioxo-1,2-dihydropyrimidin-5-y1]methylene}-1,3-thiazolidine-2,4-dione (**8**)*

A mixture of **3** (0.546 g, 2 mmol) and thiourea (0.152 g, 2 mmol) in ethanolic KOH (5%, 30 mL) was refluxed for 6 h. After cooling the reaction mixture was poured onto ice/water and neutralized with dilute HCl. The formed precipitate was filtered, washed with water and crystallized from ethanol to give **8** as yellow crystals (0.43 g, 65%), mp 140 °C. IR (KBr) ν_{max}/cm^{-1}: 3375 (OH), 3325 (NH), 3244 (NH), 1705 (C=O$_{thiazolidinedione}$), 1612 (C=N), 1199 (C=S). ^{1}H NMR (DMSO-d_6) δ 6.92-7.00 (m, 2H, Ar-H), 7.46-7.48 (m, 2H, Ar-H), 7.88 (s, 1H, H$_{enone}$), 8.41 (s, 1H, H-4$_{pyrimidine}$), 10.44 (br, 1H, OH exchangeable with D_2O), 12.31 (br, 2NH exchangeable with D_2O). Anal. Calc. for $C_{14}H_9N_3O_3S_2$ (331.37): C, 50.75; H, 2.74; N, 12.68; S, 19.35%. Found: C, 50.54; H, 2.61; N, 12.60; S, 19.14%.

*5-{[2-Amino-4-(2-hydroxyphenyl)pyrimidin-5-yl]methylene}-1-3-thiazolidin-2,4-dione (**9**)*

A mixture of compound **3** (0.546 g, 2 mmol) and guanidine hydrochloride (0.168 g, 2 mmol) in ethanolic KOH (5%, 30 mL) was refluxed for 6 h. After cooling, the reaction mixture was poured onto ice/water and neutralized with dilute HCl. The solid obtained was filtered, washed with water and crystallized from dioxane to give **9** as pale brown crystals, yield (0.39 g, 62%), mp 132 °C.

UV λ_{max}/nm: 210, 320, 440. IR (KBr) ν_{max}/cm^{-1}: 3400, 3250 (OH, NH, NH_2), 3088 ($CH_{arom.}$), 1692 ($C=O_{thiazolidinedione}$), 1610 (C=N). ^{1}H NMR (DMSO-d_6) δ 3.37 (br, 2H, NH_2 exchangeable with D_2O), 6.92-7.00 (m, 2H, Ar-H), 7.42-7.48 (m, 2H, Ar-H), 7.88 (s, 1H, H_{enone}), 8.40 (s, 1H, H-$4_{pyrimidine}$), 10.44 (br, 1H, OH exchangeable with D_2O). Anal. Calc. for $C_{14}H_{10}N_4O_3S$ (314.25): C, 53.20; H, 3.20; N, 17.82; S, 10.20%. Found: C, 53.00; H, 3.49; N, 17.74; S, 10.10%.

*5-{[2,4-Dioxo-1,3-thiazolidin-5-ylidene]methyl}-6-[(2-hydroxyphenyl)pyrimidin-2(1H)-yl]cyanamide (**10**)*

A mixture of compound **3** (0.546 g, 2 mmol) and cyanoguanidine (0.168 g, 2 mmol) in ethanolic KOH (5%, 30 mL) was refluxed for 6 h. After cooling, the reaction mixture was poured onto ice/water and neutralized with dilute HCl. The resulting precipitate was filtered and crystallized from ethanol to give **10** as yellow crystals, yield (0.32 g, 47%), mp 168 °C. UV λ_{max}/nm: 260, 335, 460. IR (KBr) ν_{max}/cm^{-1}: 3347 (OH), 3158 (2 NH), 3048 ($CH_{arom.}$), 2190 (C≡N), 1696 ($C=O_{thiazolidinedione}$), 1607 (C=N). ^{1}H NMR (DMSO-d_6) δ 6.85-7.09 (m, 2H, Ar-H), 7.16-7.54 (m, 2H, Ar-H), 7.88 (s, 1H, H_{enone}), 8.13 (s, 1H, H-$4_{pyrimidine}$), 10.45 (br, 1H, OH exchangeable with D_2O), 11.42 (br, 1H, NH exchangeable with D_2O), 12.15 (br, 1H, NH exchangeable with D_2O). Anal. Calc. for $C_{15}H_9N_5O_3S$ (339.33): C, 53.09; H, 2.67; N, 20.64, S; 9.45%. Found: C, 53.20; H, 2.70; N, 20.32, S; 9.50%.

*2-{(4-Methoxyphenyl)-7-[2,4-dioxo-1,3-thiazolidin-5-ylidine]methyl}-6-(2-hydroxyphenyl)-4-oxo-4H-pyrimido[1,2-a]pyrimidine-3-carbonitrile (**12**)*

A mixture of compound **3** (0.546 g, 2 mmol) and 2-amino-4-(4-methoxyphenyl-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**11**) (0.484 g, 2 mmol) in ethanolic KOH (5%, 30 mL) was refluxed for 4 h. After cooling the reaction mixture was poured onto ice/water and neutralized with dilute HCl. The precipitated so formed was filtered, washed with water and crystallized from DMF to give **12** as orange red crystals, yield (0.67 g, 67%), mp 208 °C. IR (KBr) ν_{max}/cm^{-1}: 3410 (OH), 3337 (NH), 2925, 2890 (CH_3), 2214 (C≡N), 1684 ($C=O_{thiazolidinedione}$), 1650 ($C=O_{pyrimidine}$), 1610 (C=N). ^{1}H NMR (DMSO-d_6, δ): 3.82 (s, 3H, OCH_3), 6.89-7.32 (m, 4H, Ar-H), 7.43 (d, 2H, *J* 7.5 Hz, Ar-H), 7.83 (d, 2H, *J* 8.4 Hz, Ar-H), 7.88 (s, 1H, H_{enone}), 8.40 (s, 1H, H-$4_{pyrimidine}$), 10.42 (br, 1H, OH exchangeable with D_2O), 12.30 (br, 1H, NH exchangeable with D_2O). MS (*m/z*, %): 497 (1), 455 (4), 437 (24), 394 (6), 363 (8), 302 (4), 297 (7), 185 (13), 171 (9), 116 (7), 104 (37), 93 (8), 77 (20), 65 (9), 55 (100). Anal. Calc. for $C_{25}H_{15}N_5O_5S$ (497.49): C, 60.36; H, 3.04; N, 14.08; S, 6.45%. Found: C, 60.00; H, 3.25; N, 13.91; S, 6.80%.

*5-{[2-(2-Hydroxyphenyl)-1H-1,5-benzodiazepin-3-yl]methylene}-1,3-thiazolidine-2,4-dione (**15**)*

A mixture of compound **3** (0.546 g, 2 mmol) and *o*-phenylenediamine (**13**) (0.216 g, 2 mmol) in ethanolic KOH (5%, 30 mL) was heated under reflux for 6 h. After cooling the reaction mixture was poured onto ice/water and neutralized with dilute HCl. The resulting precipitate was filtered, washed with water and crystallized from DMF/H_2O to give **15** as orange crystals, yield (0.48 g, 66%), mp 128 °C. IR (KBr) ν_{max}/cm^{-1}: 3400 (OH), 3200 (NH), 3056 ($CH_{arom.}$), 1695 ($C=O_{thiazolidinedione.}$), 1615 (C=N). ^{1}H NMR (DMSO-d_6) δ 6.92-7.06 (m, 3H, Ar-H), 7.25-7.59 (m, 5H, Ar-H), 7.88 (s, 1H, H_{enone}), 8.21 (s, 1H, $NH_{diazepine}$ exchangeable with D_2O), 8.40 (s, 1H, H-$4_{diazepine}$), 10.44 (s, 1H, OH exchangeable with D_2O), 12.58 (br, 1H, NH exchangeable with D_2O). Anal. Calc. for $C_{19}H_{13}N_3O_3S$ (363.40); C, 62.80; H, 3.61; N, 11.56; S, 8.83%. Found: C, 62.62; H, 3.38; N, 11.19; S, 8.58%.

*9-(4-Chlorophenyl-3[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-4-(2-hydroxy- phenyl)-7-oxo-5,7-dihydropyrido[1,2-b][1,2,4]triazepine-8,10-dicarbonitrile (**16**)*

A mixture of compound **3** (0.546 g, 2 mmol) and 4-(chlorophenyl)-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**14**) (0.571 g, 2 mmol) in ethanolic KOH (5%, 30 mL) was heated under reflux for 4 h. After cooling, the reaction mixture was poured onto ice/water and neutralized with dilute HCl. The formed precipitate was filtered, washed with water and crystallized from ethanol to give **16** as pale brown crystals, yield (0.57 g, 53%), mp 189 °C. IR (KBr) ν_{max}/cm^{-1}: 3350 (OH), 3270 (NH), 3202 (NH), 2216 (2C≡N), 1690 ($C=O_{thiazolidinedione}$), 1630 ($C=O_{pyridine}$), 1603 (C=N). ^{1}H NMR (DMSO-d_6) δ 6.97-7.60 (m, 8H, Ar-H), 7.90 (s, 1H, H_{enone}), 8.21 (s, 1H, H-$5_{triazepine}$), 8.56 (s, 1H, $NH_{triazepine}$ exchangeable with D_2O), 10.49 (br, 1H, OH exchangeable with D_2O), 12.15 (br, 1H, NH exchangeable with D_2O). MS (*m/z*, %): 540 (2), 447 (2), 321 (3), 282 (3), 171 (7), 121 (100), 93 (21), 78 (47), 65 (44). Anal. Calc. for $C_{26}H_{13}N_6O_4SC1$ (540.95): C, 57.73; H, 2.42; N, 15.54; S, 5.93. Found: C, 57.79; H, 2.49; N, 15.37; S, 5.81%.

*5-{[1-(3-Phenyl-8-(2-hydroxyphenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepin-7-yl] methylidene}-1,3-thiazolidine-2,4-dione (**19**)*

A mixture of compound **3** (0.546 g, 2 mmol) and 4-amino-5-phenyl-2,4-dihydro-[1,2,4]triazole-3-thione (**17**) (0.364 g, 2 mmol) in ethanolic KOH (5%, 30 mL) was refluxed for 4 h. After cooling, the reaction mixture was poured onto ice/water and neutralized with dilute

HCl. The formed precipitate was filtered, washed with water and crystallized from dioxane to give **19** as yellow crystals, yield (0.64 g, 72%), mp 223 °C. UV λ_{max}/nm: 265, 345. IR (KBr) ν_{max}/cm^{-1}: 3337 (OH), 3186 (NH), 3061 ($CH_{arom.}$), 1678 ($2C{=}O_{thiazolidinedione}$), 1593 (C=N). ^{1}H NMR (DMSO-d_6) δ 6.97-7.21 (m, 8H, Ar-H), 7.48-7.78 (m, 2H, 1Ar-H and H-$5_{thiadiazepine}$), 7.88 (s, 1H, H_{enone}), 9.98 (br, 1H, OH exchangeable with D_2O), 12.14 (br, 1H, NH exchangeable with D_2O). Anal. Calc. for $C_{21}H_{13}N_5O_3S_2$ (447.50): C, 56.37; H, 2.93; N, 15.65; S, 14.33%. Found: C, 56.32; H, 2.84; N, 15.48; S, 14.00%.

*5-[9-(2-Hydroxyphenyl)-3-methyl-2-oxo-2H-[1,2,4] triazino[3,2-b][1,3,4] thiadiazepin-8-yl]methylene]-1.3-thiazolidine-2,4-dione (**20**)*

A mixture of compound **3** (0.546 g, 2 mmol) and 4-amino-6-methyl-3-mercapto-1,2,4-triazin-5-one (**18**) (0.32 g, 2 mmol) in ethanolic KOH (5%, 30 mL) was refluxed for 6 h. After cooling the reaction mixture was poured onto ice/water and neutralized with dilute HCl. The formed precipitate was filtered and crystallized from ethanol to give **20** as orange crystals, yield (0.43 g, 52%), mp 152 °C. UV λ_{max}/nm: 270, 360. IR (KBr) ν_{max}/cm^{-1}: 3191 (OH, NH), 2925, 2880 (CH_3), 1697 (3C=O), 1615 (C=N). ^{1}H NMR (DMSO-d_6, δ): 2.07 (s, 3H, CH_3), 6.97-7.60 (m, 4H, Ar-H), 7.89 (s, 1H, H_{enone}), 8.19 (s, 1H, H-$5_{thiadiazepine}$), 9.98 (br, 1H, OH exchangeable with D_2O), 12.38 (br, 1H, NH exchangeable with D_2O). Anal. Calc. for $C_{17}H_{11}N_5O_4S_2$ (413.44): C, 49.39; H, 2.68; N, 16.94; S, 15.51%. Found: C, 49.20; H, 2.60; N, 16.81; S, 15.28%.

*5-[(2,4-Dioxo(1,3-thiazolidin-5-ylidene))methyl]-6-(2-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**22**)*

A mixture of compound **3** (0.546 g, 2 mmol) and cyanoacetamide or malononitrile (2 mmol) in sodium ethoxide (0.26 g of sodium in 40 mL ethanol) was refluxed for 2 h. After cooling the reaction mixture was poured onto ice/water and neutralized with dilute HCl. The solid obtained was filtrated and crystallized from dioxane to give **22** as yellow crystals, yield (0.43 g, 63%), mp 212 ºC. IR (KBr) ν_{max}/cm^{-1}: 3405 (OH), 3332, 3208 (2NH), 2202 (C≡N), 1710, 1699 ($2C{=}O_{thiazolidinedione}$ and $C{=}O_{cyclic\ amide}$). ^{1}H NMR (DMSO-d_6, δ): 6.98-7.46 (m, 3H, Ar–H), 7.89 (s, 1H, H_{enone}), 8.14 (s, 1H, H-$4_{pyridine}$), 8.43 (d, 1H, Ar–H), 10.50 (br, 1H, OH exchangeable with D_2O), 12.60 (br, 2H, exchangeable with D_2O, 2NH). MS (*m/z*, %: 339 (4), 313 (2), 262 (8), 247 (25), 215 (58), 211 (3), 203 (24), 185 (6), 171 (11), 147 (29), 121 (100), 93 (33), 78 (27), 65 (56). Anal. Calc. for $C_{16}H_9N_3O_4S$ (339.33); C, 56.63; H, 2.67; N, 12.38; S, 9.45%. Found: C, 56.45; H, 2.64; N, 12.27; S, 9.37%.

*5-{6-(2-Hydroxyphenyl)-3-oxo-2-phenyl-2,3-dihydropyrano[2,3-c]pyrazolin-5-y1] methylidene}-1,3-thiazolidine-2,4-dione (**23**)*

A mixture of compound **3** (0.546 g, 2 mmol) and 1-phenylpyrazolidine-3,5-dione (0.352 g, 2 mmol) in sodium ethoxide (0.26 g sodium in 40 mL ethanol) was heated under reflux for 4 h. After cooling, the reaction mixture was poured onto ice/water and neutralized with dilute HCl. The formed precipitate was filtered, washed with water and crystallized from ethanol to give **23** as yellow crystals, yield (0.45 g, 55%), mp 122 ºC. IR (KBr) ν_{max}/cm^{-1}: 3380 (OH), 3170 (NH), 3055 ($CH_{arom.}$), 1698 (2 $C{=}O_{thiazolidinedione}$ and $C{=}O_{pyrazole}$), 1598 (C=N). ^{1}H NMR (DMSO-d_6) δ 6.97-7.48 (m, 8H, Ar–H), 7.89 (s, 1H, H_{enone}), 8.15 (s, 1H, H–4_{pyran}), 8.42 (d, 1H, Ar–H), 10.48 (br, 1H, OH exchangeable with D_2O), 12.21 (br, 1H, NH exchangeable with D_2O). MS (*m/z*, %): 431 (2), 403 (2), 354 (21), 338 (8), 321 (3), 293 (7), 264 (16), 202 (14), 147 (47), 121 (100), 93 (35), 77 (61), 65 (90). Anal. Calc. for $C_{22}H_{13}N_3O_5S$ (431.43): C, 61.25; H, 3.04; N, 9.74; S, 7.43%. Found: C, 61.12; H, 3.00; N, 9.58; S, 7.46%.

*5-[2-(2-Hydroxyphenyl)-7,7-dimethyl-5-oxo-6,7-dihydro-5H-chromen-3-y1] methylidene]-1,3-thiazolidine-2,4-dione (**24**)*

A mixture of compound **3** (0.546 g, 2 mmol) and 5,5-dimethyl-cyclohexane-1,3-dione (0.28 g, 2 mmol) in sodium ethoxide (0.26 g of sodium in 40 mL ethanol) was refluxed for 4 h. After cooling, the reaction mixture was poured onto ice/water and neutralized with dilute HCl. The formed product was filtered, air dried and recrystallized from DMF to give **24** as yellow crystals, yield (0.40 g, 51%), mp 112 ºC. IR (KBr) ν_{max}/cm^{-1}: 3420 (OH), 3161 (NH), 3045 ($CH_{arom.}$), 2924, 2910 (CH_2, CH_3), 1697 ($2C{=}O_{thiazolidinedione}$), 1620 (C=O). ^{1}H NMR (DMSO-d_6) δ 0.80 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 2.87 (s, 2H, CH_2), 5.18 (s, 1H, H-1), 6.97-7.78 (m, 4H, Ar–H), 7.88 (s, 1H, H_{enone}), 8.42 (s,1H, H-4_{pyran}), 10.52 (br, 1H, OH exchangeable with D_2O), 12.33 (br, 1H, NH exchangeable with D_2O). Anal. Calc. for $C_{21}H_{17}NO_5S$ (395.44): C, 63.79; H, 4.33; N, 3.54; S, 8.11%. Found: C, 63.70; H, 4.00; N, 3.42; S, 8.08%.

*5-{[7-(2-Hydroxyphenyl)-2,4-dioxo-3-hydropyrano[2,3-d] pyrimidin-6-y1] methylene]-1,3-thiazolidine-2,4-dione (**25**)*

A mixture of compound **3** (0.546 g, 2 mmol) and barbituric acid (0.256 g, 2 mmol) in sodium ethoxide (0.26 g sodium in 40 mL ethanol) was refluxed for 4 h. After cooling, the reaction mixture was poured onto ice/water and neutralized with dilute HCl. The resulting precipitate was filtered, washed with water and crystallized from DMF to give **25** as pale red crystals, yield (0.46 g, 60%), mp 147 ºC.

IR (KBr) ν_{max}/cm^{-1}: 3425 (OH), 3211 (2NH), 3050 ($CH_{arom.}$), 1700 (br, 4 C=O), 1617 (C=N). ^{1}H NMR (DMSO-d_6) δ 6.94-7.53 (m, 4H, Ar–H), 7.86 (s, 1H, H_{enone}), 8.40 (s, 1H, H-4_{pyran}), 10.42 (br, 1H, OH exchangeable with D_2O), 11.09 (bs, 1H, NH exchangeable with D_2O), 12.38 (br, 1H, NH exchangeable with D_2O). Anal. Calc. for $C_{17}H_9N_3O_6S$ (383.34): C, 53.27; H, 2.37; N, 10.96; S, 8.36%. Found: C, 53.19; H, 2.33; N, 10.76; S, 8.25%.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as a PDF file.

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Supplementary Information

A New Approach for the Synthesis of Bioactive Heteroaryl Thiazolidine-2,4-diones

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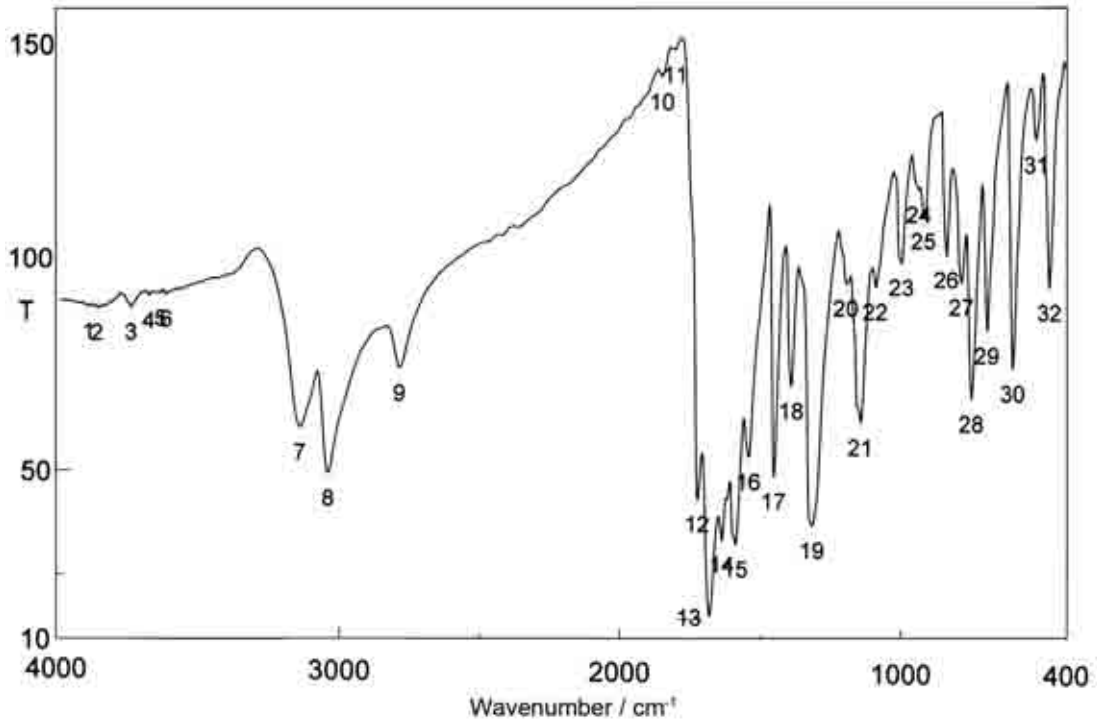

Figure S1. IR spectrum of compound **3**.

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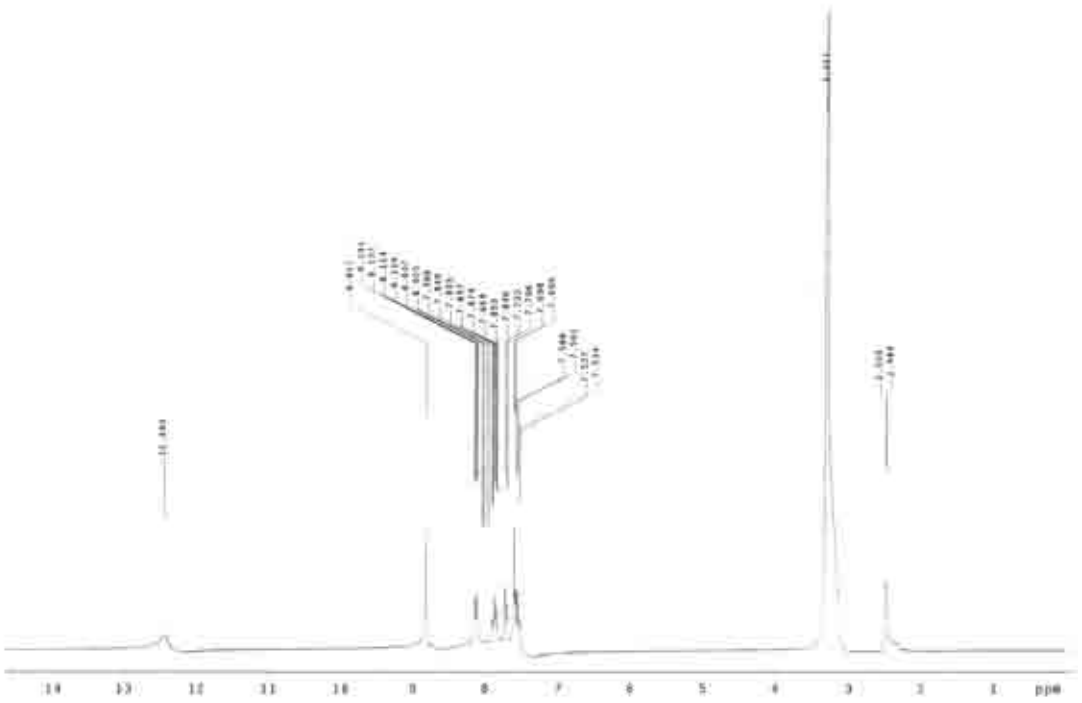

Figure S2. ^{1}H NMR spectrum of compound **3**.

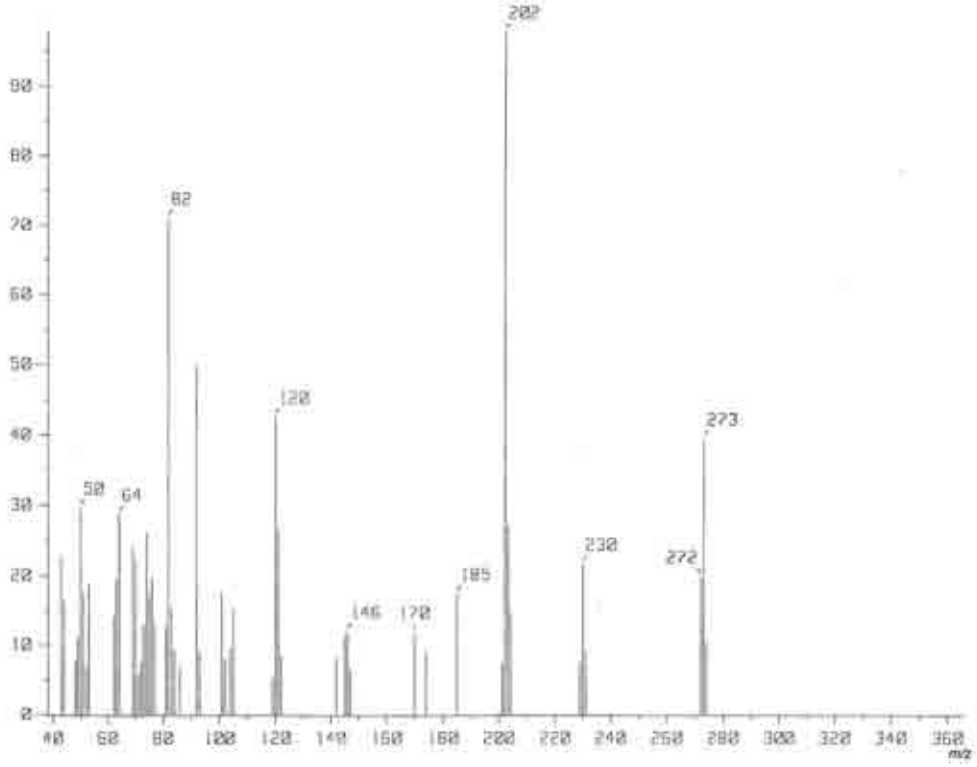

Figure S3. Mass spectrum of compound **3**.

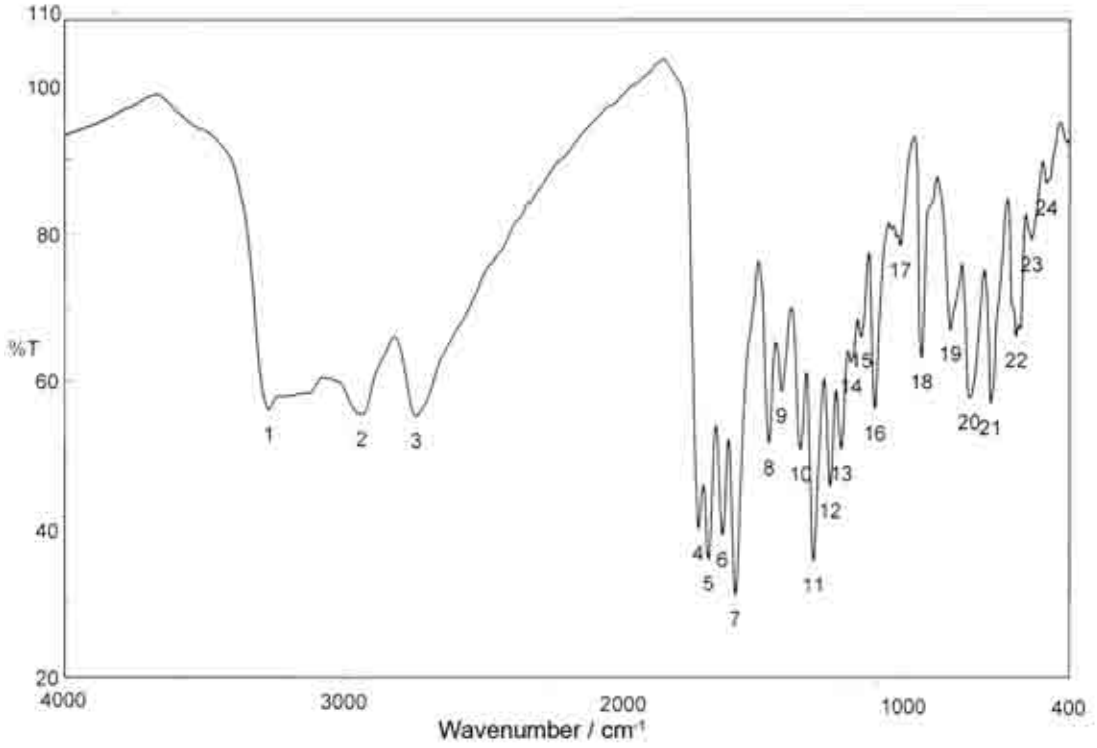

Figure S4. IR spectrum of compound **4**.

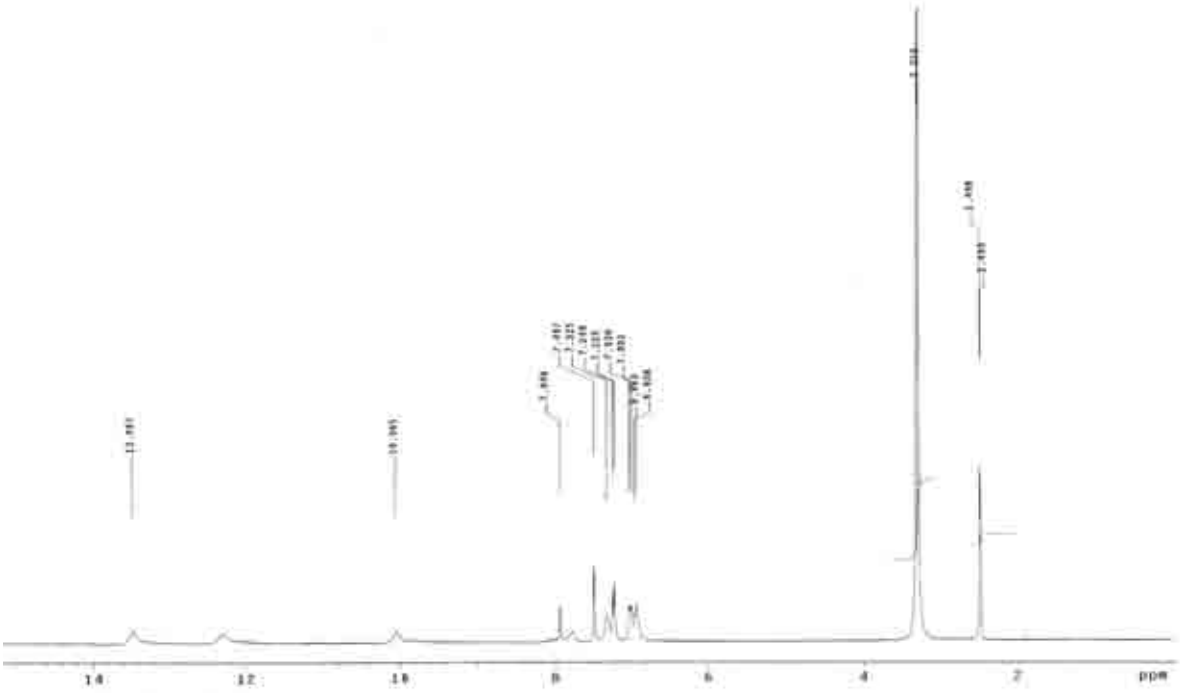

Figure S5. ^{1}H NMR spectrum of compound **4**.

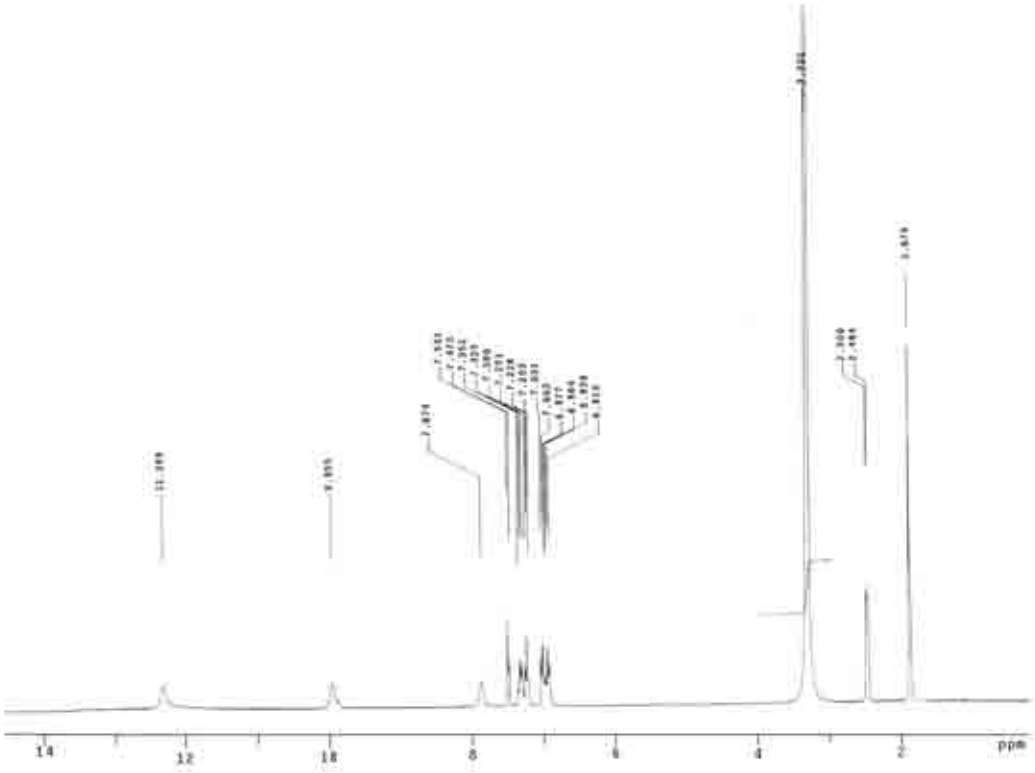

Figure S6. ^{1}H NMR spectrum of compound **5**.

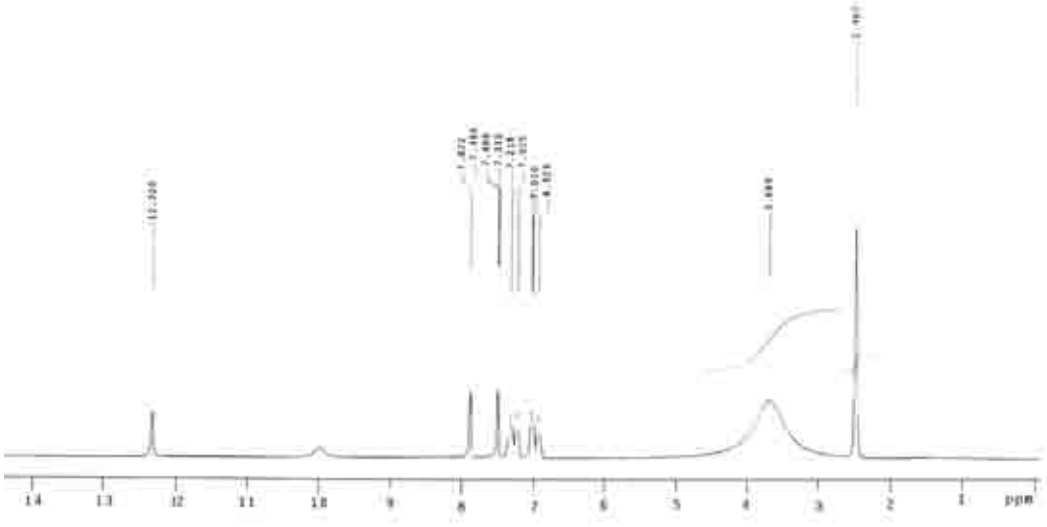

Figure S7. ^{1}H NMR spectrum of compound **7**.

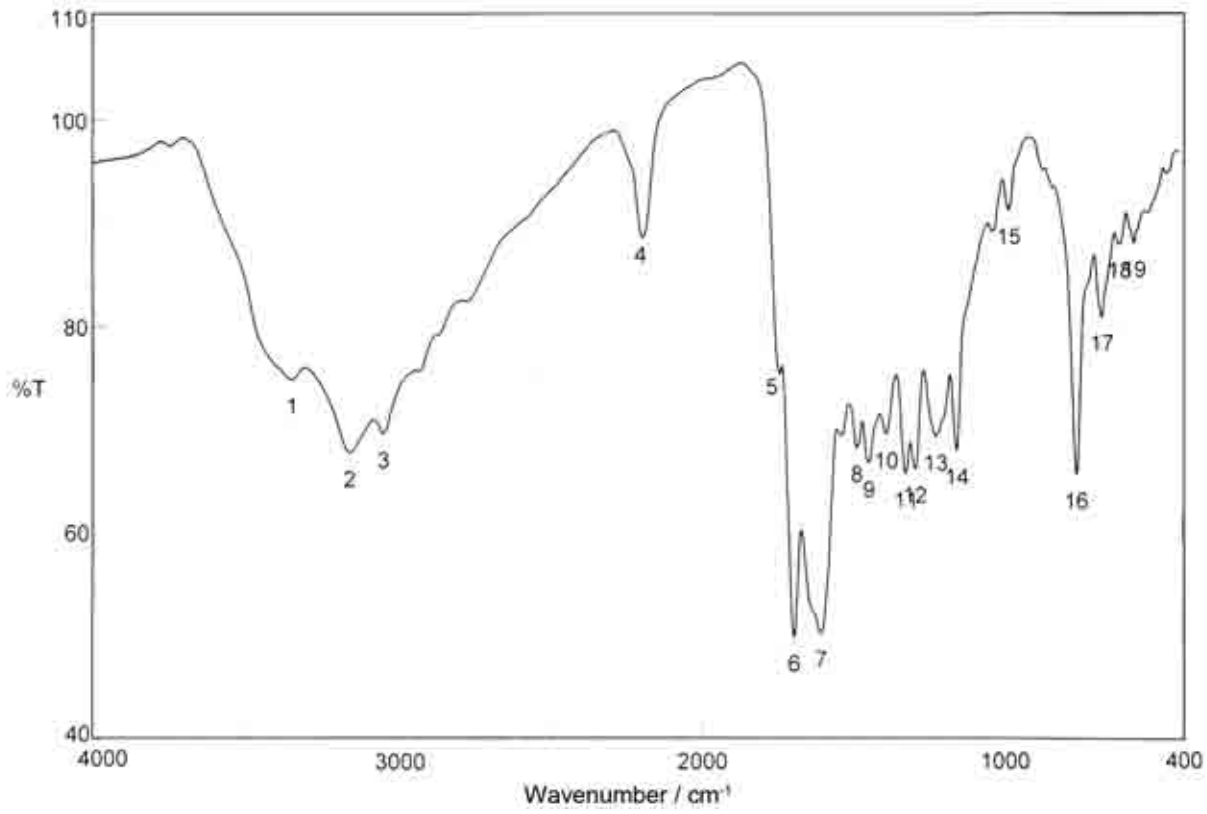

Figure S8. IR spectrum of compound **10**.

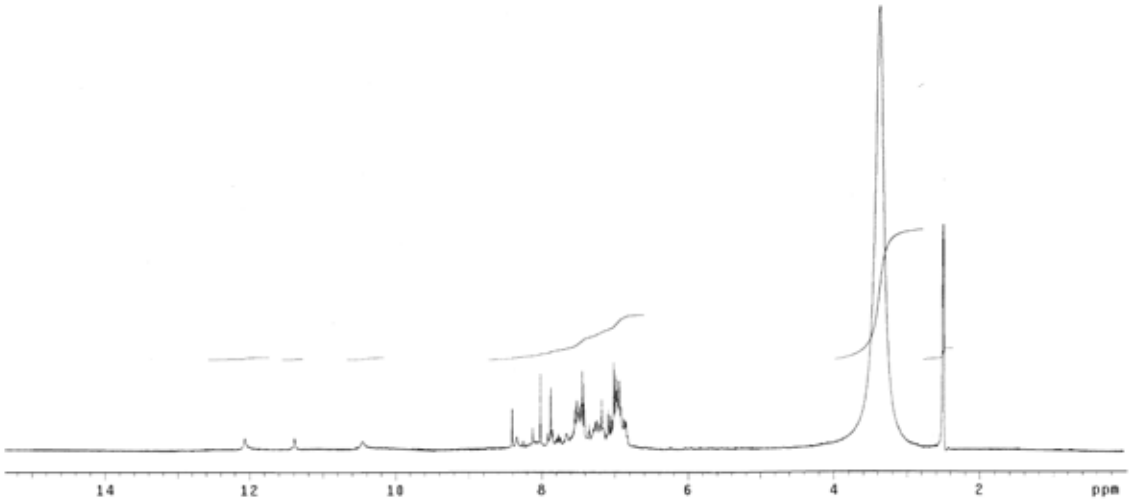

Figure S9. ^{1}H NMR spectrum of compound **10**.

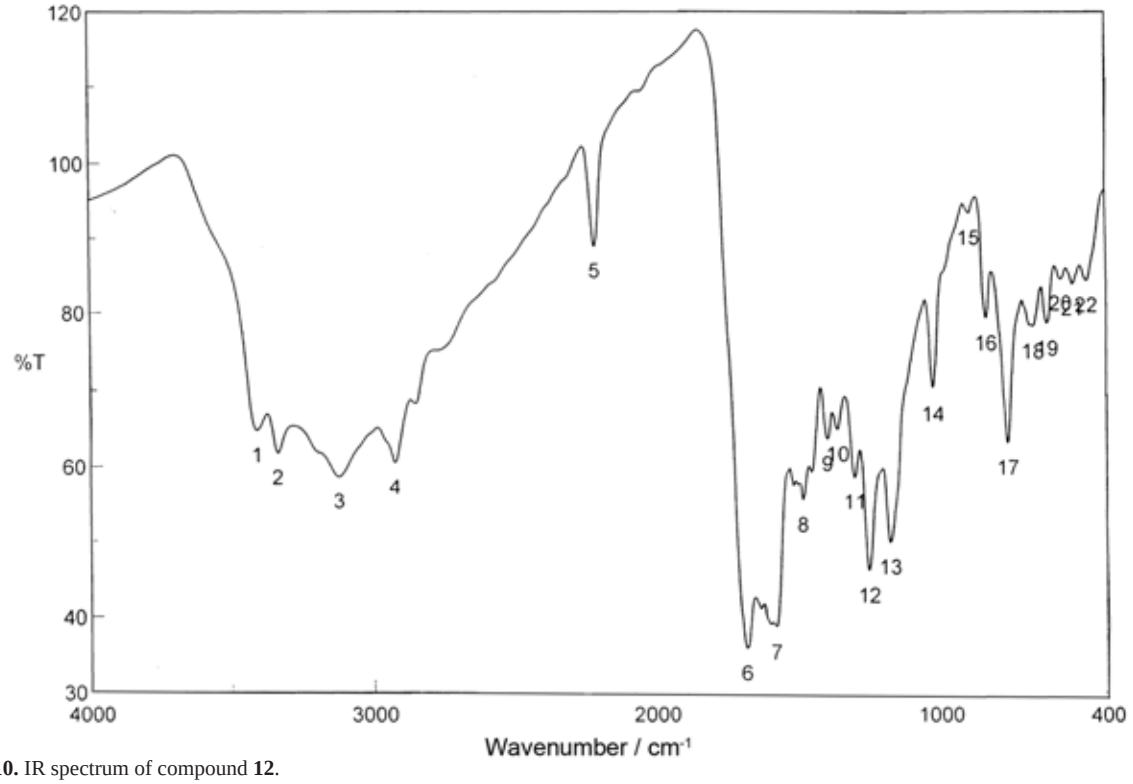

Figure S10. IR spectrum of compound **12**.

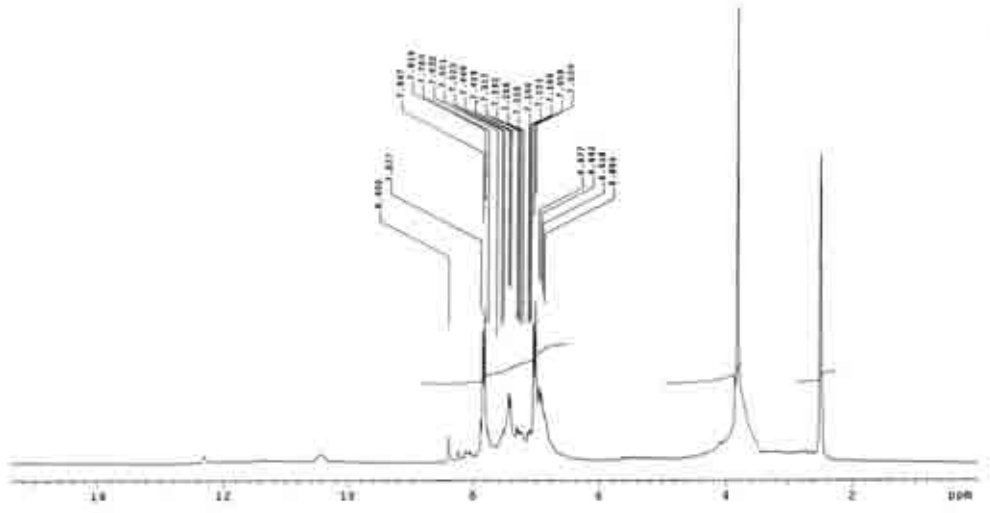

Figure S11. ^{1}H NMR spectrum of compound **12**.

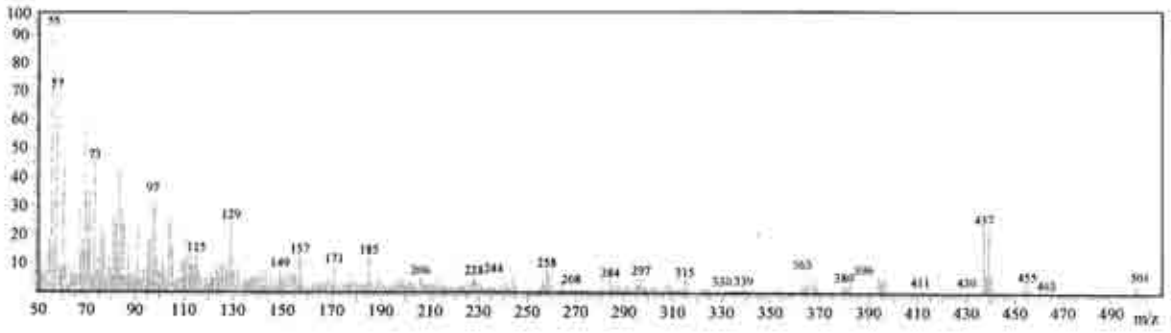

Figure S12. Mass spectrum of compound **12**.

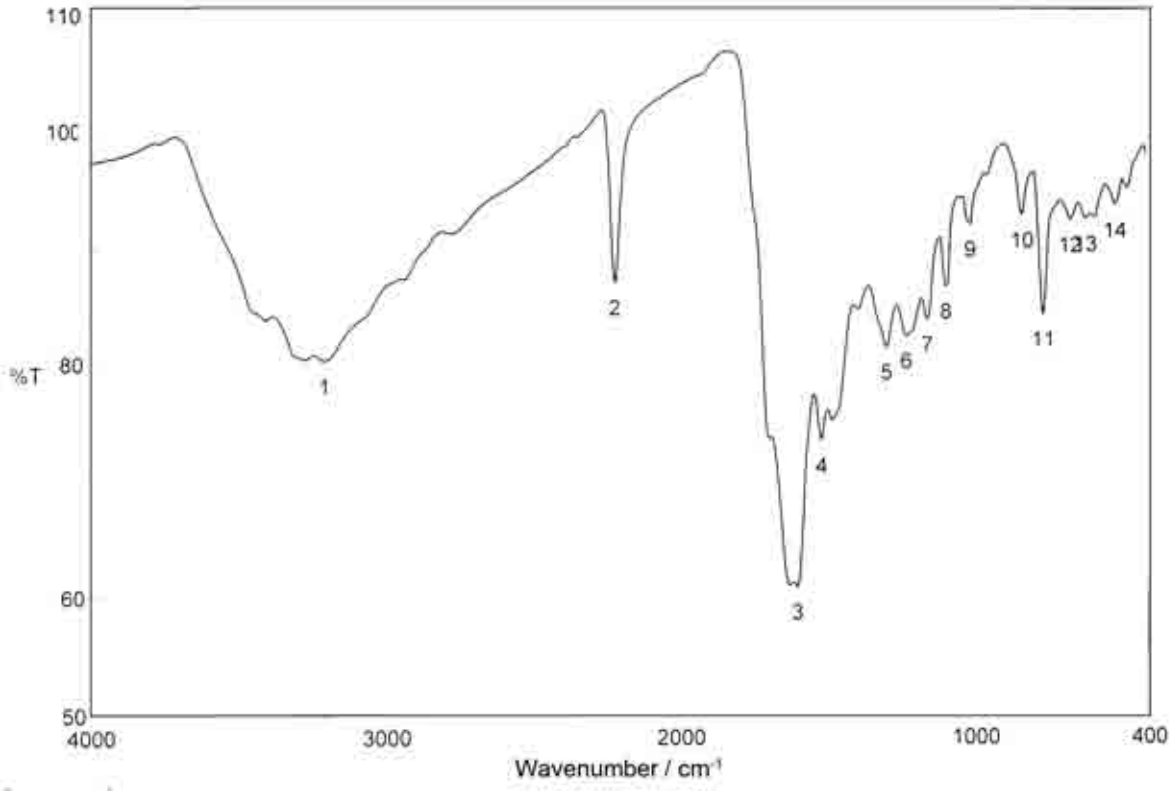

Figure S13. IR spectrum of compound **16**.

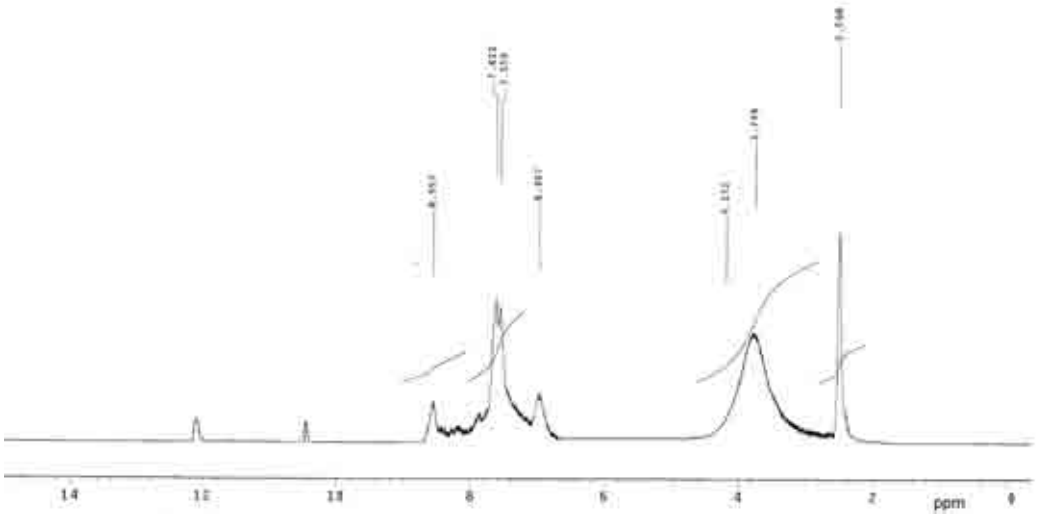

Figure S14. ^{1}H NMR spectrum of compound **16**.

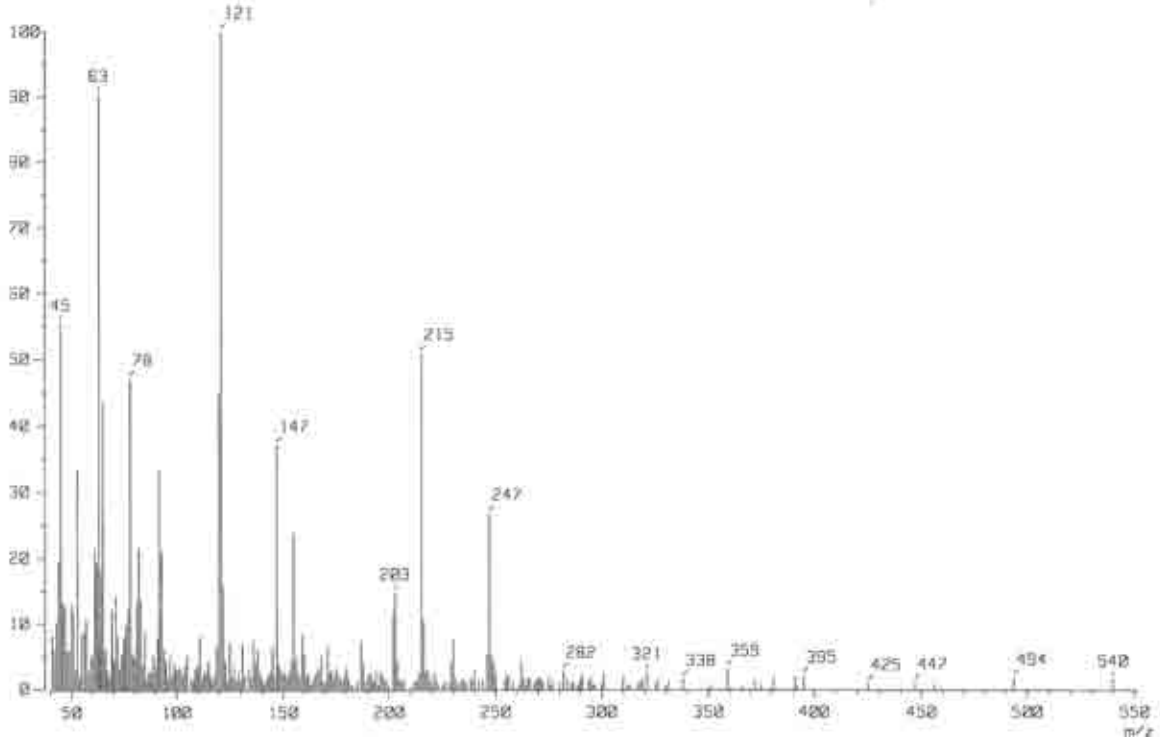

Figure S15. Mass spectrum of compound **16**.

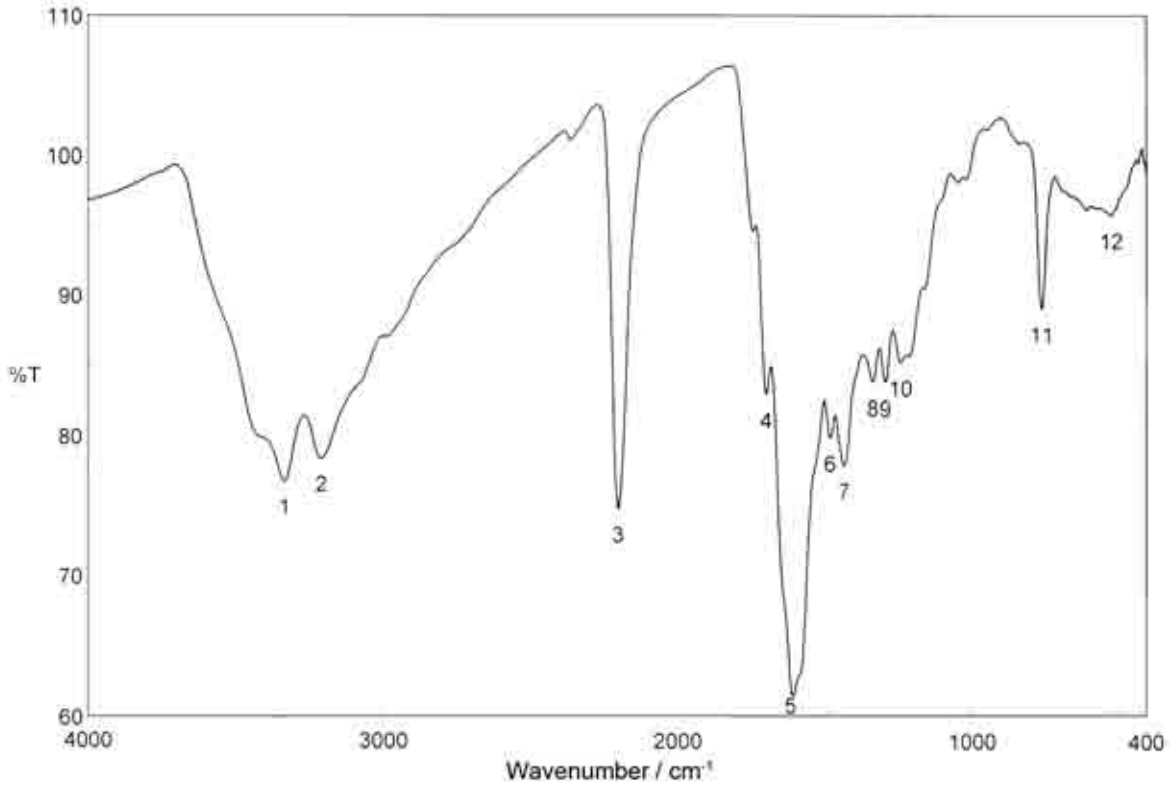

Figure S16. IR spectrum of compound **22**.

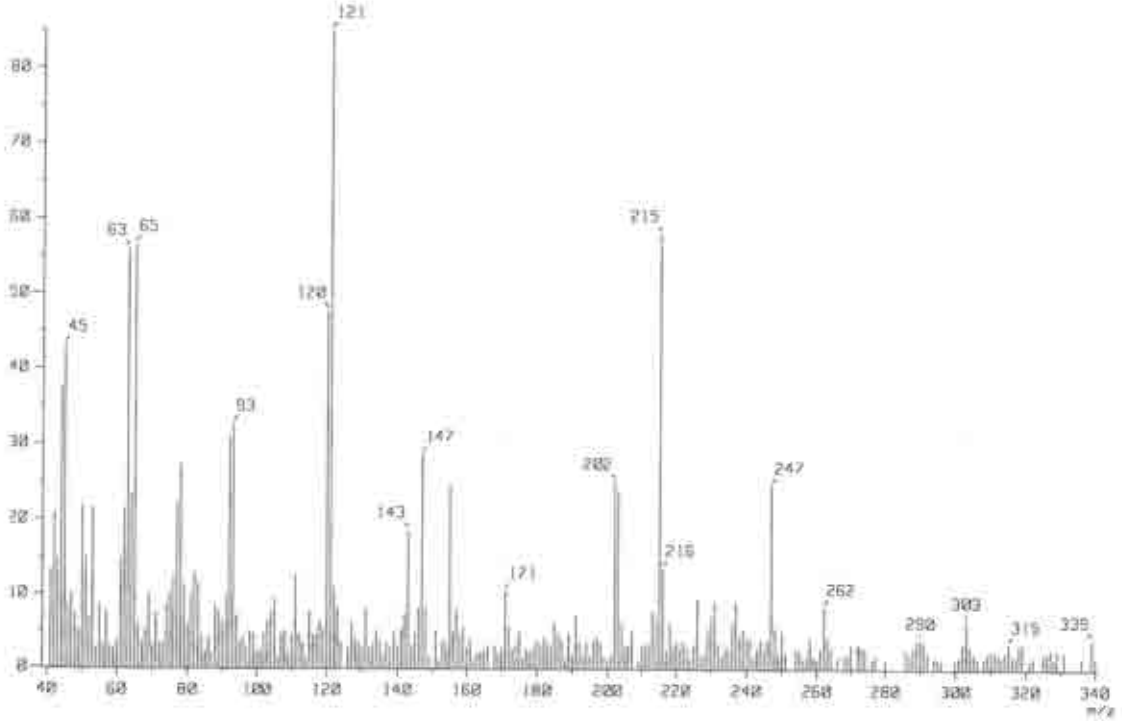

Figure S17. Mass spectrum of compound **22**.