Scientific paper

Anti-inflammatory and Anti-Ulcer activities of New fused thiazole derivatives derived from 2-(2-oxo-2H-chromen-3-yl)thiazol-4(5H)-one

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Abstract

The reaction 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 latter reacted with different reagents to give pyrano[4,5-*b*]thiazole, pyrido[4,5-*b*]thiazole and thieno[5,4-*b*]thaizole dereivatives. The anti-inflammatory and anti-ulcer evaluations of the newly synthesized products were evaluated and the results showed that compounds **7a**, **8a**, **10b**, **13b**, **15b**, **17a**, **18b**, **18c**, and **18d** 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 **17a**, **18c** and **18d** showed non-toxicity against the tested organisms.

Keywords: 4,5-dihydrothiazol, coumarin, pyrimidine, anti-inflammatory, antiulcer 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] neuropeptide[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,[12] and 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.

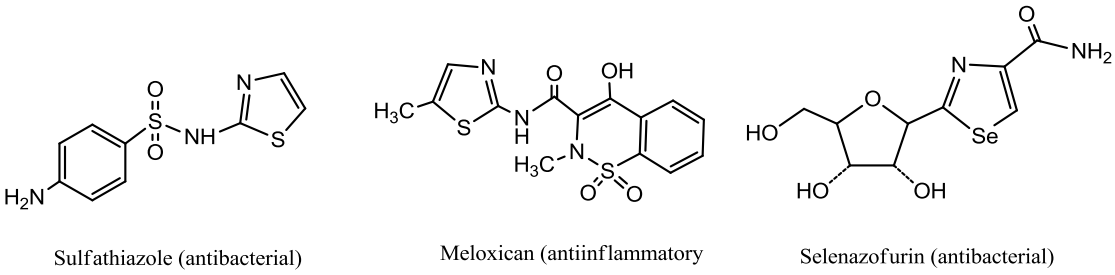
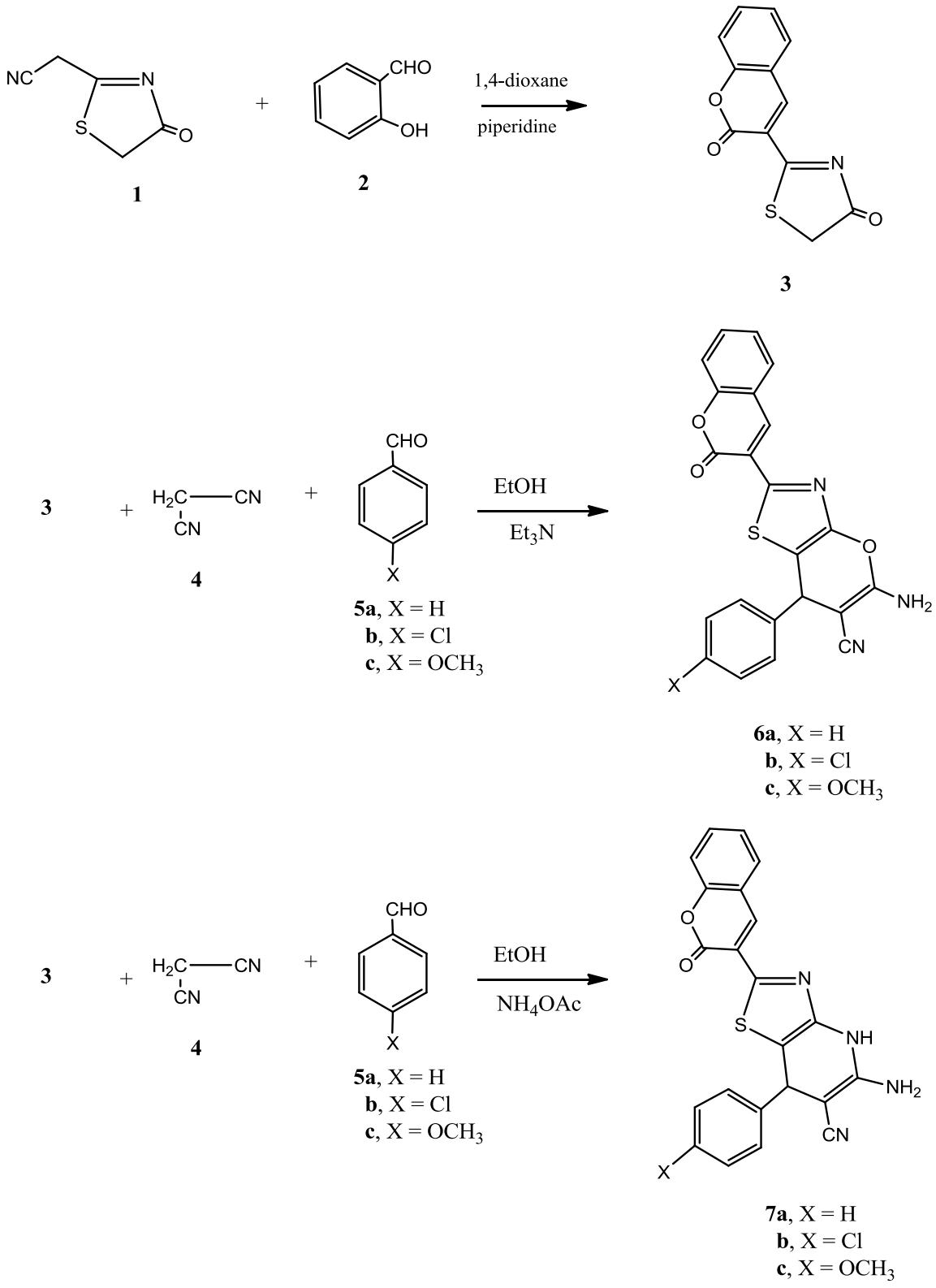


Fig. 1 Biologically active thiazole and selenazole drivatives

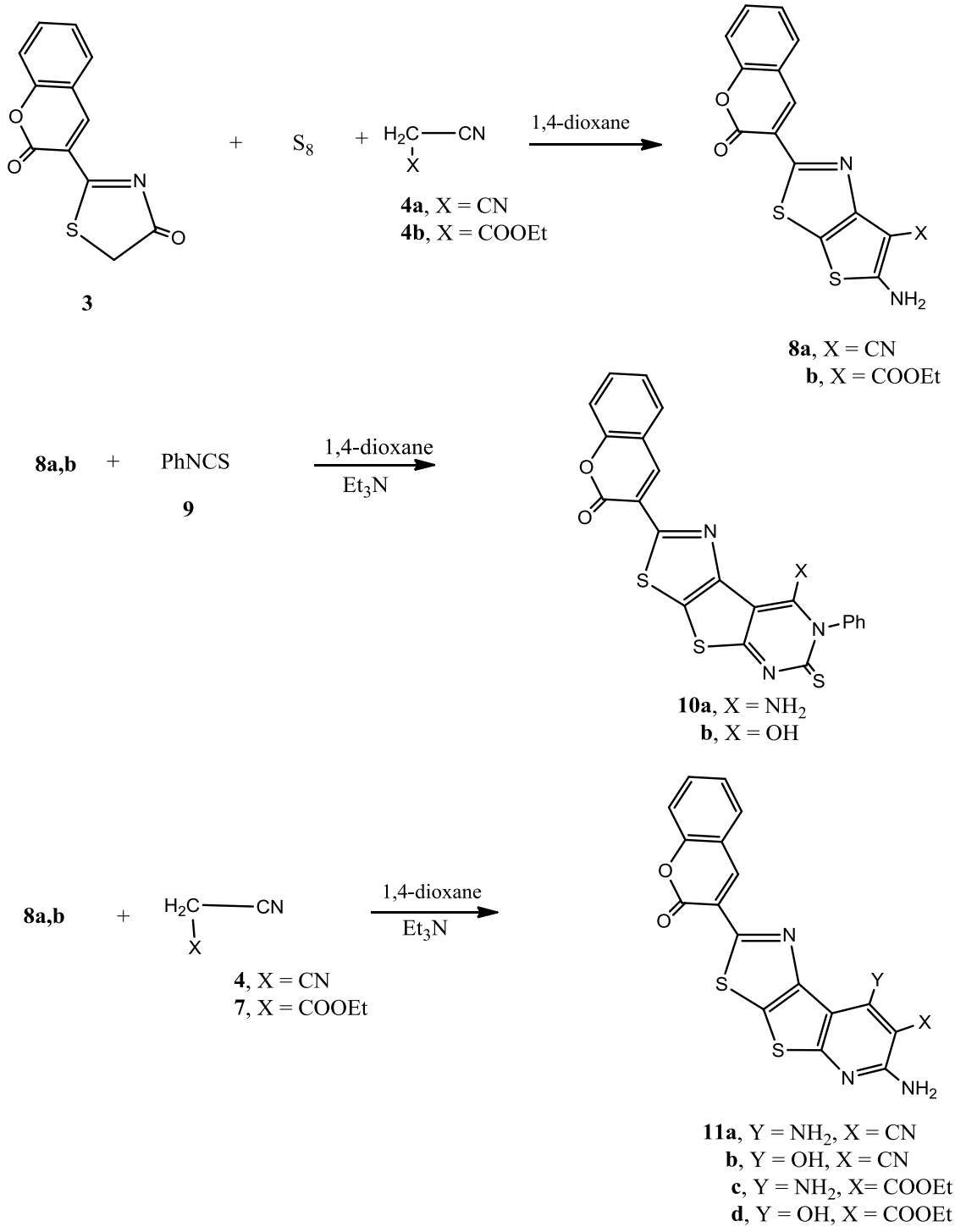
2. Results and discussion

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 compound **3** was based on its analytical and spectral data. Thus, the ^{1}H NMR spectrum showed δ 4.28 ppm equivalent to the CH2 group, a singlet at δ 6.52 ppm indicating the coumarin H-4 a multiplet at δ 6.52 ppm for coumarin H-4, amultiplet at δ 7.28-7.38 for the C_6H_4 group. Moreover, the ^{13}C NMR spectrum showed: δ 58.6 (CH_2), 118.3, 120.3, 123.6, 126.3, 130.1, 133.8, 139.5, 144.1 (coumarin C), 164.3, 168.6 (2 × CO), 170.3 (C=N). Compound **3** underwent multicomponent reactions through its reaction with malononitrile and any of benzaldehyde (**5a**), 4-chlorobenzaldehyde (**5b**) or 4-methoxybenzaldehyde (**5c**) to give the 5-amino-7H-pyrano[2,3-*d*]thiazole-6-carbonitrile derivatives **6a-6c**, respectively. On the other hand, carrying the same reaction, but using ammonium acetate instead of piperidine gave the pyrido[2,3-*d*]thiazole derivatives **7a-7c**, respectively (Scheme 1).



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

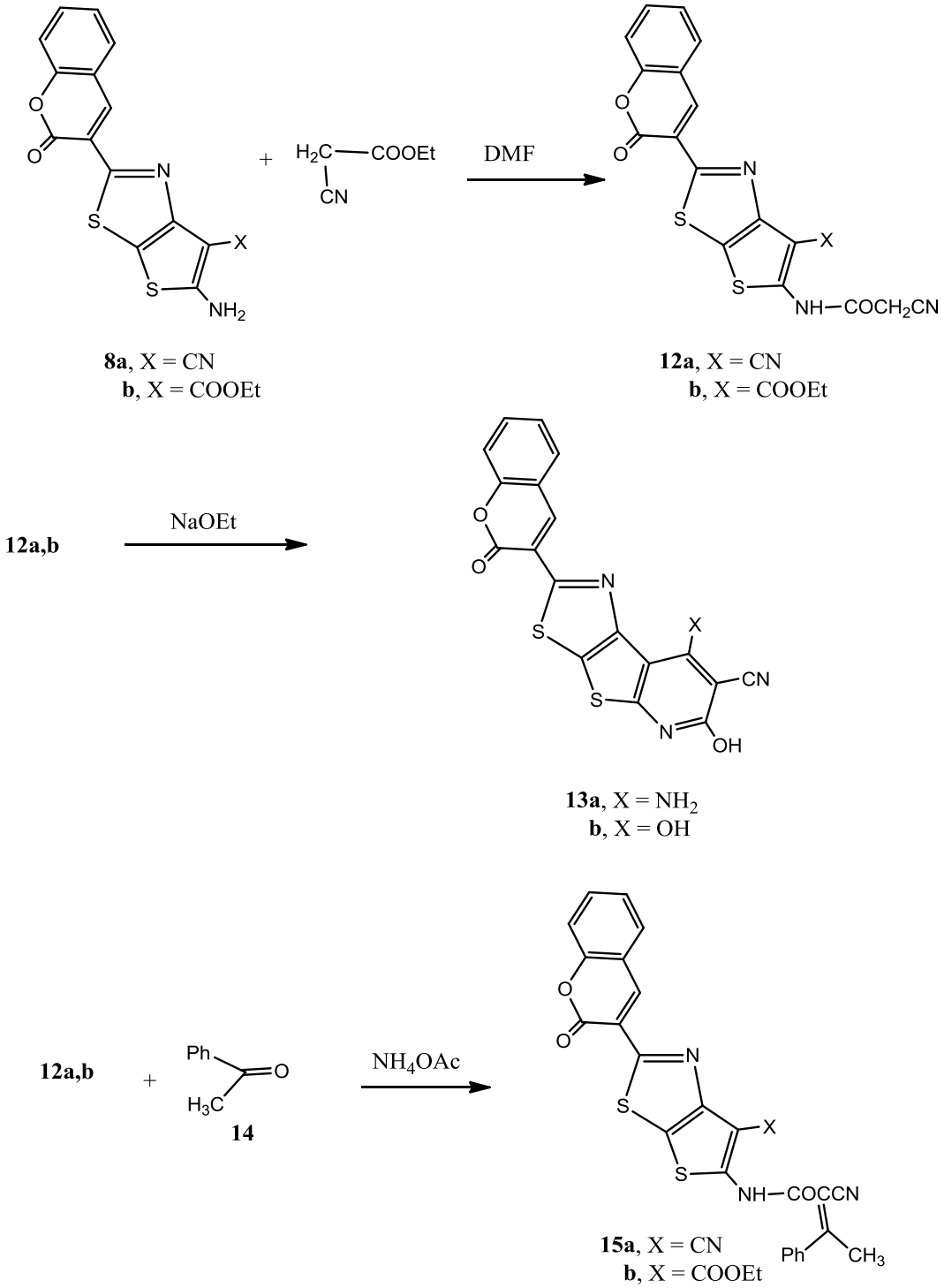
Compound **3** was ready for thiophene formation through the well known Gewald's thiophene synthesis.[15,16] Thus, the reaction of compound **3** with elemental sulfur and either malononitrile (**4a**) or ethyl cyanoacetate (**4b**) gave the thieno[2,3-*d*]thiazole derivatives **8a** and **8b**, respectively. The analytical and spectral data of compounds **8a,b** were the tools of their structural elucidation. Thus, the ^{1}H NMR spectrum of compound **8a** showed δ 4.93 ppm equivalent to the NH_2 group (D_2O exchangeable), a singlet at δ 6.62 ppm indicating the coumarin H-4 and a multiplet at δ 7.26-7.40 ppm for the C_6H_4 group. The ^{13}C NMR spectrum showed δ 117.3 (CN), 119.7, 122.0, 123.9, 126.2, 128.4, 130.5, 132.8, 133.2, 136.2, 138.1, 141.8, 142.3 equivalent to the coumarin, thiazole and thiophene carbons, 164.8 (CO) and 172.8 (C=N). The reaction of either compound **8a** or **8b** with phenylisohiocyanate gave the 7-phenylthiazolo[4',5':4,5]thieno[2,3-*d*]pyrimidine-6(7H)-thione derivatives **10a** and **10b**, respectively. On the other hand, the reaction of either compound **8a** or **8b** with either malononitrile or ethyl cyanoacetate gave the 7-phenylthiazolo[4',5':4,5]thieno[2,3-*d*]pyridin-6(7H)-thione derivatives **11a-d**, respectively (Scheme 2). The analytical and spectral data of the latter products were consistent with their respective structures (see experimental section).



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

The 2-amino group present in compounds **8a** and **8b** capable for amide formation. Thus, the reaction of either **8a** or **8b** with ethyl cyanoacetate in refluxing

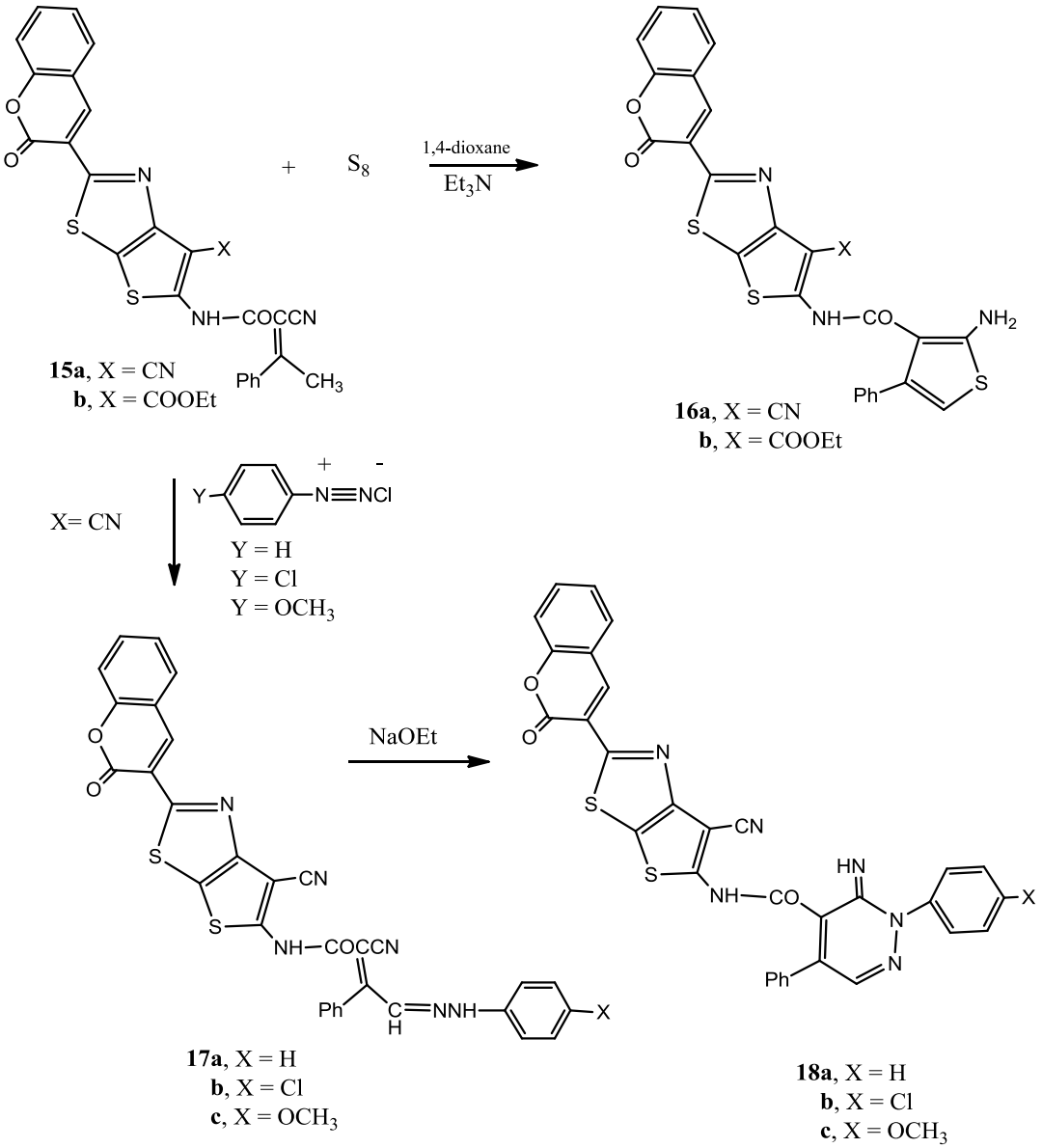
dimethylformamide gave the amide derivatives **12a** and **12b**, respectively. The latter compounds underwent ready cyclization when heated in sodium ethoxide solution to give the 7-phenylthiazolo[4',5':4,5]thieno[2,3-*d*]pyridine derivatives **13a** and **13b**, respectively. On the other hand, the reaction of either compound **12a** or **12b** with acetophenone (**14**) gave the Knoevenagel condensation products **15a** and **15b**, respectively (Scheme 3).



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

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 **15a** or **15b** with any of benzenediazonium chloride, 4-chlorobenzeediazonium chloride, or 4-methoxybenzenediazonium chloride gave the arylhydrazone derivatives **17a-c**, respectively (Scheme 4). The spectral and analytical data of compounds 17a-c were in agreement with their respective structures (see experimental section.



Scheme 4. Synthesis of compounds **16a,b**; **17a-c** and **18a-c**

2.1. Anti-inflammatory evaluation method

Carrageenin-induced rat hind paw oedema model. The method adopted resembles essentially that described by Winter.[17] 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 +/- 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, % anti-inflammatory activity = 100 X (1 - Vt/Vc) where Vt and Vc are the volume of oedema in test compounds and control groups, respectively.

2.2. Antiulcer evaluation method

Animals Wistar albino rats weighing 150-200 g of either sex maintained under standard husbandary conditions (temp 23±2 ^{o}C, relative humidity 55±10% and 12 hours light dark cycle) were used for the screening. Animals were fed with standard laboratory food and 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 1h 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

method of Shay[18] 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 four hours 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 of 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 1mL gastric juice was diluted with 1mL of distilled water and pH of the solution was measured using pH meter.

2.3. Toxicity method

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 Revcos Environmental Chamber at 25 ^{o}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 400mL of media with 10 larvae/beaker and three replicates/concentration. Larvae were fed newly hatched Artemia after daily media change. The concentration of each compound was taken in terms 10, 100 and 100 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, modified from Delorenzo[19] 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**, **17a**, **18b and 18c** showed high anti-inflammotry activity but compounds **6b**, **6c**, **7a**, **8b**, **11a**, **11b**, **13a**, **16b** and **17c** 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 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 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 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 among the four compounds.

The reaction of either compound **8a** or **8b** with ethyl cyanoacetate gave the N-cyanoacetamido derivatives **12a** or **12b**, respectively showed a remarkable decrease of anti-inflammatory in case of **12a**. On the other hand, it showed an increase of anti-inflammatory of **12b**. For the thiazolo[4',5':4,5]thieno[2,3-*b*]pyridine derivatives **13a,b** the presence of the OH group present in compound **13b** is responsible for its higher anti-inflammatory 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 was higher than compound **15a** with the CN group. However, the thiophene derivatives **16a,b** derived from **15a,b** showed the reverse where compound **16a** with the CN group showed higher anti-inflammatory activity than compound **16b** with the COOEt moiety. Considering the arylhydrazone derivatives **17a-c**, it is clear from Table 1 that compound **17a** with the unsubstituted aryl moiety has the maximum anti-inflammatory activity among the three compounds. However, cyclization of compounds **17a-c** in sodium ethoxide solution gave the pyridazine derivatives **18a-c** where compound **18b** with 4-chloroaryl group showed the highest anti-inflammatory activity among the three compounds then compound **18c** with the 4-methoxyaryl group being the middle of the three compounds.

2.5. Antiulcer activity

From Table 2, it is clear that compounds **6a**, **6b**, **6c**, **7a-c**, **8b, 10b**, **13a**, **16b**, **18b** and **18c** showed the maximum antiulcer activity. Moreover, these twelve compounds showed

inhibition effect higher than the reference drug ranitidine. On the other hand most of the newly synthesized product showed a moderate antiulcer activity at concentrations 250 and 500 mg/kg. Moreover, compounds **18b** and **18c** 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 10X magnifier lens to assess the formation of ulcers. The numbers of ulcers were counted.

Scoring of ulcer will be made as follows:

Normal colored stomach..... (0)

Red coloration..... (0.5)

Spot ulcer.....… (1)

Hemorrhagic streak... (1.5)

Deep Ulcers.....… (2)

Perforation.....… (3)

Mean ulcer score for each animal will be expressed as ulcer index. The percentage of ulcer protection was determined as follows:

Ulcer index (UI) was measured by using following formula:

$UI = UN + US + UP \times 10^{-1}$

Where,

UI= Ulcer Index; UN = Average number of ulcers per animal;

US = Average number of severity score; UP = Percentage of animals with ulcers

Percentage inhibition of ulceration was calculated as below:

% Inhibition of Ulceration = (Ulcer index Control-Ulcer index Test) × 100 /Ulcer index Control

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 LC_{50} program to determine LC_{50} values and 95% confidence intervals.[20] Results are given in Table 4 for the compounds which exhibited optimal anti-inflammatory and antiulcer activity which are the eleven compounds **7b**, **8a**, **10a**, **10b**, **13a**, **13b**, **15b**, **17d**, **18**, **18c** and **18d**. 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,[21] natural and synthetic organic compounds.[22] 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 man, including A. salina toxicity test, was slightly better than the rat test for test compounds.[23]

In order to prevent the toxicity results from possible false effects originated from solubility of compounds and DMSO's possible toxicity effect, compounds were prepared by dissolving in DMSO in the suggested DMSO volume ranges. It is clear from Table 4 compounds **17a**, **18c** and **18d** showed non 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.

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)
17a	0.13 ± 0.07(94)	0.24 ± 0.04 (89)	0.07 ± 0.03 (97)
17b	0.73 ± 0.18 (68)	0.52± 0.15 (77)	0.29 ±0.02 (87)
17c	1.39 ± 0.26 (39)	1.52± 0.16 (34)	1.44 ± 0.29 (37)
18a	0.89 ± 0.17 (61)	0.62 ± 0.08 (73)	0.29± 0.01 (87)
18b	0.18 ± 0.03 (92)	0.18 ± 0.09 (92)	0.09 ±0.01 (96)
18c	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%).

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	Dos (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	250 500	0.43±0.08 0.18±0.01	88 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±021	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
17a	250	0.92±0.13	66
	500	0.62±0.23	74
17b	250	2.88±0.53	20
	500	2.21±0.09	39
17c	250	1.42±0.96	60
	500	0.89±0.25	72
18a	250	2.89±0.68	20

	500	1.63±0.71	55
18b	250	0.22±0.05	94
	500	0.29±0.09	92
18c	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

Compd No.	Cons. (μg/ml)	Mortality[a]	Toxicity	LC_{50}	Upper 95% lim.	Lower 95% lim
7b	10 100 1000	2 4 10	Very toxic	120.29	-	-
8a	10 100 1000	1 4 7	Harmful	210.55	197.22	148.38
10b	10 100 1000	0 2 4	nontoxic	818.15	112.40	72.73
13b	10 100	3 6	Very toxic	112.49	276.40	66.30

	1000	10				
15b	10 100 1000	2 5 10	Very toxic	109.06	220.31	80.45
17a	10 100 1000	0 1 4	Non toxic	909.28	-	-
18b	10 100 1000	1 4 10	Harmful	133.40	236..50	93.28
18c	10 100 1000	0 3 5	Non toxic	910.63	-	-
18d	10 100 1000	0 2 6	Non toxic	890.63	-	-

[a]Ten organisms (*A. salina*) tested for each concentration.

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). ^{1}H NMR and ^{13}C 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 solvent, using TMS as internal standard chemical shifts are expressed as δ ppm. The 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 on 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 formed solid product, 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) νmax 3054, 2933, 1690, 1687, 1660, 1638 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 7.28-7.38 (4H, m, Bz), 6.52 (1H, s, H-4), 4.28 (2H, s, H-5); ^{13}C 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); EIMMS: m/z 245 $[M]^+$ (18); Analysis Calcd for $C_{12}H_7NO_3S$ (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 was collected by filtration.

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) νmax 3477, 3329, 3056, 2220, 1693, 1654, 1635 cm^{-1}; ^{1}H 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, NH_2, D_2O exchangeable); ^{13}C 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); EIMMS: m/z 399 $[M]^+$ (42 %); Analysis Calcd for $C_{22}H_{13}N_3O_3S$ (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) νmax 3493, 3326, 3054, 2223,1690, 1656, 1633 (C=C) cm^{-1}; ^{1}H 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, NH_2, D_2O exchangeable); ^{13}C 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); EIMMS: m/z 433 $[M]^+$ (30 %); Analysis Calcd for $C_{22}H_{12}ClN_3O_3S$ (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) νmax 3475, 3318, 3056, 2221, 1692, 1658,1630 cm^{-1}; ^{1}H 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, NH_2, D_2O exchangeable), 3.14 (3H, s, OCH_3); ^{13}C 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, OCH_3); EIMMS: m/z 429 $[M]^+$ (22 %); Analysis Calcd for $C_{23}H_{15}N_3O_4S$ (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 either 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 formed solid product 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) νmax 3466-3380, 3059, 2222, 1688, 1652, 1633 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ = 8.23 (s, 1H, D_2O 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, NH_2, D_2O exchangeable); ^{13}C 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) ; EIMMS: m/z 398 $[M]^+$ (28 %); Analysis Calcd for $C_{22}H_{14}N_4O_2S$ (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) νmax 3493-3327, 3056, 2220, 1688, 1653, 1630 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ = 8.25 (s, 1H, D_2O 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, NH_2, D_2O exchangeable); ^{13}C 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); EIMMS: m/z 432 $[M]^+$ (38 %); Analysis Calcd for $C_{22}H_{13}ClN_4O_2S$ (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 from ethanol yield 79 % (3.38 g), mp 255-258 °C; IR (KBr) νmax 3488-3359, 3052, 2220, 1689, 1654, 1632 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ = 8.22 (s, 1H, D_2O 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, NH_2, D_2O exchangeable), 3.20 (s, 3H, CH_3); ^{13}C 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, OCH_3), EIMMS: m/z 428 $[M]^+$ (20 %); Analysis Calcd for $C_{23}H_{16}N_4O_3S$ (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 4h then left to cool. The formed solid product, in each case, 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) νmax 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, NH_2, D_2O exchangeable); ^{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); EIMMS: m/z 325 $[M]^+$ (15 %); Analysis Calcd for $C_{15}H_7N_3O_2S_2$ (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) νmax 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, NH_2, D_2O exchangeable), 4.20 (2H, q, J = 7.29 Hz, $O\underline{CH_2}CH_3$), 1.14 (3H, t, J = 7.29 Hz, $OCH_2\underline{CH_3}$); ^{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, CH_2, OCH_2CH_3), 16.9 (C, CH_3, OCH_2CH_3); EIMMS: m/z 372 $[M]^+$ (30 %); Analysis Calcd for $C_{17}H_{12}N_2O_4S_2$ (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 the 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 compound **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 few drops of hydrochloric acid and the formed solid product, formed 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)

Pal yellow crystals (1,4-dioxane), 74 % (3.40 g), mp 222-225 °C; IR (KBr) νmax 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, NH_2, D_2O exchangeable); ^{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'); EIMMS: m/z 460 $[M]^+$ (35

%); Analysis Calcd for $C_{22}H_{12}N_4O_2S_3$ (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) νmax 3473-3340, 3052, 2220, 1689, 1652, 1632, 1223 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ = 10.31 (1H, s, D_2O 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'); EIMMS: m/z 462 $[M]^+$ (18 %); Analysis Calcd for $C_{22}H_{11}N_3O_3S_3$ (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 formed solid product 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) νmax 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, $2NH_2$, D_2O exchangeable); ^{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); EIMMS: m/z 391 $[M]^+$ (24 %);

Analysis Calcd for $C_{18}H_9N_5O_2S_2$ (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) νmax 3574-3332, 3054, 2222, 1686, 1651, 1631 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ = 10.30 (1H, s, OH), 7.25-7.36 (4H, m, Bz), 6.63 (1H, s, H-4'), 4.87 (2H, s, NH_2, D_2O exchangeable); ^{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); EIMMS: m/z 392 $[M]^+$ (18 %); Analysis Calcd for $C_{18}H_8N_4O_3S_2$ (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) νmax 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, $2NH_2$, D_2O exchangeable), 4.20 (2H, q, J = 7.08 Hz, CH_2, OCH_2CH_3), 1.14 (3H, t, J = 7.08 Hz, CH_3, 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); EIMMS: m/z 438 $[M]^+$ (23 %); Analysis Calcd for $C_{20}H_{14}N_4O_4S_2$ (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) νmax 3520-3336, 3058, 1689, 1651, 1632 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ = 10.22 (1H, s, OH, D_2O exchangeable), 7.28-7.39 (4H, m, Bz), 6.62 (1H, s, H-4'), 4.48 (2H, s,

NH_2, D_2O exchangeable), 4.20 (2H, q, J = 7.22 Hz, CH_2, OCH_2CH_3), 1.15 (3H, t, J = 7.22 Hz, CH_3, 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); EIMMS: m/z 439 $[M]^+$ (18 %); Analysis Calcd for $C_{20}H_{13}N_3O_5S_2$ (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 poured onto ice/water containing a few drops of hydrochloric acid and the formed solid product 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) νmax 3468-3326, 3054, 2223, 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 (CN), 62.5 (C, CH_2, $COCH_2$); EIMMS: m/z 392 $[M]^+$ (18 %); Analysis Calcd for $C_{18}H_8N_4O_3S_2$: 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) νmax 3462-3329, 3057, 1689-1706, 1646, 1628 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ = 8.31 (1H, s, 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, CH_2, OCH_2CH_3), 1.38 (3H, t, J = 6.83 Hz, CH_3, 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, CH_2, OCH_2CH_3), 16.5 (C, CH_3, OCH_2CH_3); EIMMS: m/z 439 $[M]^+$ (37 %); Analysis Calcd for $C_{20}H_{13}N_3O_5S_2$ (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 through the 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 few drops of hydrochloric acid (till pH 6). The formed solid product 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) νmax 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, NH_2, D_2O exchangeable); ^{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); EIMMS: m/z 392 $[M]^+$ (32 %); Analysis Calcd for $C_{18}H_8N_4O_3S_2$ (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 °C; IR (KBr) νmax 3542-3318 (2OH), 3054 (CH aromatic), 1686 (CO), 1642 (C=N), 1628 (C=C); ^1H

NMR (DMSO-d_6, 200 MHz): δ = 10.32, 10.11 (2H, 2s, D_2O exchangeble, 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); EIMMS: m/z 393 $[M]^+$ (44 %); Analysis Calcd for $C_{18}H_7N_3O_4S_2$ (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 ^oC for 0.5 h and the formed solid product 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 °C; IR (KBr) νmax 3472-3318, 3057, 2222, 2220, 1689, 1690, 1642, 1627; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 10.22 (1H, s, NH, D_2O exchangeable), 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); EIMMS: m/z 494 $[M]^+$ (23 %); Analysis Calcd for $C_{26}H_{14}N_4O_3S_2$ (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 °C; IR (KBr) νmax 3488-3326, 3052, 2221, 1682, 1690, 1638, 1628 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz): δ

= 8.31 (1H, s, NH, D_2O exchangeble), 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, CH_2, OCH_2CH_3), 2.68 (3H, s, CH_3), 1.13 (t, 3H, J = 6.88 Hz, CH_3, 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, CH_2, OCH_2CH_3), 19.2 (CH_3), 16.8 (C, CH_3, OCH_2CH_3), EIMMS: m/z 541 $[M]^+$ (28 %); Analysis Calcd for $C_{28}H_{19}N_3O_5S_2$ (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 2h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product, 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 °C; IR (KBr) νmax 3494-3326, 3053, 2224,1687, 1694, 1646, 1629 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 10.28 (1H, s, NH, D_2O exchangeable), 7.23-7.39 (9H, m, 2Bz), 6.61 (1H, s, H-4'), 6.24 (1H, s, H-5"), 4.68 (2H, s, NH_2, D_2O exchangeable); ^{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); EIMMS: m/z 526 $[M]^+$ (38 %); Analysis Calcd for $C_{26}H_{14}N_4O_3S_3$ (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 °C; IR (KBr) νmax 3462-3346, 3056, 1689-1696, 1641, 1632 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 8.33 (1H, s, NH, D_2O exchangeble), 7.23-7.37 (9H, m, 2Bz), 6.63 (1H, s, H-4'), 6.28 (1H, s, H-5''), 4.82 (2H, s, NH_2, D_2O exchangeable), 4.20 (2H, q, J = 7.39 Hz, CH_2, OCH_2CH_3), 1.14 (3H, t, J= 7.39 Hz, CH_3, 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, COEt), 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, CH_2, OCH_2CH_3), 16.4 (C, CH_3, OCH_2CH_3); EIMMS: m/z 573 $[M]^+$ (31 %); Analysis Calcd for $C_{28}H_{19}N_3O_5S_3$ (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 17a-17c

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 ^{o}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 in a portion wise with continuous stirring. The whole reaction mixture was stirred at room for 2 h and the formed solid product, in each case, was collected by filtration.

2-Cyano-N-(6-cyano-2-(2-oxo-2H-chromen-3-yl)thieno[3,2-d]thiazol-5-yl)-3-phenyl-4-(2-phenylhydrazono)but-2-enamide (17a)

Yellow (1,4-dioxane), yield 76 % (4.54 g) mp133-137 °C; IR (KBr) νmax 3469-3341, 3056, 2221, 2220, 1689, 1691, 1648, 1631 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz): δ =10.23, 8.33 (2H, 2s, 2NH, D_2O exchangeable), 7. 48-7.25 (14H, m, 2Bz), 5.93 (1H, s, CH=N), 6.63 (1H, s, H-4'); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 173.1 (C-2), 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); EIMMS: m/z 598 $[M]^+$ (28 %); Analysis Calcd for $C_{32}H_{18}N_6O_3S_2$ (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-2H-chromen-3-yl)thieno[3,2-d]thiazol-5-yl)-3-phenylbut-2-enamide (17b)

Yellow crystals (1,4-dioxane) 89 % (5.63 g), mp 123-125 °C; IR (KBr) νmax 3473-3341, 3058, 2220, 1688, 1696, 1642, 1635 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ = 10.21, 8.36 (2H, 2s, 2NH, D_2O exchangeable), 7.45-7.26 (13H, m, 3Bz), 6.62 (1H, s, H-4'), 5.90 (1H, s, CH=N); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 173.3 (C-2), 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 8 (Bz, C-3, C-4, C-6, C-7, C-3', C-4', C-2", C-3", C-4", C-5"), 116.7 (CN),; 88.4, 90.6 (C=C); EIMMS: m/z 633 $[M]^+$ (41 %); Analysis Calcd for $C_{32}H_{17}ClN_6O_3S_2$ (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-2H-chromen-3-yl)thieno[3,2-d]thiazol-5-yl)-4-(2-(4-methoxyphenyl)hydrazono)-3-phenylbut-2-enamide (17c)

Yellow crystals (1,4-dioxane), yield 68 %, (4.27 g), mp 203-207 °C; IR (KBr) νmax 3489-3324, 3055, 2222, 1690, 1693, 1640, 1631 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ = 10.25, 8.33 (2H, 2s, 2NH, D_2O exchangeable), 7.48-7.28 (13H, m, 3Bz), 6.60 (1H, s, H-4'), 5.88 (1H, s, CH=N),1.12 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 173.1 (C-2), 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"), 116.3 (CN), 90.3, 88.7 (C=C); EIMMS: m/z 628 $[M]^+$ (33 %); Analysis Calcd for $C_{33}H_{20}N_6O_4S_2$ (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 18a-18c

To a suspension of any of compound **17a** (5.98 g, 0.01 mol), **17b** (6.33 g, 0.01 mol) or **17c** (6.28 g, 0.01 mol) in sodium ethoxide solution [prepared through 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 few drops of hydrochloric acid (till pH 6). The formed solid product was collected by filtration.

N-(6-Cyano-2-(2-oxo-2H-chromen-3-yl)thieno[3,2-d]thiazol-5-yl)-3-imino-2,5-diphenyl-2,3-dihydropyridazine-4-carboxamide (18a)

Yellow crystals (1,4-dioxane), yield 82 % (4.90 g), mp 287-293 °C; IR (KBr) νmax 3477-3321, 3053, 2220, 1689, 1691, 1648, (C=N), 1631 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 10.41, 8.31 (2H, 2s, 2NH, D_2O exchangeable), 7.45-7.22 (14H, m, 3Bz), 6.60 (1H, s, H-4'), 6.02 (1H, s, H-3"); ^{13}C 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), EIMMS: m/z 598 $[M]^+$ (20 %); Analysis Calcd for $C_{32}H_{18}N_6O_3S_2$ (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 (18b)

Pale yellow crystals (1,4-dioxane), yield 69 %(4.12 g), mp 244-147 °C; IR (KBr) νmax 3482-3329, 3057, 2221, 1689, 1696, 1640, 1632 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 10.20, 8.38 (2H, 2s, 2NH, D_2O exchangeable), 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); EIMMS: m/z 633 $[M]^+$ (23 %); Analysis Calcd for $C_{32}H_{17}ClN_6O_3S_2$ (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 (18c)

Yellow crystals (1,4-dioxane), yield 73 % (4.58 g), mp 192-196 °C; IR (KBr) νmax 3479- 3320, 3056, 2220, 1687, 1691, 1637, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 10.26, 8.31 (2H, 2s, 2NH, D_2O exchangeable), 7.23-7.45 (13H, m, 3Bz), 7.03 (1H, s, H-3"), 6.71 (1H, s, H-4'), 3.13 (3H, s, CH_3); ^{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, OCH_3); EIMMS: m/z 628 $[M]^+$ (33 %); Analysis Calcd for $C_{33}H_{20}N_6O_4S_2$ (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 compatible with the synthesis of a wide range of thiazole derivatives and particularly when being corporate to heterocyclic and fused derivatives. Compounds **10b**, **13b**, **17a**, **18b and 18c** showed the maximum anti-inflammatory activities while compounds **6a**, **6b**, **6c**, **7a-c**, **8b, 10b**, **13a**, **16b**, **18b** and **18c** showed high anti-ulcer evaluations among the synthesized compounds. The toxicity of selective compounds was studied against shrimp larvae where compounds **17a**, **18c** and **18d** showed non-toxicity against the tested organisms.

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