New Approaches for the Synthesis of Thiazoles and Their Fused Derivatives with Antimicrobial Activities

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The 2-ethoxy carbonyl methylene thiazol-4-one (**3**) reacts with acetophenone (**4**) to give the ethyl 2-(4-oxo-4,5-dihydro-thiazol-2-yl)-3-phenyl-2-butenoate (**5**). The reactivity of the latter product towards aromatic aldehydes **6a-d**, cyanomethylene reagents **9a**,**b**, aromatic aldehydes **13a-d**, phenylisothiocyanate (**16**), elemental sulfur and aromatic amines (**20a-c**) was studied to give arylidene, pyridine, thiophene and anilide derivatives. Some of the newly synthesized derivatives were used to synthesize fused derivatives. The antimicrobial activities of the newly synthesized products were tested in vitro for antimicrobial activity against two bacterial isolates, one saprophytic (Escherichia coli) and the other parasitic (Xanthomonas citri) and for antifungal activity against one saprophytic (Aspergillus fumigatus) and two phytopathogenics (Rhizoctonia solani and Fusarium oxysporum).

Keywords: Thiazole; Pyrazole; Pyridazine; Antimicrobial.

INTRODUCTION

Thiazoles play a prominent role in nature. For example, the thiazolium ring present in vitamin B1 serves as an electron sink and its coenzyme form is important for the decarboxylation of α-keto acids.[1] Various pesticides possessing a thiazole nucleus are well known in agriculture. Large numbers of thiazole derivatives have emerged as active pharmaceutical ingredients in several drugs for their potential anti-inflammatory,[2] anti-tumour,[3] anti-hyperlipidemic,[4] anti-hypertensive[5] and several other biological properties.[6] Besides, thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds.[7-14] Thus, the thiazole nucleus has been much studied in the field of organic and medicinal chemistry.

RESULTS AND DISCUSSION

In this work we describe the uses of 2-ethoxy carbonyl methylene thiazol-4-one (**3**), which was obtained earlier,[15,16] through the reaction of ethyl cyanacetate (**1**) with thioglycollic acid (**2**) in the presence of ethanol and triethylamine in many heterocyclic transformations. Compound **3** reacts with acetophenone (**4**) in the presence of ammonium acetate at 140 °C to give the Knoevenagel condensation product **5**. The structure of compound **5** was based on analytical and spectral data. Thus, the ^{1}H NMR spectrum showed a triplet at δ 1.12 corresponding to ester CH_3, a singlet at δ 2.50 for CH_3 group, a quartet at δ 4.22 for the ester CH_2, a singlet at δ 5.41 for CH_2 group and a multiplet at δ 7.33-7.40 for phenyl protons. Moreover, the ^{13}C NMR spectrum showed δ at 14.28, 19.99 (2 CH_3); 32.37, 59.25 (2 CH_2); 87.39, 88.38 (2 CH); 121.58 (C-Phenyl); 126.74, 128.95 (2 CH); 142.45, 146.39 (2 C=C); 166.26 (C=N); 167.01 (C=O); 174.21 (C=O). ^{13}C NMR δ (DMSO) (DEPT), *up lines*: 14.28 (CH_3); 19.99 (CH_3); 87.39 (CH); 88.38 (CH), 126.74 (CH); 128.95 (CH), *down lines*: 32.37 (CH_2); 59.25 (CH_2).

The reaction of compound **5** with aromatic aldehydes was studied to give arylidine derivatives with potential biological activities. Thus, compound **5** reacts with either benzaldehyde (**6a**), 4-chlorobenzaldehyde (**6b**), 4-methoxybenzaldehyde (**6c**) or salicylaldehyde (**6d**), in each case a single product with molecular formula $C_{22}H_{19}NO_3S$, $C_{22}H_{18}NO_3SCl$, $C_{23}H_{21}NO_4S$ and $C_{22}H_{19}NO_4S$, respectively. Two possible isomeric structures were considered for the reaction products, either **7a-d** or **8a-d**. The possibility of compounds **7a-d** was ruled out on the basis of ^{13}C NMR which showed in the case of **8c** (as an example) δ at

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14.3 (CH_3), 43.5 (ester CH_2), 55.3 (CH_3), 55.46 (OCH_3), 59.5 (CH_2), 89.48, 114.8 (2 CH); 120.4 (C=C), 126.1, 129.3, 131.8 (3CH), 152.1 (C=C); 160.4 (C=N); 166.8, 167.1 (2 C=O). ^{13}C NMR δ (DMSO) (DEPT): *Up lines*; 14.3 (CH_3); 55.3 (CH_3); 55.4 (OCH_3); 89.4 (CH); 114.8 (CH); 126.1 (CH); 129.3 (CH); 131.8 (CH). *Down lines*; 43.5 (CH_2); 59.5 (CH_2). The reaction of compound **8a** with either malononitrile (**9a**) or ethyl cyanoacetate (**9b**) gave the polyfunctionally substituted pyrano[2,3-d]thiazole derivatives **11a,b**. The reaction took place via the intermediate formation of **10a**,**b** (see Scheme I). Structures of compounds **11a** and **11b** were established on the basis of analytical and spectral data. Thus, the ^{1}H NMR spectrum of **11a** showed a triplet at δ 1.21 corresponding to the CH_3 ester group, a singlet at δ 2.66 for the CH_3 group, quartet at δ 4.24 for the ester CH_2 group, a singlet at δ 5.43 for the NH_2 group, and a multiplet at δ 7.37-7.58 for the phenyl and pyran protons. Further confirmation for structures **11a**,**b** was obtained through the synthesis of these compounds using other reaction routes. Thus, the reaction of compound **5** with either α-cyano cinmamonitrile (**12a**) or ethyl α-cyanocinmamate (**12b**) (Scheme I) in the presence of 1,4-dioxan and a catalytic amount of triethylamine gave the same polyfunctionally substituted pyrano[2,3-d]thiazole derivatives **11a** and **11b**, respectively (finger print IR spectrum, m.p. and mixed m.p.).

The reaction of compound **5** with either benzenediazonium chloride (**13a**), 4-chlorobenzenediazonium chloride (**13b**), 4-methybenzenediazonium chloride (**13c**) or 4-methoxybenzenediazonium chloride (**13d**) gave arylhydrazone derivatives **14a-d**, respectively. The analytical and spectral data of the latter products are consistent with the proposed structures (see experimental section). Compounds **14a-d** underwent ready cyclization when heated under reflux in ethanolic/NaOH solution to give the 4-thiazol-2-yl-pyridazine derivatives **15a-d**, respectively. The reaction of compound **5** with phenylisothiocyanate (**16**) in 1,4-dioxan containing triethylamine gave the 3-thiazol-2-yl-pyridine derivative **17**, the structure of which was based on analytical and spectral data. Thus, the ^{1}H NMR spectrum showed a singlet at δ 3.89 corresponding to pyridine CH_2, a singlet at δ 5.77 for the thiazole CH_2 and a multiplet at δ 7.29-7.38 corresponding to the phenyl protons. The reaction of compound **5** with either malononitrile (**9a**) or ethyl cyanoacetate (**9b**) gave the polyfunctionally substituted pyrano[2,3-d]thiazole derivatives **18a** and **18b**, respectively. The analytical and spectral data of the latter products are in agreement with the proposed structures. Thus, the ^{1}H NMR spectrum of **18a** showed a triplet at δ 1.16 corresponding to the ester CH_3 group, a singlet at δ 2.59 for the CH_3 group, a quartet at δ 4.22 for the ester CH_2 group, a singlet (D_2O exchangeable) at δ 4.88 for the NH_2 group, a singlet at δ 5.99 for the pyran H-3 and a multiplet at δ 7.35-7.47 for the phenyl and pyran protons and a singlet (D_2O exchangeable) at δ 8.92 for the NH group. The reaction of compound **5** with elemental sulfur in 1,4-dioxan containing triethylamine gave thiophene derivative **19** (see Scheme III). On the other hand, the reaction of compound **5** with either aniline (**20a**), 2-amino-3-cyano-4,5,6,7-tetrahydro-benzo[b]thiophene (**20b**) or ethyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**20c**) in an oil bath at 140 °C gave the anilide derivatives **21a-c**, respectively. The structures of the latter products were established on the basis of analytical and spectral data (see Scheme III).

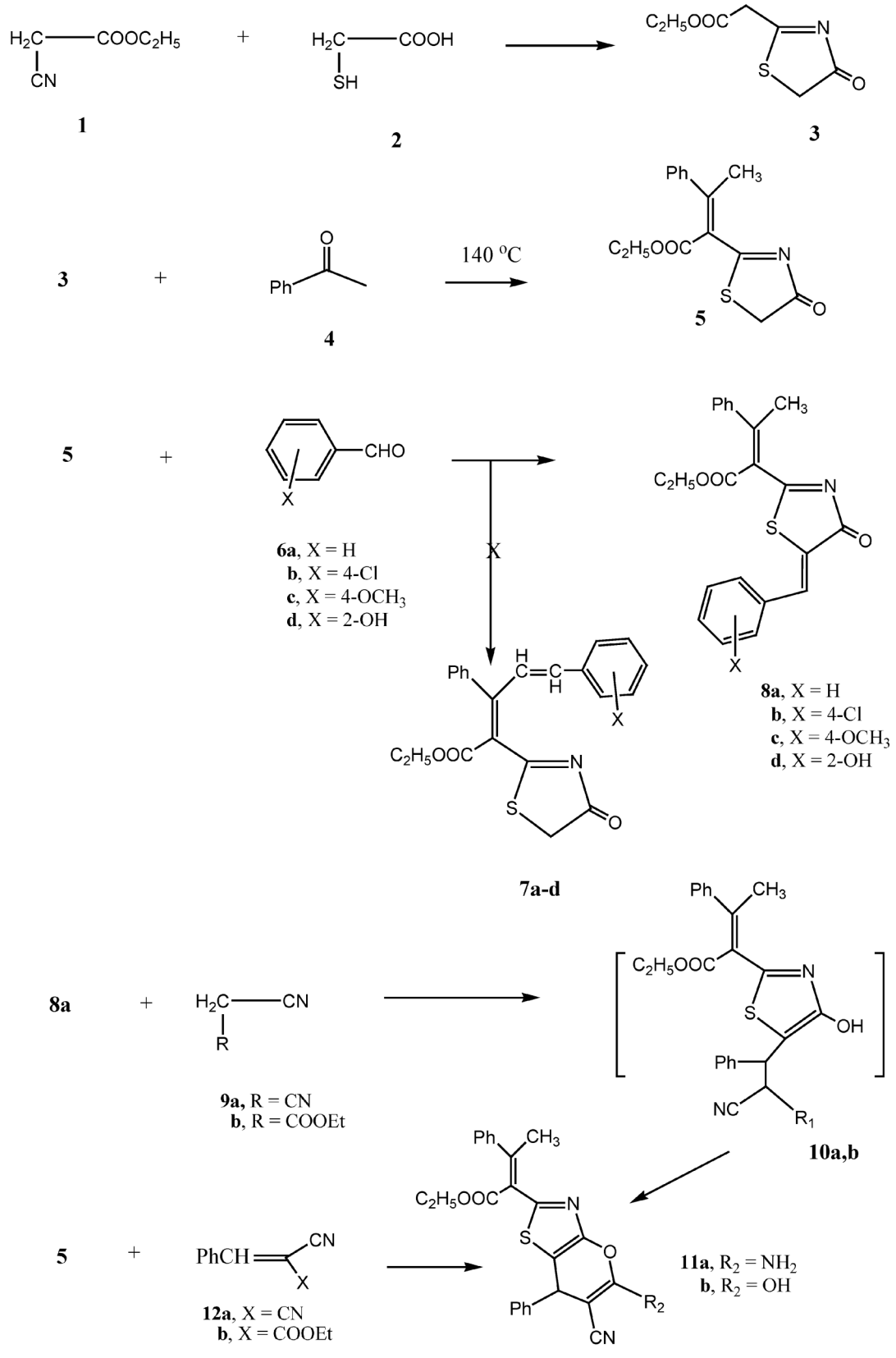
Compound **21a** reacts with either benzaldehyde (**6a**), p-chlorobenzaldehyde (**6b**), p-methoxybenzaldehyde (**6c**) or salicyaldehyde (**6d**) to give the arylidene derivatives **22a-d**, respectively. On the other hand, the reaction of compound **21a** with either malononitrile (**9a**), or ethylcyanoacetate (**9b**) gave the substituted pyrano[2,3-d]thiazole derivatives **23a**,**b**.

It is convenient to notice that compounds, **5**, **8a-d**, **11a**,**b**, **14a-d**, **18a-d**, **21a-c**, **22a-d** and **23a**,**b** can exist in either Z or E structures. However, according to the concept of push-pull alkenes that was reviewed by Sandstrom,[17] where the physicochemical properties and chemical reactivity of numerous functionalized compounds of that type have been extensively studied,[18-23] and the recent studies which showed that the 4-oxothiazolidines with one and two exocyclic double bonds attached to a thiazolidine ring, respectively, exemplify typical push-pull compounds which can exist in Z/E equilibrium depending on temperature and the nature of the solvent.[24] One can say that compounds **5**, **8a-d**, **11a**,**b**, **14a-d**, **18a**,**b**, **21a-c**, **22a-d** and **23a**,**b** are examples of push-pull conjugated alkenes which are existing in a Z/E equilibrium mixture. Moreover, the resonance effect existing in these compounds due to the presence of the phenyl-diene moiety enhances such equilibrium.

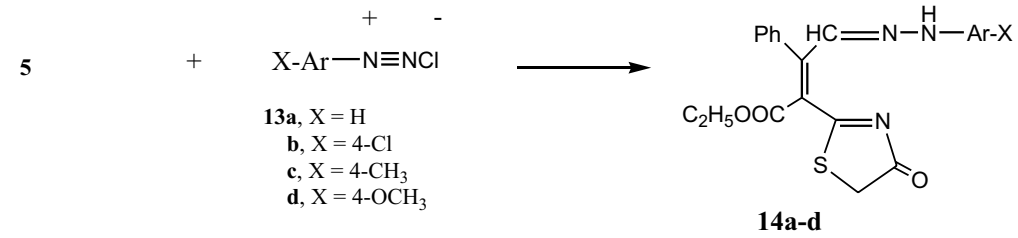
Biological Activity

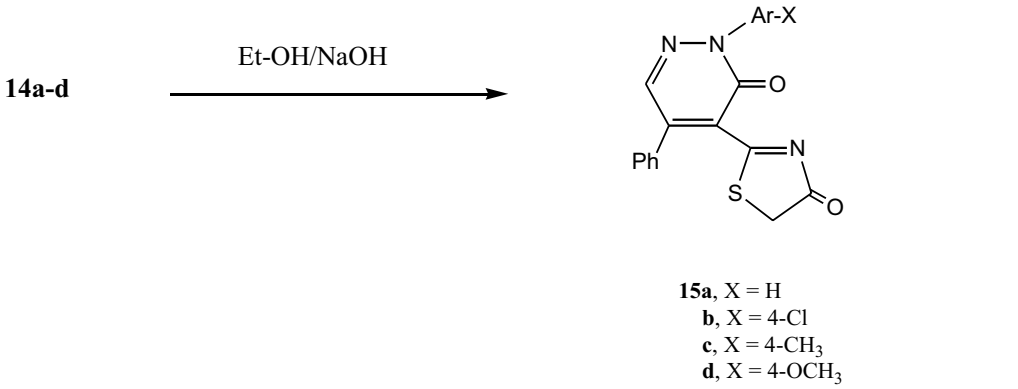
The diverse biological activities of thiazoles and their fused derivatives encouraged us to test and study the biological activities of some newly synthesized products. The antibacterial and antifungal activities were tested.

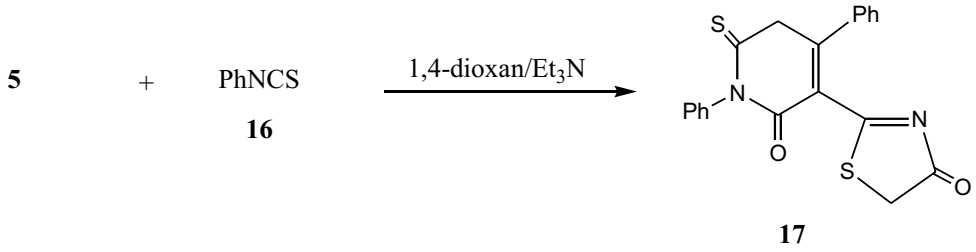
Scheme I

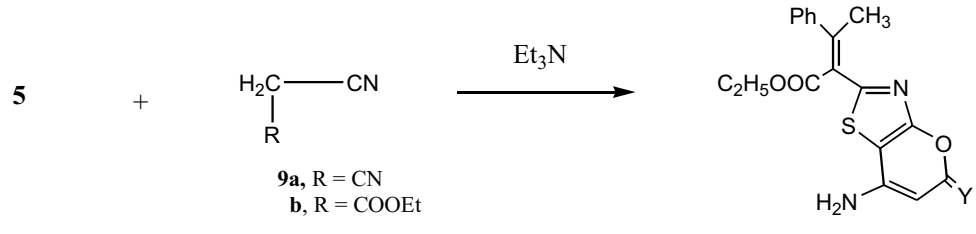

1
2
3
4
5
140 °C
6a, X = H
b, X = 4-Cl
c, X = 4-OCH3
d, X = 2-OH
8a, X = H
b, X = 4-Cl
c, X = 4-OCH3
d, X = 2-OH
7a-d
9a, R = CN
b, R = COOEt
10a,b
12a, X = CN
b, X = COOEt
11a, R2 = NH2
b, R2 = OH

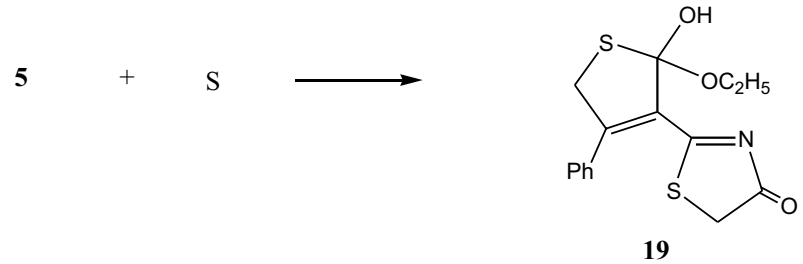
Scheme II


5
+
X-Ar—N≡NCl
13a, X = H
b, X = 4-Cl
c, X = 4-CH3
d, X = 4-OCH3
Ph HC=N—N—Ar-X
H
C2H5OOC
N
S
O
14a-d

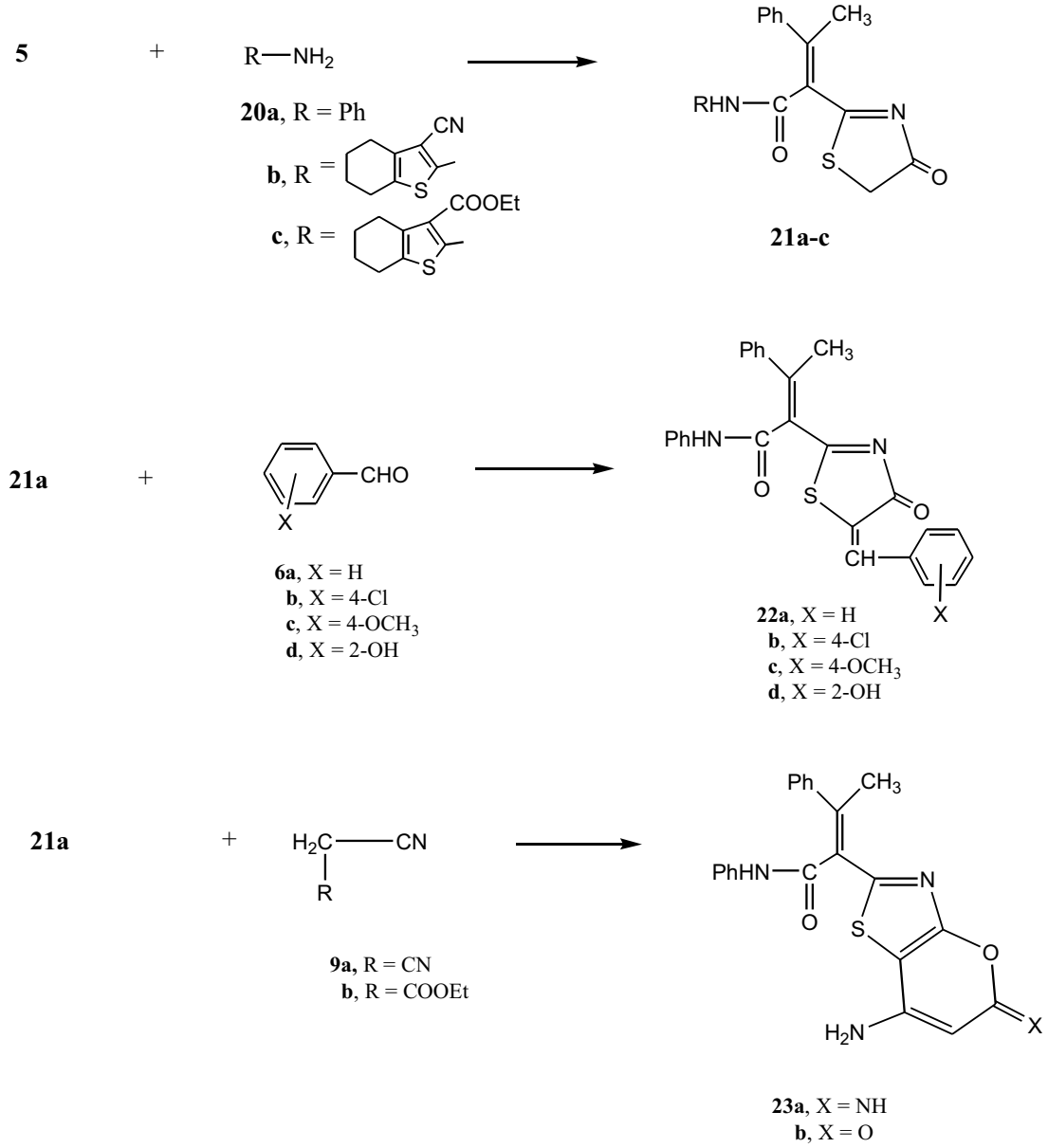

14a-d
Et-OH/NaOH
Ar-X
N—N
O
Ph
N
S
O
15a, X = H
b, X = 4-Cl
c, X = 4-CH3
d, X = 4-OCH3


5
+
PhNCS
16
1,4-dioxan/Et3N
S
Ph
Ph
N
O
N
S
O
17


5
+
H2C—CN
R
9a, R = CN
b, R = COOEt
Et3N
Ph
CH3
C2H5OOC
N
S
O
H2N
Y
18a, Y = NH
b, Y = O


5
+
S
OH
S
OC2H5
Ph
N
S
O
19

Scheme III



Biological Screening

All described compounds were tested in vitro for antimicrobial activity against two bacterial isolates, one saprophytic (*Escherichia coli*) and the other parasitic (*Xanthomonas citri*) and for antifungal activity against one saprophytic (*Aspergillus fumigatus*) and two phytopathogenics *(Rhizoctonia solani* and *Fusarium oxysporum)*.

The culture medium was the nutrient agar for bacteria and Czapek's Dox agar medium for fungi. The sterile medium was inoculated with the test organism so that each 100 mL of the medium received 1 mL of a 24-hour culture of the bacterium or 7-day-old culture of spore suspension of the fungus. The solutions of the tested compounds at 25 ug/mL in dimethylformamide (DMF) were placed separately in the cup (8 mm diameter). The plates were incubated at 28 °C and the resulting inhibition zones were measured.

DMF as a blank exhibited no antimicrobial activity against any of the tested organisms used.

As can be seen from the results, most of the synthesized compounds showed antibacterial and/or antifungal activities. Compounds **5**, **8a**, **8d**, **11a**, **16**, **21b**, **22c**, **22d**,

23a and **23b** were highly active against *Escherichia coli* and *Xanthomonas citri*, whereas **8b**, **8c**, **11b** and **17** showed moderate activity against this microorganism. And **14a** and **22b** showed the lowest activities. Compounds **8a**, **8d**, **14c** and **14d** were highly active against *A-fumigatus*, compounds **5**, **14b**, **17**, **21b**, **22a**, **22d**, **23a** and **23b** showed moderate activity against *A. fumigatus*, *R. solani* and *F. oxysparum* and compounds **8b**, **8c** and **19** were not active against either *R. solani* or *F. oxysparum.* The bacterial isolates were more susceptible to the synthesized compounds than isolated fungals. The recorded inhibition zones are summarized in Table 1.

Compounds **14c** and **14d** which have 4-methyl or 4-methoxy instead of 4-chloro on the benzene ring, showed higher activity than the corresponding compounds **14a** and **14b**. Compound **14c** showed the highest activity against the two bacteria, *E. coli*, *X. citri* and also towards the three fungi *A. fumigatums*, *R. solani*, and *F. oxysporum*.

Table 1. Inhibition zones in mm for some of the synthesized compounds at a concentration level of 25 ug/mL

Compound	*E.coli*	*X.citri*	*A.fumigatus*	*R.solani*	*F.oxysporum*
5	26	26	12	10	12
8a	28	26	19	17	13
8b	18	10	6	5	0
8c	16	12	8	0	4
8d	28	29	30	15	18
11a	26	26	16	18	19
11b	21	16	5	3	0
14a	13	12	6	5	4
14b	18	20	16	4	4
14c	32	34	32	20	17
14d	28	30	28	18	18
16	34	30	18	14	18
17	22	15	14	14	18
19	34	14	12	6	0
21a	28	26	16	15	16
21b	32	30	17	16	18
21c	11	11	4	5	4
22a	26	18	14	13	18
22b	12	10	8	8	8
22c	38	28	18	16	16
22d	26	28	15	18	16
23a	26	20	14	16	17
23b	26	20	16	13	17

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded for (KBr) discs on a Pye Unicam SP-1000 Spectrophotometer. ^{1}H NMR Spectra were measured on a Varian EM-390-200 MHz and Bruker AVANCE DRX-500-300 MHz in CD_3SOCD_3 as solvent, using TMS as internal standard, and chemical shifts are expressed as δ. ^{13}C NMR spectra were measured on a Bruker AVANCE DRX-500. Analytical data were obtained from the Micro Analytical Data Unit at Cairo University, Giza, Egypt.

Ethyl 2-(4,5-dihydro-4-oxothiazol-2-yl)-3-phenyl-2-butenoate (5)

Procedure for the Synthesis of (5)

To a dry mixture of compound **3** (0.01 mol, 1.87 g), acetophenone (1.20 g, 0.01 mol) was added in the presence of ammonium acetate (2.0 g). The reaction mixture was heated in an oil bath (at 140 °C) for 1 h, then left to cool. The solid product formed after boiling in ethanol was collected by filtration.

Compound 5

Yellow crystals from ethanol, yield 76% (2.19 g) and m.p. 130 °C. IR (υ/cm^{-1}) = 2994-2899 (CH_3, CH_2), 1715 (2 C=O), 1677 (C=N), 1630 (C=C). MS: *m/z* (%) = 289 (20.8%), 243 (44.6%), 148 (100%), 103 (11.2%). ^{1}H NMR δ = 1.12 (t, 3H, *J* = 7.61 Hz, CH_3), 2.50-2.61 (s, 3H, CH_3), 4.22 (q, 2H, *J* = 7.61 Hz, CH_2), 5.41 (s, 2H, CH_2), 7.33-7.40 (m, 5H, C_6H_5). ^{13}C NMR δ = 14.2, 19.9 (2 CH_3), 32.37, 59.2 (2 CH_2), 87.3, 88.3 (2 CH), 121.58 (C-phenyl), 126.74, 128.95 (2 CH), 142.45, 146.39 (2 C=C), 166.26 (C=N), 167.01 (C=O), 174.21 (C=O). ^{13}C NMR δ (DMSO) (DEPT): *Up lines*: 14.28 (CH_3), 19.99 (CH_3), 87.39 (CH), 88.38 (CH), 126.74 (CH), 128.95 (CH). *Down lines*: 32.37 (CH_2), 59.25 (CH_2). *Calculated for* $C_{15}H_{15}NO_3S$ (289.35): C, 62.26; H, 5.23; N, 4.84; S, 11.08. Found: C, 62.10; H, 5.26; N, 5.02; S, 10.88.

Ethyl 2-(5-benzylidene-4,5-dihydro-4-oxothiazol-2-yl)-3-phenyl-2-butenoate (8a), ethyl 2-[5-(4-chlorobenzylidene)-4,5-dihydro-4-oxothiazol-2-yl]-3-phenyl-2-butenoate (8b), ethyl 2-[5-(4-methoxybenzylidene)-4,5-dihydro-4-oxothiazol-2-yl]-3-phenyl-2-butenoate (8c), ethyl 2-[5-(2-hydroxy-benzylidene)-4,5-dihydro-4-oxothiazol-2-yl]-3-phenyl-2-butenoate (8d), 5-benzylidene-4,5-dihydro-4-oxothiazol-2-yl)-N,3-diphenylbut-2-enamide (22a), 5-(4-chlorobenzylidene)-4,5-dihydro-4-oxothiazol-2-yl)-N,3-diphenylbut-2-enamide (22b), 5-(4-methoxybenzylidene-4,5-dihydro-4-oxothiazol-2-yl)-N,3-diphenylbut-2-enamide (22c), 5-(2-hydroxy-benzylidene-4,5-dihydro-4-oxothiazol-2-yl)-N,3-diphenylbut-2-enamide (22d)

General procedure

An equimolar amount of either compound **5** (0.01

mol, 2.89 g) or **21a** (3.36 g, 0.01 mol), in ethanol (30 mL) containing pipridine (0.5 mL) either benzaldehyde (0.01 mol, 1.06 mL), p-chlorobenzaldehyde (1.40 g, 0.01 mol), p-methoxy-benzaldhyde (1.36 g, 0.01 mol), or salicylaldehyde (1.22 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. then poured into an ice/water mixture containing a few drops of hydrochloric acid. The solid product formed, in each case, was collected by filtration.

Compound 8a

Yellow crystals from ethanol, yield 61% (2.3 g), m.p. 106-108 °C. IR (υ/cm^{-1}) = 3056 (CH aromatic), 2976-2869 (CH_3, CH_2), 1690, 1685 (2 C=O), 1668 (C=N), 1633 (C=C). ^{1}H NMR δ = 1.36 (t, 3H, *J* = 7.02), 2.66 (s, 3H, CH_3), 4.21 (q, 2H, *J* = 7.02 Hz, CH_2), 7.28-7.39 (m, 11H, C_6H_4, C_6H_5, CH). ^{13}C NMR δ = 13.6, 14.6 (2 CH_3), 60.8 (CH_2), 120.6, 122.8, 124.7, 126.4, 126.8, 128.0, 135.8, (2 C_6H_5), 155.8, 156.8, 158.2 (C=C), 166.1 (C=N), 169.7, 188.9 (2 C=O). *Calculated for* $C_{22}H_{19}NO_3S$ (377.11): C, 70.00; H, 5.07; N, 3.71; S, 8.50. Found: C, 69.76; H, 4.95; N, 4.02; S, 8.73.

Compound 8b

Yellow crystals from ethanol, yield 67% (3.0 g), m.p. 180 °C. IR (υ/cm^{-1}) = 3060 (CH aromatic), 2939-2862 (CH_3, CH_2), 1685 (C=O), 1660 (C=N), 1593 (C=C). ^{1}H NMR δ = 1.36 (t, 3H, *J* = 6.59 Hz, CH_3), 2.49 (s, 3H, CH_3), 4.22 (q, 2H, *J* = 6.59 Hz, CH_2), 7.25-7.46 (m, 10H, C_6H_4, Ph, CH). ^{13}C NMR δ = 13.8, 14.9 (2 CH_3), 61.3 (CH_2), 122.6, 123.3, 123.9, 126.0, 127.1, 127.5, 134.6, 144.9 (2 C_6H_5), 156.5, 157.2, 159.9 (C=C), 166.8 (C=N), 170.6, 187.4 (2 C=O). *Calculated for* $C_{22}H_{18}ClNO_3S$ (411.90). C, 64.15; H, 4.40; N, 3.40; S, 7.78. Found: C, 64.15; H, 4.54; N, 3.73; S, 8.02.

Compound 8c

Yellow crystals from ethanol; yield 86% (3.5 g) and m.p. 180 °C. IR (υ/cm^{-1}) = 3056 (CH aromatic), 2932-2835 (CH_3, CH_2), 1685 (C=O), 1660 (C=N), 1592 (C=C). ^{1}H NMR δ = 1.40 (t, 3H, *J* = 7.01 Hz, CH_3), 2.51, 3.04 (2s, 6H, 2CH_3), 4.22 (q, 2H, *J* = 7.01 Hz, CH_2), 7.32-7.44 (m, 10H, C_6H_4, Ph, CH). ^{13}C NMR δ = 14.3, 18.6 (2 CH_3), 43.5 (ester CH_2), 55.3 (CH_3), 55.4 (OCH_3), 59.5 (CH_2), 89.4, 114.8 (2 CH), 120.4 (C=C), 122.5, 124.9, 126.1, 129.3, 131.8 (C_6H_5, C_6H_4), 152.1 (C=C), 160.4 (C=N), 166.8, 167.1 (2 C=O). ^{13}C NMR δ (DEPT): *Up lines*: 14.3 (CH_3), 55.3 (CH_3), 55.4 (OCH_3), 89.4, 114.8, 124.9, 126.1, 129.3 (CH aromatic); 131.8 (CH). *Down lines*: 59.5 (CH_2). *Calculated for* $C_{23}H_{21}NO_4S$ (407.48): C, 67.79; H, 5.19; N, 3.44; S, 7.87. Found: C, 67.91; H, 5.43; N, 3.71; S, 8.22.

Compound 8d

Yellow crystals from ethanol, yield 53.6% (2.3 g) and m.p. 175 °C. IR (υ/cm^{-1}) = 3056 (CH aromatic), 2932, 2835 (CH_3, CH_2), 1685 (C=O), 1660 (C=N), 1592 (C=C). ^{1}H NMR δ = 1.38 (t, 3H, *J* = 5.99 Hz, CH_3), 2.54 (s, 3H, CH_3), 4.24 (q, 2H, *J* = 5.99 Hz, CH_2), 7.28-7.38 (m, 10H, C_6H_5, C_6H_4, CH), 10.01 (s, 1H, OH). ^{13}C NMR (DMSO) δ (ppm) = 14.3, 18.9 (2 CH_3), 55.3 (CH_3), 55.46 (OCH_3), 59.56 (CH_2), 89.48, 114.86 (2 CH), 120.49 (C=C), 126.18, 129.38, 131.82 (3CH), 152.19 (C=C), 160.46 (C=N), 166.83, 167.14 (2 C=O).^{13}C NMR δ (DMSO) (DEPT): *Up lines*: 14.32 (CH_3), 55.3 (CH_3), 55.46 (OCH_3), 89.48 (CH), 114.86 (CH), 126.18 (CH), 129.38 (CH), 131.82 (CH). *Down lines*: 59.56 (CH_2). *Calculated for* $C_{22}H_{19}NO_4S$ (393.46): C, 67.16; H, 4.87; N, 3.56; S, 8.15. Found: C, 67.63; H, 4.80; N, 3.87; S, 7.99.

Compound 22a

Pale yellow crystals from 1,4-dioxan, yield 70% (2.96 g), m.p. 201-204 °C. IR (υ/cm^{-1}) = 3465-3321 (NH), 3053 (CH aromatic), 2860 (CH_3), 1688, 1687 (2 C=O), 1655 (C=N), 1638 (C=C). ^{1}H NMR δ = 2.66 (s, 3H, CH_3), 7.26-7.38 (m, 16H, 3C_6H_5, CH), 8.26 (s, 1H, NH). ^{13}C NMR δ = 16.3 (CH_3), 120.8, 121.8, 122.7, 122.8, 124.4, 126.6, 126.9, 127.8, 129.0, 129.3, 136.7, 146.1 (3C_6H_5), 157.3, 158.1, 159.6 (C=C), 166.4 (C=N), 171.4, 186.9 (2 C=O). *Calculated for* $C_{26}H_{20}N_2O_2S$ (424.51): C, 73.56; H, 4.75; N, 6.60; S, 7.55. Found: C, 73.85; H, 4.88; N, 6.31; S, 7.73.

Compound 22b

Yellow crystals from 1,4-dioxan, yield 64% (2.93 g), m.p. 222-225 °C. IR (υ/cm^{-1}) = 3473-3327 (NH), 3060 (CH aromatic), 2880 (CH_3), 1689, 2685 (2 C=O), 1657 (C=N), 1622 (C=C). ^{1}H NMR δ = 2.67 (s, 3H, CH_3), 7.29-7.43 (m, 15H, 2C_6H_5, C_6H_4, CH), 8.29 (s, 1H, NH). ^{13}C NMR δ = 16.7 (CH_3), 120.4, 120.9, 121.6, 122.6, 123.8, 125.3, 126.6, 127.3, 129.1, 129.7, 138.9, 147.9 (3C_6H_5), 157.0, 158.8, 159.8 (C=C), 166.7 (C=N), 170.9, 186.4 (2 C=O). *Calculated for* $C_{26}H_{19}ClN_2O_2S$ (458.96). C, 68.04; H, 4.17; N, 6.10; S, 6.99. Found: C, 68.33; H, 4.24; N, 5.83; S, 7.32.

Compound 22c

Orange crystals from acetic acid; yield 72% (3.27 g) and m.p. 170-174 °C. IR (υ/cm^{-1}) = 3469-3331 (NH), 3059 (CH aromatic), 2896 (CH_3), 1689, 1687 (2 C=O), 1658 (C=N), 1633 (C=C). ^{1}H NMR δ = 2.58, 3.16 (2s, 6H, 2CH_3), 7.29-7.40 (m, 15H, 2C_6H_5, C_6H_4, CH), 8.33 (s, 1H, NH). ^{13}C NMR δ = 16.4, 22.9 (2 CH_3), 121.3, 121.9, 122.0, 122.3, 123.2, 124.9, 126.5, 127.1, 128.5, 129.3, 139.2,

146.4 (3C_6H_5), 156.8, 158.4, 159.5 (C=C), 166.9 (C=N), 169.5, 187.2 (2 C=O). *Calculated for* $C_{27}H_{22}N_2O_3S$ (454.54): C, 71.34; H, 4.88; N, 6.16; S, 7.05. Found: C, 71.65; H, 5.21; N, 6.37; S, 6.7.

Compound 22d

Yellow crystals from ethanol/1,4-dioxan mixture, yield 52% (2.28 g) and m.p. 150 °C. IR (υ/cm^{-1}) = 3473-3329 (NH), 3050 (CH aromatic), 2946 (CH_3) 1688, 1686 (2 C=O), 1654 (C=N), 1623 (C=C). ^{1}H NMR δ = 2.66 (s, 3H, CH_3), 7.32-7.42 (m, 15H, 2C_6H_5, C_6H_4, CH), 8.23 (s, 1H, NH), 10.26 (s, 1H, OH). ^{13}C NMR δ = 16.4 (CH_3), 120.0, 122.3, 122.9, 122.1, 123.8, 123.9, 125.8, 127.1, 127.3, 127.2, 138.2, 148.4 (3 C_6H_5), 156.8, 158.4, 159.5 (C=C), 166.9 (C=N), 169.5, 187.2 (2 C=O). *Calculated for* $C_{26}H_{20}N_2O_3S$ (440.51): C, 70.89; H, 4.58; N, 6.36; S, 7.28. Found: C, 71.16; H, 4.83; N, 6.87; S, 7.07.

Ethyl 2-(5-amino-6-cyano-7-phenyl-7H-pyrano[2,3-d]-thiazol-2-yl)-3-phenyl-2-butenoate (11a) and Ethyl 2-(6-cyano-5-hydroxy-7-phenyl-7H-pyrano[2,3-d]thiazol-2-yl)-3-phenyl-2-butenoate (11b)

General procedure: Method A

To a solution of compound **8a** (0.01 mol, 3.77 g) in ethanol (30 mL) containing triethylamine (0.5 mL), either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added; the reaction mixture was heated under reflux for 4 h. The solid product formed upon pouring onto ice/water mixture was collected by filtration.

Method B

To a solution of compound **5** (0.01 mol, 2.89 g) in ethanol (30 mL) containing triethylamine (0.5 mL), either α-cyanocinnamonitrile (1.70 g, 0.01 mol) or ethyl α-cyanocinnamate (1.97 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 5 h and then the reaction mixture was poured onto an ice/water mixture containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound 11a

Orange crystals from ethanol, yield 56% (2.5 g) and m.p. 164-166 °C. IR (υ/cm^{-1}) = 3455-3379 (NH_2); 3059 (CH aromatic), 2931-2897 (CH_3, CH_2), 2197 (CN), 1694 (C=O); 1641 (C=N), 1595 (C=C). ^{1}H NMR δ = 1.21 (t, 3H, *J* = 6.32 Hz, CH_3), 2.66 (s, 3H, CH_3), 4.24 (q, 2H, *J* = 6.32 Hz, CH_2), 5.43 (s, 2H, NH_2), 7.37-7.58 (m, 11H, 2C_6H_5, pyran H-4). ^{13}C NMR δ = 16.3, 18.9 (2 CH_3), 60.8 (CH_2), 59.2, 80.3 (pyran C-3, C-4), 116.9 (CN), 119.3, 120.8, 122.6, 122.8, 123.2, 123.6, 124.6, 125.5, 127.8, 128.3, 129.0, 129.9, 133.5, 138.9, 141.2, 146.4 (2 C_6H_5, thiazole C), 154.9, 167.9 (C=C), 166.4 (C=N), 169.9 (C=O). *Calculated for* $C_{25}H_{21}N_3O_3S$ (443.52): C, 67.70; H, 4.77; N, 9.47; S, 7.23. Found: C, 67.52; H, 4.50; N, 9.31; S, 7.07.

Compound 11b

Yellow crystals from ethanol, yield 56% (2.53 g) and m.p. 90 °C. IR (υ/cm^{-1}) = 3575-3163 (OH), 3065 (CH, aromatic), 2989, 2899 (CH_3, CH_2), 2195 (CN), 1677 (C=O), 1650 (C=N), 1633(C=C). ^{1}H NMR δ = 1.02-1.14 (t, 3H, *J* = 5.44 Hz, CH_3), 3.30 (s, 3H, CH_3), 4.23 (q, 2H, *J* = 5.44 Hz, CH_2), 7.12-7.51 (m, 11H, 2C_6H_5, pyrane H-4), 8.56 (s, 1H, OH). ^{13}C NMR δ = 16.0, 18.6 (2 CH_3), 60.4 (CH_2), 59.0, 80.6 (pyran C-3, C-4), 116.6 (CN), 119.0, 121.8, 122.4, 122.9, 123.0, 123.4, 124.3, 124.7, 125.5, 127.6, 128.0, 129.3, 129.9, 133.5, 138.7, 140.9, 156.6 (2 C_6H_5, thiazole C), 154.7, 167.3 (C=C), 166.0 (C=N), 169.5 (C=O). *Calculated for* $C_{25}H_{20}N_2O_4S$ (444.11): C, 67.55; H, 4.54; N, 6.30; N, 7.21. Found: C, 67.34; H, 4.28; N, 6.57; N, 7.48.

Ethyl 2-(4-oxo-4,5-dihydro-thiazol-2-yl)-3-phenyl-4-(phenyl-hydrazono)-2-butenoate (14a). Ethyl 4-[(4-chloro-phenyl)-hydrazono]-2-(4-oxo-4,5-dihydro-thiazol-2-yl)-3-phenyl-2-butenoate (14b). Ethyl 2-(4-oxo-4,5-dihydro-thiazol-2-yl)-3-phenyl-4-(p-tolyl-hydrazono)-2-butenoate (14c). Ethyl 4-[(4-methoxy-phenyl)-hydrazono]-2-(4-oxo-4,5-dihydro-thiazol-2-yl)-3-phenyl-2-butenoate (14d)

General Procedure

To a cold solution (0-5 °C) of compound **5** (2.89 g, 0.01 mol g) in acetic acid/ethanol (1:4) (50 mL) containing sodium hydroxide (5 mL, 10%) either benzenediazonium chloride (0.01 mol), 4-chlorobenzene-diazonium chloride (0.01 mol), 4-methylbenzenediazonium chloride (0.01 mol) or 4-methoxy-benzenediazonium chloride (0.01 mol) [prepared by adding sodium nitrite (0.02 mol, 1.38 g) solution to a cold solution (0-5 °C) of aniline (0.93 g, 0.01 mol), 4-chloroaniline (1.27 g, 0.01 mol), 4-methylaniline (1.07 g, 0.01 mol) or 4-methoxyaniline (1.23 g, 0.01 mol) containing the appropriate amount of hydrochloric acid with continuous stirring] was added with stirring. The reaction mixture was left at 0-5 °C for 4 h and the formed solid product, in each case, was collected by filtration.

Compound 14a

Red crystals from ethanol, yield 84% (3.30 g) and m.p. 92 °C. IR (υ/cm^{-1}) = 3450-3325 (NH), 3066 (CH aromatic), 2993, 2900 (CH_3, CH_2), 1684, 1674 (2 C=O), 1660 (C=N), 1633 (C=C). ^{1}H NMR δ = 1.36 (t, 3H, *J* = 6.41 Hz, CH_3), 4.23 (q, 2H, *J* = 6.41 Hz, CH_2), 5.33 (s, 2H, thiazole CH_2), 6.34 (s, 1H, CH=N), 7.32-7.41 (m, 10H, 2C_6H_5),

8.21 (s, 1H, NH). ^{13}C NMR δ = 19.0 (CH_3), 39.8 (thiazole CH_2), 60.8 (CH_2), 119.8, 120.3, 122.9, 123.9, 124.0, 124.2, 125.3, 126.6, 128.0, 129.0, 134.9, 138.9, 140.0, 143.2 (2 C_6H_5, thiazole C-2), 153.7, 166.4 (C=C), 159.3, 163.1 (2 C=N), 169.3, 198.5 (2 C=O). *Calculated for* $C_{21}H_{19}N_3O_3S$ (393.46): C, 64.10; H, 4.87; N, 10.68; S, 8.15. Found: C, 63.87; H, 4.76; S, 8.44.

Compound 14b

Dark brown powder from ethanol, yield 70% (2.89 g), m.p. 155 °C. IR (υ/cm^{-1}) = 3460-3326 (NH), 3066 (CH aromatic), 2970, 2900 (CH_3, CH_2), 1687, 1679 (2 C=O), 1650 (C=N), 1632 (C=C). ^{1}H NMR δ = 1.34 (t, 3H, *J* = 7.05 Hz, CH_3), 4.21 (q, 2H, *J* = 7.05 Hz, CH_2), 5.31 (s, 2H, thiazole CH_2), 6.22 (s, 1H, CH=N), 7.24-7.38 (m, 9H, C_6H_5, C_6H_4), 8.29 (s, 1H, NH). ^{13}C NMR δ = 18.8 (CH_3), 39.1 (thiazole CH_2), 60.5 (CH_2), 119.6, 120.8, 121.3, 123.3, 124.6, 124.9, 126.2, 128.1, 129.6, , 137.3, 142.4, 148.7 (2 C_6H_5, thiazole C-2), 153.5, 166.8 (C=C), 159.1, 163.3 (2 C=N), 169.7, 198.0 (2 C=O). *Calculated for* $C_{21}H_{18}ClN_3O_3S$ (427.90): C, 58.94; H, 4.24; N, 9.82; S, 7.49. Found: C, 58.89; H, 4.69; N, 9.67; S, 7.82.

Compound 14c

Brown crystals from ethanol, yield 76% (3.10 g), m.p. 162 °C. IR (υ/cm^{-1}) = 3448-3321 (NH), 3066 (CH aromatic), 2969, 2908 (CH_3, CH_2), 1688, 1680 (2 C=O), 1661 (C=N), 1638 (C=C). ^{1}H NMR δ = 1.33 (t, 3H, *J* = 7.33 Hz, CH_3), 3.01 (s, 3H, CH_3), 4.25 (q, 2H, *J* = 7.33 Hz, CH_2), 5.42 (s, 2H, thiazole CH_2), 6.28 (s, 1H, CH=N), 7.26-7.35 (m, 9H, C_6H_5, C_6H_4), 8.32 (s, 1H, NH). ^{13}C NMR δ = 18.6, 24.8 (2 CH_3), 39.0 (thiazole CH_2), 60.7 (CH_2), 119.4, 120.4, 123.6, 125.8, 126.1, 128.3, 128.9, 130.2.6, 137.6, 144.4, 148.9 (C_6H_5, C_6H_4, thiazole C-2), 153.2, 166.3 (C=C), 159.0, 163.8 (2 C=N), 168.2, 198.6 (2 C=O). *Calculated for* $C_{22}H_{21}N_3O_3S$ (407.49): C, 64.85; H, 5.19; N, 10.31; S, 7.87. Found: C, 64.60; H, 5.10; N, 10.55; S, 8.16.

Compound 14d

Brown crystals from ethanol, yield 89% (3.76 g) and m.p. 148 °C. IR (υ/cm^{-1}) = 3466-3321 (NH), 3067 (CH aromatic), 2970, 2900 (CH_3, CH_2), 1677 (C=O), 1650 (C=N), 1588 (C=C). ^{1}H NMR δ = 1.19 (t, 3H, *J* = 6.52 Hz, CH_3), 3.22 (s, 3H, CH_3), 4.28 (q, 2H, *J* = 6.49 Hz, CH_2), 5.46 (s, 2H, CH_2), 6.26 (s, 1H, CH=N), 7.32-7.41 (m, 9H, C_6H_4, C_6H_5), 8.67 (s, 1H, NH). ^{13}C NMR δ = 18.6, 29.3 (2 CH_3), 39.2 (thiazole CH_2), 60.8 (CH_2), 119.1, 120.6, 123.8, 125.9, 126.2, 128.6, 128.9, 130.2, 137.8, 144.0, 149.4 (C_6H_5, C_6H_4, thiazole C-2), 153.1, 166.2 (C=C), 159.2, 163.6 (2 C=N), 168.1, 198.3 (2 C=O). *Calculated for* $C_{22}H_{21}N_3O_4S$ (423.48): C, 62.40; H, 5.00; N, 9.92; S, 7.57. Found: C, 62.14; H, 5.35; N, 10.27; S, 7.79.

4-(4,5-Dihydro-4-oxothiazol-2-yl)-2,5-diphenylpyridazin-3(2H)-one (15a), 4-(4,5-dihydro-4-oxothiazol-2-yl)-2-(4-chlorophenyl)-5-phenylpyridazin-3(2H)-one (15b), 4-(4,5-dihydro-4-oxothiazol-2-yl)-2-(4-methylphenyl)-5-phenylpyridazin-3(2H)-one (15c) and 4-(4,5-dihydro-4-oxothiazol-2-yl)-2-(4-methoxyphenyl)-5-phenylpyridazin-3(2H)-one (15d)

General procedure

A solution of either **14a** (3.93 g, 0.01 mol), **14b** (4.27 g, 0.01 mol), **14c** (4.07 g, 0.01 mol) or **14d** (4.23 g, 0.01 mol) in ethanol (50 mL) containing sodium hydroxide (0.50 g) was heated under reflux for 4 h. The formed solid product, upon pouring onto ice/water mixture containing hydrochloric acid (till pH 6), was collected by filtration.

Compound 15a

Pale yellow crystals from 1,4-dioxane, yield 66% (2.29 g) and m.p. 177 °C. IR (υ/cm^{-1}) = 3054 (CH aromatic), 2876 (CH_2), 1685, 1682 (2 C=O), 1659 (C=N), 1630 (C=C). ^{1}H NMR δ = 5.36 (s, 2H, thiazole CH_2), 6.29 (s, 1H, pyridine H-6), 7.35-7.40 (m, 10H, 2 C_6H_5). ^{13}C NMR δ = 39.5 (thiazole CH_2), 120.2, 120.6, 121.8, 122.6, 124.0, 124.7, 126.0, 127.6, 137.3, 142.5, 148.1 (2 C_6H_5, pyridazine C, thiazole C-2), 154.5, 164.9 (2 C=N), 165.3, 198.6 (2 C=O). *Calculated for* $C_{19}H_{13}N_3O_2S$ (347.39): C, 65.69; H, 3.77; N, 12.10; S, 9.23. Found: C, 65.44; H, 4.01; S, 9.01.

Compound 15b

Yellowish brown crystals from ethanol, yield 66% (2.51 g), m.p. 186-189 °C. IR (υ/cm^{-1}) = 3052 (CH aromatic), 2877 (CH_2), 1689, 1681 (2 C=O), 1656 (C=N), 1638 (C=C). ^{1}H NMR δ = 5.35 (s, 2H, thiazole CH_2), 6.27 (s, 1H, pyridine H-6), 7.28-7.35 (m, 9H, C_6H_5, C_6H_4). ^{13}C NMR δ = 39.8 (thiazole CH_2), 120.8, 121.6, 121.9, 122.2, 123.8, 124.5, 126.7, 132.3, 134.0, 140.6, 147.8 (2 C_6H_5, pyridazine C, thiazole C-2), 153.6, 163.7 (2 C=N), 163.7, 198.9 (2 C=O). *Calculated for* $C_{19}H_{12}ClN_3O_2S$ (381.84): C, 59.76; H, 3.17; N, 11.00; S, 8.40. Found: C, 60.03; H, 2.89; N, 10.83; S, 8.27.

Compound 15c

Brown crystals from 1,4-dioxane, yield 79% (2.85 g), m.p. 162 °C. IR (υ/cm^{-1}) = 3053 (CH aromatic), 2908 (CH_2), 1689, 1683 (2 C=O), 1655 (C=N), 1636 (C=C). ^{1}H NMR δ = 5.39 (s, 2H, thiazole CH_2), 6.29 (s, 1H, pyridazine H-6), 7.26-7.39 (m, 9H, C_6H_5, C_6H_4). ^{13}C NMR δ = 20.8 (CH_3), 39.6 (thiazole CH_2), 119.6, 121.0, 122.6,

123.3, 123.8, 124.2, 125.7, 126.7, 139.2, 143.6, 149.0 (2 C_6H_5, pyridazine C, thiazole C-2), 155.5, 165.0 (2 C=N), 166.4, 198.2 (2 C=O). *Calculated for* $C_{20}H_{15}N_3O_2S$ (361.42): Calcd: C, 66.46; H, 4.18; N, 11.63; S, 8.87. Found: C, 66.78; H, 3.89; N, 11.57; S, 8.69.

Compound 15d

Yellow crystals from dimethylformamide, yield 69% (2.55 g) and m.p. 220-224 °C. IR (υ/cm^{-1}) = 3061 (CH aromatic), 2893 (CH_2), 1689, 1681 (2 C=O), 1658 (C=N), 1633 (C=C). ^{1}H NMR δ = 3.01 (s, 3H, CH_3), 5.53 (s, 2H, CH_2), 6.28 (s, 1H, pyridazine H-6), 7.27-7.38 (m, 9H, C_6H_4, C_6H_5). ^{13}C NMR δ = 24.6 (CH_3), 39.8 (thiazole CH_2), 119.8, 120.2, 120.8, 121.9, 123.8, 124.0, 125.7, 126.7, 139.6, 143.5, 149.3 (2 C_6H_5, pyridazine C, thiazole C-2), 155.8, 165.2 (2 C=N), 166.6, 198.1 (2 C=O). *Calculated for* $C_{20}H_{15}N_3O_3S$ (377.42): Calcd: C, 63.65; H, 4.01; N, 11.13; S, 8.50. Found: C, 63.83; H, 4.35; N, 11.27; S, 8.42.

5,6-dihydro-3-(4,5-dihydro-4-oxothiazol-2-yl)-1,4-diphenyl-6-thioxopyridin-2(1H)-one (17)

Equimolar amounts of compound **5** (2.89 g, 0.01 mol), and phenylisothiocyanate (1.35 g, 0.01 mol), in 1,4-dioxan (30 mL) containing triethylamine (0.50 mL), were heated under reflux for 3 hr. The reaction mixture was poured onto an ice/water mixture containing a few drops of hydrochloric acid. And the formed solid product was collected by filtration.

Compound 17

Orange crystals from ethanol, yield 78% (2.94 g) and m.p. 180-184 °C. IR (υ/cm^{-1}) = 2894 (CH_2), 1689, 1682 (2 C=O); 1659 (C=N), 1636 (C=C). ^{1}H NMR δ = 3.89 (s, 2H, pyridine CH_2), 5.77 (s, 2H, thiazole CH_2), 7.29-7.38 (m, 10H, 2 C_6H_5). ^{13}C NMR δ = 39.6 (thiazole CH_2), 120.5, 121.6, 122.8, 123.1, 123.8, 125.0, 126.1, 134.3, 136.2, 141.1, 143.6 (2 C_6H_5, pyridazine C, thiazole C-2), 166.4 (C=N), 163.5, 197.9 (2 C=O). *Calculated for* $C_{20}H_{14}N_2O_2S_2$ (378.47): C, 63.47; H, 3.73; N, 7.40; S, 16.94. Found: C, 63.36; H, 3.89; N, 7.65; S, 17.25.

Ethyl 2-(7-amino-5-imino-5H-pyrano[2,3-d]thiazol-2-yl)-3-phenyl-2-butenoate (18a) and ethyl 2-(7-amino-5-oxo-5H-pyrano[2,3-d]thiazol-2-yl)-3-phenyl-2-butenoate (18b)

General Procedure

An equimolar amount of compound **5** (2.89 g, 0.01 mol) in ethanol (20 mL) containing triethylamine (0.5 mL) and either malononitrile (0.66 g, 0.01 mol) or ethylcyanoacetate (1.13 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 6 h, and then the mixture was poured onto ice/water mixture containing a few drops of hydrochloric acid. The solid product formed, in each case, was collected by filtration.

Compound 18a

Yellow crystals from methanol yield 65% (2.34 g), m.p. 148-150 °C. IR (υ/cm^{-1}) = 3480-3321 (NH_2, NH), 3054 (CH aromatic), 2987, 2880 (CH_3, CH_2), 1688 (C=O), 1666 (C=N); 1638 (C=C). ^{1}H NMR δ = 1.16 (t, 3H, J = 6.69 Hz, CH_3), 2.59 (s, 3H, CH_3), 4.22 (q, 2H, J = 6.69 Hz, CH_2), 4.88 (s, 2H, NH_2), 5.99 (s, 1H, pyran H-3), 7.35-7.47 (m, 5H, C_6H_5), 8.92 (s, 1H, NH). ^{13}C NMR δ = 16.3, 24.1 (2 CH_3), 56.8 (CH_2), 119.2, 122.4, 123.0, 124.9, 130.1, 143.5 (C_6H_5, thiazole C), 162.8 (C=N), 168.8 (C=O). *Calculated for* $C_{18}H_{17}N_3O_3S$ (355.41): Calcd: C, 60.83; H, 4.82; N, 11.82; S, 9.02. Found: C, 60.75; H, 5.04; N, 12.21; S, 8.84.

Compound 18b

Yellow crystals (from ethanol), yield 53% (1.9 g) and m.p. 145-148 °C. IR (υ/cm^{-1}) = 3058 (CH aromatic), 2990, 2876 (CH_3, CH_2), 1685, 1679 (2 C=O), 1661 (C=N), 1633 (C=C). ^{1}H NMR δ = 1.14 (t, 3H, J = 5.77 Hz, CH_3), 2.33 (s, 3H, CH_3), 4.26 (q, 2H, J = 5.77 Hz, CH_2), 4.68 (s, 2H, NH_2), 5.87 (s, 1H, pyran H-2), 7.32-7.42 (m, 5H, C_6H_5). ^{13}C NMR δ = 16.0, 24.5 (2 CH_3), 56.3 (CH_2), 120.5, 122.9, 123.7, 124.1, 132.6, 143.8 (C_6H_5, thiazole C), 166.3, 168.0 (C=O). *Calculated for* $C_{18}H_{16}N_2O_4S$ (356.43): C, 60.66; H, 4.53; N, 7.86; S, 9.00. Found: C, 60.87; H, 4.44; N, 8.04; 8.79.

2-(2-ethoxy-2,5-dihydro-2-hydroxy-4-phenylthiophen-3-yl)thiazol-4-(5H)-one (19)

An equimolar amount of compound **5** (2.89 g, 0.01 mol) in 1,4-dioxan (30 mL) containing triethylamine (0.5 mL) and elemental sulfur (0.32 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The reaction mixture was poured onto ice/water mixture containing a few drops of hydrochloric acid. The solid product formed was collected by filtration.

Compound 19

Orange crystals (from ethanol), yield 56% (1.80 g) and m.p. 170 °C. IR (υ/cm^{-1}) = 3444 (OH), 3064 (CH aromatic), 2991-2899 (CH_3, CH_2), 1683 (C=O), 1640 (C=N), 1588 (C=C). ^{1}H NMR δ = 1.36 (t, 3H, J = 6.11 Hz, CH_3), 4.24 (q, 2H, J = 6.11 Hz, CH_2), 4.84, 5.31 (2s, 4H, thiazole CH_2, thiophene CH_2), 7.34-7.41 (m, 5H, C_6H_5), 10.13 (s, 1H, OH). ^{13}C NMR: δ = 16.7 (CH_3), 27.4 (thiophene CH_2), 38.8 (thiazole CH_2), 112.0 (thiophene C-2), 117.8, 122.3, 123.9, 125.3, 127.1, 128.0, 128.8 130.9, 133.4 (C_6H_5, thiophene C-3, C-4), 165.2 (C=N). *Calculated for*

$C_{15}H_{15}NO_3S_2$ (321.41): Calcd: C, 56.05; H, 4. 70; N, 14.93; S, 19.95. Found: C, 55.93; H, 4.83; N, 15.21; S, 20.26.

Ethyl 2-(4-oxo-4,5-dihydro-thiazol-2-yl)-3-phenyl-but-2-enoic acid phenylamide (21a). 2-(4-Oxo-4,5-dihydro-thiazol-2-yl)-3-phenyl-but-2-enoic acid-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-amide (21b). Ethyl 2-[2-(4-oxo-4,5-dihydro-thiazol-2-yl)-3-phenyl-but-2-enoyl amino]-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (21c)

General Procedure

An equimolar amount of compound **5** (2.89 g, 0.01 mol), in dimethylformamide (30 mL), either aniline (0.93 g, 0.01 mol), 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo-[b]thiophene (1.80 g, 0.01 mol) or ethyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (2.38 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 h and then the reaction mixture was poured onto an ice/water mixture containing a few drops of hydrochloric acid. The solid product formed, in each case, was collected by filtration.

Compound 21a

Yellow crystals (from ethanol), yield 71% (2.34 g), m.p. 190 °C. IR (υ/cm^{-1}) = 3058 (CH aromatic), 2924, 2870 (CH_3, CH_2), 1688, 1682 (3C=O), 1658 (C=N), 1623 (C=C). ^{1}H NMR δ = 2.78 (s, 3H, CH_3), 5.31 (s, 2H, thiazole CH_2), 7.31-7.37 (m, 10H, C_6H_5), 8.28 (s, 1H, NH). MS: *m/z* = 336 (18%), 289 (33.9%), 243 (58.8%), 148 (100%), 93 (52.2%). ^{13}C NMR δ = 13.8 (CH_3), 40.1 (thiazole CH_2), 119.6, 124.8, 125.7, 126.4, 126.8, 128.6, 128.8, 135.6, 139.0 (2 C_6H_5), 154.9, 156.5 (C=C), 166.5 (C=N), 164.7, 198.9 (2 C=O). *Calculated for* $C_{19}H_{16}N_2O_2S$ (336.41): C, 67.84; H, 4.79; N, 8.33; S, 9.53. Found: C, 67.61; H, 4.86; N, 8.03; S, 9.72.

Compound 21b

Orange-red crystals from acetic acid yield 63% (2.75 g), m.p. 108 °C. IR (υ/cm^{-1}) = 3058 (CH aromatic), 2944, 2875 (CH_3, CH_2), 1686, 1680 (2 C=O), 1655 (C=N), 1624 (C=C). ^{1}H NMR δ = 2.02-2.22 (s, 4H, 2CH_2), 2.31-2.36 (m, 4H, CH_2), 2.73 (s, 3H, CH_3), 5.31 (s, 2H, thiazole CH_2), 7.30-7.39 (m, 5H, C_6H_5), 8.31 (s, 1H, NH). ^{13}C NMR δ = 14.2 (CH_3), 19.1 (thiazole CH_2), 20.1, 23.0, 23.1, 24.0 (cyclohexene CH_2), 116.3 (CN), 120.5, 123.7, 124.0, 126.2, 128.0, 128.3 (C_6H_5), 154.2, 156.8 (C=C), 166.1 (C=N), 165.3, 199.0 (2 C=O). *Calculated for* $C_{22}H_{19}N_3O_2S_2$ (421.54): C, 62.68; H, 4.54; N, 9.97; S, 15.21. Found: C, 62.41; H, 4.56; N, 10.27; S, 14.85.

Compound 21c

Yellow crystals yield 68% (3.29 g), m.p. 178 °C. IR (υ/cm^{-1}) = 3053 (CH aromatic), 2941, 2885 (CH_3, CH_2), 1689, 1682 (2 C=O), 1665 (C=N), 1631 (C=C). ^{1}H NMR δ = 1.16 (t, 3H, *J* = 7.01 Hz, CH_3), 2.04-2.24 (s, 4H, 2 CH_2), 2.30-2.37 (m, 4H, CH_2), 2.73 (s, 3H, CH_3), 4.22 (q, 2H, *J* = 7.01 Hz, CH_2), 5.31 (s, 2H, thiazole CH_2), 7.30-7.39 (m, 5H, C_6H_5), 8.31 (s, 1H, NH). ^{13}C NMR δ = 14.0, 22.6 (2 CH_3), 19.3 (thiazole CH_2), 20.1, 23.0, 23.1, 24.0 (cyclohexene CH_2), 60.9 (ester CH_2), 119.9, 123.7, 124.9, 126.2, 128.0, 129.6 (C_6H_5), 154.6, 155.9 (C=C), 166.3 (C=N), 165.8, 198.6 (2 C=O). *Calculated for* $C_{24}H_{24}N_2O_4S_2$ (468.59): Calcd: C, 61.52; H, 5.16; N, 5.98; S, 13.69. Found: C, 61.75; H, 5.44; N, 6.06; S, 13.99.

2-(7-Amino-5-imino-5H-pyrano[2,3-d]thiazol-2-yl)-N,3-diphenylbut-2-enamide (23a) and 2-(7-Amino-5-oxo-5H-pyrano[2,3-d]thiazol-2-yl)-N,3-diphenylbut-2-enamide (23b)

General Procedure

An equimolar amount of compound **21a** (3.36 g, 0.01 mol) in ethanol (20 mL) containing triethylamine (0.5 mL) and either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 6 h, and then the mixture was poured onto an ice/water mixture containing a few drops of hydrochloric acid. The solid product formed, in each case, was collected by filtration.

Compound 23a

Pale brown crystals from 1,4-dioxane, yield 59% (3.53 g), m.p. 166 °C. IR (υ/cm^{-1}) = 3480-3311 (NH_2, NH), 3058 (CH aromatic), 2971, 2880 (CH_3, CH_2), 1683 (C=O), 1668 (C=N), 1634 (C=C). ^{1}H NMR δ = 2.77 (s, 3H, CH_3), 4.61 (s, 2H, NH_2), 5.48 (s, 1H, pyrane H-3), 7.30-7.37 (m, 10H, 2 C_6H_5), 8.22, 8.36 (2s, 2H, 2NH). ^{13}C NMR δ = 14.3 (CH_3), 122.8, 124.9, 125.0, 125.6, 125.7, 126.4, 126.7, 128.4, 128.7, 134.3, 139.6, 140.1 (2 C_6H_5), 153.9, 156.2 (C=C), 160.1, 164.6 (2 C=N), 171.9 (C=O). *Calculated for* $C_{22}H_{18}N_4O_2S$ (402.47): Calcd: C, 65.65; H, 4.51; N, 13.92; S, 7.97. Found: C, 65.81; H, 4.81; N, 14.22; S, 8.27.

Compound 23b

Pale brown crystals from 1,4-dioxan, yield 59% (3.53 g), m.p. 166 °C. IR (υ/cm^{-1}) = 3440-3321 (NH_2, NH), 3053 (CH aromatic), 2978, 2883 (CH_3, CH_2), 1686, 1683 (2 C=O), 1655 (C=N), 1636 (C=C). ^{1}H NMR δ = 2.77 (s, 3H, CH_3), 4.68 (s, 2H, NH_2), 5.48 (s, 1H, pyrane H-3), 7.30-7.37 (m, 10H, 2 C_6H_5), 8.36 (s, 1H, NH). ^{13}C NMR δ = 14.0

(CH_3), 120.3, 122.6, 124.8, 125.0, 125.2, 125.9, 126.2, 127.9, 128.7, 134.0, 139.3, 141.8 (2 C_6H_5), 153.9, 156.2 (C=C), 160.6 (C=N), 166.4, 169.8 (2 C=O). *Calculated for* $C_{22}H_{17}N_3O_3S$ (403.45): Calcd: C, 65.49; H, 4.25; N, 10.42; S, 7.95. Found: C, 65.81; H, 4.81; N, 10.33; S, 8.77.

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