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# Green chemistry: A facile synthesis of polyfunctionally substituted thieno[3,4-c]pyridinones and thieno[3,4-d]pyridazinones under neat reaction conditions

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ABSTRACT

A facile, solvent free, ecofriendly approach for the synthesis of pyridine-2,6-diones **4a–d**, pyridazinone derivatives **8a–c** and thienoazines **6** and **9** is herein described employing neat reaction conditions under both microwave and ultrasound irradiations. This solventless methodology is environmentally benign as it completely eliminates the use of solvent from the reaction procedure.



## 1. Introduction

Industrial chemistry in the new millennium is widely adopting the concept of "Green Chemistry" [1] to meet the fundamental scientific challenges of protecting the human health and environment while maintaining commercial viability. One of the advances in this area where substantial progress has been made is the microwave assisted [2–4]. But this technique does not meet the ecofriendly goal of clean synthesis as an appreciable amount of solvent is required for the adsorption of reactants and elution of products. The "neat reaction" technique is an alternative solvent free approach in which the reaction is carried out in the absence of solvent. Further coupling of this solventless synthesis with microwaves and ultrasound has the associated benefits of shorter reaction time, uniform heating and better yields in comparison to conventional heating.

The importance of pyridines and fused pyridines as calcium antagonists [5] and hypertensives [6] are well known. Moreover, pyridazines belong among the most significant heterocyclic rings, which are frequently employed for the preparation of a variety of important products [7]. Pyridazine derivatives have only recently been discovered among the natural products, such as pyridazinomycin, antifungal antibiotic isolated from *Streptomyces violacoeniger*, and tetrahydropyridazine- and hexahydropyridazine-6-carboxylic acid structural element containing peptides, exhibiting antibiotic, antitumor, and collagenase inhibition activity [7]. On the other hand, a variety of synthetic pyridazine derivatives found use in agrochemical, pharmaceutical, and other applications [7–9]. Keeping in view the biological importance of the above mentioned heterocyclic compounds and in continuation to our endeavor towards environmentally benign synthesis [10–16], we report herein the synthesis of alkyl azinylcarbonitriles **4** and **8** as a good precursors to polyfunctionally substituted thienoazines, under neat reaction conditions, utilizing both microwave irradiation and ultrasound as ecofriendly energy sources.

## 2. Results and discussion

Our initial strategy aimed to synthesize the pyridine-3-carbonitriles **4** and convert them to the corresponding 5-arylhydrazonopyridine-3-carbonitriles **5**, which assumed to be very important synthon for the synthesis of the desired polyfunctionally substituted thieno-[3,4-c]pyridinones. Cyanoacetamides **2a–d** have been prepared in our laboratory via treatment of ethyl cyanoacetate with primary aliphatic amines **3a–d** either at room temperature for long time or via irradiation with microwave (MW) for 1–4 min at 100 W or with ultrasound (US) for 2–10 min at 40 °C. Reacting ethyl 3-oxohexanoate (**1**) with cyanoacetamides **2a–d** also either via long reflux of neat reagents or by short time microwave or by US for 5–7 h at 40 °C furnished the intermediate

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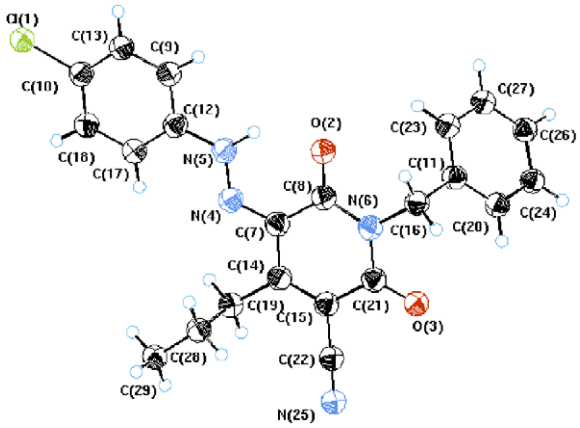



**Fig. 1.** X-ray crystal structure of 5 h.

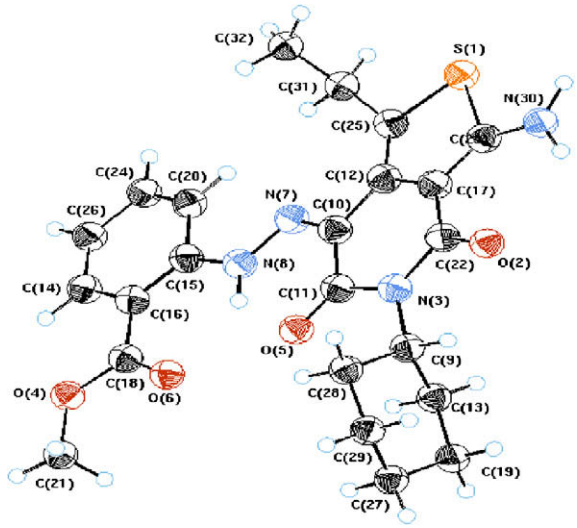
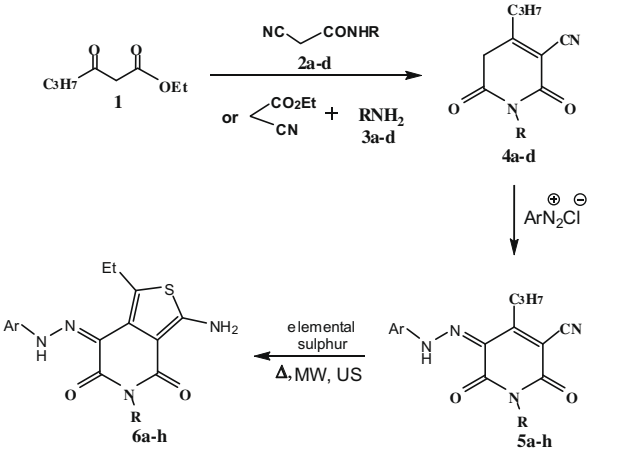


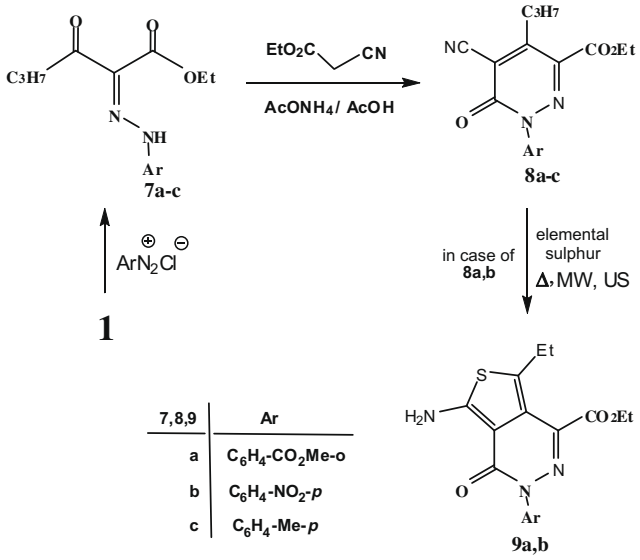

**Fig. 2.** X-ray crystal structure of **6c**.




| 2,3,4 | R |
|---|---|
| a | butyl |
| b | hexyl |
| c | cyclohexyl |
| d | benzyl |

| 5,6 | R | Ar |
|---|---|---|
| a | butyl | $C_6H_4$-$CO_2$Me-*o* |
| b | hexyl | $C_6H_4$-$CO_2$Me-*o* |
| c | cyclohexyl | $C_6H_4$-$CO_2$Me-*o* |
| d | benzyl | $C_6H_4$-$CO_2$Me-*o* |
| *e* | butyl | $C_6H_4$-Cl-*p* |
| f | hexyl | $C_6H_4$-Cl-*p* |
| *g* | cyclohexyl | $C_6H_4$-Cl-*p* |
| h | benzyl | $C_6H_4$-Cl-*p* |

**Scheme 1.**




| 7,8,9 | Ar |
|---|---|
| a | $C_6H_4$-$CO_2$Me-o |
| b | $C_6H_4$-$NO_2$-*p* |
| c | $C_6H_4$-Me-*p* |

**Scheme 2.**

pyridine-3-carbonitriles **4a–d**, as viscous oils, which were subjected to reaction without further purification. Alternatively, compounds **4a–d** could also be obtained by reacting compound **1** with primary aliphatic amines **3a–d** and ethyl cyanoacetate in the presence of ceric ammonium nitrate by US for 5 h at 40 °C.

Thus, coupling of **4a–d** with aromatic diazonium salts afforded the corresponding 5-arylhydrazono-pyridinones **5a–h**. Correct elemental analyses and spectral data of **5a–h** substantiated their structures (see Section 4). Furthermore, the structure of compounds **5a–h** could be unambiguously confirmed by single crystal X-ray diffraction of compound **5h** [17] (Fig. 1). Single crystal X-ray diffraction of compound **5h** add a strong evidence for the proposed structure (Scheme 1).

Next we examined the reaction of aryl hydrazones **5** with elemental sulphur with a view to synthesize new derivatives of the interesting polyfunctionally substituted thieno[3,4-c]pyridinones, with expected significant biological activity. Thus, the reaction of aryl hydrazones **5a–g** with elemental sulphur either by heating with microwave or by US and conventional heating gave the corresponding aminothienopyridinones **6a–g**. The structure of compounds **6a–g** was established and confirmed for the reaction products on the basis of their elemental analyses and spectral data (MS, IR, $^1$H and $^{13}$C NMR) (see Section 4). Moreover, the structure of compounds **6a–g** could be unequivocally established by single crystal X-ray diffraction of compound **6c** [18] (Fig. 2). Single crystal X-ray diffraction of compound **6c** adds a sharp evidence for the proposed structure (Scheme 1).

As the synthesis of fused heterocyclic ring systems containing the azine moiety is the main target of this program, we therefore considered the possibility that this design strategy could be extended to the synthesis of new thienoazines ring systems that incorporate a thiophene nucleus in addition to pyridazine moiety, utilizing compound **1** as starting material. Thus, coupling compound **1** with aromatic diazonium salts gave the corresponding aryl hydrazones **7a–c**, in excellent yields. When aryl hydrazones

**Table 1**
Formation of compounds **4–9** under three methodologies (thermal, microwave irradiation, and ultrasound).

| No. | Time | | | Yield (%) | | |
|---|---|---|---|---|---|---|
| | Δ (h) | μω (min) | US | Δ | μω | US |
| **4a** | 8 | 10 | 5 h | 72 | 94 | 89 |
| **4b** | 8 | 10 | 5 h | 73 | 95 | 91 |
| **4c** | 8 | 10 | 5 h | 75 | 95 | 90 |
| **4d** | 8 | 10 | 5 h | 69 | 92 | 88 |
| **6a** | 3 | 5 | 30 min | 73 | 90 | 84 |
| **6b** | 3 | 5 | 30 min | 78 | 96 | 88 |
| **6c** | 3 | 5 | 30 min | 80 | 92 | 89 |
| **6d** | 3 | 5 | 30 min | 70 | 93 | 87 |
| **6e** | 3 | 5 | 30 min | 73 | 90 | 81 |
| **6f** | 3 | 5 | 30 min | 76 | 90 | 85 |
| **6g** | 3 | 5 | 30 min | 88 | 92 | 81 |
| **8a** | 12 | 20 | – | 50 | 70 | – |
| **8b** | 12 | 20 | – | 55 | 78 | – |
| **8c** | 12 | 20 | – | 54 | 80 | – |
| **9a** | 3 | 5 | 1 h | 80 | 97 | 78 |
| **9b** | 3 | 5 | 1 h | 83 | 98 | 85 |

**7a–c** were reacted with ethyl cyanoacetate by heating the neat reagents with microwave or by conventional heating, an intramolecular condensation took place that led directly to the new ethyl 1-aryl-5-cyano-6-oxo-4-propyl-1,6-dihydropyridazine-3-carboxylate **8a–c** (Scheme 2), in good yields. The structural assignment of **8a–c** was based on spectral and analytical data. The molecular formula was confirmed by elemental analyses and mass spectroscopy ($M^+$/m/e). Under analogous experimental conditions that described above for the synthesis of compounds **6a–g**, pyridazinones **8a,b** were reacted with elemental sulphur to give the polyfunctionally substituted thieno[3,4-d]pyridazinones **9a,b**.

Table 1 shows yields and reaction times by the three methodologies are compared.

In order to construct new derivatives of the interesting thienoazine ring systems, we investigated the reaction of compounds **8** with acrylonitrile and maleic anhydride, as electron poor dienophiles. Thus, the reaction of compound **8b**, as example, with acrylonitrile gave an addition intermediate **10** which lose one molecule of hydrogen sulphide to yield the new polyfunctionally substituted phthalazine **11** (Scheme 3). On the other hand, the cycloaddition reaction between compound **8b** and maleic anhydride furnished the corresponding cycloadduct **12** (Scheme 3). The synthesis of compounds **11** and **12** was achieved by heating the neat reagent with microwave irradiation for 5 min at 440 W.

All reaction times were determined by follow the reaction progress via thin layer chromatography (TLC).

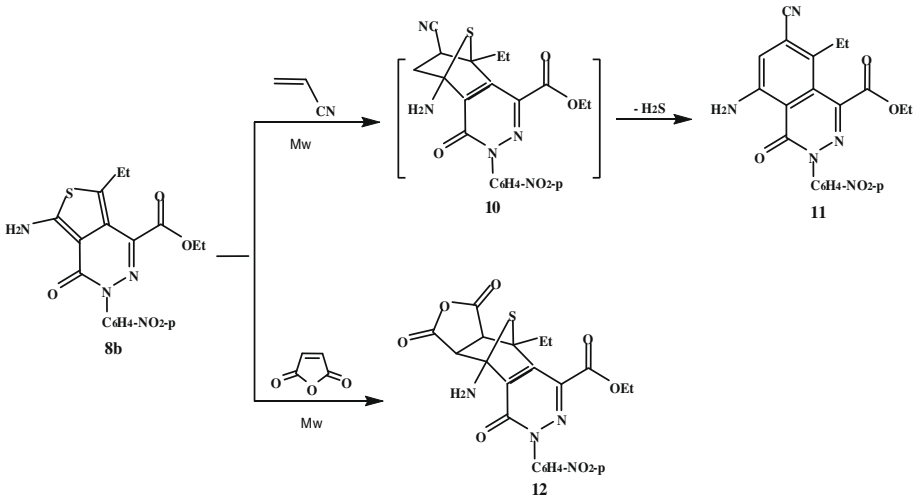
## 3. Conclusion

A novel environmentally benign methodology for the synthesis of pyridinones, pyridazinones, thieno[3,4-c]pyridines and thieno[3,4-d]pyridazines has been developed avoiding volatile and toxic organic solvents. This neat reaction under MWs not only gave excellent yield of products with lesser reaction time but is also devoid of hazardous solvents and reagents.

## 4. Experimental

### 4.1. Materials and methods

All melting points were measured on Gallenkamp electrothermal melting point apparatus and are uncorrected. The IR absorption spectra were measured on a Nicollet Magna 520FT IR Spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded in deuterated dimethylsulfoxide (DMSO-$d_6$) or deuterated chloroform ($CDCl_3$) at 200 MHz on a Varian Gemini NMR spectrometer and a Bruker DPX 400 MHz spectrometer using tetramethylsilane (TMS) as an internal reference and results are expressed as $\delta$ values. Mass spectra were performed on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Microwave irradiation was carried out using the commercial microwave oven (SGO 1000W). Ultrasonic irradiation was carried out using Sonics and Materials device, 750 W ultrasonic processor VCX 750, solid probe with non-replaceable tip, with processing capability: 10–250 ml, length: 53/8″ (136 mm), weight: 3/4 lb (340 g), titanium alloy Ti-6Al-4V, with integrated temperature control, allows sample temperature to be monitored up to 100 °C. Control temperature of reaction at 40 °C via cooling the reaction vessel in a bath of cold water to maintain desired temperature. The shape and the size of reactor dimensions ($H \times W \times D$) 91/4″ × 71/2″ × 131/2″ (235 × 190 × 340 mm) weight: 15 lb (6.8 kg) with sealed converter piezoelectric lead zirconate titanate crystals (PZT) of diameter: 21/2″ (63.5 mm), length: 71/4″ (183 mm), weight: 2 lb (900 g) all reactions undergo at 300 W power (40%).




**Scheme 3.**

Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University, Egypt. Compound **1** is commercially available from Merck Company, Germany, and used as it is without further purification, compounds **2a–d** were prepared in our laboratory [15].

### 4.2. Typical procedure for reactions

#### 4.2.1. Synthesis of pyridinone derivatives 4a–d

*4.2.1.1. Method I (Δ).* Ethyl 3-oxohexanoate (**1**) (0.1 mol) was added to cyanoacetamides **2a–d** (0.1 mol) and then the reaction mixture was heated to reflux for 8 h. The mixture was evaporated to dryness in vacuo to give compounds **4a–d** as clear oils.

*4.2.1.2. Method II (μω).* A mixture of compound **1** (0.1 mol) and cyanoacetamides **2a–d** (0.1 mol) was placed in the microwave oven and irradiated at 460 W for 10 min to give compounds **4a–d** as clear oils.

*4.2.1.3. Method III (US).* Compound **1** (0.1 mol) was added to a mixture of primary aliphatic amines **3a–d** (0.1 mol) and ethyl cyanoacetate (0.1 mol). The reaction mixture was catalyzed by (0.1 mol) of ceric ammonium nitrate under ultrasound irradiation at 40 °C for 5 h. Then, compounds **4a–d** were isolated as clear oils and used in the next step without further purification.

#### 4.2.2. General procedure for the synthesis of aryl hydrazone compounds 5a–h

A cold solution of aryldiazonium salt (10 mmol), prepared by adding a solution of sodium nitrite (1 g into 10 ml $H_2O$) to a cold solution of aryl amine hydrochloride or aryl amine nitrate (10 mmol) with stirring as described earlier [11,12]. The resulting solution of the aryldiazonium was then added to a cold solution of pyridine-3-carbonitriles **4a–d** or compound **1 (0.1 mol)** in ethanol (50 ml) containing sodium acetate (1 g in 10 ml $H_2O$). The mixture was stirred at room temperature for 1 h and the solid product so-formed was collected by filtration and recrystallized from ethanol to give compounds **5a–h** and **7a–c**, respectively.

*4.2.2.1. 2-[N-(1-Butyl-5-cyano-2,6-dioxo-4-propyl-1,6-dihydro-2H-pyridine-3-ylidene)hydrazine]-benzoic acid methyl ester (**5a**).* Yellow crystals; m.p. 199 °C. Yield 82%. IR (KBr): $\nu$ = 3470 (NH, broadened due to H-bond between O and NH), 3100 (CH aromatic), 2956 (CH aliphatic), 2223 (CN), 1680 (ester CO), 1640 (amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.91 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.01 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.31 (sextet, 2H, $J$ = 7 Hz, $CH_2$), 1.52 (quintet, 2H, $J$ = 7 Hz, $CH_2$), 1.71 (sextet, 2H, $J$ = 7 Hz, $CH_2$), 2.49 (t, 2H, $J$ = 7 Hz, $CH_2$), 3.84 (t, 2H, $J$ = 7 Hz, $CH_2N$), 3.96 (s, 3H, $CO_2CH_3$), 7.39 (t, 1H, $J$ = 7 Hz, Ar–H), 7.81 (t, 1H, $J$ = 7 Hz, Ar–H), 7.99 (d, 1H, $J$ = 8 Hz, Ar–H), 8.06 (d, 1H, $J$ = 8 Hz, Ar–H), 15.66 (s, 1H, NH) ppm. MS: $m/z$ (%) = 396. Anal. Calcd. for $C_{21}H_{24}N_4O_4$ (396.45): C, 63.62; H, 6.10; N, 14.13. Found: C, 63.60; H, 6.25; N, 14.15.

*4.2.2.2. 2-[N-(5-Cyano-1-hexyl-2,6-dioxo-4-propyl-1,6-dihydro-2H-pyridine-3-ylidene)hydrazine]-benzoic acid methyl ester (**5b**).* Yellow crystals; m.p. 160 °C. Yield 86%. IR (KBr): $\nu$ = 3390 (NH), 3102 (CH aromatic), 2961 (CH aliphatic), 2220 (CN), 1675 (ester CO), 1649 (amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.86 (t, 3H, $J$ = 6 Hz, $CH_3$), 1.08 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.27–1.30 (m, 6H, 3 hexyl-$CH_2$), 1.60 (quintet, 2H, $J$ = 7 Hz, $CH_2$), 1.76 (sextet, 2H, $J$ = 7 Hz, $CH_2$), 3.01 (t, 2H, $J$ = 7 Hz, $CH_2$), 4.0 (t, 2H, $J$ = 7 Hz, $CH_2N$), 4.04 (s, 3H, $CO_2CH_3$), 7.31 (t, 1H, $J$ = 7 Hz, Ar–H), 7.64 (t, 1H, $J$ = 7 Hz, Ar–H), 7.93 (d, 1H, $J$ = 8 Hz, Ar–H), 8.10 (d, 1H, $J$ = 8 Hz, Ar–H), 15.85 (s, 1H, NH) ppm. $^{13}C$ NMR: $\delta$ = 14.4, 22.6, 26.7 (propyl carbons), 14.1, 23.6, 27.8, 31.5, 32.7, 40.2 (hexyl carbons), 53.0 ($CO_2CH_3$), 102.8 (C-3), 114.4, 116.3 123.8, 125.8, 131.8, 134.8 ($C_6H_4$–$CO_2CH_3$-*o*), 116.9 (CN), 143.2 (C-4), 160.3 (C-5), 160.5, 162.6 (2CO), 166.9 ($CO_2CH_3$). MS: $m/z$ (%) = 424. Anal. Calcd. for $C_{23}H_{28}N_4O_4$ (424.50): C, 65.08; H, 6.65; N, 13.20. Found: C, 65.15; H, 6.60; N, 13.15.

*4.2.2.3. 2-[N-(5-Cyano-1-cyclohexyl-2,6-dioxo-4-propyl-1,6-dihydro-2H-pyridine-3-ylidene) hydrazine]benzoic acid methyl ester (**5c**).* Yellow crystals; m.p. 253 °C. Yield 88%. IR (KBr): $\nu$ = 3434 (NH, broadened due to H-bond between O and NH), 3062 (CH aromatic), 2938 (CH aliphatic), 2223 (CN), 1698 (CO ester), 1661 (amide CO), 1642 (amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.99 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.29–2.90 (m, 10H, cyclohexyl-H), 1.72 (sextet, 2H, $J$ = 7 Hz, $CH_2$), 3.23 (t, 2H, $J$ = 7 Hz, $CH_2$), 3.95 (s, 3H, $CO_2CH_3$), 4.66 (m, 1H, cyclohexyl-H), 7.35 (t, 1H, $J$ = 7 Hz, Ar–H), 7.77 (t, 1H, $J$ = 7 Hz, Ar–H), 7.96 (d, 1H, $J$ = 8 Hz, Ar–H), 8.04 (d, 1H, $J$ = 8 Hz, Ar–H), 15.57 (s, 1H, NH) ppm. MS: $m/z$ (%) = 422. Anal. Calcd. for $C_{23}H_{26}N_4O_4$ (422.49): C, 65.39; H, 6.20; N, 13.26. Found: C, 65.45; H, 6.29; N, 13.40.

*4.2.2.4. 2-[N-(1-Benzyl-5-cyano-2,6-dioxo-4-propyl-1,6-dihydro-2H-pyridine-3-ylidene) hydrazine]benzoic acid methyl ester (**5d**).* Orange crystals; m.p. 217 °C. Yield 89%. IR (KBr): $\nu$ = 3329 (NH, broadened due to H-bond between O and NH), 3095 (CH aromatic), 2955 (CH aliphatic), 2221 (CN), 1687 (ester CO), 1645, 1638 (amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.96 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.37 (sextet, 2H, $J$ = 7 Hz, $CH_2$), 1.96 (t, 2H, $J$ = 7 Hz, $CH_2$), 3.88 (s, 3H, $CO_2CH_3$), 5.05 (s, 2H, $CH_2$ph), 6.57–7.72 (m, 9H, Ar–H), 15.50 (s, 1H, NH) ppm. $^{13}C$ NMR: $\delta$ = 14.1, 19.5, 25.3 (propyl carbons), 46.1 ($CH_2$ph), 52.3 ($CO_2CH_3$), 116.8 (CN), 115.0, 117.1, 118.4, 130.5, 133.6, 147.9 ($C_6H_4CO_2CH_3$), 126.5, 127.1, 128.4, 142.4 ($C_6H_5CH_2$), 105.1 (*C*-3), 145.3 (*C*-4), 155.3 (*C*-5), 162.5, 164.1 (2CO), 167.6 ($CO_2CH_3$) ppm. MS: $m/z$ (%) = 430. Anal. Calcd. for $C_{24}H_{22}N_4O_4$ (430.47): C, 66.97; H, 5.15; N, 13.02. Found: C, 66.85; H, 5.20; N, 13.10.

*4.2.2.5. 1-Butyl-5-[(4-chlorophenyl)-hydrazono]-2,6-dioxo-4-propyl-1,2,5,6-tetrahydro-pyridine-3-carbonitrile (**5e**).* Dark yellow crystals; m.p. 182 °C. Yield 80%. IR (KBr): $\nu$ = 3455 (NH, broadened due to H-bond between O and NH), 3077 (CH aromatic), 2946 (CH aliphatic), 2216 (CN), 1641 (amid CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.90 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.0 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.30 (sextet, 2H, $J$ = 7 Hz, $CH_2$), 1.52 (quintet, 2H, $J$ = 7 Hz, $CH_2$), 1.67 (sextet, 2H, $J$ = 7 Hz, $CH_2$), 2.90 (t, 2H, $J$ = 7 Hz, $CH_2$), 3.82 (t, 2H, $J$ = 7 Hz, $CH_2N$), 7.54 (d, 2H, $J$ = 8 Hz, Ar–H), 7.73 (d, 2H, $J$ = 8 Hz, Ar–H), 14.41 (s, 1H, NH) ppm. MS: $m/z$ (%) = 374, 372. Anal. Calcd. for $C_{19}H_{21}ClN_4O_2$ (372.86): C, 61.21; H, 5.68; N, 15.03. Found: C, 61.30; H, 5.45; N, 15.16.

*4.2.2.6. 5-[(4-Chlorophenyl)-hydrazono]-1-hexyl-2,6-dioxo-4-propyl-1,2,5,6-tetrahydro-pyridine-3-carbonitrile (**5f**).* Orange crystals; m.p. 152 °C. Yield 88%. IR (KBr): $\nu$ = 3414 (NH, broadened due to H-bond between O and NH), 3089 (CH aromatic), 2954 (CH aliphatic), 2219 (CN), 1647 (amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.83 (t, 3H, $J$ = 6 Hz, $CH_3$), 0.99 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.26 (m, 6H, 3 hexyl-$CH_2$), 1.52 (quintet, 2H, $J$ = 7 Hz, $CH_2$), 1.66 (sextet, 2H, $J$ = 7 Hz, $CH_2$), 2.88 (t, 2H, $J$ = 7 Hz, $CH_2$), 3.79 (t, 2H, $J$ = 7 Hz, $CH_2N$), 7.51 (d, 2H, $J$ = 8 Hz, Ar–H), 7.71 (d, 2H, $J$ = 8 Hz, Ar–H), 14.50 (s, 1H, NH) ppm. MS: $m/z$ (%) = 402, 400. Anal. Calcd. for $C_{21}H_{25}Cl\ N_4O_2$ (400.91): C, 62.92; H, 6.29; N, 13.97. Found: C, 62.88; H, 6.30; N, 13.89.

*4.2.2.7. 1-Benzyl-5-[(4-chlorophenyl)-hydrazono]-2,6-dioxo-4-propyl-1,2,5,6-tetrahydro-pyridine-3-carbonitrile (**5g**).* Orange crystals; m.p. 203 °C. Yield 79%. IR (KBr): $\nu$ = 3465 (NH, broadened due to H-bond between O and NH), 3061 (CH aromatic), 2966 (CH aliphatic), 2223 (CN), 1641 (amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.01 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.71 (sextet, 2H, $J$ = 7 Hz, $CH_2$), 2.92 (t, 2H, $J$ = 7 Hz, $CH_2$), 5.03 (s, 2H, $CH_2$ph), 7.25–7.32 (m, 5H, Ar–H), 7.52

(d, 2H, *J* = 8 Hz, Ar–H), 7.73 (d, 2H, *J* = 8 Hz, Ar–H), 14.45 (s, 1H, NH) ppm. MS: *m*/*z* (%) = 408, 406. Anal. Calcd. for $C_{22}H_{19}Cl\ N_4O_2$ (406.88): C, 64.95; H, 4.71; N, 13.77. Found: C, 64.78; H, 4.80; N, 13.69.

*4.2.2.8. 5-[(4-Chlorophenyl)-hydrazono]-1-cyclohexyl-2,6-dioxo-4-propyl-1,2,5,6-tetrahydro-pyridine-3-carbonitrile (**5h**).* Yellow crystals; m.p. 227 °C. Yield 91%. IR (KBr): *ν* = 3455 (NH, broadened due to H-bond between O and NH), 3041 (CH aromatic), 2940 (CH aliphatic), 2220 (CN), 1645 (amide CO) $cm^{-1}$. $^1H$ NMR; *δ* = 1.07 (t, 3H, *J* = 7 Hz, $CH_3$), 1.24–2.38 (m, 10H, cyclohexyl-H), 1.74 (sextet, 2H, *J* = 7 Hz, $CH_2$), 2.95 (t, 2H, *J* = 7 Hz, $CH_2$), 4.78 (m, 1H, cyclohexyl C*H*–N), 7.35–7.43 (m, 4H, Ar–H), 15.02 (s, 1H, NH) ppm. MS: *m*/*z* (%) = 400, 398. Anal. Calcd. for $C_{21}H_{23}ClN_4O_2$ (398.90): C, 63.23; H, 5.81; N, 14.05. Found: C, 63.38; H, 5.75; N, 14.20.

*4.2.2.9. 2-[N-(1-Ethoxycarbonyl-2-oxo-pentylidene)hydrazino]benzoic acid methyl ester (**7a**).* Yellow crystals; m.p. 178 °C. Yield 93%. IR (KBr): *ν* = 3310 (NH), 3012 (CH aromatic), 2940 (CH aliphatic), 1686 (ester CO), 1669 (Ketonic CO) $cm^{-1}$. $^1H$ NMR: *δ* = 0.96 (t, 3H, *J* = 7 Hz, $CH_3$), 1.38 (t, 3H, *J* = 7 Hz, $CH_3$), 1.71 (sextet, 2H, *J* = 7 Hz, $CH_2$), 2.91 (t, 2H, *J* = 7 Hz, $CH_2$), 3.96 (s, 3H, $OCH_3$), 4.35 (q, 2H, *J* = 7 Hz, $CH_2$), 7.08–8.03 (m, 4H, Ar–H), 14.06, 15.50 (s, 1H, N*H*) ppm; *Z*, *E* isomers. $^{13}C$ NMR; 14.1 ($CO_2CH_2CH_3$), 61.2 ($COOCH_2CH_3$), 17.8, 18.1, 40.7 ($COCH_2CH_2CH_3$), 52.7 ($CO_2CH_3$), 114.6, 115.3, 122.9, 123.7, 131.2, 134.5 ($C_6H_4$–$CO_2CH_3$-*o*), 144.5 (*C*=N–NH), 162.5, 167.5 (2 CO ester), 197.4 (CO) ppm. MS: *m*/*z* (%) = 320. Anal. Calcd. for $C_{16}H_{20}N_2O_5$ (320.35): C, 59.99; H, 6.29; N, 8.74. Found: C, 59.82; H, 6.18; N, 8.91.

*4.2.2.10. 2-[(4-Nitrophenyl)hydrazono]-3-oxo-hexanoic acid ethyl ester (**7b**).* Yellow crystals; m.p. 202 °C. Yield 90%. IR (KBr): *ν* = 3325 (NH), 3010 (CH aromatic), 2953 (CH aliphatic), 1715 (ester CO), 1670 (ketonic CO) $cm^{-1}$. $^1H$ NMR: *δ* = 0.99 (t, 3H, *J* = 7 Hz, $CH_3$), 1.39 (t, 3H, *J* = 7 Hz, $CH_3$), 1.73 (sextet, 2H, *J* = 7 Hz, $CH_2$), 2.89 (t, 2H, *J* = 7 Hz, $CH_2$), 4.37 (q, 2H, *J* = 7 Hz, $CH_2$), 7.37 (d, 2H, *J* = 8 Hz, Ar–H), 8.27 (d, 2H, *J* = 8 Hz, Ar–H), 12.65, 14.45 (s, 1H, NH) ppm; *Z*, *E* isomers. $^{13}C$ NMR; 14.0 ($CO_2CH_2CH_3$), 62.1 ($CO_2CH_2CH_3$), 14.1, 22.4, 40.7 ($COCH_2CH_2CH_3$), 115.0, 125.6, 134.8, 138.2 ($C_6H_4$–$NO_2$-*p*), 146.8 (*C*=N–NH), 196.7 (CO ester), 220.1 (CO) ppm. MS: *m*/*z* (%) = 307. Anal. Calcd. for $C_{14}H_{17}N_3O_5$ (307.31): C, 54.72; H, 5.58; N, 13.67. Found: C, 54.59; H, 5.50; N, 13.77.

*4.2.2.11. 3-Oxo-2-(4-tolylhydrazono)hexanoic acid ethyl ester (**7c**).* Brown crystals; m.p. 240 °C. Yield 94%. IR (KBr): *ν* = 3325 (NH), 3001 (CH aromatic), 2962 (CH aliphatic), 1696 (ester CO), 1667 (ketonic CO) $cm^{-1}$. $^1H$ NMR: *δ* = 0.96 (t, 3H, *J* = 7 Hz, $CH_3$), 1.36 (t, 3H, *J* = 7 Hz, $CH_3$), 1.67 (sextet, 2H, *J* = 7 Hz, $CH_2$), 2.32 (s, 3H, $CH_3$), 2.87 (t, 2H, *J* = 7 Hz, $CH_2$), 4.30 (q, 2H, *J* = 7 Hz, $CH_2$), 7.14–7.29 (m, 4H, Ar–H), 12.77, 14.88 (s, 1H, NH) ppm; *Z*, *E* isomers. $^{13}C$ NMR: 14.1 ($COOCH_2CH_3$), 61.3 ($COOCH_2CH_3$), 14.2, 18.2, 40.5 ($COCH_2CH_2CH_3$), 21.0 $C_6H_4$–$CH_3$-*p*), 115.5, 126.3, 130.2, 134.7 ($C_6H_4$–$CH_3$-*p*), 139.6 (*C*=N–NH), 164.1 (CO ester), 196.9 (CO) ppm. MS: *m*/*z* (%) = 276. Anal. Calcd. for $C_{15}H_{20}N_2O_3$ (276.34): C, 65.20; H, 7.30; N, 10.14. Found: C, 65.32; H, 7.17; N, 10.24.

*4.2.3. General procedure for the synthesis of pyridazinone compounds **8a–c***

*4.2.3.1. Method I (Δ).* To a mixture of aryl hydrazone derivatives **7a–c** (0.1 mol) and ethyl cyanoacetate (0.1 mol) in dry benzene and glacial acetic acid (10 mL), ammonium acetate (4 g) was added. Then, the reaction mixture was heated to reflux for 12 h. After cooling to room temperature, the resulting solid product was collected by filtration and dried.

*4.2.3.2. Method II (μω).* A mixture of ethyl cyanoacetate (0.1 mol), aryl hydrazone derivatives **7a–c** (0.1 mol), ammonium acetate (0.1 mol) and a few drops of glacial acetic acid was placed in the microwave oven and irradiated at 440 W for 20 min. After cooling to room temperature. The solid product so-formed was filtered off, dried and recrystallized from ethanol.

*4.2.3.3. 5-Cyano-1-(2-methoxycarbonylphenyl)-6-oxo-4-propyl-1,6-dihydropyridazine-3-carboxylic acid ethyl ester (**8a**).* Yellow crystals; m.p. 190 °C. IR (KBr): *ν* = 3091 (CH aromatic), 2934 (CH aliphatic), 2220 (CN), 1720 (ester CO), 1685 (ester CO), 1641 (amide CO) $cm^{-1}$. $^1H$ NMR: *δ* = 1.08 (t, 3H, *J* = 7 Hz, $CH_3$), 1.34 (t, 3H, *J* = 7 Hz, $CH_3$), 1.75 (sextet, 2H, *J* = 7 Hz, $CH_2$), 3.06 (t, 2H, *J* = 7 Hz, $CH_2$), 3.76 (s, 3H, $CO_2CH_3$), 4.35 (q, 2H, *J* = 7 Hz, $CH_2$), 7.44 (d, 1H, *J* = 8 Hz, Ar–H), 7.54 (t, 1H, *J* = 7 Hz, Ar–H), 7.66 (t, 1H, *J* = 7 Hz, Ar–H), 8.06 (d, 1H, *J* = 8 Hz, Ar–H) ppm. $^{13}C$ NMR: 14.1 ($CO_2CH_2CH_3$), 62.8 ($CO_2CH_2CH_3$), 14.2, 23.5, 34.2 ($COCH_2CH_2CH_3$), 52.6 ($C_6H_4$–$CO_2CH_3$-*o*), 112.4 (*C*-5), 114.7 (*C*N), 127.1, 128.1, 130.2, 131.4, 133.6, 137.1 ($C_6H_4$–$CO_2CH_3$-*o*), 139.7 (*C*-3), 155.2 (*C*-4), 156.6 (CO ring), 162.1, 164.7 (2CO ester) ppm. MS: *m*/*z* (%) = 369. Anal. Calcd. for $C_{19}H_{19}N_3O_5$ (369.38): C, 61.78; H, 5.18; N, 11.38. Found: C, 61.70; H, 5.25; N, 11.45.

*4.2.3.4. 5-Cyano-1-(4-nitrophenyl)-6-oxo-4-propyl-1,6-dihydro-pyridazine-3-carboxylic acid ethyl ester (**8b**).* Brown crystals; m.p. 192 °C; IR (KBr): *ν* = 3010 (CH aromatic), 2985 (CH aliphatic), 2214 (CN), 1689 (ester CO), 1642 (amide CO) $cm^{-1}$. $^1H$ NMR: *δ* = 0.99 (t, 3H, *J* = 7 Hz, $CH_3$), 1.29 (t, 3H, *J* = 7 Hz, $CH_3$), 1.67 (sextet, 2H, *J* = 7 Hz, C*H*$_2$), 2.94 (t, 2H, *J* = 7 Hz, $CH_2$), 4.37 (q, 2H, *J* = 7 Hz, $CH_2$), 7.92 (d, 2H, *J* = 8 Hz, Ar–H), 8.43 (d, 2H, *J* = 8 Hz, Ar–H) ppm. MS: *m*/*zm*/*z* (%) = 356. Anal. Calcd. for $C_{17}H_{16}N_4O_5$(356.34): C, 57.30; H, 4.53; N, 15.72. Found: C, 57.45; H, 4.60; N, 15.59.

*4.2.3.5. 5-Cyano-6-oxo-4-propyl-1-(4-methylphenyl)-1,6-dihydropyridazine-3-carboxylic acid ethyl ester (**8c**).* Brown crystals; m.p. > 300 °C. IR (KBr): *ν* = 3021 (CH aromatic), 2805 (CH aliphatic), 2210 (CN), 1658 (ester CO), 1645 (amide CO) $cm^{-1}$. $^1H$ NMR: *δ* = 1.04 (t, 3H, *J* = 7 Hz, $CH_3$), 1.30 (t, 3H, *J* = 7 Hz, $CH_3$), 1.69 (sextet, 2H, *J* = 7 Hz, $CH_2$), 3.04 (t, 2H, *J* = 7 Hz, $CH_2$), 3.94 (s, 3H, $CH_3$), 4.07 (q, 2H, *J* = 7 Hz, $CH_2$), 7.68 (d, 2H, *J* = 7 Hz, Ar–H), 7.96 (d, 2H, *J* = 8 Hz, Ar–H) ppm. MS: *m*/*z* (%) = 325. Anal. Calcd. for $C_{18}H_{19}N_3O_3$ (325.37): C, 66.45; H, 4.89; N, 12.91. Found: C, 66.59; H, 5.77; N, 12.90.

*4.2.4. General procedure for the reaction of **5a–h** and **8a,b** with elemental sulphur*

*4.2.4.1. Method I (Δ).* To a solution of arylazopyridinone derivatives **5a–g** or pyridazinones **8a,b** (0.1 mol) in ethanol (30 ml), elemental sulphur (0.1 mol) and a catalytic amount of triethylamine were added. The reaction mixture was heated to reflux for 3 h. The solid product so-formed was collected by filtration and dried.

*4.2.4.2. Method II (μω).* A mixture of **5a–g** or **8a,b** (0.1 mol), elemental sulphur (0.1 mol) and a few drops of triethylamine was placed in the microwave oven and irradiated at 440 W for 10 min. Then, the reaction mixture was left to cool to room temperature. The solid product so-formed was filtered off and dried.

*4.2.4.3. Method III (US).* To a solution of **5a–g** or **8a,b** (0.1 mol) in ethanol (30 ml), elemental sulphur (0.1 mol) and a catalytic amount of triethylamine were added. The reaction mixture was heated under ultrasound irradiation at 40 °C for 90 min and then left to cool to room temperature. The solid product so-formed was collected by filtration, dried and recrystallized from ethanol.

*4.2.4.4. 2[2-(3-Amino-5-butyl-1-ethyl-4,6-dioxo-5,6-dihydrothieno[3,4-c]pyridine-7(4H)-ylidene)-hydrazinyl]benzoic acid methyl ester (**6a**).* Brown crystals; m.p. 113 °C. IR (KBr): $\nu$ = 3447, 3343, 3144 (($NH_2$, NH), 3049 (CH aromatic), 2952 (CH aliphatic), 1702 (ester CO), 1660, 1639 (2 amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.93 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.08 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.37 (sextet, 2H, $J$ = 7 Hz, $CH_2$), 1.61 (quintet, 2H, $J$ = 7 Hz, $CH_2$), 1.76 (q, 2H, $J$ = 7 Hz, $CH_2$), 3.01 (t, 2H, $J$ = 7 Hz, $CH_2N$), 4.03 (s, 3H, $CO_2CH_3$), 7.29 (t, 1H, $J$ = 7 Hz, Ar–H), 7.66 (t, 1H, $J$ = 7 Hz, Ar–H), 7.72 (s, 2H, $NH_2$), 7.93 (d, 1H, $J$ = 8 Hz, Ar–H), 8.11 (d, 1H, $J$ = 8 Hz, Ar–H), 15.85 (s, 1H, NH) ppm. $^{13}C$ NMR: $\delta$ = 13.9, 23.6, 32.7, 40.0 (butyl carbons), 14.4, 20.3 ($CH_3CH_2$), 53.1 ($CO_2CH_3$), 102.8 (C-3), 114.4, 116.3, 116.9, 123.8, 125.8, 143.2 ($C_6H_4$–$COOCH_3$-*o*), 131.8, 134.7 (thienyl carbons), 145.0 (C-4), 160.3 (C-5), 160.5, 162.6 (2CO), 166.9 ($CO_2CH_3$) ppm. MS: *m*/*z* (%) = 428. Anal. Calcd. for $C_{21}H_{24}N_4O_4S$ (428.51): C, 58.86; H, 5.65; N, 13.07. Found: C, 58.78; H, 5.60; N, 13.33.

*4.2.4.5. 2[2-(3-Amino-1-ethyl-5-hexyl-4,6-dioxo-5,6-dihydrothieno[3,4-c]pyridine-7(4H)-ylidene)-hydrazinyl]benzoic acid methyl ester (**6b**).* Dark brown crystals; m.p. 138 °C. IR (KBr): $\nu$ = 3444, 3344, 3300 (($NH_2$, NH), 3095 (CH aromatic), 2925 (CH aliphatic), 1705 (ester CO), 1662, 1641 (2 amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.86 (t, 3H, $J$ = 6 Hz, $CH_3$), 1.24 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.29 (m, 6H, 3 hexyl-$CH_2$), 1.51 (quintet, 2H, $J$ = 7 Hz, $CH_2$), 2.66 (q, 2H, $J$ = 7 Hz, $CH_2$), 3.83 (t, 2H, $J$ = 7 Hz, $CH_2N$), 3.92 (s, 3H, $CO_2CH_3$), 7.70 (s, 2H, $NH_2$) 7.08 (t, 1H, $J$ = 7 Hz, Ar–H), 7.67 (t, 1H, $J$ = 7 Hz, Ar–H), 7.74 (d, 1H, $J$ = 8 Hz, Ar–H), 7.98 (d, 1H, $J$ = 8 Hz, Ar–H), 14.87 (s, 1H, NH) ppm. MS: *m*/*z* (%) = 456. Anal. Calcd. for $C_{23}H_{28}N_4O_4S$ (456.57): C, 60.51; H, 6.18; N, 12.27. Found: C, 60.58; H, 6.25; N, 12.15.

*4.2.4.6. 2[2-(3-Amino-5-cyclohexyl-1-ethyl-4,6-dioxo-5,6-dihydrothieno[3,4-c]pyridine-7(4H)-ylidene)hydrazinyl]benzoic acid methyl ester (**6c**).* Brown crystals; m.p. 222 °C. IR (KBr): $\nu$ = 3444, 3325, 3302 ($NH_2$, NH), 3045 (aromatic CH), 2931 (aliphatic CH), 1697 (ester CO), 1660, 1641 (2 amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.01 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.23–2.37 (m, 10H cyclohexyl-H), 2.99 (q, 2H, $J$ = 7 Hz, $CH_2$), 3.93 (s, 3H, $CO_2CH_3$), 4.69 (m, 1H cyclohexyl-H), 7.08 (s, 2H, $NH_2$), 7.29–7.98 (m, 4H, Ar–H), 14.80 (s, 1H, NH) ppm. MS: *m*/*z* (%) = 454. Anal. Calcd. for $C_{23}H_{26}N_4O_4S$ (454.55): C, 60.78; H, 5.77; N, 12.33. Found: C, 60.75; H, 5.89; N, 12.40.

*4.2.4.7. 2[2-(3-Amino-5-benzyl-1-ethyl-4,6-dioxo-5,6-dihydrothieno[3,4-c]pyridine-7(4H)-ylidene)-hydrazinyl]benzoic acid methyl ester (**6d**).* Dark brown crystals; m.p. 221 °C. IR (KBr): $\nu$ = 3534, 3449, 3344 ($NH_2$, NH), 3050 (aromatic CH), 2950 (aliphatic CH), 1701 (ester CO), 1666 (2 amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.27 (t, 3H, $J$ = 7 Hz, $CH_3$), 3.02 (q, 2H, $J$ = 7 Hz, $CH_2$), 3.89 (s, 3H, $CO_2CH_3$), 5.06 (s, 2H, $CH_2$ph), 7.07 (s, 2H, $NH_2$), 7.23–7.96 (m, 9H, Ar–H), 14.83 (s, 1H, NH) ppm. MS: *m*/*z* (%) = 462. Anal. Calcd. for $C_{24}H_{22}N_4O_4S$ (462.53): C, 62.32; H, 4.79; N, 12.11. Found: C, 62.44; H, 4.65; N, 12.27.

*4.2.4.8. 3-Amino-5-butyl-7-[2-(4-chlorophenyl)-hydrazono]-1-ethyl-7H-thieno[3,4-c]pyridine-4,6-dione (**6e**).* Light brown crystals; m.p. 179 °C. IR (KBr): $\nu$ = 3442, 3315, 3302 ($NH_2$, NH) 3090 (aromatic CH), 2957 (aliphatic CH), 1665, 1640 (2 amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.88 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.20 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.27 (sextet, 2H, $J$ = 7 Hz, $CH_2$), 1.49 (quintet, 2H, $J$ = 7 Hz, $CH_2$), 2.95 (q, 2H, $J$ = 7 Hz, $CH_2$), 3.78 (t, 2H, $J$ = 7 Hz, $CH_2N$), 7.30–7.38 (m, 4H, Ar–H), 7.62 (s, 2H, $NH_2$), 13.52 (s, 1H, NH) ppm. MS: *m*/*z* (%) = 406, 404. Anal. Calcd. for $C_{19}H_{21}ClN_4O_2S$ (404.92): C, 56.36; H, 5.23; N, 13.84. Found: C, 56.42; H, 5.15; N, 13.89.

*4.2.4.9. 3-Amino-7-[2-(4-chlorophenyl)-hydrazono]-1-ethyl-5-hexyl-7H-thieno[3,4-c]pyridine-4,6-dione (**6f**).* Dark red crystals; m.p. 161 °C. IR (KBr): $\nu$ = 3411, 3324, 3302 ($NH_2$, NH), 3092 (aromatic CH), 2926 (aliphatic CH), 1663, 1645 (2 amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 0.85 (t, 3H, $J$ = 6 Hz, $CH_3$), 1.23 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.27 (m, 6H, 3 hexyl-$CH_2$), 1.51 (quintet, 2H, $J$ = 7 Hz, $CH_2$), 2.95 (q, 2H, $J$ = 7 Hz, $CH_2$), 3.79 (t, 2H, $J$ = 7 Hz, $CH_2N$), 7.34 (d, 2H, $J$ = 8 Hz, Ar–H), 7.42 (d, 2H, $J$ = 8 Hz, Ar–H), 7.68 (s, 2H, $NH_2$), 13.55 (s, 1H, NH) ppm. MS: *m*/*z* (%) = 434, 432. Anal. Calcd. for $C_{21}H_{25}ClN_4O_2S$ (432.98): C, 58.26; H, 5.82; N, 12.94. Found: C, 58.30; H, 5.76; N, 12.85.

*4.2.4.10. 3-Amino-5-benzyl-7-[2-(4-chlorophenyl)-hydrazono]-1-ethyl-7H-thieno[3,4-c]pyridine-4,6-dione (**6g**).* Red crystals; m.p. 244 °C. IR (KBr): $\nu$ = 3510, 3441, 3317 ($NH_2$, NH), 3050 (aromatic CH), 2949 (aliphatic CH), 1658 (2 amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.24 (t, 3H, $J$ = 7 Hz, $CH_3$), 2.99 (q, 2H, $J$ = 7 Hz, $CH_2$), 5.03 (s, 2H, $CH_2$ph), 7.35 (m, 9H, Ar–H), 7.73 (s, 2H, $NH_2$), 13.48 (s, 1H, NH) ppm. MS: *m*/*z* (%) = 440, 438. Anal. Calcd. for $C_{22}H_{19}ClN_4O_2S$ (438.94): C, 60.20; H, 4.36; N, 12.76. Found: C, 60.33; H, 4.47; N, 12.55.

*4.2.4.11. 5-Amino-7-ethyl-3-(2-methoxycarbonylphenyl)-4-oxo-3,4-dihydrothieno[3,4-d]-pyridazine-1-carboxylic acid ethyl ester (**9a**).* Brown crystals; m.p. 122 °C. IR (KBr): $\nu$ = 3412, 3314 ($NH_2$), 3091 (aromatic CH), 2921 (aliphatic CH), 1722 (2 ester CO), 1651 (amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.17 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.30 (t, 3H, $J$ = 7 Hz, $CH_3$), 2.71 (q, 2H, $J$ = 7 Hz, $CH_2$), 3.67 (s, 3H, $CO_2CH_3$), 4.32 (q, 2H, $J$ = 7 Hz, $CH_2$), 7.48–7.88 (m, 6H, 4 Ar–H + $NH_2$) ppm. MS: *m*/*z* (%) = 401. Anal. Calcd. for $C_{19}H_{19}N_3O_5S$ (401.44): C, 56.85; H, 4.77; N, 10.47. Found: C, 56.80; H, 4.88; N, 10.33.

*4.2.4.12. 5-Amino-7-ethyl-3-(4-nitrophenyl)-4-oxo-3,4-dihydrothieno[3,4-d]pyridazine-1-carboxylic acid ethyl ester (**9b**).* Brown crystals; m.p.159 °C. IR (KBr): $\nu$ = 3452, 3343 ($NH_2$), 3088 (aromatic CH), 2922 (aliphatic CH), 1715 (ester CO), 1663 (amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.22 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.38 (t, 3H, $J$ = 7 Hz, $CH_3$), 2.79 (q, 2H, $J$ = 7 Hz, $CH_2$), 4.39 (q, 2H, $J$ = 7 Hz, $CH_2$), 6.17 (s, 2H, $NH_2$), 7.84 (d, 2H, $J$ = 8 Hz, Ar–H), 8.21 (d, 2H, $J$ = 8 Hz, Ar–H) ppm. $^{13}C$ NMR: $\delta$ = 14.1 ($CO_2CH_2CH_3$), 16.5, 21.7 ($CH_2CH_3$), 62.6 ($CO_2CH_2CH_3$), 120.5, 123.9, 125.2, 138.2 ($C_6H_4$–$NO_2$-*p*), 106.3, 127.0, 145.5 (pyridazine carbons), 145.9, 159.2 (thienyl carbons), 159.6 (CO ring), 164.2 (CO ester) ppm. MS: *m*/*z* (%) = 388. Anal. Calcd. for $C_{17}H_{16}N_4O_5S$ (388.40): C, 52.57; H, 4.15; N, 14.42. Found: C, 52.43; H, 4.32; N, 14.35.

*4.2.4.13. Synthesis of 5-Amino-7-cyano-8-ethyl-3-(4-nitrophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid ethyl ester (**11**).* A mixture of compound **8b** (0.1 mol) and acrylonitrile (0.1 mol) was placed in the microwave oven and irradiated at 440 W for 5 min. Then, the reaction mixture left to cool to room temperature. The solid product so-formed was filtered off and recrystallized from ethanol to yield compound **11** as brown crystals.

Yield 83%; m.p. 163 °C. IR (KBr): $\nu$ = 3436, 3322 ($NH_2$), 3033 (aromatic CH), 2974 (aliphatic CH), 2221 (CN), 1718 (ester CO), 1657 (amide CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.24 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.45 (t, 3H, $J$ = 7 Hz, $CH_3$), 2.82 (q, 2H, $J$ = 7 Hz, $CH_2$), 4.44 (q, 2H, $J$ = 7 Hz, $CH_2$), 6.22 (s, 2H, $NH_2$), 7.27 (s, 1H, H-6), 7.89 (d, 2H, $J$ = 8 Hz, Ar–H), 8.26 (d, 2H, $J$ = 8 Hz, Ar–H) ppm. MS: *m*/*z* (%) = 408. Anal. Calcd. for $C_{20}H_{17}N_5O_5$(407.39): C, 58.97; H, 4.21; N, 17.19. Found: C, 58.82; H, 4.30; N, 17.25.

*4.2.4.14. Synthesis of 1-Amino-7-ethyl-4-oxo-10-thiatricyclo [5.2.1.02,6] deca-8-diene-3,5-dione;1-(4-nitro-phenyl)-6-oxo-1,6-dihydro-pyridazine-3-carboxylic acid ethyl ester (**12**).* A mixture of compound **8b** (0.1 mol) and maleic anhydride (0.1 mol) was placed

in the microwave oven and irradiated at 440 W for 5 min. Then, it left to cool to room temperature. The solid product so-formed was filtered off and recrystallized from ethanol to give compound **12** as brown crystals.

Yield 70%; m.p. 103 °C. IR (KBr): $\nu$ = 3422, 3331 ($NH_2$), 3088 (aromatic CH), 2918 (aliphatic CH), 1728 (ester CO), 1676, 1664, 1642 (3 CO) $cm^{-1}$. $^1H$ NMR: $\delta$ = 1.06 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.19 (t, 3H, $J$ = 7 Hz, $CH_3$), 1.28 (q, 2H, $J$ = 7 Hz, $CH_2$), 3.41, 3.48 (s, 2H, maleic anhydride), 4.39 (q, 2H, $J$ = 7 Hz, $CH_2$), 6.17 (s, 2H, $NH_2$), 7.86 (d, 2H, $J$ = 8 Hz, Ar–H), 8.26 (d, 2H, $J$ = 8 Hz, Ar–H) ppm. MS: $m/z$ (%) = 486. Anal. Calcd. for $C_{21}H_{18}N_4O_8S$ (486.46): C, 51.85; H, 3.73; N, 11.52. Found: C, 51.66; H, 3.82; N, 11.39.

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[18] Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary Publications Nos. CCDC 687579. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk)