

Scientific paper

Anti-inflammatory and Anti-ulcer Activities of New Fused Thiazole Derivatives Derived from 2-(2-Oxo-2*H*-chromen-3-yl)thiazol-4(5*H*)-one

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Abstract

The reaction of the 2-(4-oxo-4,5-dihydrothiazol-2-yl)acetonitrile (**1**) with salicylaldehyde (**2**) in 1,4-dioxane containing a catalytic amount of piperidine gave the coumarin derivative **3**. The latter reacted with different reagents to give pyrido[4,5-*b*]thiazole, pyrido[4,5-*b*]thiazole and thieno[5,4-*b*]thiazole derivatives. The anti-inflammatory and anti-ulcer activities of the newly synthesized products were evaluated and the results showed that compounds **7a**, **8a**, **10b**, **13b**, **15b**, **18a**, **19b**, **19c**, and **19d** showed higher activity compared to the rest of the compounds. In addition to this, toxicity of such active compounds was studied against shrimp larvae where compounds **10b**, **18a**, **19c** and **19d** showed to be non-toxic against the tested organisms.

Keywords: 4,5-dihydrothiazol, coumarin, pyrimidine, anti-inflammatory, anti-ulcer activity

1. Introduction

Thiazole is a core structural motif present in a variety of natural products, such as vitamin B1 (thiamine) and penicillin. Thiazole derivatives also exhibit a broad spectrum of medicinal and biological properties, such as antibacterial, antifungal,¹ anti-inflammatory,² antiviral,³ antimalarial,⁴ and anti-HIV activities.⁵ Thiazole analogs have also been reported as ligands at estrogen receptors,⁶

neuropeptides,⁷ Y5 adenosine receptors,⁸ and act as inhibitors of human platelet aggregation factor,⁹ urokinase,¹⁰ and poly(ADP-ribose) polymerase-1.¹¹ Selenazoles have been reported to possess antibacterial properties,¹² superoxide-anion-scavenging activity,¹³ and exhibit cytotoxicity and DNA fragmentation effects in human HT-1080 fibrosarcoma cells.¹⁴ The structures of sulfathiazole, meloxicam, and selenazofurin and their pharmacological activities are given in Fig. 1.

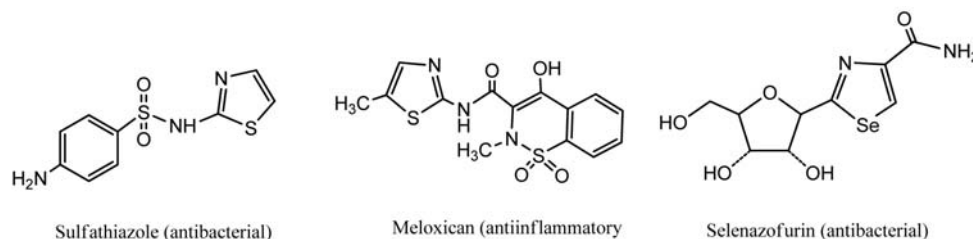
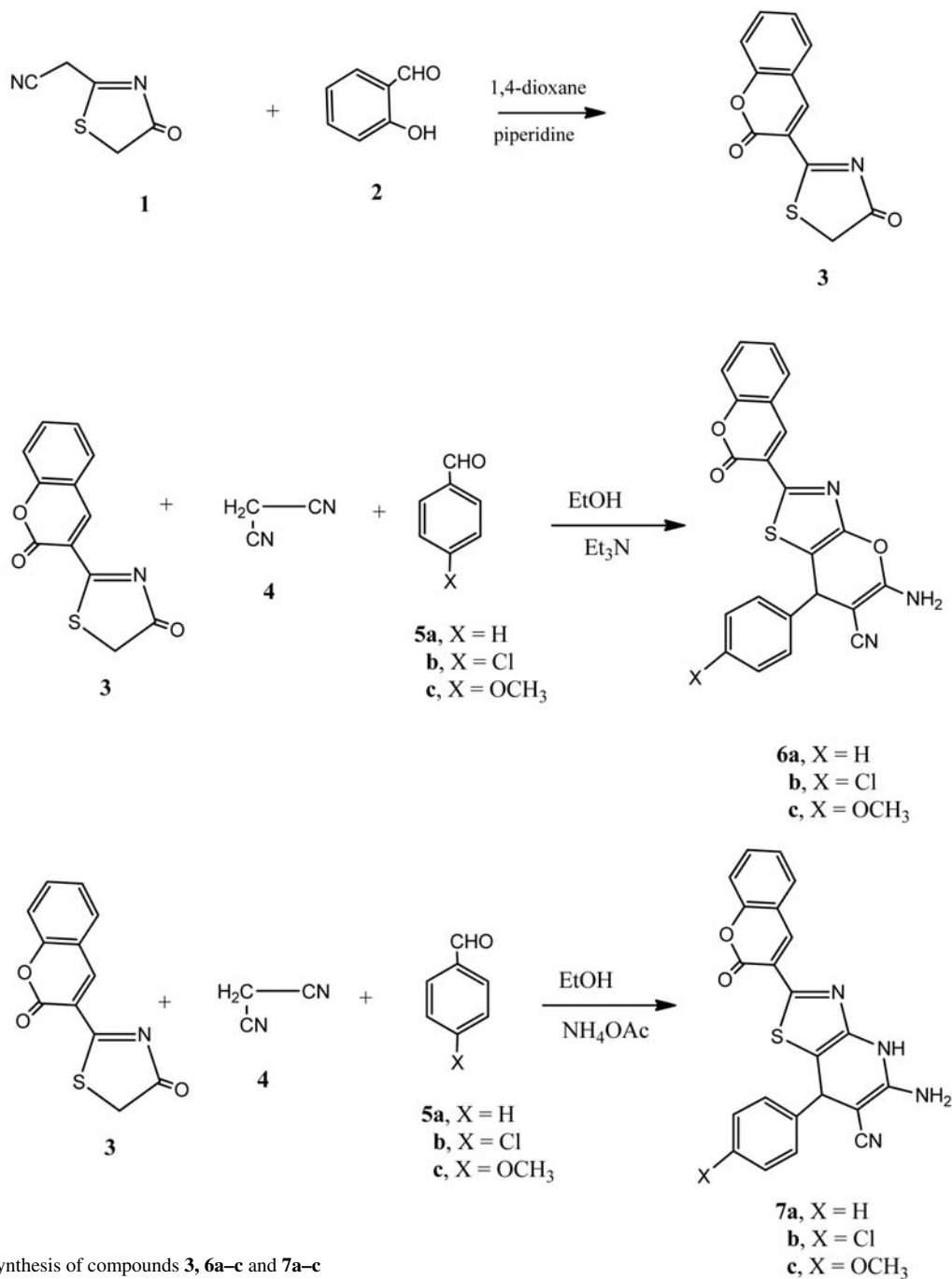


Fig 1. Biologically active thiazole and senazole drivatives

In many report structural modification of the heterocyclic rings through the construction of new heterocyclic nuclei enhances the pharmaceutical applications of the resulting molecules.^{15,16} This encouraged our efforts in this work to modify 2-(4-oxo-4,5-dihydrothiazol-2-yl)acetonitrile through its reaction with salicylaldehyde to produce a chromen-3-yl)thiazol which was used as the key starting compound for many further heterocyclic transformations. The anti-inflammatory and anti-ulcer evaluations of the newly synthesized compounds were studied.

2. Results and Discussion

In the present work the 2-(4-oxo-4,5-dihydrothiazol-2-yl)acetonitrile (**1**) reacted with salicylaldehyde (**2**) in 1,4-dioxane containing a catalytic amount of piperidine to give the coumarin derivative **3**. The structure of **3** was based on its analytical and spectral data. Thus, the ¹H NMR spectrum showed a singlet at δ 4.28 ppm equivalent to the thiazole CH₂ group, a singlet at δ 6.52 ppm indicating the coumarin 4H, a multiplet at δ 7.28–7.38 ppm for the C₆H₄ group. Moreover, the ¹³C NMR spectrum sho-



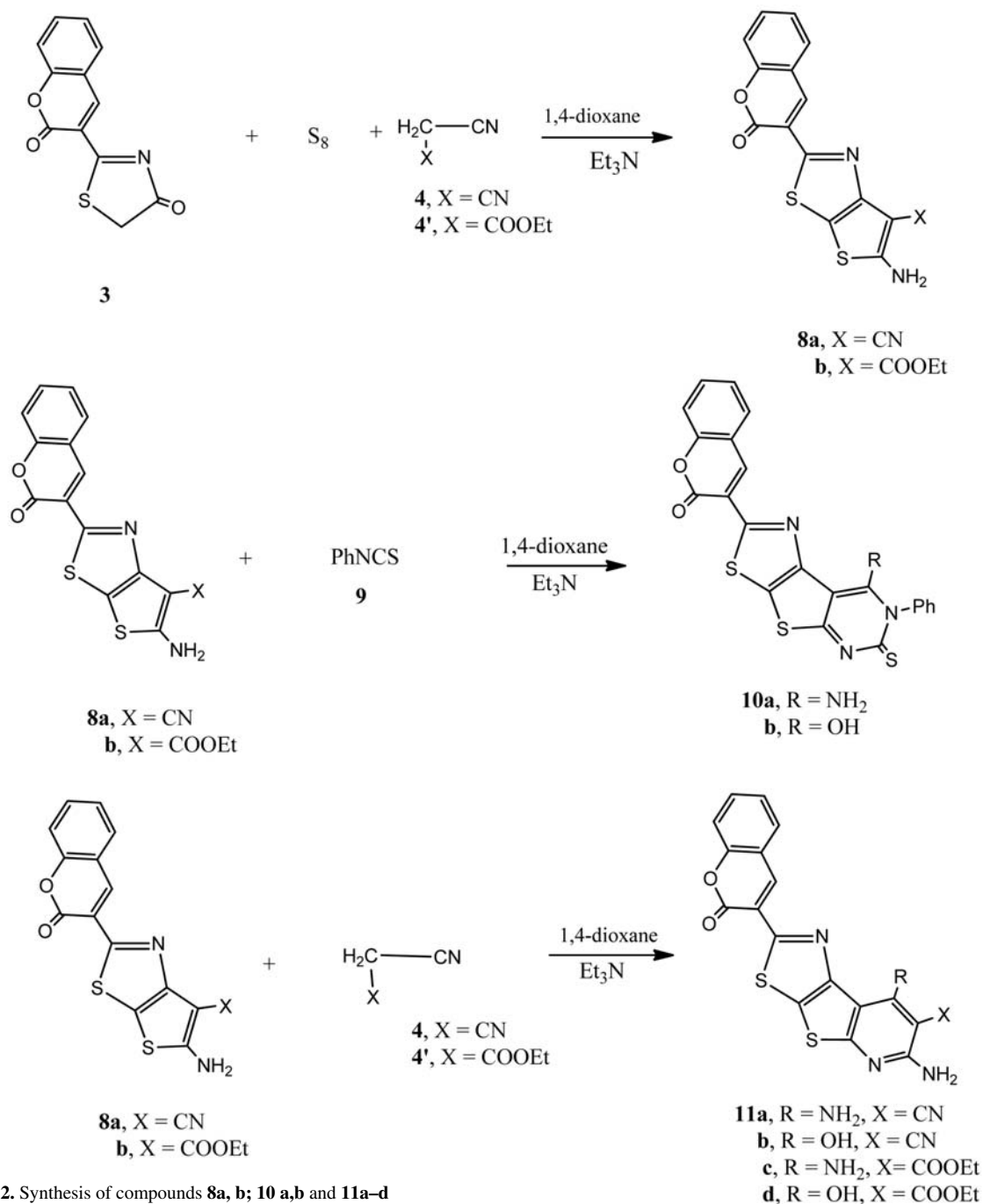
Scheme 1. Synthesis of compounds **3**, **6a–c** and **7a–c**

wed beside the expected signals, δ 58.6 ppm indicating the presence of the thiazole CH_2 , two signals at δ 164.3, 168.6 ppm equivalent to the two CO groups and a signal at δ 170.3 ppm for the $\text{C}=\text{N}$.

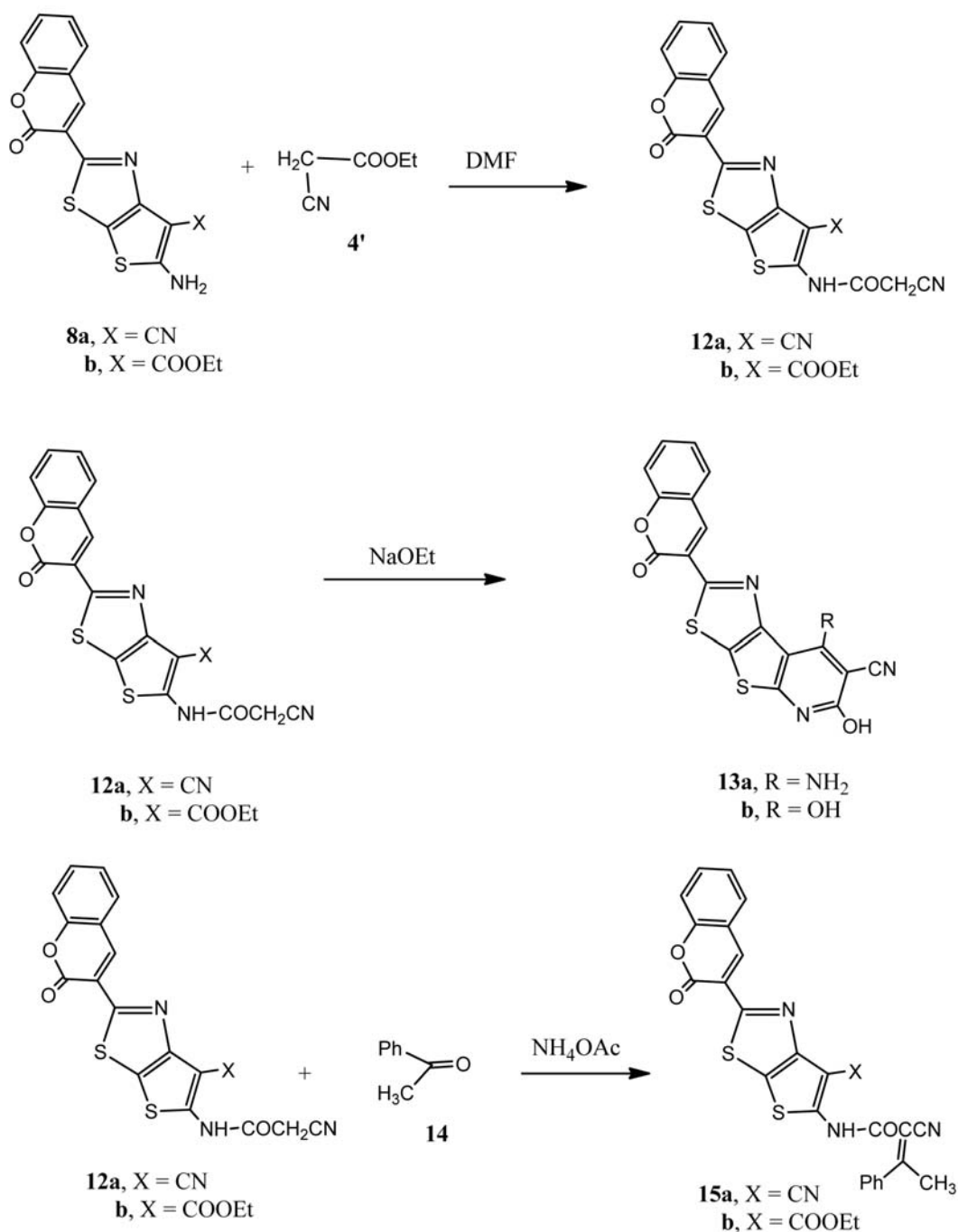
Compound **3** underwent multi-component reactions through its transformation with malonitrile (**4**) and any of benzaldehyde (**5a**), 4-chlorobenzaldehyde (**5b**) or 4-methoxybenzaldehyde (**5c**) to give the 5-amino-7*H*-pyrido[2,3-*d*]thiazole-6-carbonitrile derivatives **6a–c**, respectively. On the other hand, carrying out the same reaction, but using ammonium acetate instead of piperidine gave

the pyrido[2,3-*d*]thiazole derivatives **7a–c**, respectively (Scheme 1).

Compound **3** was ready for thiophene formation through the well known Gewald's thiophene synthesis.^{17,18} Thus, the reaction of **3** with elemental sulfur and either malonitrile (**4**) or ethyl cyanoacetate (**4'**) gave the thieno[2,3-*d*]thiazole derivatives **8a** and **8b**, respectively. The analytical and spectral data of **8a,b** were the tools of their structural elucidation. Thus, the ^1H NMR spectrum of **8a** showed a signal at δ 4.93 ppm equivalent to the NH_2 group (D_2O exchangeable), a singlet at δ 6.62 ppm indica-



Scheme 2. Synthesis of compounds **8a, b**; **10 a,b** and **11a–d**

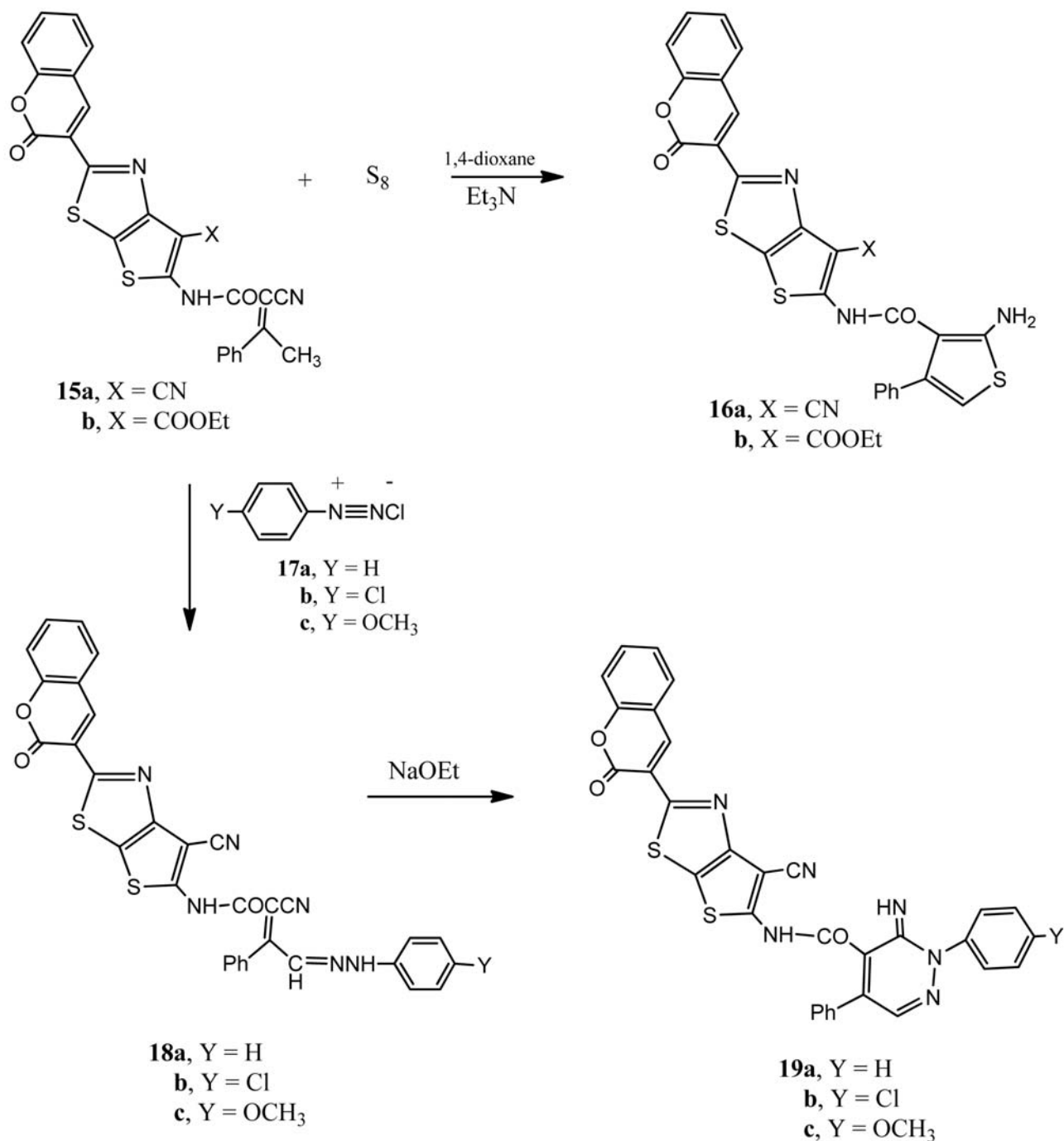


Scheme 3. Synthesis of compounds **12a, b**; **13 a, b** and **15a, b**

ting the coumarin H-4 and a multiplet at δ 7.26–7.40 ppm for the C₆H₄ group. In addition, the ¹³C NMR spectrum signals were consistent with the assigned structure. The reaction of either compound **8a** or **8b** with phenylisothiocyanate (**9**) gave the 7-phenylthiazolo[4',5':4,5]thieno[2,3-*d*]pyrimidin-6(7*H*)-thione derivatives **10a** and **10b**, respectively. On the other hand, the reaction of either compound **8a** or **8b** with either malononitrile (**4**) or ethyl cyanoacetate (**4'**) gave the 7-phenylthiazolo[4',5':4,5]thieno[2,3-*d*]pyrimidin-6(7*H*)-thione derivatives **11a–d**, res-

pectively (Scheme 2). The analytical and spectral data of the latter products were consistent with their respective structures (see experimental section).

The 2-amino group present in compounds **8a** and **8b** is capable for the amide group formation. Thus, the reaction of either **8a** or **8b** with ethyl cyanoacetate in refluxing dimethylformamide gave the amide derivatives **12a** and **12b**, respectively. The latter compounds readily underwent cyclization when heated in sodium ethoxide solution to give the 7-phenylthiazolo[4',5':4,5]thieno



Scheme 4. Synthesis of compounds **16a, b**; **18 a, c** and **19a–c**

[2,3-*d*]pyridine derivatives **13a** and **13b**, respectively. On the other hand, the reaction of either compound **12a** or **12b** with acetophenone (**14**) gave the Knoevenagel condensation products **15a** and **15b**, respectively (Scheme 3).

The presence of the but-2-enenitrile moiety in compounds **15a** and **15b** is suitable for thiophene synthesis. Thus, the reaction of either compound **15a** or **15b** with elemental sulfur gave the thiophene derivatives **16a** and **16b**, respectively. On the other hand, the reaction of either

her **15a** or **15b** with any of benzenediazonium chloride (**17a**), 4-chlorobenzenediazonium chloride (**17b**), or 4-methoxybenzenediazonium chloride (**17c**) gave the arylhydrazone derivatives **18a–c**, respectively (Scheme 4). The spectral and analytical data of compounds **18a–c** were in agreement with their respective structures (see experimental section). The latter compounds underwent cyclization when heated in sodium ethoxide solution to give corresponding pyridazine derivatives **19a–c**, respectively.

2. 1. Anti-inflammatory Evaluation Method

Carrageenin-induced rat hind paw oedema model was used. The method adopted resembles essentially that described by Winter.¹⁹ The animals were studied for toxicity of DMSO up to 10% v/v in saline, and 5% DMSO was selected as a vehicle to suspend the standard drugs and the test compounds.

Albino rats weighing between 150 and 250 g of either sex were starved for 18 h prior to the experiment. The animals were weighed, marked for identification and divided into groups of six. The standard drugs, ibuprofen (20 mg/kg body weight), mefenamic acid (100 mg/kg body weight) and three graded doses (10, 20 and 40 mg/kg body weight) of the test compounds were given orally as a suspension using 5% DMSO as a vehicle.

One hour later foot paw oedema was induced by injecting 0.1 mL of 1% carrageenin subcutaneously into the planter portion of the right hind paw of each rat. Initial foot paw volume was measured immediately by mercury plethysmometer. Oedema was measured 3 h after carrageenin administration. The swelling in test group animals was used to calculate the % inhibition \pm SEM of oedema achieved by the compound at the test dose compared with the vehicle control group. The % protection of oedema was calculated according to the formula:

$$\% \text{ anti inflammatory activity} = 100 \left(\frac{1 - V_t}{V_c} \right) \quad (1)$$

where V_t and V_c are the volume of oedema in test compounds and control groups, respectively.

2. 2. Anti-ulcer Evaluation Method

Animals Wistar albino rats weighing 150–200 g of either sex maintained under standard husbandary conditions (temperature 23 ± 2 °C, relative humidity $55 \pm 10\%$ and 12 h light/dark cycle) were used for the screening. Animals were fed with standard laboratory food *ad libitum* during the study period.

Albino rats of either sex were divided into four groups of six animals each. Animals were fasted for 24 h before the study, but had free access to water. Animals in the control group received only distilled water. Each of the given compounds at 250 and 500 mg/kg, (p. o.) were given to the animals in the treatment group. Ranitidine (50 mg/kg) was used as a standard. After 1 h of drugs treatment, they were anaesthetized with the help of anesthetic ether; the abdomen was opened by a small midline incision below the xiphoid process. Pyloric portion of the stomach was slightly lifted out and ligated according to the method of Shay²⁰ avoiding traction to the pylorus or damage to its blood supply. The stomach was replaced carefully and the abdominal wall was closed by interrupted sutures. Rats were sacrificed by an over dose of anaesthetic ether after 4 h of pyloric ligation. The abdomen was

opened, cardiac end of the stomach was dissected out and the contents were drained into a glass tube. The volume of the gastric juice was measured and centrifuged at 2000 rpm for 10 min. From the supernatant, aliquots (1 mL each) were taken for the determination of pH, total and free acidity. Each stomach was examined for lesions in the fore stomach portion and indexed according to severity.

Determination of pH: an aliquot of 1 mL gastric juice was diluted with 1 mL of distilled water and pH of the solution was measured using pH meter.

2. 3. Toxicity Method on Shrimp Larvae

All toxicity tests were 96-h static renewal tests and water quality measurements (dissolved oxygen, pH, temperature, salinity) were taken in the control containers each day. Tests were run in a Revco's Environmental Chamber at 25 °C, 20% salinity, and a 16 h light/8 h dark cycle. A media change was made every 24 h. Larvae used for all tests were one to two days old and exposed in 600 mL glass beakers containing 400 mL of media with 10 larvae/beaker and three replicates/concentration. Larvae were fed newly hatched *Artemia* after daily media exchange. The concentration of each compound was taken in terms 10, 100 and 1000 mg/mL. Adult shrimp toxicity tests were also run to complete the grass shrimp toxicity profile. Adult shrimp (acclimated for two weeks before testing) were exposed in 4 L wide mouth glass jars containing 2 L of media and 10 shrimp/jar with two replicates/concentration, according to the modified method published by DeLorenzo²¹ and were run under conditions as described above for larvae.

2. 4. Biological Evaluation

2. 4. 1. Anti-inflammatory Evaluations

From Table 1 it is clear that compounds **10b**, **13b**, **18a**, **19b** and **19c** showed high anti-inflammatory activity, but compounds **6b**, **6c**, **7a**, **8b**, **11a**, **11b**, **13a**, **16b** and **18c** showed low anti-inflammatory effect. Considering the 4,7-dihydrothiazolo[4,5-*b*]pyridine derivatives **7a–c**, compound **7b** with the 4-chlorophenyl moiety showed the highest anti-inflammatory activity among the three compounds. On the other hand, for the thieno[3,2-*d*]thiazole derivatives **8a,b**, compound **8a** with the 3-cyano group showed higher anti-inflammatory activity than compound **8b** with the COOEt moiety. For the thiazolo[4',5':4,5]thieno[2,3-*d*]pyrimidine derivatives **10a** and **10b**, it is obvious that compound **10b** with the hydroxyl group showed higher anti-inflammatory activity than compound **10a** with the amino group. Similarly for compounds **11a–d**, compound **11d** with the OH and COOEt moieties has the highest anti-inflammatory activity among the four compounds.

The reaction of either compound **8a** or **8b** with ethyl cyanoacetate gave the *N*-cyanoacetamido derivatives **12a**

or **12b**, respectively. Such change showed a remarkable decrease of anti-inflammatory activity in the case of **12a**. On the other hand, it showed an increase of anti-inflammatory activity of **12b**. For the thiazolo[4',5':4,5]thieno[2,3-*b*]pyridine derivatives **13a,b** the presence of the OH group in compound **13b** is responsible for its higher anti-inflammatory activity than compound **13a**. The reaction of either compound **12a** or **12b** with acetophenone gave the condensation products **15a** and **15b**, respectively, where compound **15b** with the COOEt had higher activity than compound **15a** with the CN group. However, the thiophene derivatives **16a,b** obtained from **15a,b** showed the reverse: compound **16a** with the CN group showed higher anti-inflammatory activity than compound **16b** with the COOEt moiety. Considering the arylhydrazine derivatives **18a–c**, it is clear from Table 1 that compound **18a** with the unsubstituted aryl moiety has the maximum anti-inflammatory activity among the three compounds. However, cyclization of compounds **18a–c** in sodium ethoxide solution gave the pyridazine derivatives **19a–c** where compound **19b** with 4-chloroaryl group showed the highest anti-inflammatory activity among the three compounds, followed by the compound **19c** with the 4-methoxyaryl group having the intermediate activity of the three compounds.

2. 5. Anti-ulcer Activity

From Table 2 it is clear that compounds **6a–c**, **7a–c**, **8b**, **10b**, **13a**, **16b**, **19b** and **19c** showed the maximum anti-ulcer activity. Moreover, these twelve compounds showed inhibition effect higher than the reference drug ranitidine. On the other hand, most of the newly synthesized products showed a moderate anti-ulcer activity at concentrations 250 and 500 mg/kg. Moreover, compounds **19b** and **19c** showed the maximum antiulcer activity among the tested compounds.

2. 5. 1. Macroscopic Evaluation of Stomach

The stomachs were opened along the greater curvature, rinsed with saline to remove gastric contents and blood clots and examined by a 10× magnifier lens to assess the formation of ulcers. The numbers of ulcers were counted. Scoring of ulcer was made as follows: (0) ... normal colored stomach; (0.5) ... red coloration; (1) ... spot ulcer; (1.5) ... hemorrhagic streak; (2) ... deep ulcers; (3) ... perforation. Mean ulcer score for each animal was expressed as ulcer index (UI). The percentage of ulcer protection was determined as follows. UI was measured by using the following formula:

$$UI = UN + US + (10^{-1}UP) \quad (2)$$

where UI is ulcer index; UN average number of ulcers per animal; US average number of severity score; UP percent-

age of animals with ulcers. Percentage inhibition of ulceration was calculated as below:

$$\begin{aligned} \% \text{ inhibition of ulceration} &= \quad (3) \\ &= [UI(\text{control}) - UI(\text{text})] \frac{100}{UI(\text{control})} \end{aligned}$$

2. 6. Toxicity

Bioactive compounds are often toxic to shrimp larvae. Thus, in order to monitor these chemicals *in vivo* lethality to shrimp larvae (*Artemia salina*), brine shrimp lethality assay was used. Results were analyzed with LC₅₀ program to determine LC₅₀ values and 95% confidence intervals.²² Results are given in Table 4 for the compounds which exhibited optimal anti-inflammatory and anti-ulcer activity, that is the eleven compounds **7b**, **8a**, **10a**, **10b**, **13a**, **13b**, **15b**, **18a**, **19b**, **19c** and **19d**. The shrimp lethality assay is considered as a useful tool for preliminary assessment of toxicity, and it has been used for the detection of fungal toxins, plant extract toxicity, heavy metals, cyanobacteria toxins, pesticides, and cytotoxicity testing of dental materials,²³ natural and synthetic organic compounds.²⁴ It has also been shown that *A. salina* toxicity test results have a correlation with rodent and human acute oral toxicity data. Generally, a good correlation was obtained between *A. salina* toxicity test and the rodent data. Likewise, the predictive screening potential of the aquatic invertebrate tests for acute oral toxicity in humans, including *A. salina* toxicity test, was slightly better than the rat test for test compounds.²⁵

In order to prevent the toxicity results from possible false effects originating from solubility of compounds and possible toxicity effect of DMSO, compounds were prepared by dissolving in DMSO in the suggested DMSO volume ranges. It is clear from Table 3 that compounds **10b**, **18a**, **19c** and **19d** showed no toxicity against the tested organisms. On the other hand, compound **7b**, **13b** and **15b** are very toxic compounds, while the rest of compounds are harmful.

3. Experimental

3. 1. General

All melting points were determined on an Electrothermal digital melting point apparatus and are uncorrected. IR spectra (KBr discs) were recorded on a FTIR plus 460 or Pye Unicam SP-1000 spectrophotometer (Pye Unicam, UK, Cambridge). ¹H NMR and ¹³C NMR spectra were recorded with Varian Gemini-200 (200 MHz, Varian UK) and JEOL AS 500 MHz (JEOL, Japan) instruments in DMSO-*d*₆ as the solvent, using TMS as the internal standard, chemical shifts are expressed as δ ppm. The

Table 1. Anti-inflammatory evaluation of the newly synthesis products

Compound	Anti-inflammatory activity ^a carrageenin-induced rat hind paw oedema Mean value of Oedema volume (% protection)		
	10 mg/kg	20 mg/kg	40 mg/kg
3	0.60 ± 0.04 (74)	0.38 ± 0.06 (83)	0.19 ± 0.07 (92)
6a	0.55 ± 0.18 (76)	0.22 ± 0.02 (90)	0.23 ± 0.11 (90)
6b	0.99 ± 0.23 (57)	0.68 ± 0.08 (70)	1.13 ± 0.38 (51)
6c	0.98 ± 0.28 (57)	0.82 ± 0.03 (64)	0.63 ± 0.18 (72)
7a	0.82 ± 0.15 (64)	0.60 ± 0.13 (73)	0.92 ± 0.18 (58)
7b	0.38 ± 0.08 (83)	0.36 ± 0.07 (84)	0.29 ± 0.04 (87)
7c	0.80 ± 0.15 (65)	0.66 ± 0.12 (71)	0.52 ± 0.05 (77)
8a	0.44 ± 0.08 (81)	0.51 ± 0.09 (78)	0.05 ± 0.04 (98)
8b	0.93 ± 0.14 (59)	0.81 ± 0.20 (65)	1.22 ± 0.30 (48)
10a	1.30 ± 0.04 (43)	0.48 ± 0.06 (79)	0.93 ± 0.14 (59)
10b	0.09 ± 0.02 (96)	0.16 ± 0.08 (93)	0.19 ± 0.06 (92)
11a	1.22 ± 0.18 (47)	1.09 ± 0.23 (53)	1.19 ± 0.37 (48)
11b	1.08 ± 0.11 (53)	1.04 ± 0.18 (55)	1.09 ± 0.21 (53)
11c	0.83 ± 0.17 (64)	0.92 ± 0.20 (60)	0.69 ± 0.30 (70)
11d	0.68 ± 0.03 (70)	0.29 ± 0.04 (87)	0.59 ± 0.23 (74)
12a	0.83 ± 0.19 (64)	1.29 ± 0.36 (44)	1.33 ± 0.46 (42)
12b	0.60 ± 0.10 (74)	0.88 ± 0.08 (62)	0.49 ± 0.06 (79)
13a	1.54 ± 0.20 (33)	1.01 ± 0.23 (56)	0.51 ± 0.13 (78)
13b	0.39 ± 0.02 (83)	0.09 ± 0.01 (96)	0.39 ± 0.13 (83)
15a	0.63 ± 0.15 (73)	0.82 ± 0.21 (64)	0.65 ± 0.16 (72)
15b	0.33 ± 0.02 (86)	0.29 ± 0.07 (87)	0.40 ± 0.09 (83)
16a	0.75 ± 0.19 (67)	0.32 ± 0.04 (86)	0.22 ± 0.06 (90)
16b	1.39 ± 0.21 (39)	1.08 ± 0.25 (53)	1.19 ± 0.12 (48)
18a	0.13 ± 0.07(94)	0.24 ± 0.04 (89)	0.07 ± 0.03 (97)
18b	0.73 ± 0.18 (68)	0.52 ± 0.15 (77)	0.29 ± 0.02 (87)
18c	1.39 ± 0.26 (39)	1.52 ± 0.16 (34)	1.44 ± 0.29 (37)
19a	0.89 ± 0.17 (61)	0.62 ± 0.08 (73)	0.29 ± 0.01 (87)
19b	0.18 ± 0.03 (92)	0.18 ± 0.09 (92)	0.09 ± 0.01 (96)
19c	0.29 ± 0.11 (87)	0.37 ± 0.07(84)	0.49 ± 0.11 (79)
DMSO control	2.30	–	–
Indomethacin	0.32 ± 0.09 (86)	0.31 ± 0.07 (88)	0.09 ± 0.29 (96)

^a Oral administration for all test compounds, P < 0.05, the standard drugs (dose and % protection) were ibuprofen (20 mg/kg, 33%) and mefenamic acid (100 mg/kg, 39%).

mass spectra were recorded with Hewlett Packard 5988 A GC/MS system (Hewlett Packard, Agilent, USA) and GCMS-QP 1000Ex Shimadzu (EI, 70 eV) (Shimadzu, Japan) instruments. Analytical data were obtained from Vario EL III Elemental CHNS analyzer (Germany).

3. 1. 1. 2-(2-Oxo-2H-chromen-3-yl)thiazol-4(5H)-one (3)

To a solution of compound **1** (1.40 g, 0.01 mol) in 1,4-dioxane (30 mL) containing piperidine (1.0 mL) salicylaldehyde (1.22 g, 0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 1 h, left to cool and the solid product formed, in each case, was collected by filtration and crystallized from ethanol.

Yellow crystals (ethanol), yield 82% (2.45 g), mp 166–168 °C; IR (KBr) ν_{max} 3054, 2933, 1690, 1687, 1660, 1638 cm^{-1} ; ¹H NMR (DMSO-*d*₆, 200 MHz): δ

7.28–7.38 (4H, m, Bz), 6.52 (1H, s, H-4), 4.28 (2H, s, CH₂); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 170.3 (C-2'), 168.6, 164.3 (C-2, C-4'), 58.6 (C-5'), 144.1, 139.5, 133.8, 130.1, 126.3, 123.6, 120.3 (C-3, C-4, C-5, C-6, C-7, C-8, C-9, C-10); EI-MS: *m/z* 245 [M]⁺ (18); Analysis Calcd for C₁₂H₇NO₃S (245.25): C, 58.77; H, 2.88; N, 5.71; S, 13.07%. Found: C, 58.85; H, 3.03; N, 5.92; S, 12.89%.

3. 1. 2. General Procedure for the Synthesis of the Pyrano[2,3-*d*]thiazole Derivatives 6a–c

To a solution of compound **3** (2.45 g, 0.01 mol) in ethanol (50 mL) containing triethylamine (0.50 mL) malononitrile (0.66 g, 0.01 mol) and any of benzaldehyde (1.06 g, 0.01 mol), 4-chlorobenzaldehyde (1.40 g, 0.01 mol) or 4-methoxybenzaldehyde (1.37 g, 0.01 mol) were added. The whole reaction mixture was heated under reflux for 4 h then left to cool. The formed solid product, in each case, was collected by filtration.

Table 2. Effect of DMSO solution of the given compounds on gastric ulcer induced by pylorus ligation in rats, pH, total and free acidity in pyloric ligation induced ulceration in rats

Treatment	Dose (mg/kg)	Ulcer index	% ulcer inhibition
Control (distilled water)	10	3.6 ± 0.45	–
3	250	1.91 ± 0.53	47
	500	0.98 ± 0.19	73
6a	250	0.43 ± 0.08	88
	500	0.18 ± 0.01	95
6b	250	0.32 ± 0.28	91
	500	0.82 ± 0.08	77
6c	250	0.77 ± 0.19	79
	500	0.59 ± 0.08	84
7a	250	0.66 ± 0.42	82
	500	0.49 ± 0.52	86
7b	250	0.88 ± 0.30	75
	500	0.38 ± 0.21	89
7c	250	0.58 ± 0.27	84
	500	0.32 ± 0.19	91
8a	250	1.29 ± 0.27	64
	500	1.38 ± 0.36	62
8b	250	0.13 ± 0.08	96
	500	0.19 ± 0.05	95
10a	250	1.86 ± 0.63	48
	500	0.82 ± 0.17	77
10b	250	0.80 ± 0.25	78
	500	0.32 ± 0.09	91
11a	250	1.77 ± 0.83	51
	500	1.20 ± 0.39	67
11b	250	1.83 ± 0.29	49
	500	0.66 ± 0.13	82
11c	250	1.73 ± 0.42	52
	500	1.39 ± 0.62	61
11d	250	1.23 ± 0.64	66
	500	0.88 ± 0.12	75
12a	250	1.93 ± 0.25	46
	500	0.83 ± 0.26	77
12b	250	1.82 ± 0.63	49
	500	1.94 ± 0.08	46
13a	250	0.63 ± 0.09	82
	500	1.19 ± 0.16	67
13b	250	1.09 ± 0.15	70
	500	0.86 ± 0.26	76
15a	250	1.73 ± 0.41	52
	500	1.63 ± 0.22	55
15b	250	1.87 ± 0.48	48
	500	1.29 ± 0.27	64
16a	250	1.53 ± 0.42	57
	500	0.89 ± 0.04	75
16b	250	0.63 ± 0.12	82
	500	0.58 ± 0.20	84
18a	250	0.92 ± 0.13	66
	500	0.62 ± 0.23	74
18b	250	2.88 ± 0.53	20
	500	2.21 ± 0.09	39
18c	250	1.42 ± 0.96	60
	500	0.89 ± 0.25	72

Treatment	Dose (mg/kg)	Ulcer index	% ulcer inhibition
19a	250	2.89 ± 0.68	20
	500	1.63 ± 0.71	55
19b	250	0.22 ± 0.05	94
	500	0.29 ± 0.09	92
19c	250	0.26 ± 0.06	93
	500	0.19 ± 0.01	95
Ranitidine	50	1.65 ± 0.49	54

Values are expressed as mean ± S.E.M., $n = 6$, * $p < 0.05$ when compared with control group.

Table 3. Toxicity of the most potent compounds

Compound	Conc. (µg/mL)	Mortality ^a	Toxicity	LC ₅₀	Upper 95% lim.	Lower 95% lim.
7b	10	2	very toxic	120.29	–	–
	100	4				
	1000	10				
8a	10	1	harmful	210.55	197.22	
	148.38					
	100	4				
	1000	7				
10b	10	0	nontoxic	818.15	112.40	72.73
	100	2				
	1000	4				
13b	10	3	very toxic	112.49	276.40	66.30
	100	6				
	1000	10				
15b	10	2	very toxic	109.06	220.31	80.45
	100	5				
	1000	10				
18a	10	0	non toxic	909.28	–	–
	100	1				
	1000	4				
19b	10	1	harmful	133.40	236.50	93.28
	100	4				
	1000	10				
19c	10	0	non toxic	910.63	–	–
	100	3				
	1000	5				
19d	10	0	non toxic	890.63	–	–
	100	2				
	1000	6				

^aTen organisms (*A. salina*) tested for each concentration.

5-Amino-2-(2-oxo-2H-chromen-3-yl)-7-phenyl-7H-pyrano[2,3-d]thiazole-6-carbonitrile (6a)

Yellow crystals (ethanol), yield 80% (3.19 g), mp 188–191 °C; IR (KBr) ν_{\max} 3477, 3329, 3056, 2220, 1693, 1654, 1635 cm^{-1} ; ¹H NMR (DMSO-*d*₆, 200 MHz): δ 7.42–7.25 (9H, m, 2Bz), 6.58 (1H, s, H-4'), 6.18 (1H, s, H-7), 4.82 (2H, s, D₂O exchangeable, NH₂); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 86.4 (C-7), 116.8 (CN), 144.4, 143.1, 142.8, 138.8, 135.2, 130.3, 129.4, 128.9, 127.2,

126.3, 126.2, 125.4, 124.8, 122.8, 119.8 (Bz, C-8,C-9, C-5, C-6, C-1', C-2', C3', C-4', C-5', C-6'), 165.2 (C-7'), 173.2 (C-2); EI-MS: m/z 399 [M]⁺ (42%); Analysis Calcd for C₂₂H₁₃N₃O₃S (399.42): C, 66.15; H, 3.28; N, 10.52; S, 8.03. Found: C, 66.29; H, 3.41; N, 10.73; S, 7.92.

5-Amino-7-(4-chlorophenyl)-2-(2-oxo-2H-chromen-3-yl)-7H-pyrano[2,3-d]thiazole-6-carbonitrile (6b)

Pale yellow crystals (ethanol), yield 73% (3.16 g), mp 166–169 °C; IR (KBr) ν_{\max} 3493, 3326, 3054, 2223, 1690, 1656, 1633 (C=C) cm⁻¹; ¹H NMR (DMSO-*d*₆, 200 MHz): δ 7.24–7.40 (8H, m, 2Bz), 6.61 (1H, s, H-4'), 6.15 (1H, s, H-7), 4.80 (s, 2H, D₂O exchangeable, NH₂); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 86.8 (C-7), 116.6 (CN), 120.4, 122.6, 123.9, 124.3, 124.9, 125.2, 125.7, 126.9, 129.2, 130.5, 133.9, 135.2, 138.1, 140.2, 142.9, 143.6 (Bz, C-8,C-9,C-5, C-6, C-1', C-2', C3', C-4', C-5', C-6'), 165.4 (C-7'), 173.0 (C-2); EI-MS: m/z 433 [M]⁺ (30%); Analysis Calcd for C₂₂H₁₂ClN₃O₃S (433.03): C, 60.90; H, 2.79; N, 9.69; S, 7.39%. Found: C, 61.28; H, 2.91; N, 9.49; S, 7.44%.

5-Amino-7-(4-methoxyphenyl)-2-(2-oxo-2H-chromen-3-yl)-7H-pyrano[2,3-d]thiazole-6-carbonitrile (6c)

Orange crystals (ethanol), yield 88% (3.77 g), mp 211–213 °C; IR (KBr) ν_{\max} 3475, 3318, 3056, 2221, 1692, 1658, 1630 cm⁻¹; ¹H NMR (DMSO-*d*₆, 200 MHz): δ 7.29–7.41 (m, 8H, 2Bz), 6.63 (1H, s, H-4'), 6.18 (1H, s, H-7), 4.86 (2H, s, D₂O exchangeable, NH₂), 3.14 (3H, s, OCH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 173.3 (C-2), 165.4 (C-7'), 143.6, 143.0, 139.2, 138.7, 134.6, 133.7, 132.2, 131.8, 129.8, 127.4, 126.0, 125.7, 125.1, 124.6, 123.2, 120.7 (Bz, C-8,C-9,C-5, C-6, C-1', C-2', C3', C-4', C-5', C-6'), 116.8 (CN), 86.6 (C-7), 34.6 (C, OCH₃); EI-MS: m/z 429 [M]⁺ (22%); Analysis Calcd for C₂₃H₁₅N₃O₄S (429.45): C, 64.33; H, 3.52; N, 9.78; S, 7.47%. Found: C, 64.40; H, 3.66; N, 9.83; S, 7.54%.

3. 1. 3. General procedure for the synthesis of the pyridino[2,3-d]thiazole derivatives 7a–c

To a solution of compound **3** (2.45 g, 0.01 mol) in ethanol (50 mL) containing ammonium acetate (0.50 mL) malononitrile (0.66 g, 0.01 mol) and any of benzaldehyde (1.06 g, 0.01 mol), 4-chlorobenzaldehyde (1.40 g, 0.01 mol) or 4-methoxybenzaldehyde (1.37 g, 0.01 mol) was added. The whole reaction mixture was heated under reflux for 4 h then left to cool. The solid product formed upon pouring onto ice/water containing a few drops of hydrochloric acid was collected by filtration.

5-Amino-2-(2-oxo-2H-chromen-3-yl)-7-phenyl-4,7-dihydrothiazolo[4,5-*b*]pyridine-6-carbonitrile (7a)

Yellow crystals (ethanol), yield 77% (3.06 g), mp 201–203 °C; IR (KBr) ν_{\max} 3466–3380, 3059, 2222, 1688, 1652, 1633 cm⁻¹; ¹H NMR (DMSO-*d*₆, 200 MHz):

δ 8.23 (s, 1H, D₂O exchangeable, NH), 7.28–7.39 (m, 9H, 2Bz), 6.54 (1H, s, H-7), 6.16 (1H, s, H-4'), 4.80 (s, 2H, D₂O exchangeable, NH₂); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 173.0 (C-2), 165.8 (C-7'), 142.6, 141.3, 140.2, 139.4, 136.2, 134.9, 133.8, 128.7, 128.2, 126.8, 126.0, 125.3, 124.5, 121.5, 120.3 (Bz, C-8,C-9,C-5, C-6, C-1', C-2', C3', C-4', C-5', C-6'), 116.9 (CN), 86.2 (C-7); EI-MS: m/z 398 [M]⁺ (28%); Analysis Calcd for C₂₂H₁₄N₄O₂S (398.44): C, 66.32; H, 3.54; N, 14.06; S, 8.05%. Found: C, 66.59; H, 3.33; N, 14.18; S, 7.98%.

5-Amino-7-(4-chlorophenyl)-2-(2-oxo-2H-chromen-3-yl)-4,7-dihydrothiazolo[4,5-*b*]pyridine-6-carbonitrile (7b)

Pale yellow crystals (ethanol), yield 73% (3.15 g), mp 241–243 °C; IR (KBr) ν_{\max} 3493–3327, 3056, 2220, 1688, 1653, 1630 cm⁻¹; ¹H NMR (DMSO-*d*₆, 200 MHz): δ 8.25 (s, 1H, D₂O exchangeable, NH), 7.26–7.39 (m, 8H, 2Bz), 6.63 (1H, s, H-7), 6.18 (1H, s, H-4'), 4.83 (s, 2H, D₂O exchangeable, NH₂); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 173.2 (C-2), 165.6 (C-7'), 142.8, 141.4, 140.8, 137.2, 135.6, 134.3, 132.8, 128.7, 126.4, 126.0, 125.2, 123.9, 123.2, 122.4, 120.3 (Bz, C-8,C-9,C-5, C-6, C-1', C-2', C3', C-4', C-5', C-6'), 116.9 (CN), 86.2 (C-7); EI-MS: m/z 432 [M]⁺ (38%); Analysis Calcd for C₂₂H₁₃ClN₄O₂S (432.88): C, 61.04; H, 3.03; N, 12.94; S, 7.41%. Found: C, 61.29; H, 2.88; N, 12.72; S, 7.39%.

5-Amino-7-(4-methoxyphenyl)-2-(2-oxo-2H-chromen-3-yl)-4,7-dihydrothiazolo[4,5-*b*]pyridine-6-carbonitrile (7c)

Orange crystals (ethanol), yield 79% (3.38 g), mp 255–258 °C; IR (KBr) ν_{\max} 3488–3359, 3052, 2220, 1689, 1654, 1632 cm⁻¹; ¹H NMR (DMSO-*d*₆, 200 MHz): δ 8.22 (s, 1H, D₂O exchangeable, NH), 7.25–7.45 (8H, m, 2Bz), 6.62 (1H, s, H-7), 6.20 (1H, s, H-4'), 4.83 (s, 2H, D₂O exchangeable, NH₂), 3.70 (s, 3H, CH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 173.2 (C-2), 165.6 (C-7'), 142.9, 142.8, 139.9, 139.1, 136.0, 134.2, 132.8, 132.4, 130.2, 128.8, 126.2, 125.6, 125.2, 123.8, 122.0, 121.2 (Bz, C-8,C-9,C-5, C-6, C-1', C-2', C3', C-4', C-5', C-6'), 116.9 (CN), 86.6 (C-7), 34.8 (C, OCH₃); EI-MS: m/z 428 [M]⁺ (20%); Analysis Calcd for C₂₃H₁₆N₄O₃S (428.46): C, 64.47; H, 3.76; N, 13.08; S, 7.48%. Found: C, 64.53; H, 3.80; N, 12.93; S, 7.62%.

3. 1. 4. General Procedure for the Synthesis of the Thieno[3,2-*d*]thiazole Derivatives 8a and 8b

To a solution of compound **3** (2.45 g, 0.01 mol) in 1,4-dioxane (40 mL) containing (0.01 mol) triethylamine, either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) and elemental sulfur (0.32 g, 0.01 mol) were added. The whole reaction mixture was heated under reflux for 4 h then left to cool. The solid product

formed upon pouring onto ice/water containing a few drops of hydrochloric acid was collected by filtration.

5-Amino-2-(2-oxo-2H-chromen-3-yl)thieno[3,2-d]thiazole-6-carbonitrile (**8a**)

Orange crystals (1,4-dioxane), yield 82% (2.66 g), mp 189–193 °C; IR (KBr) ν_{max} 3488–3342, 3057, 2220, 1690, 1655, 1632 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 7.40–7.26 (4H, m, Bz), 6.62 (1H, s, H-4'), 4.93 (2H, s, D₂O exchangeable, NH₂); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 172.8 (C-2), 164.8 (C-2'), 142.3, 141.8, 138.1, 136.2, 133.2, 132.8, 130.5, 128.4, 126.2, 123.9, 122.0, 119.7 (Bz, C-4, C-5, C-7, C-8, C-3', C-4'), 117.3 (CN); EI-MS: m/z 325 [M]⁺ (15%); Analysis Calcd for C₁₅H₇N₃O₂S₂ (325.36): C, 55.37; H, 2.17; N, 12.91; S, 19.71%. Found: C, 55.52; H, 2.28; N, 13.18; S, 19.88%.

Ethyl 5-amino-2-(2-oxo-2H-chromen-3-yl)thieno[3,2-d]thiazole-6-carboxylate (8b**)** Yellow crystals (1,4-dioxane), yield 77% (3.86 g), mp 142–145 °C; IR (KBr) ν_{max} 3493–3338, 3055, 1688, 1653, 1630 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 7.38–7.23 (4H, m, Bz), 6.64 (1H, s, H-4'), 4.96 (2H, s, D₂O exchangeable, NH₂), 4.20 (2H, q, $J = 7.29$ Hz, OCH₂CH₃), 1.14 (3H, t, $J = 7.29$ Hz, OCH₂CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 172.9 (C-2), 164.8 (C-2'), 142.6, 141.2, 138.3, 136.0, 133.6, 132.5, 130.3, 128.3, 126.4, 123.7, 122.2, 119.3 (Bz, C-4, C-5, C-7, C-8, C-3', C-4'), 56.2 (C, CH₂, OCH₂CH₃), 16.9 (C, CH₃, OCH₂CH₃); EI-MS: m/z 372 [M]⁺ (30%); Analysis Calcd for C₁₇H₁₂N₂O₄S₂ (372.42): C, 54.83; H, 3.25; N, 7.52; S, 17.22%. Found: C, 54.76; H, 3.19; N, 7.73; S, 17.08%.

3. 1. 5. General Procedure for the Synthesis of 7-phenylthiazolo[4',5':4,5]-thieno[2,3-d]pyrimidine-6(7H)-thione Derivatives **10a** and **10b**

To a solution of either compound **8a** (3.25 g, 0.01 mol) or **8b** (3.72 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL), phenylisothiocyanate (1.30 g, 0.01 mol) was added. The whole reaction mixture was heated under reflux for 4 h then poured onto ice/water containing a few drops of hydrochloric acid and the formed solid product, in each case, was collected by filtration.

3-(8-Amino-7-phenyl-6-thioxo-6,7-dihydrothiazolo[4',5':4,5]thieno[2,3-d]pyrimidin-2-yl)-2H-chromen-2-one (**10a**)

Pale yellow crystals (1,4-dioxane), 74% (3.40 g), mp 222–225 °C; IR (KBr) ν_{max} 3459–3326, 3054, 2223, 1687, 1653, 1630, 1220 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 7.25–7.42 (m, 9H, 2Bz), 6.62 (1H, s, H-4'), 4.92 (2H, s, D₂O exchangeable, NH₂); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 178.2 (C-6), 170.8, 172.4 (C-2, C-10), 164.3

(C-2'), 142.6, 140.4, 139.2, 138.1, 136.2, 133.2, 132.8, 131.8, 130.2, 129.3, 128.6, 127.3, 125.8, 123.3, 121.8, 120.3 (2Bz, C-4, C-8, C-9, C-11, C-3', C-4'); EI-MS: m/z 460 [M]⁺ (35%); Analysis Calcd for C₂₂H₁₂N₄O₂S₃ (460.55): C, 57.37; H, 2.63; N, 12.17; S, 20.89%. Found: C, 57.50; H, 2.58; N, 12.22; S, 20.69%.

3-(8-Hydroxy-7-phenyl-6-thioxo-6,7-dihydrothiazolo[4',5':4,5]thieno[2,3-d]pyrimidin-2-yl)-2H-chromen-2-one (**10b**)

Yellow crystals (1,4-dioxane), yield 69% (3.18 g), mp 180–184 °C; IR (KBr) ν_{max} 3473–3340, 3052, 2220, 1689, 1652, 1632, 1223 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 10.31 (1H, s, D₂O exchangeable, OH), 7.46–7.28 (9H, m, 2Bz), 6.64 (1H, s, H-4'); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 178.2 (C-6), 170.5, 172.2 (C-2, C-10), 164.4 (C-2'), 143.1, 140.6, 138.0, 137.4, 136.1, 134.9, 132.6, 132.3, 130.6, 129.0, 126.1, 124.2, 123.6, 122.8, 120.5, 118.5 (2Bz, C-4, C-8, C-9, C-11, C-3', C-4'); EI-MS: m/z 462 [M]⁺ (18%); Analysis Calcd for C₂₂H₁₁N₃O₃S₃ (462.54): C, 57.25; H, 2.40; N, 9.10; S, 20.84%. Found: C, 57.39; H, 2.29; N, 9.28; S, 20.77%.

3. 1. 6. General Procedure for the Synthesis of the Thiazolo[4',5':4,5]thieno[2,3-b]pyridine Derivatives **11a–d**

To a solution of either compound **8a** (3.25 g, 0.01 mol) or **8b** (4.61 g, 0.01 mol) in 1,4-dioxane (30 mL) containing triethylamine (0.50 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 2 h then poured onto ice/water containing a few drops of hydrochloric acid and the solid product formed was collected by filtration.

6,8-Diamino-2-(2-oxo-2H-chromen-3-yl)thiazolo[4',5':4,5]thieno[2,3-b]pyridine-7-carbonitrile (**11a**)

Orange crystals (1,4-dioxane), yield 78% (4.83 g), mp 243–246 °C; IR (KBr) ν_{max} 3488–3336, 3056, 2221, 1689, 1653, 1632 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 7.40–7.28 (4H, m, Bz), 6.65 (1H, s, H-4'), 5.21, 4.89 (4H, 2s, D₂O exchangeable, 2NH₂); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 171.8, 170.3 (C-2, C-6), 164.6 (C-2'), 140.5, 138.2, 136.4, 135.2, 134.6, 132.7, 130.2, 129.7, 127.8, 125.0, 124.6, 122.7, 120.1, 119.2 (Bz, C-4, C-5, C-8, C-9, C-10, C-11, C-3', C-4'), 116.9 (CN); EI-MS: m/z 391 [M]⁺ (24%); Analysis Calcd for C₁₈H₉N₅O₂S₂ (391.43): C, 55.23; H, 2.32; N, 17.89; S, 16.38%. Found: C, 55.36; H, 2.41; N, 18.29; S, 16.29%.

6-Amino-8-hydroxy-2-(2-oxo-2H-chromen-3-yl)thiazolo[4',5':4,5]thieno[2,3-b]pyridine-7-carbonitrile (**11b**)

Pale yellow crystals (1,4-dioxane), yield 66% (2.58 g), mp 210–213 °C; IR (KBr) ν_{max} 3574–3332, 3054,

2222, 1686, 1651, 1631 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 10.30 (1H, s, D_2O exchangeable, OH), 7.25–7.36 (4H, m, Bz), 6.63 (1H, s, H-4'), 4.87 (2H, s, D_2O exchangeable, NH_2); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 171.5, 170.2 (C-2, C-6), 164.3 (C-2'), 141.8, 137.0, 136.4, 133.0, 132.8, 131.9, 130.2, 125.7, 125.1, 124.6, 123.4, 121.8, 120.6 (Bz, C-4, C-5, C-8, C-9, C-10, C-11, C-3', C-4'), 116.5 (CN); EI-MS: m/z 392 $[\text{M}]^+$ (18%); Analysis Calcd for $\text{C}_{18}\text{H}_8\text{N}_4\text{O}_3\text{S}_2$ (392.41): C, 55.09; H, 2.05; N, 14.28; S, 16.34%. Found: C, 55.18; H, 2.21; N, 14.50; S, 16.48%.

Ethyl 6,8-diamino-2-(2-oxo-2H-chromen-3-yl)thiazolo[4',5':4,5]thieno[2,3-b]pyridine-7-carboxylate (11c)

Yellowish white (1,4-dioxane), yield 73% (3.19 g), mp 188–192 °C; IR (KBr) ν_{max} 3464–3328, 3056, 1688, 1653, 1629 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 7.37–7.27 (4H, m, Bz), 6.60 (1H, s, H-4'), 4.45, 5.28 (4H, 2s, D_2O exchangeable, 2NH_2), 4.20 (2H, q, $J = 7.08$ Hz, OCH_2CH_3), 1.14 (3H, t, $J = 7.08$ Hz, OCH_2CH_3); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 170.4, 171.4 (C-2, C-6), 164.2 (C-2'), 120.5, 121.8, 121.9, 122.8, 123.9, 124.2, 127.3, 127.8, 128.0, 129.3, 130.3, 131.3, 134.9, 139.2 (Bz, C-4, C-5, C-8, C-9, C-10, C-11, C-3', C-4'), 54.2 (C, CH_2 , OCH_2CH_3), 16.8 (C, CH_3 , OCH_2CH_3); EI-MS: m/z 438 $[\text{M}]^+$ (23%); Analysis Calcd for $\text{C}_{20}\text{H}_{14}\text{N}_4\text{O}_4\text{S}_2$ (438.48): C, 54.78; H, 3.22; N, 12.78; S, 14.63%. Found: C, 54.91; H, 3.40; N, 12.91; S, 14.80%.

Ethyl 6-amino-8-hydroxy-2-(2-oxo-2H-chromen-3-yl)thiazolo[4',5':4,5]thieno[2,3-b]pyridine-7-carboxylate (11d)

Yellow crystals (1,4-dioxane), yield 78% (3.42 g), mp 205–208 °C; IR (KBr) ν_{max} 3520–3336, 3058, 1689, 1651, 1632 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 10.22 (1H, s, D_2O exchangeable, OH), 7.28–7.39 (4H, m, Bz), 6.62 (1H, s, H-4'), 4.48 (2H, s, D_2O exchangeable, NH_2), 4.20 (2H, q, $J = 7.22$ Hz, OCH_2CH_3), 1.15 (3H, t, $J = 7.22$ Hz, OCH_2CH_3); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 171.6, 170.2 (C-2, C-6), 164.4, 164.2 (C-2'), 142.7, 134.9, 132.6, 131.8, 131.2, 129.7, 119.3, 126.7, 126.5, 124.8, 124.0, 123.6, 122.8, 121.6, (Bz, C-4, C-5, C-8, C-9, C-10, C-11, C-3', C-4'), 54.6 (C, CH_2 , OCH_2CH_3), 16.7 (C, CH_3 , OCH_2CH_3); EI-MS: m/z 439 $[\text{M}]^+$ (18%); Analysis Calcd for $\text{C}_{20}\text{H}_{13}\text{N}_3\text{O}_5\text{S}_2$ (439.46): C, 54.66; H, 2.98; N, 9.56; S, 14.59%. Found: C, 54.79; H, 3.17; N, 9.29; S, 14.63%.

3. 1. 7. General Procedure for the Synthesis of the 2-cyanoacetylthieno[3,2-d]thiazole Derivatives 12a and 12b

To a solution of either compound **8a** (3.25 g, 0.01 mol) or **8b** (4.61 g, 0.01 mol) in dimethylformamide (30 mL) ethyl cyanoacetate (1.13 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 h then pou-

red onto ice/water containing a few drops of hydrochloric acid and the solid product formed was collected by filtration.

2-Cyano-N-[6-cyano-2-(2-oxo-2H-chromen-3-yl)thieno[3,2-d]thiazol-5-yl]acetamide (12a)

Yellow crystals (1,4-dioxane), yield 83% (3.25 g), mp 188–191 °C; IR (KBr) ν_{max} 3468–3326, 3054, 2223, 2220, 1688, 1705, 1655, 1634 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 8.20 (1H, s, NH, D_2O exchangeable), 7.26–7.36 (4H, m, Bz), 6.63 (1H, s, H-4'), 5.30 (2H, s, CH_2); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 170.1 (C-2), 164.4, 165.2 (C-2', C, CO, COCH_2), 141.2, 134.9, 134.8, 132.9, 131.9, 128.3, 126.9, 125.3, 124.7, 122.3, 121.9, 120.8 (Bz, C-4, C-5, C-7, C-8, C-3', C-4'), 116.6, 115.8 (2CN), 62.5 (C, CH_2 , COCH_2); EI-MS: m/z 392 $[\text{M}]^+$ (18%); Analysis Calcd for $\text{C}_{18}\text{H}_8\text{N}_4\text{O}_3\text{S}_2$ (392.41): C, 55.09; H, 2.05; N, 14.28; S, 16.34%. Found: C, 55.28; H, 2.26; N, 14.25; S, 16.52%.

Ethyl 5-(2-cyanoacetamido)-2-(2-oxo-2H-chromen-3-yl)thieno[3,2-d]thiazole-6-carboxylate (12b)

Pale brown crystals (1,4-dioxane), yield 80% (3.51 g), mp 166–169 °C; IR (KBr) ν_{max} 3462–3329, 3057, 2222, 1689–1706, 1646, 1628 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 8.31 (1H, s, D_2O exchangeable, NH), 7.39–7.26 (4H, m, Bz), 6.61 (1H, s, H-4'), 5.28 (2H, s, CH_2), 4.22 (2H, q, $J = 6.83$ Hz, OCH_2CH_3), 1.38 (3H, t, $J = 6.83$ Hz, OCH_2CH_3); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 170.0 (C-2), 162.3, 163.0, 164.4 (C-2', COOEt, NHCO), 140.3, 134.8, 131.9, 128.4, 126.9, 126.0, 125.3, 124.1, 123.1, 122.2, 121.3, 120.8 (Bz, C-4, C-5, C-7, C-8, C-3', C-4'), 116.8 (CN), 62.8 (C, CH_2 , COCH_2), 54.2 (C, OCH_2CH_3), 16.5 (C, OCH_2CH_3); EI-MS: m/z 439 $[\text{M}]^+$ (37%); Analysis Calcd for $\text{C}_{20}\text{H}_{13}\text{N}_3\text{O}_5\text{S}_2$ (439.46): C, 54.66; H, 2.98; N, 9.56; S, 14.59%. Found: C, 54.80; H, 3.11; N, 9.73; S, 14.79%.

3. 1. 8. General Procedure for the Synthesis of the Thiazolo[4',5':4,5]thieno[2,3-b]pyridine-7-carbonitrile Derivatives 13a and 13b

To a suspension of either compound **12a** (3.92 g, 0.01 mol) or **12b** (4.39 g, 0.01 mol) in sodium ethoxide solution [prepared by dissolving metallic sodium (0.46 g, 0.02 mol) in absolute ethanol (40 mL)] was heated in a boiling water bath for 3 h then poured onto ice/water containing a few drops of hydrochloric acid (till pH 6). The formed solid product, in each case, was collected by filtration.

8-Amino-6-hydroxy-2-(2-oxo-2H-chromen-3-yl)thiazolo[4',5':4,5]thieno[2,3-b]pyridine-7-carbonitrile (13a)

Yellow crystals (1,4-dioxane), yield 73% (2.86 g), mp 245–247 °C; IR (KBr) ν_{max} 3533–3341, 3058, 2220,

1693, 1653, 1632 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 10.19 (1H, s, OH, D_2O exchangeable), 7.39–7.28 (4H, m, Bz), 6.60 (1H, s, H-4'), 4.80 (2H, s, D_2O exchangeable, NH_2); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 171.8, 170.5 (C-2, C-6), 164.2 (C-2'), 139.8, 137.9, 132.4, 131.9, 130.3, 129.7, 127.8, 127.1, 124.9, 124.2, 123.8, 122.3, 121.6, 120.2 (Bz, C-4, C-5, C-8, C-9, C-10, C-11, C-3', C-4'), 116.8 (CN); EI-MS: m/z 392 $[\text{M}]^+$ (32%); Analysis Calcd for $\text{C}_{18}\text{H}_8\text{N}_4\text{O}_3\text{S}_2$ (392.41): C, 55.09; H, 2.05; N, 14.28; S, 16.34%. Found: C, 54.89; H, 2.31; N, 14.44; S, 16.41%.

6,8-Dihydroxy-2-(2-oxo-2H-chromen-3-yl)thiazolo [4',5':4,5]thieno[2,3-b]pyridine-7-carbonitrile (13b)

Yellow crystals (1,4-dioxane), yield 73% (2.86 g), mp 262–265 $^\circ\text{C}$; IR (KBr) ν_{max} 3542–3318, 3054, 1686, 1642, 1628 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 10.32, 10.11 (2H, 2s, D_2O exchangeable, 2OH), 7.36–7.28 (4H, m, C_6H_4), 6.64 (1H, s, H-4'); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 171.0, 170.2 (C-2, C-6), 164.2 (C-2'), 142.0, 138.3, 130.9, 130.6, 129.4, 128.3, 127.3, 126.3, 125.8, 125.4, 125.0, 123.9, 123.5, 122.6, 122.0, 120.2 (Bz, C-4, C-5, C-8, C-9, C-10, C-11, C-3', C-4'), 116.6 (CN); EI-MS: m/z 393 $[\text{M}]^+$ (44%); Analysis Calcd for $\text{C}_{18}\text{H}_7\text{N}_3\text{O}_4\text{S}_2$ (393.40): C, 54.96; H, 1.79; N, 10.68; S, 16.30%. Found: C, 54.77; H, 2.01; N, 10.29; S, 16.42%.

3. 1. 9. General Procedure for the Synthesis of the Thieno[3,2-d]thiazole Derivatives 15a and 15b

To a dry solid of either **12a** (3.92 g, 0.01 mol) or **12b** (4.39 g, 0.01 mol) acetophenone (1.20 g, 0.01 mol) and ammonium acetate (0.50 g) was added. The whole reaction mixture was heated in an oil bath at 120 $^\circ\text{C}$ for 0.5 h and the solid product formed upon trituration with ethanol was collected by filtration.

2-Cyano-N-[6-cyano-2-(2-oxo-2H-chromen-3-yl)thieno[3,2-d]thiazol-5-yl]-3-phenylbut-2-enamide (15a)

Yellow crystals (1,4-dioxane), yield 73% (3.60 g), mp 221–223 $^\circ\text{C}$; IR (KBr) ν_{max} 3472–3318, 3057, 2222, 2220, 1689, 1690, 1642, 1627 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 10.22 (1H, s, D_2O exchangeable, NH), 7.26–7.46 (9H, m, 2Bz), 6.59 (1H, s, H-4'), 2.88 (3H, s, CH_3); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 170.2 (C-2), 164.5, 162.8 (C-2, NHCO), 140.5, 138.7, 136.2, 133.4, 132.6, 132.1, 130.8, 128.9, 127.8, 127.4, 126.1, 125.6, 124.2, 123.7, 122.1, 121.9, 120.9, 120.5 (2Bz, C-3, C-4, C-6, C-7, C-3', C-4'), 117.0, 116.4, (2CN), 90.6, 86.7 (C=C), 19.5 (C, CH_3); EI-MS: m/z 494 $[\text{M}]^+$ (23%); Analysis Calcd for $\text{C}_{26}\text{H}_{14}\text{N}_4\text{O}_3\text{S}_2$ (494.54): C, 63.14; H, 2.85; N, 11.33; S, 12.97%. Found: C, 62.98; H, 2.69; N, 11.41; S, 13.08%.

Ethyl 2-[[6-cyano-2-(2-oxo-2H-chromen-3-yl)thieno[3,2-d]thiazol-5-yl]carbamoyl]-3-phenylbut-2-enoate (15b)

Yellow crystals (1,4-dioxane), yield 68% (3.67 g), mp 189–192 $^\circ\text{C}$; IR (KBr) ν_{max} 3488–3326, 3052, 2221, 1690, 1682, 1638, 1628 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 8.31 (1H, s, D_2O exchangeable, NH), 7.39–7.26 (9H, m, C_6H_5 , C_6H_4), 6.63 (1H, s, H-4'), 4.22 (q, 2H, J = 6.88 Hz, OCH_2CH_3), 2.68 (3H, s, CH_3), 1.13 (t, 3H, J = 6.88 Hz, OCH_2CH_3); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 170.4 (C-2), 164.2 (C-2'), 163.9, 162.3 (C-2, NHCO), 141.2, 134.7, 132.6, 130.8, 129.2, 128.3, 127.1, 126.8, 125.8, 124.9, 124.2, 123.9, 123.5, 123.1, 122.2, 119.6 (2Bz, C-3, C-4, C-6, C-7, C-3', C-4'), 90.8, 86.3 (C=C), 52.3 (C, OCH_2CH_3), 19.2 (CH_3), 16.8 (C, OCH_2CH_3); EI-MS: m/z 541 $[\text{M}]^+$ (28%); Analysis Calcd for $\text{C}_{28}\text{H}_{19}\text{N}_3\text{O}_5\text{S}_2$ (541.60): C, 62.09; H, 3.54; N, 7.76; S, 11.84%. Found: C, 61.95; H, 3.72; N, 8.02; S, 12.03%.

3. 1. 10. General Procedure for the Synthesis of Thiophene Derivatives 16a and 16b

To a solution of either compound **15a** (4.94 g, 0.01 mol) or **15b** (5.41 g, 0.01 mol) in 1,4-dioxane (30 mL) containing triethylamine (0.50 mL) elemental sulfur (3.2 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 h then poured onto ice/water containing a few drops of hydrochloric acid and the solid product formed, in each case, was collected by filtration.

2-Amino-N-[6-cyano-2-(2-oxo-2H-chromen-3-yl)thieno[3,2-d]thiazol-5-yl]-4-phenylthiophene-3-carboxamide (16a)

Yellow crystals (acetic acid), 82% (4.31 g), mp 187–190 $^\circ\text{C}$; IR (KBr) ν_{max} 3494–3326, 3053, 2224, 1687, 1694, 1646, 1629 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 10.28 (1H, s, D_2O exchangeable, NH), 7.23–7.39 (9H, m, 2Bz), 6.61 (1H, s, H-4'), 6.24 (1H, s, H-5''), 4.68 (2H, s, D_2O exchangeable, NH_2); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 170.3 (C-2), 162.5, 164.3 (C-2', CONH), 143.8, 142.6, 138.7, 133.4, 132.6, 132.4, 131.9, 130.6, 128.3, 127.4, 126.8, 125.9, 124.2, 123.9, 123.6, 122.3, 121.9, 120.9, 120.6, 119.6 (Bz, C-3, C-4, C-6, C-7, C-3', C-4', C-2'', C-3'', C-4'', C-5''), 116.8 (CN); EI-MS: m/z 526 $[\text{M}]^+$ (38%); Analysis Calcd for $\text{C}_{26}\text{H}_{14}\text{N}_4\text{O}_3\text{S}_3$ (526.61): C, 59.30; H, 2.68; N, 10.64; S, 18.27%. Found: C, 59.52; H, 2.72; N, 10.39; S, 18.44%.

Ethyl 5-(2-amino-4-phenylthiophene-3-carboxamido)-2-(2-oxo-2H-chromen-3-yl)thieno[3,2-d]thiazole-6-carboxylate (16b)

Yellow (1,4-dioxane), yield 73% (4.18 g), mp 203–207 $^\circ\text{C}$; IR (KBr) ν_{max} 3462–3346, 3056, 1689–1696, 1641, 1632 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 8.33 (1H, s, D_2O exchangeable, NH), 7.23–7.37 (9H, m, 2Bz), 6.63 (1H, s, H-4'), 6.28 (1H, s, H-5''), 4.82 (2H, s, D_2O exchangeable, NH_2), 4.20 (2H, q, J = 7.39 Hz, OCH_2CH_3), 1.14 (3H, t, J = 7.39 Hz, OCH_2CH_3); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 170.2 (C-2), 162.5, 164.0,

164.3 (C-2', CONH, COOEt), 143.1, 142.4, 136.1, 132.8, 131.6, 130.3, 129.6, 129.2, 128.4, 128.7, 126.7, 125.9, 125.3, 125.2, 124.9, 123.8, 123.8, 123.1, 122.9, 121.8 (Bz, C-3, C-4, C-6, C-7, C-3', C-4', C-2'', C-3'', C-4'', C-5''), 52.3 (C, OCH₂CH₃), 16.4 (C, OCH₂CH₃); EI-MS: *m/z* 573 [M]⁺ (31%); Analysis Calcd for C₂₈H₁₉N₃O₅S₃ (573.66): C, 58.62; H, 3.34; N, 7.32; S, 16.77%. Found: C, 58.39; H, 3.51; N, 7.48; S, 16.91%.

3. 1. 11. General Procedure for the Synthesis of the Arylhydrazone Derivatives 18a–c

To a solution of compound **15a** (4.94 g, 0.01 mol) in ethanol (50 mL) containing sodium hydroxide (10 mL, 10%) any of benzenediazonium chloride, 4-chlorobenzenediazonium chloride or 4-methoxybenzenediazonium chloride [prepared through the addition of sodium nitrite solution (0.70 g, 0.01 mol) to a cold solution (0–5 °C) of the appropriate aromatic amine, namely aniline (0.93 g, 0.01 mol), 4-chloroaniline (1.27 g, 0.01 mol) or 4-methoxyaniline (1.24 g, 0.01 mol), dissolved in concentrated hydrochloric acid (10 mL, 18 mol) with continuous stirring] was added portion-wise with continuous stirring. The whole reaction mixture was stirred at room for 2 h and the solid product formed, in each case, was collected by filtration.

2-Cyano-*N*-[6-cyano-2-(2-oxo-2*H*-chromen-3-yl)thieno[3,2-*d*]thiazol-5-yl]-3-phenyl-4-(2-phenylhydrazono)but-2-enamide (18a)

Yellow (1,4-dioxane), yield 76% (4.54 g) mp 133–137 °C; IR (KBr) *v*_{max} 3469–3341, 3056, 2221, 2220, 1689, 1691, 1648, 1631 cm⁻¹; ¹H NMR (DMSO-*d*₆, 200 MHz): δ 10.23, 8.33 (2H, 2s, D₂O exchangeable, 2NH), 7.48–7.25 (14H, m, 2Bz), 5.93 (1H, s, CH=N), 6.63 (1H, s, H-4'); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 173.1, 171.6 (C-2, C=N), 164.9, 162.8 (C-2', NHCO), 142.5, 141.3, 139.5, 138.2, 131.8, 131.2, 130.8, 127.6, 126.4, 125.2, 124.8, 124.6, 124.2, 123.3, 122.8, 122.0, 121.3, 120.8, 120.3, 119.8 (Bz, C-3, C-4, C-6, C-7, C-3', C-4', C-2'', C-3'', C-4'', C-5''), 116.8, 116.4 (2CN), 90.6, 88.3 (C=C); EI-MS: *m/z* 598 [M]⁺ (28%); Analysis Calcd for C₃₂H₁₈N₆O₃S₂ (598.65): C, 64.20; H, 3.03; N, 14.04; S, 10.71%. Found: C, 64.49; H, 2.97; N, 14.22; S, 10.64%.

4-[2-(4-Chlorophenyl)hydrazono]-2-cyano-*N*-[6-cyano-2-(2-oxo-2*H*-chromen-3-yl)thieno[3,2-*d*]thiazol-5-yl]-3-phenylbut-2-enamide (18b)

Yellow crystals (1,4-dioxane), 89% (5.63 g), mp 123–125 °C; IR (KBr) *v*_{max} 3473–3341, 3058, 2223, 2220, 1688, 1696, 1642, 1635 cm⁻¹; ¹H NMR (DMSO-*d*₆, 200 MHz): δ 10.21, 8.36 (2H, 2s, 2NH, D₂O exchangeable), 7.45–7.26 (13H, m, 3Bz), 6.62 (1H, s, H-4'), 5.90 (1H, s, CH=N); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 173.3, 171.8 (C-2, C=N), 164.6, 162.6 (C-2', NHCO), 142.2,

140.8, 132.3, 131.8, 130.8, 128.4, 127.9, 126.4, 125.9, 125.4, 124.9, 124.8, 124.2, 123.1, 122.9, 122.4, 121.3, 120.8, 120.1, 119.9 (Bz, C-3, C-4, C-6, C-7, C-3', C-4', C-2'', C-3'', C-4'', C-5''), 116.7, 115.8 (2CN); 88.4, 90.6 (C=C); EI-MS: *m/z* 633 [M]⁺ (41%); Analysis Calcd for C₃₂H₁₇ClN₆O₃S₂ (633.10): C, 60.71; H, 2.71; N, 13.27; S, 10.13%. Found: C, 60.83; H, 2.83; N, 13.99; S, 10.28%.

2-Cyano-*N*-[6-cyano-2-(2-oxo-2*H*-chromen-3-yl)thieno[3,2-*d*]thiazol-5-yl]-4-[2-(4-methoxyphenyl)hydrazono]-3-phenylbut-2-enamide (18c)

Yellow crystals (1,4-dioxane), yield 68%, (4.27 g), mp 203–207 °C; IR (KBr) *v*_{max} 3489–3324, 3055, 2222, 2220, 1690, 1693, 1640, 1631 cm⁻¹; ¹H NMR (DMSO-*d*₆, 200 MHz): δ 10.25, 8.33 (2H, 2s, D₂O exchangeable, 2NH), 7.48–7.28 (13H, m, 3Bz), 6.60 (1H, s, H-4'), 5.88 (1H, s, CH=N), 1.12 (3H, s, CH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 173.1, 171.9 (C-2, C=N), 162.8, 164.9 (C-2', NHCO), 141.6, 140.4, 132.8, 131.3, 130.9, 130.2, 129.4, 126.8, 126.0, 125.6, 125.3, 124.9, 124.4, 123.7, 123.0, 122.8, 121.4, 120.9, 120.3, 119.7 (Bz, C-3, C-4, C-6, C-7, C-3', C-4', C-2'', C-3'', C-4'', C-5''), 116.6, 116.3 (2CN), 90.3, 88.7 (C=C); EI-MS: *m/z* 628 [M]⁺ (33%); Analysis Calcd for C₃₃H₂₀N₆O₄S₂ (628.68): C, 63.05; H, 3.21; N, 13.37; S, 10.20%. Found: C, 63.22; H, 3.51; N, 13.53; S, 10.42%.

3. 1. 12. General Procedure for the Synthesis of the Pyridazine Derivatives 19a–c

To a suspension of any of compound **18a** (5.98 g, 0.01 mol), **18b** (6.33 g, 0.01 mol) or **17c** (6.28 g, 0.01 mol) in sodium ethoxide solution [prepared via dissolving metallic sodium (0.46 g, 0.02 mol) in absolute ethanol (60 mL)] was heated in a boiling water bath for 3 h then poured onto ice/water containing a few drops of hydrochloric acid (till pH 6). The solid product formed was collected by filtration.

N-[6-Cyano-2-(2-oxo-2*H*-chromen-3-yl)thieno[3,2-*d*]thiazol-5-yl]-3-imino-2,5-diphenyl-2,3-dihydropyridazine-4-carboxamide (19a)

Yellow crystals (1,4-dioxane), yield 82% (4.90 g), mp 287–293 °C; IR (KBr) *v*_{max} 3477–3321, 3053, 2220, 1689, 1691, 1648, (C=N), 1631 (C=C) cm⁻¹; ¹H NMR (DMSO-*d*₆, 200 MHz): δ 10.41, 8.31 (2H, 2s, D₂O exchangeable, 2NH), 7.45–7.22 (14H, m, 3Bz), 6.60 (1H, s, H-4'), 6.02 (1H, s, H-3''); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ 173.0, 170.3, 169.6 (C-3, C-3'', C-6''), 164.6, 162.6 (C-2', NHCO), 142.9, 140.2, 133.4, 132.6, 131.8, 131.2, 130.8, 128.2, 127.9, 126.7, 125.5, 124.8, 124.9, 123.0, 122.8, 122.3, 121.9, 120.9, 120.8, 119.2 (Bz, C-3, C-4, C-6, C-7, C-3', C-4', C-4'', C-5''), 116.2 (CN), EI-MS: *m/z* 598 [M]⁺ (20%); Analysis Calcd for C₃₂H₁₈N₆O₃S₂ (598.65): C, 64.20; H, 3.03; N, 14.04; S, 10.71%. Found: C, 64.33; H, 3.19; N, 14.38; S, 10.54%.

2-(4-Chlorophenyl)-N-[6-cyano-2-(2-oxo-2H-chromen-3-yl)thieno[3,2-d]thiazol-5-yl]-3-imino-5-phenyl-2,3-dihydropyridazine-4-carboxamide (19b)

Pale yellow crystals (1,4-dioxane), yield 69% (4.12 g), mp 244–147 °C; IR (KBr) ν_{max} 3482–3329, 3057, 2221, 1689, 1696, 1640, 1632 (C=C) cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 10.20, 8.38 (2H, 2s, D₂O exchangeable, 2NH), 7.42–7.23 (13H, m, 3Bz), 7.03 (1H, s, H-3''), 6.64 (1H, s, H-4'); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 173.1, 170.2, 169.7 (C-3', C-3'', C-6''), 162.8, 164.3 (C-2', NHCO), 142.6, 140.2, 139.5, 138.6, 132.9, 131.8, 131.6, 130.8, 127.6, 126.4, 125.7, 125.6, 124.9, 124.8, 124.2, 123.1, 122.9, 122.4, 120.8, 120.1, 121.3, 119.9 (Bz, C-3, C-4, C-6, C-7, C-3', C-4', C-4'', C-5''), 116.6 (CN); EI-MS: m/z 633 [M]⁺ (23%); Analysis Calcd for C₃₂H₁₇ClN₆O₃S₂ (633.10): C, 60.71; H, 2.71; N, 13.27; S, 10.13%. Found: C, 60.92; H, 2.94; N, 13.40; S, 10.45%.

N-[6-Cyano-2-(2-oxo-2H-chromen-3-yl)thieno[3,2-d]thiazol-5-yl]-3-imino-2-(4-methoxyphenyl)-5-phenyl-2,3-dihydropyridazine-4-carboxamide (19c)

Yellow crystals (1,4-dioxane), yield 73% (4.58 g), mp 192–196 °C; IR (KBr) ν_{max} 3479–3320, 3056, 2220, 1687, 1691, 1637, 1630 cm^{-1} ; ^1H NMR (DMSO- d_6 , 200 MHz): δ 10.26, 8.31 (2H, 2s, D₂O exchangeable, 2NH), 7.23–7.45 (13H, m, 3Bz), 7.03 (1H, s, H-3''), 6.71 (1H, s, H-4'), 3.13 (3H, s, CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 173.5, 170.2, 169.6 (C-2', C-3'', C-6''), 164.3, 163.2 (C-2', NHCO), 141.3, 140.2, 130.3, 130.2, 128.6, 128.3, 127.1, 126.9, 126.2, 125.6, 125.2, 124.6, 124.4, 123.7, 123.0, 122.8, 121.7, 120.3, 120.3, 119.2 (Bz, C-3, C-4, C-6, C-7, C-3', C-4', C-4'', C-5''), 116.6 (CN), 32.6 (C, OCH₃); EI-MS: m/z 628 [M]⁺ (33%); Analysis Calcd for C₃₃H₂₀N₆O₄S₂ (628.68): C, 63.05; H, 3.21; N, 13.37; S, 10.20%. Found: C, 63.31; H, 3.38; N, 13.42; S, 10.32%.

4. Conclusions

In summary, we have shown herein that our strategy is applicable for the synthesis of a wide range of thiazole derivatives and particularly of such which are incorporated into heterocyclic cores and for fused derivatives. Compounds **10b**, **13b**, **18a**, **19b** and **19c** showed the maximum anti-inflammatory activities while compounds **6–c**, **7a–c**, **8b**, **10b**, **13a**, **16b**, **19b** and **19c** showed high anti-ulcer activities among the synthesized compounds. The toxicity of selected compounds was studied against shrimp larvae where compounds **10b**, **18a**, **19c** and **19d** showed to be non toxic against the tested organisms.

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Povzetek

Reakcija 2-(4-okso-4,5-dihidrotiazol-2-il)acetonitrila (**1**) s salicilaldehidom (**2**) v 1,4-dioksanu ob dodatku katalitske množine piridina daje kumarinske derivate **3**. Ob reakciji le-teh z različnimi reagenti nastanejo pirano[4,5-*b*]tiazolni, pirido[4,5-*b*]tiazolni in tieno[5,4-*b*]tiazolni derivati. Za novo pripravljene spojine smo raziskali učinkovitost delovanja proti vnetjem in želodčnim razjedam ter ugotovili, da so spojine **7a**, **8a**, **10b**, **13b**, **15b**, **18a**, **19b**, **19c**, in **19d** pokazale bistveno večje aktivnosti kot ostale pripravljene spojine. Poleg tega smo raziskali tudi strupenost aktivnih spojin za ličinke morskih rakcev ter ugotovili, da spojine **10b**, **18a**, **19c** in **19d** ne kažejo strupenosti za testirane organizme.