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Three practical approaches for the synthesis of novel 4,7-dihetarylpyrazolo[1,5-*a*][1,3,5]triazines

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ABSTRACT

Novel 4,7-dihetarylpyrazolo[1,5-*a*][1,3,5]triazines were synthesized from three different approaches. The first one, involved a one-step reaction between 5-amino-3-hetaryl-1*H*-pyrazoles and *O,S*-diethyl hetaroylimidothiocarbonates or *S,S*-diethyl hetaroylimidodithiocarbonates under solvent-free conditions employing microwave irradiation as the energy source. In the second approach, conventional heating under reflux in DMF as solvent was used instead of the microwave irradiation; and the third one was achieved from a two-step sequence through the treatment of 5-amino-3-hetaryl-1*H*-pyrazoles with hetaroyl isothiocyanates and the subsequent S-alkylation and cyclization process in DMF as solvent. Some intermediates were isolated and characterized to support the regiochemistry of the studied reactions. The structures of the new compounds were unambiguously established by spectroscopic and analytical techniques.

1. Introduction

The pyrazolo[1,5-*a*][1,3,5]triazine core may be found in the structure of different biologically active molecules including inhibitors of protein kinase CK2 and cyclin-dependent kinases (CDKs),[1] which exhibit high antiproliferative activity in tumor cell lines and high potential as cancer chemotherapy agents (compound **1**, Fig. 1).[2] Some pyrazolotriazines act as inhibitors of phosphodiesterase type 4 (PDE4),[3] potential therapeutic agents for the control of autoimmune and inflammatory diseases and more recently, it was reported the activity of some of them against the herpes simplex viruses HSV-1 and HSV-2.[4] A variety of corticotrophin releasing factor CRF_1 receptor antagonists containing the pyrazolo[1,5-*a*][1,3,5]triazine framework have been studied over the last years.[5] Among them is the Pexacerfont (compound **2**, Fig. 1), which has been tested as a potential agent for the control and treatment of some diseases related to stress such as anxiety and depression.[5e]

It is also worth mentioning that the presence of the 2-thienyl and 2-furyl moieties in the structure of purines **3**,[6] pyrazolopyrimidines **4**,[7] and triazolotriazine **5**[8] (Fig. 1), was determinant for their biological properties displayed.[6–8] The insertion of the 2-thienyl and 2-furyl units into such interesting compounds has been usually mediated by a common C–C coupling process based on the Stille reaction of the corresponding hetarylstannic derivatives and the appropriate starting chloro-compounds[6a,7] or by a cross-coupling reaction between a hetarylzinc halide and the adequate chlorinated compound.[6b]

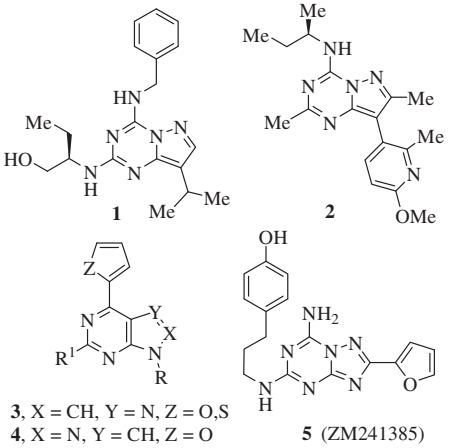

Fig. 1. Pyrazolo[1,5-*a*][1,3,5]triazines and analogue ring systems with pharmacological activity.

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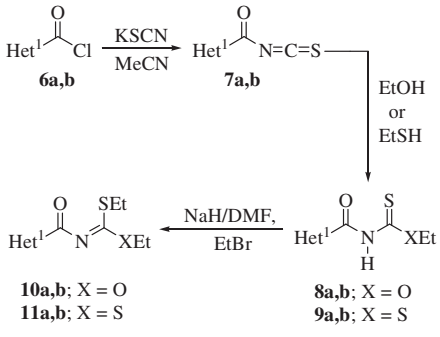
In connection with our current studies on the synthesis of fused heterocycles containing the pyrazole moiety,[9] we are describing here the synthesis and interaction of hetaroyl (furoyl and thenoyl) isothiocyanates **7**, *O*,*S*-diethyl hetaroylimidothiocarbonates **10**, and *S*,*S*-diethyl hetaroylimidodithiocarbonates **11** with 5-amino-3-hetaryl-1*H*-pyrazoles **12** as efficient and metal catalyst-free approaches to obtain novel 4,7-dihetarylpyrazolo[1,5-*a*][1,3,5]triazines **13** and **14**, bearing the well known 2-thienyl and 2-furyl pharmacophores as part of their structures.

2. Results and discussion

2.1. Synthesis of *O*,*S*-diethyl hetaroylimidothiocarbonates and *S*,*S*-diethyl hetaroylimidodithiocarbonates

We have developed a convenient procedure for the synthesis of *O*,*S*-diethyl hetaroylimidothiocarbonates **10a**,**b** and *S*,*S*-diethyl hetaroylimidodithiocarbonates **11a**,**b** (Scheme 1). The starting precursors **10a**,**b** and **11a**,**b** were prepared by the addition of the appropriate hetaroyl chlorides **6a**,**b** to a solution of potassium thiocyanate in acetonitrile to provide the hetaroyl isothiocyanates **7a**,**b**, which were immediately treated with ethanol or ethanethiol to afford the corresponding *O*-ethyl hetaroylthiocarbamates **8a**,**b** or *S*-ethyl hetaroyldithiocarbamates **9a**,**b**. Alkylation of the sulfur atom of **8a**,**b** and **9a**,**b** with ethyl bromide in the presence of sodium hydride at room temperature led to the corresponding thiocarbonates **10a**,**b** and dithiocarbonates **11a**,**b** (Scheme 1, Table 1). The main difference between our protocol and the previous reported method for the synthesis of *S*,*S*-dialkyl aroylimidodithiocarbonates[10] consisted in using a stronger base for the S-alkylation reaction, which permitted us to obtain the precursors **10** and **11** in shorter reaction times (1–1.5 h), and with excellent yields (89–95%), Table 1.



In all cases: **a,** Het[1] = 2-furyl; **b,** Het[1] = 2-thienyl

Scheme 1. Synthesis of thio- and dithiocarbonates **10** and **11**.

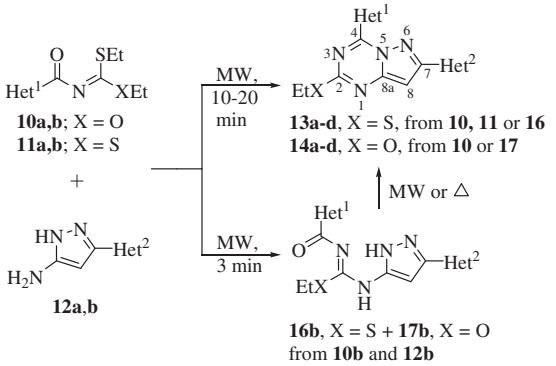
Table 1
Synthesis of thio-/dithiocarbamates **8**, **9** and thio-/dithiocarbonates **10**, **11**

Product	Het[1]	X	Yield, %	Time, h
8a	2-Furyl	O	91	12
8b	2-Thienyl	O	93	12
9a	2-Furyl	S	95	12
9b	2-Thienyl	S	93	12
10a	2-Furyl	O	94	1
10b	2-Thienyl	O	90	1
11a	2-Furyl	S	95	1.5
11b	2-Thienyl	S	89	1.5

2.2. Synthesis of 4,7-dihetarylpyrazolo[1,5-*a*][1,3,5]triazines

Compounds **10** and **11** were employed as starting materials to obtain the desired pyrazolotriazines **13a**–**d** and **14a**–**d** (Scheme 2).

The reaction of thiocarbonates **10a**,**b** with the commercially available 5-aminopyrazoles **12a**,**b** under solvent-free conditions using microwave irradiation (300 watts of power and 160–180 °C, during 10–20 min) afforded a mixture of two new products (TLC control), which were separated by column chromatography (it will be referred to as approach A). The new compounds corresponded to 2-ethylthio-4,7-dihetarylpyrazolo[1,5-*a*][1,3,5]triazines **13a**–**d** and 2-ethoxy-4,7-dihetarylpyrazolo[1,5-*a*][1,3,5]triazines **14a**–**d** (Scheme 2).



In all cases: **a,** Het[1] = Het[2] = 2-furyl; **b,** Het[1] = Het[2] = 2-thienyl; **c,** Het[1] = 2-furyl, Het[2] = 2-thienyl; **d,** Het[1] = 2-thienyl, Het[2] = 2-furyl

Scheme 2. Synthesis of pyrazolo[1,5-*a*][1,3,5]triazines **13** and **14** from the reaction of thiocarbonates **10**, **11** with 5-aminopyrazoles **12**.

When the mixture of thiocarbonate **10b** and 5-aminopyrazole **12b** was irradiated for 3 min, the intermediates 2-ethyl-1-(2-thenoyl)-3-(3-(2-thienyl)pyrazol-5-yl)isothiourea **16b** and 2-ethyl-1-(2-thenoyl)-3-(3-(2-thienyl)pyrazol-5-yl)isourea **17b** were isolated in 10% and 24% yields, respectively. The ^{1}H and ^{13}C NMR spectra of **16b** and **17b** taken in DMSO-d_6 at room temperature confirmed the structures of such intermediates (see ^{1}H NMR spectrum of **17b**, Fig. 2a).

In order to confirm the intermediacy of **17b** in the formation of product **14b**, once the NMR spectra was run at ambient temperature, the probe of the NMR spectrometer was heated at 100 °C and the NMR experiment was repeated for the same sample, to induce, in situ, its cyclization. After five consecutive runs, the progressive disappearance of the N–H signals, notorious changes of the thienyl signals and an increasing of the water signal, corroborated that **17b** was cyclized to pyrazolotriazine **14b** (see spectrum (b) in Fig. 2). Alternatively, a sample of **17b** dissolved in DMSO was cyclized to **14b** by heating it in an oil bath at 180 °C for 10 min. It was also found that intermediates **16b** and **17b** can be cyclized to **13b** and **14b**, respectively, employing microwave irradiation without using solvent, at 180 °C and during 10 min of reaction.

To avoid the mixture of both final products **13** and **14**, and to improve the yields of the target pyrazolotriazines, the microwave-assisted reaction between dithiocarbonates **11a**,**b** and 5-aminopyrazoles **12a**,**b** under solvent-free conditions to obtain exclusively the pyrazolotriazines **13a**–**d** was then studied. It was found that this reaction is highly efficient and selectively generated compounds **13a**–**d** as unique products, in excellent yields (90–95%) (Scheme 2, Table 2).

To evaluate the efficacy of the reaction mediated by microwave irradiation, all reactions depicted in Scheme 2 were repeated under conventional heating using DMF as solvent (it will be referred to as approach B, see Experimental section). Table 2 summarizes the comparative results and the evident improved yields and shorter reaction times when reactions were carried out by microwave irradiation rather than by conventional heating.

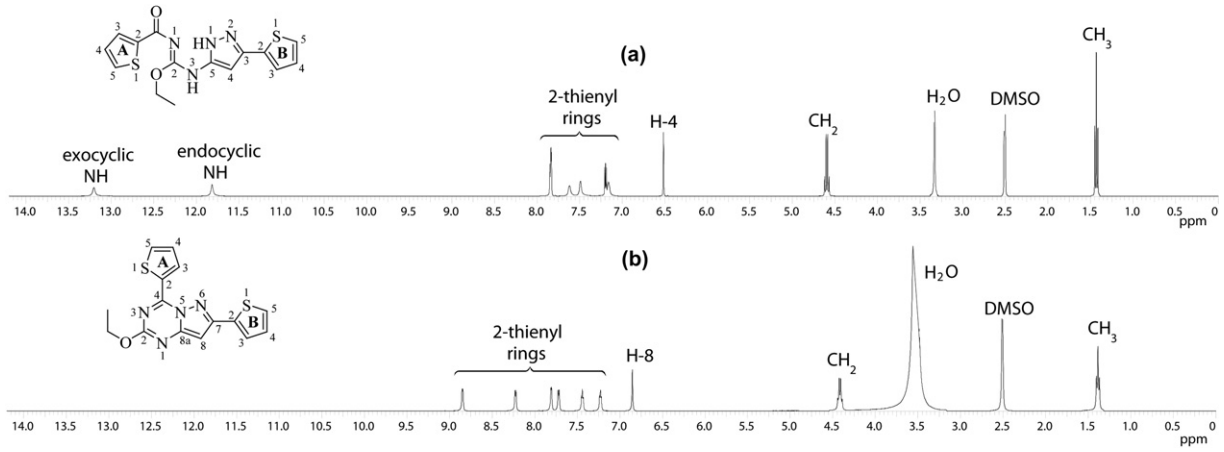
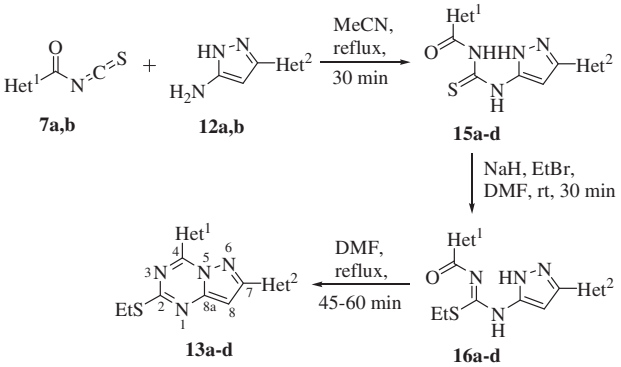


Fig. 2. ^{1}H NMR spectra of intermediate **17b** in DMSO-d_6, (a) at room temperature, (b) at 100 °C into the probe of the NMR spectrometer.

Table 2
Synthesis of pyrazolo[1,5-*a*][1,3,5]triazines **13** and **14**

Product	Het^1	Het^2	X	Yield,[a,b] %		Time, min	
				MW	DMF	MW	DMF
13a	2-Furyl	2-Furyl	S	16(95)	10(83)	15	90
13b	2-Thienyl	2-Thienyl	S	20(90)	12(71)	20	110
13c	2-furyl	2-Thienyl	S	15(93)	9(79)	10	65
13d	2-Thienyl	2-Furyl	S	11(91)	5(75)	12	75
14a	2-Furyl	2-Furyl	O	48	39	15	90
14b	2-Thienyl	2-Thienyl	O	50	41	20	110
14c	2-Furyl	2-Thienyl	O	65	53	10	65
14d	2-Thienyl	2-Furyl	O	46	36	12	75

[a] For products **13a**–**d**, values out of parenthesis are referred to reactions between **10** and **12**. Values in parenthesis correspond to reactions between **11** and **12**.
[b] Yields after isolation by column chromatography.



In all cases: **a**, Het^1 = Het^2 = 2-furyl; **b**, Het^1 = Het^2 = 2-thienyl; **c**, Het^1 = 2-furyl, Het^2 = 2-thienyl; **d**, Het^1 = 2-thienyl, Het^2 = 2-furyl

Scheme 3. Synthesis of pyrazolo[1,5-*a*][1,3,5]triazines **13** via pyrazolylthioureas **15**.

Formation of compounds **13** and **14** should involve an addition–elimination process. Firstly, the C=N double bond of the starting materials **10** and **11** should suffer a nucleophilic attack from the 5-NH_2 of pyrazole **12** with subsequent elimination of a molecule of ethanol or ethanethiol leading to adducts **16** and **17**, respectively (Scheme 2). For reaction between **10** and **12**, adduct **17** should be the main intermediate because ethanethiol (pK_a=10.6) is a better leaving group than ethanol (pK_a=15.9). Finally, adducts **16** and **17** should be intramolecularly cyclized after the attack of 1-NH of pyrazole moiety over the C=O functionality with elimination of a molecule of water to afford the isolated pyrazolotriazines **13** and **14**. Previous reports showing the higher electrophilicity of the C=N double bond than the carbonyl group in compounds type **10**,**11**[11] supports the postulated sequence of steps depicted in Scheme 2.

In order to provide further evidence to support the selectivity and mechanism of this process, an alternative two-step sequence to prepare selectively the target compounds **13a**–**d**, (it will be referred to as approach C) was devised. In the first step, hetaroyl isothiocyanates **7a**,**b** and 5-aminopyrazoles **12a**,**b** were heated under reflux in acetonitrile for 30 min to afford the thiourea derivatives **15a**–**d** (Scheme 3, Table 3). In the second step, compounds **15a**–**d** were treated with ethyl bromide in the presence of sodium hydride in DMF and stirred at room temperature for 30 min to generate the intermediate isothioureas **16a**–**d**, which without isolation were heated under reflux for 45–60 min to produce the desired compounds **13a**–**d** (Scheme 3, Table 3). Products **13a**–**d** obtained by this approach had the same physical and spectroscopic characteristics of those pyrazolotriazines **13a**–**d** resulting from the direct reaction of thiocarbonates **10** or **11** and 5-aminopyrazoles **12**, as mentioned above.

Table 3
Synthesis of pyrazolotriazines **13** via pyrazolylthioureas **15**

Product	Het^1	Het^2	Yield,[a] %	Time, min
15a	2-Furyl	2-Furyl	97	30
15b	2-Thienyl	2-Thienyl	95	30
15c	2-Furyl	2-Thienyl	92	30
15d	2-Thienyl	2-Furyl	93	30
13a	2-Furyl	2-Furyl	70	60
13b	2-Thienyl	2-Thienyl	75	60
13c	2-Furyl	2-Thienyl	85	45
13d	2-Thienyl	2-Furyl	78	45

[a] The yields for products **13a**–**d** correspond to their conversion from **15**.

To corroborate the intermediacy of **16a**–**d** in the formation of products **13a**–**d** (Scheme 3), the isothiourea **16d**, the most stable of the series, was initially isolated and characterized. Then, it was cyclized to its corresponding compound **13d** by conventional heating in DMF under reflux for 45 min, confirming that the conversion of **15** to **13** passed through adducts **16**.

A comparison of the overall yields among the three approaches for the synthesis of pyrazolotriazines **13a**–**d** (calculated on the basis of the stages of formation of precursors and products), allowed us to establish that the synthesis of compounds **13a**–**d** starting from dithiocarbonates **11a**,**b** and 5-aminopyrazoles **12a**,**b** in the absence of solvent employing microwave irradiation gave an overall yield in the range of 75–84%. Conventional heating in DMF gave yield in the range of 59–71%, while reactions performed in two steps starting from the hetaroyl isothiocyanates **7** gave an overall yield in the range of 68–78%. These findings demonstrated

that all three studied synthetic approaches are really useful for the synthesis of the pyrazolotriazines **13a**–**d**, although the first approach should be considered the best, because it is carried out under solvent-free conditions, employs microwaves as energy source and proceeds in shorter reaction times.

The structures of the obtained compounds **8**–**17** were unambiguously established by IR, ^{1}H and 13C NMR spectroscopic techniques, COSY ^{1}H–^{1}H, HSQC, and HMBC experiments, mass spectrometry, and elemental analyses.

3. Conclusions

A practical synthesis of *O*,*S*-diethyl hetaroylimidothiocarbonates **10** and *S*,*S*-diethyl hetaroylimidodithiocarbonates **11** displaying high yields (89–95%) and under mild reaction conditions has been implemented. Besides, three simple and versatile approaches for the synthesis of novel 4,7-dihetarylpyrazolo[1,5-*a*][1,3,5]triazines **13** exhibiting good yields, from the reaction of the starting thiocarbonates **10**, **11** and isothiocyanates **7** with 5-aminopyrazoles **12** in both solution and solvent-free conditions have been developed. Experimental evidence about reaction intermediates allowed us to confirm the regiochemistry as well as the mechanistic approximation for this kind of reactions.

4. Experimental section

4.1. General

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR 8400 instrument using KBr disks (or CH_2Cl_2 as solvent for compounds **11a**,**b**). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 and 100 MHz, respectively, using $CDCl_3$ or DMSO-d_6 as solvent. Mass spectra were run on a Hewlett Packard HP Engine-5989 spectrometer (equipped with a direct inlet probe) operating at 70 eV. Microanalyses were performed on a LECO CHNS-900 elemental analyzer and the values are within ±0.4% of the theoretical values. Silica gel aluminum plates 60-F_{254} (Merck) were used for analytical TLC. *O*,*S*-Diethyl hetaroylimidothiocarbonates **10** and *S*,*S*-diethyl hetaroylimidodithiocarbonates **11** were obtained according to a modification of published procedure.[10] 5-Amino-3-hetaryl-1*H*-pyrazoles **12** were purchased from Sigma–Aldrich Chemical Co. Ltd. Reactions under microwave irradiation were improved using a CEM Discover oven in open glass vessels. For describing the spectroscopic data of compounds **13**–**17**, the heteroaromatic rings (Het^1 and Het^2) have been denoted by the letters A and B, respectively.

4.2. Procedure for the synthesis of *O*-ethyl hetaroylthiocarbamates 8 and *S*-ethyl hetaroyldithiocarbamates 9

A solution of potassium thiocyanate (0.043 mol) in acetonitrile (50 mL) was heated under reflux for 10 min, then, the heating was turned off and the appropriate hetaroyl chlorides **6a**,**b** (0.043 mol) were added to afford the corresponding hetaroyl isothiocyanates **7a**,**b**, which were not isolated. Then, an excess of ethanol or ethanethiol (0.40 mol) was added and the reaction mixture was stirred for 12 h to afford the carbamates **8a**,**b** and **9a**,**b**, respectively. After dilution of the reaction mixture with ice water, the resulting solid was collected by filtration, washed with hexane, and dried at room temperature.

*4.2.1. O-Ethyl 2-furoylthiocarbamate (**8a**).* White solid, mp 69–70 °C. IR (KBr): ν 3413 (NH), 1719 (C=O), 1583 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.46 (t, 3H, CH_3), 4.66 (q, 2H, CH_2), 6.58 (dd, J=1.7, 3.5 Hz, 1H, H-4), 7.31 (d, J=3.5 Hz, 1H, H-5), 7.54 (d, J=1.7 Hz, 1H, H-3), 9.34 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.7 (CH_3), 69.2 (CH_2), 113.2 (C-4), 118.1 (C-3), 145.4 (C-5), 146.1 (C-2), 152.3 (C=O), 188.6 (C=S). MS (70 eV) *m*/*z* (%): 199 (19, M$^+$), 171 (29), 143 (23), 111 (18), 95 (100), 39 (33). Anal. Calcd for $C_8H_9NO_3S$: C, 48.23; H, 4.55; N, 7.03. Found: C, 48.31; H, 4.49; N, 7.11.

*4.2.2. O-Ethyl 2-thenoylthiocarbamate (**8b**).* Green solid, mp 74–75 °C. IR (KBr): ν 3235 (NH), 1678 (C=O), 1568 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.47 (t, 3H, CH_3), 4.67 (q, 2H, CH_2), 7.14 (t, J=3.7 Hz, 1H, H-4), 7.64 (d, J=4.0 Hz, 1H, H-5), 7.65 (d, J=3.7 Hz, 1H, H-3), 9.05 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.7 (CH_3), 69.5 (CH_2), 128.1 (C-4), 130.2 (C-5), 133.4 (C-3), 137.5 (C-2), 156.4 (C=O), 189.0 (C=S). MS (70 eV) *m*/*z* (%): 215 (12, M$^+$), 187 (25), 127 (24), 111 (100), 83 (18), 39 (22). Anal. Calcd for $C_8H_9NO_2S_2$: C, 44.63; H, 4.21; N, 6.51. Found: C, 44.59; H, 4.26; N, 6.47.

*4.2.3. S-Ethyl 2-furoyldithiocarbamate (**9a**).* Green solid, mp 56–57 °C. IR (KBr): ν 3388 (NH), 1688 (C=O), 1563 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.41 (t, 3H, CH_3), 3.29 (q, 2H, CH_2), 6.62 (dd, J=2.6, 4.2 Hz, 1H, H-4), 7.39 (d, J=4.2 Hz, 1H, H-5), 7.60 (d, J=2.6 Hz, 1H, H-3), 10.1 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 12.1 (CH_3), 31.5 (CH_2), 113.4 (C-4), 118.8 (C-3), 146.0 (C-5), 146.2 (C-2), 152.1 (C=O), 188.5 (C=S). MS (70 eV) *m*/*z* (%): 215 (26, M$^+$), 187 (48), 177 (65), 126 (80), 95 (100), 27 (38). Anal. Calcd for $C_8H_9NO_2S_2$: C, 44.63; H, 4.21; N, 6.51. Found: C, 44.71; H, 4.14; N, 6.58.

*4.2.4. S-Ethyl 2-thenoylthiocarbamate (**9b**).* Green solid, mp 88–89 °C. IR (KBr): ν 3216 (NH), 1653 (C=O), 1599 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.43 (t, 3H, CH_3), 3.31 (q, 2H, CH_2), 7.19 (t, J=3.9 Hz, 1H, H-4), 7.71 (d, J=5.0 Hz, 1H, H-5), 7.73 (d, J=2.7 Hz, 1H, H-3), 9.92 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.6 (CH_3), 33.0 (CH_2), 129.8 (C-4), 132.1 (C-5), 135.4 (C-3), 137.7 (C-2), 159.1 (C=O), 205.2 (C=S). MS (70 eV) *m*/*z* (%): 231 (22, M$^+$), 203 (15), 177 (81), 130 (33), 111 (100), 27 (26). Anal. Calcd for $C_8H_9NOS_3$: C, 41.53; H, 3.92; N, 6.05. Found: C, 41.59; H, 3.87; N, 6.11.

4.3. Procedure for the synthesis of *O*,*S*-diethyl hetaroylimidothiocarbonates 10 and *S*,*S*-diethyl hetaroylimidodithiocarbonates 11

A slight excess of sodium hydride (60% suspension in oil, 0.02 mol) was added to a solution of the corresponding carbamates **8a**,**b** or **9a**,**b** (0.01 mol) in DMF (6 mL). This mixture was stirred for 10 min at room temperature, then ethyl bromide (0.015 mol) was added dropwise and the stirring was continued for a further 60–90 min to afford the compounds **10a**,**b** and **11a**,**b**. For isolation of the thiocarbonates **10a**,**b**, the reaction mixture was diluted with ice water and the resulting solid was collected by filtration, dried at room temperature, and recrystallized from ethanol. Isolation of the dithiocarbonates **11a**,**b**, was made by purification of the resulting reaction's oil by column chromatography on silica gel, using a mixture of hexane/ethyl acetate (4:1) as eluent.

*4.3.1. O,S-Diethyl 2-furoylimidothiocarbonate (**10a**).* White solid, mp 82–83 °C. IR (KBr): ν 1654 (C=O), 1553, 1467 (C=C, C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.30 (t, 3H, CH_3), 1.44 (t, 3H, CH_3), 3.00 (q, 2H, CH_2S), 4.54 (q, 2H, CH_2O), 6.48 (dd, J=1.8 Hz, J=3.5, 1H, H-4), 7.20 (d, J=3.7 Hz, 1H, H-5), 7.54 (d, J=1.5 Hz, 1H, H-3). ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 14.5 (CH_3), 25.3 (CH_2S), 66.5 (CH_2O), 111.8 (C-4), 117.9 (C-3), 146.4 (C-5), 150.2 (C-2), 166.4 (C=O), 171.4 (C=N). MS (70 eV) *m*/*z* (%): 227 (25, M$^+$), 198 (15), 138 (22), 95 (100), 70 (23), 39 (15). Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.85; H, 5.77; N, 6.16. Found: C, 52.83; H, 5.83; N, 6.12.

*4.3.2. O,S-Diethyl 2-thenoylimidothiocarbonate (**10b**).* White solid, mp 39–40 °C. IR (KBr): ν 1630 (C=O), 1507, 1464 (C=C, C=N) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 1.32 (t, 3H, CH_3), 1.43 (t, 3H, CH_3), 2.96 (q, 2H, CH_2S), 4.54 (q, 2H, CH_2O), 7.09 (t, J=3.8 Hz, 1H, H-4), 7.52 (d, J=4.0 Hz, 1H, H-5), 7.82 (d, J=2.5 Hz, 1H, H-3). ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 14.4 (CH_3), 25.2 (CH_2S), 66.6 (CH_2O), 127.9 (C-4), 132.5 (C-5), 132.7 (C-3), 141.5 (C-2), 170.1 (C=O), 171.9 (C=N). MS (70 eV) m/z (%): 243 (22, M^+), 214 (16), 154 (26), 111 (100), 83 (14), 27 (22). Anal. Calcd for $C_{10}H_{13}NO_2S_2$: C, 49.36; H, 5.38; N, 5.76. Found: C, 49.28; H, 5.43; N, 5.71.

*4.3.3. S,S-Diethyl 2-furoylimidodithiocarbonate (**11a**).* Green oil, bp 139–140 °C. IR (CH_2Cl_2): ν 1622 (C=O), 1564, 1479 (C=C, C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 6H, 2×CH_3), 3.15 (q, 4H, 2×CH_2), 6.52 (dd, J=1.8, 3.5 Hz, 1H, H-4), 7.18 (d, J=3.5 Hz, 1H, H-5), 7.61 (d, J=1.8 Hz, 1H, H-3). ^{13}C NMR ($CDCl_3$): δ 13.9 (2×CH_3), 27.3 (2×CH_2), 112.0 (C-4), 118.4 (C-3), 146.8 (C-5), 149.7 (C-2), 165.4 (C=O), 178.3 (C=N). MS (70 eV) m/z (%): 243 (100, M^+), 297 (30), 156 (50), 95 (78), 27 (22). Anal. Calcd for $C_{10}H_{13}NO_2S_2$: C, 49.36; H, 5.38; N, 5.76. Found: C, 49.35; H, 5.40; N, 5.84.

*4.3.4. S,S-Diethyl 2-thenoylimidodithiocarbonate (**11b**).* Green oil, bp 127–128 °C. IR (CH_2Cl_2): ν 1620 (C=O), 1560, 1478 (C=C, C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.41 (t, 6H, 2×CH_3), 3.10 (q, 4H, 2×CH_2), 7.14 (t, J=3.8 Hz, 1H, H-4), 7.60 (d, J=5.0 Hz, 1H, H-5), 7.86 (d, J=3.8 Hz, 1H, H-3). ^{13}C NMR ($CDCl_3$): δ 13.9 (2×CH_3), 27.4 (2×CH_2), 133.0 (C-4), 133.1 (C-3), 140.8 (C-5), 168.9 (C-2), 178.3 (C=O), 179.8 (C=N). MS (70 eV) m/z (%): 259 (95, M^+), 213 (38), 172 (100), 111 (87), 27 (22). Anal. Calcd for $C_{10}H_{13}NOS_3$: C, 46.30; H, 5.05; N, 5.40. Found: C, 46.25; H, 5.12; N, 5.35.

4.4. Procedure for the synthesis of pyrazolo[1,5-*a*][1,3,5]triazines 13 and 14

Approach A: A mixture of the appropriate *O*,*S*-diethyl hetaroylimidothiocarbonates **10a**,**b** or *S*,*S*-diethyl hetaroylimidodithiocarbonates **11a**,**b** (0.015 mol) and the corresponding 5-amino-3-hetaryl-1*H*-pyrazoles **12a**,**b** (0.015 mol) was subjected to microwave irradiation in absence of solvent (maximum power 300 W for 10–20 min at a temperature in the range of 160–180 °C), using a focused microwave reactor (CEM discover). When finished (TLC control), the crude product was dissolved in chloroform (3.0 mL) and purified by column chromatography on silica gel, using a mixture of hexanes/ethyl acetate (9:1) as eluent. For reactions between **10** and **12**, the first chromatographic fraction corresponded to compound **13** and the second one to compound **14**.

Approach B: The mixture of the appropriate thiocarbonate **10** or **11** (0.015 mol), the corresponding aminopyrazoles **12a**,**b** (0.015 mol), and DMF (3 mL) was heated under reflux for 65–110 min. When finished (TLC control), the solid crudes were precipitated by adding cold water to the reaction mixture and collected by filtration. Then the crudes were purified as described in approach *A*.

Approach C: A solution of ethyl bromide (0.02 mol) was added dropwise to a suspension of the corresponding thioureas **15a**–**d** (0.015 mol) and sodium hydride (0.02 mol) in DMF (5 mL). The reaction mixture was then stirred at room temperature for 30 min and heated under reflux for 45–60 min. After dilution of the mixture with cold water, precipitate was collected by filtration and purified by column chromatography on silica gel, using a mixture of hexanes/ethyl acetate (3:2) as eluent.

*4.4.1. 2-Ethylthio-4,7-di(2-furyl)pyrazolo[1,5-a][1,3,5]triazine (**13a**).* Yellow solid, mp 148–149 °C. IR (KBr): ν 1611, 1571, 1498 (C=C, C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.48 (t, 3H, CH_3), 3.26 (q, 2H, CH_2), 6.58 (dd, J=1.8, 3.3 Hz, 1H, H_B-4), 6.65 (s, 1H, H-8), 6.77 (dd, J=1.8, 3.5 Hz, 1H, H_A-4), 7.04 (d, J=3.3 Hz, 1H, H_B-5), 7.61 (d, J=1.8 Hz, 1H, H_B-3), 7.86 (d, J=1.5 Hz, 1H, H_A-5), 8.52 (d, J=3.5 Hz, 1H, H_A-3). ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 25.6 (CH_2), 91.2 (C-8), 109.7 (C_B-3), 111.9 (C_B-5), 113.2 (C_B-4), 125.1 (C_A-4), 142.9 (C_A-2), 143.3 (C_B-2), 143.9 (C_A-5), 147.9 (C-8a), 148.2 (C_A-3), 150.3 (C-7), 150.9 (C-4), 166.9 (C-2). MS (70 eV) m/z (%): 312 (100, M^+), 297 (19), 279 (41), 191 (51), 159 (43), 133 (28), 105 (30), 90 (55), 29 (63). Anal. Calcd for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94. Found: C, 57.71; H, 3.85; N, 17.92.

*4.4.2. 2-Ethylthio-4,7-di(2-thienyl)pyrazolo[1,5-a][1,3,5]triazine (**13b**).* Yellow solid, mp 163–164 °C. IR (KBr): ν 1589, 1524, 1475 (C=C, C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.50 (t, 3H, CH_3), 3.26 (q, 2H, CH_2), 6.60 (s, 1H, H-8), 7.16 (dd, J=1.5, 3.5 Hz, 1H, H_B-4), 7.31 (dd, J=1.0, 4.0 Hz, 1H, H_A-4), 7.45 (dd, J=1.3, 3.3 Hz, 1H, H_B-5), 7.63 (dd, J=1.3, 2.5 Hz, 1H, H_B-3), 7.84 (dd, J=1.3, 3.8 Hz, 1H, H_A-5), 8.94 (dd, J=1.3, 2.8 Hz, 1H, H_A-3). ^{13}C NMR ($CDCl_3$): δ 14.4 (CH_3), 25.7 (CH_2), 90.9 (C-8), 127.1 (C_B-3), 127.4 (C_B-5), 127.9 (C_B-4), 128.5 (C_A-4), 132.3 (C_A-2), 135.5 (C_B-2), 135.9 (C_A-5), 137.2 (C_A-3), 147.4 (C-8a), 151.4 (C-7), 153.4 (C-4), 166.5 (C-2). MS (70 eV) m/z (%): 344 (41, M^+), 311 (16), 270 (16), 207 (18), 178 (35), 134 (24), 110 (48), 70 (61), 45 (54), 29 (100). Anal. Calcd for $C_{15}H_{12}N_4S_3$: C, 52.30; H, 3.51; N, 16.26. Found: C, 52.31; H, 3.52; N, 16.22.

*4.4.3. 2-Ethylthio-4-(2-furyl)-7-(2-thienyl)pyrazolo[1,5-a][1,3,5]triazine (**13c**).* Yellow solid, mp 165–166 °C. IR (KBr): ν 1606, 1577, 1455 (C=C, C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.49 (t, 3H, CH_3), 3.26 (q, 2H, CH_2), 6.64 (s, 1H, H-8), 6.78 (dd, J=1.6, 3.7 Hz, 1H, H_A-4), 7.17 (dd, J=3.5, 5.0 Hz, 1H, H_B-4), 7.45 (d, J=5.0 Hz, 1H, H_B-5), 7.63 (d, J=3.6 Hz, 1H, H_B-3), 7.87 (d, J=3.3 Hz, 1H, H_A-5), 8.53 (d, J=1.6 Hz, 1H, H_A-3). ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 25.6 (CH_2), 91.2 (C-8), 113.3 (C_A-4), 125.1 (C_A-3), 127.1 (C_B-3), 127.4 (C_B-5), 127.9 (C_B-4), 135.4 (C_B-2), 143.1 (C_A-2), 143.1 (C-4), 148.1 (C_A-5), 151.1 (C-8a), 153.7 (C-7), 166.7 (C-2). MS (70 eV) m/z (%): 328 (100, M^+), 313 (24), 295 (57), 207 (35), 175 (29), 149 (26), 134 (19), 94 (29), 70 (20). Anal. Calcd for $C_{15}H_{12}N_4OS_2$: C, 54.86; H, 3.68; N, 17.06. Found: C, 54.89; H, 3.72; N, 17.05.

*4.4.4. 2-Ethylthio-7-(2-furyl)-4-(2-thienyl)pyrazolo[1,5-a][1,3,5]triazine (**13d**).* Yellow solid, mp 108–109 °C. IR (KBr): ν 1594, 1531, 1479 (C=C, C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.50 (t, 3H, CH_3), 3.27 (q, 2H, CH_2), 6.60 (dd, J=1.8, 3.3 Hz, 1H, H_B-4), 6.64 (s, 1H, H-8), 7.07 (d, J=3.3 Hz, 1H, H_B-5), 7.32 (t, J=4.4 Hz, 1H, H_A-4), 7.62 (d, J=1.0 Hz, 1H, H_B-3), 7.84 (d, J=4.8 Hz, 1H, H_A-5), 8.97 (d, J=3.8 Hz, 1H, H_A-3). ^{13}C NMR ($CDCl_3$): δ 14.4 (CH_3), 25.7 (CH_2), 90.9 (C-8), 109.8 (C_B-3), 111.9 (C_B-5), 128.5 (C_B-4), 132.4 (C_A-2), 135.8 (C_A-4), 137.3 (C_A-5), 143.9 (C_A-3), 147.6 (C_B-2), 147.9 (C-8a), 150.3 (C-7), 151.2 (C-4), 166.5 (C-2). MS (70 eV) m/z (%): 328 (100, M^+), 313 (22), 268 (38), 219 (35), 191 (93), 94 (55), 27 (29). Anal. Calcd for $C_{15}H_{12}N_4OS_2$: C, 54.86; H, 3.68; N, 17.06. Found: C, 54.84; H, 3.65; N, 17.03.

*4.4.5. 2-Ethoxy-4,7-di(2-furyl)pyrazolo[1,5-a][1,3,5]triazine (**14a**).* Yellow solid, mp 156–157 °C. IR (KBr): ν 1613, 1572, 1497 (C=C, C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.49 (t, 3H, CH_3), 4.52 (q, 2H, CH_2), 6.57 (s, 1H, H-8), 6.58 (dd, J=1.8, 3.3 Hz, 1H, H_B-4), 6.76 (dd, J=1.8, 3.5 Hz, 1H, H_A-4), 7.02 (d, J=3.3 Hz, 1H, H_B-5), 7.60 (d, J=1.7 Hz, 1H, H_B-3), 7.84 (d, J=3.5 Hz, 1H, H_A-5), 8.52 (d, J=1.8 Hz, 1H, H_A-3). ^{13}C NMR ($CDCl_3$): δ 14.3 (CH_3), 64.1 (CH_2), 90.8 (C-8), 109.6 (C_B-3), 111.8 (C_B-5), 113.2 (C_B-4), 124.9 (C_A-4), 143.0 (C_A-2), 143.8 (C_A-5), 146.2 (C_B-2), 147.9 (C-8a), 148.1 (C_A-3), 150.9 (C-7), 152.1 (C-4), 160.1 (C-2). MS (70 eV) m/z (%): 296 (27, M^+), 281 (16), 175 (38), 119 (19), 94 (45), 63 (34), 39 (40), 29 (100). Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.83; H, 4.06; N, 18.93.

*4.4.6. 2-Ethoxy-4,7-di(2-thienyl)pyrazolo[1,5-a][1,3,5]triazine (**14b**).* Yellow solid, mp 167–168 °C. IR (KBr): ν 1610, 1562, 1491 (C=C, C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.54 (t, 3H, CH_3), 4.56 (q, 2H, CH_2), 6.56 (s, 1H, H-8), 7.17 (dd, J=1.3, 3.8 Hz, 1H, H_B-4), 7.34 (dd,

J=1.0, 4.0 Hz, 1H, H_A-4), 7.46 (d, J=3.8 Hz, 1H, H_B-5), 7.65 (d, J=1.3 Hz, 1H, H_B-3), 7.86 (d, J=4.0 Hz, 1H, H_A-5), 9.01 (d, J=1.1 Hz, 1H, H_A-3). ^{13}C NMR ($CDCl_3$): δ 14.4 (CH_3), 64.2 (CH_2), 90.7 (C-8), 127.0 (C_B-3), 127.4 (C_B-5), 127.9 (C_B-4), 128.4 (C_A-4), 132.2 (C_A-2), 135.6 (C_B-2), 136.0 (C_A-5), 137.3 (C_A-3), 150.4 (C-8a), 152.6 (C-7), 154.0 (C-4), 160.2 (C-2). MS (70 eV) m/z (%): 328 (100, M^+), 313 (18), 284 (18), 191 (73), 134 (27), 110 (64), 69 (19), 29 (43). Anal. Calcd for $C_{15}H_{12}N_4OS_2$: C, 54.86; H, 3.68; N, 17.06. Found: C, 54.89; H, 3.70; N, 17.08.

*4.4.7. 2-Ethoxy-4-(2-furyl)-7-(2-thienyl)pyrazolo[1,5-a][1,3,5]triazine (**14c**).* Yellow solid, mp 161–162 °C. IR (KBr): ν 1612, 1576, 1503 (C=C, C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.49 (t, 3H, CH_3), 4.51 (q, 2H, CH_2), 6.54 (s, 1H, H-8), 6.77 (dd, J=1.6, 3.6 Hz, 1H, H_A-4), 7.15 (dd, J=5.0, 3.5 Hz, 1H, H_B-4), 7.43 (d, J=5.0 Hz, 1H, H_B-5), 7.60 (d, J=3.8 Hz, 1H, H_B-3), 7.83 (d, J=3.6 Hz, 1H, H_A-5), 8.51 (d, J=1.6 Hz, 1H, H_A-3). ^{13}C NMR ($CDCl_3$): δ 14.3 (CH_3), 64.1 (CH_2), 90.8 (C-8), 113.3 (C_A-4), 124.9 (C_A-3), 127.0 (C_B-3), 127.3 (C_B-5), 127.9 (C_B-4), 135.5 (C_B-2), 143.0 (C-4), 146.0 (C_A-2), 148.1 (C_A-5), 152.3 (C-8a), 154.1 (C-7), 160.1 (C-2). MS (70 eV) m/z (%): 312 (100, M^+), 297 (28), 284 (18), 268 (25), 191 (98), 94 (60). Anal. Calcd for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94. Found: C, 57.65; H, 3.89; N, 17.96.

*4.4.8. 2-Ethoxy-7-(2-furyl)-4-(2-thienyl)pyrazolo[1,5-a][1,3,5]triazine (**14d**).* Yellow solid; mp 134–135 °C. IR (KBr): ν 1596, 1537, 1489 (C=C, C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.52 (t, 3H, CH_3), 4.55 (q, 2H, CH_2), 6.58 (t, J=2.8 Hz, 1H, H_B-4), 6.58 (s, 1H, H-8), 7.06 (d, J=3.0 Hz, 1H, H_B-5), 7.33 (t, J=4.0 Hz, 1H, H_A-4), 7.62 (d, J=3.8 Hz, 1H, H_B-3), 7.85 (d, J=3.7 Hz, 1H, H_A-5), 9.01 (d, J=2.8 Hz, 1H, H_A-3). ^{13}C NMR ($CDCl_3$): δ 14.4 (CH_3), 64.2 (CH_2), 90.7 (C-8), 109.8 (C_B-3), 111.8 (C_B-5), 128.5 (C_B-4), 132.2 (C_B-2), 135.9 (C_A-4), 137.3 (C_A-5), 143.9 (C_A-3), 148.0 (C_A-2), 150.6 (C-4), 150.8 (C-2a), 152.3 (C-4), 160.1 (C-2). MS (70 eV) m/z (%): 312 (100, M^+), 297 (22), 284 (19), 175 (44), 110 (65), 27 (32). Anal. Calcd for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94. Found: C, 55.71; H, 3.86; N, 17.85.

4.5. Procedure for the synthesis of 1-hetaroyl-3-(3-(2-hetaryl) pyrazol-5-yl)thioureas 15a–d

To a solution of the proper hetaroyl isothiocyanates **7a**,**b** (0.02 mol) in acetonitrile (15 mL) (prepared from reaction of the respective hetaroyl chlorides **6a**,**b** and potassium thiocyanate) were added the corresponding 5-aminopyrazoles **12a**,**b** (0.02 mol) and the reaction mixture was then heated under reflux for 30 min to obtain the thiourea derivatives **15a–d**. Ice water was added to the reaction mixture and the resulting solid was collected by filtration, washed with cold water and ethanol, and finally dried at room temperature.

*4.5.1. 1-(2-Furoyl)-3-(3-(2-furyl)pyrazol-5-yl)thiourea (**15a**).* White solid, mp 204–205 °C. IR (KBr): ν 3304 (NH), 1673 (C=O), 1578, 1530 (C=C, C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.64 (t, J=3.3 Hz, 1H, H_B-4), 6.78 (t, J=3.7 Hz, 1H, H_A-4), 6.88 (d, J=3.5 Hz, 1H, H_B-5), 7.32 (s, 1H, H-4), 7.79 (br s, 1H, H_B-3), 7.90 (d, J=3.8 Hz, 1H, H_A-5), 8.09 (br s, 1H, H_A-3), 11.42 (s. 1H, exocyclic NH-1), 12.95 (s. 1H, endocyclic NH-1), 13.34 (s. 1H, NH-3). ^{13}C NMR (DMSO-d_6): δ 79.2 (C-4), 94.7 (C_B-3), 99.5 (C_B-5), 107.1 (C_B-4), 107.1 (C_A-4), 111.8 (C_A-3), 112.7 (C_A-5), 118.9 (C_A-2), 143.2 (C_B-2), 144.5 (C-5), 148.6 (C-3), 158.0 (C=S), 176.8 (C=O). MS (70 eV) m/z (%): 302 (100, M^+), 282 (22), 191 (20), 176 (46), 111 (46), 95 (67), 74 (22). Anal. Calcd for $C_{13}H_{10}N_4O_3S$: C, 51.65; H, 3.33; N, 18.53. Found: C, 51.52; H, 3.38; N, 18.59.

*4.5.2. 1-(2-Thenoyl)-3-(3-(2-thienyl)pyrazol-5-yl)thiourea (**15b**).* White solid, mp 220–221 °C. IR (KBr): ν 3300 (NH), 1658 (C=O), 1599, 1530 (C=C, C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.17 (t, J=3.3 Hz, 1H, H_B-4), 7.27 (t, J=3.4 Hz, 1H, H_A-4), 7.32 (s, 1H, H-4), 7.51 (d, J=2.8 Hz, 1H, H_B-5), 7.63 (d, J=4.8 Hz, 1H, H_B-3), 8.07 (d, J=4.8 Hz, 1H, H_A-5), 8.42 (d, J=3.5 Hz, 1H, H_A-3), 11.70 (s, 1H, exocyclic NH-1), 13.04 (s, 1H, endocyclic NH-1), 13.31 (s, 1H, NH-3). ^{13}C NMR (DMSO-d_6): δ 79.2 (C-4), 95.8 (C_B-3), 124.8 (C_B-5), 126.3 (C_B-4), 128.2 (C_A-4), 128.8 (C_A-3), 131.0 (C_A-2), 132.9 (C_A-5), 135.5 (C_B-2), 136.3 (C-5), 147.6 (C-3), 162.5 (C=S), 176.7 (C=O). MS (70 eV) m/z (%): 334 (100, M^+), 301 (26), 254 (30), 226 (28), 111 (59), 74 (33). Anal. Calcd for $C_{13}H_{10}N_4OS_3$: C, 46.69; H, 3.01; N, 16.75. Found: C, 46.58; H, 2.92; N, 16.71.

*4.5.3. 1-(2-Furoyl)-3-(3-(2-thienyl)pyrazol-5-yl)thiourea (**15c**).* White solid, mp 214–215 °C. IR (KBr): ν 3307 (NH), 1670 (C=O), 1577, 1528 (C=C, C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.78 (dd, J=1.8, 3.5 Hz, 1H, H_B-4), 7.16 (dd, J=2.3, 4.3 Hz, 1H, H_A-4), 7.29 (s, 1H, H-4), 7.50 (d, J=3.5 Hz, 1H, H_B-5), 7.61 (d, J=1.8 Hz, 1H, H_B-3), 7.89 (d, J=4.3 Hz, 1H, H_A-5), 8.09 (d, J=2.3 Hz, 1H, H_A-3), 11.40 (s, 1H, exocyclic NH-1), 12.92 (s, 1H, endocyclic NH-1), 13.32 (s, 1H, NH-3). ^{13}C NMR (DMSO-d_6): δ 95.7 (C-4), 112.7 (C_B-3), 118.9 (C_B-5), 124.8 (C_B-4), 126.3 (C_A-4), 128.1 (C_A-3), 134.7 (C_A-5), 138.1 (C_A-2), 144.5 (C_B-2), 148.6 (C-5), 158.0 (C-3), 163.3 (C=S), 176.9 (C=O). MS (70 eV) m/z (%): 318 (98, M^+), 282 (29), 176 (100), 111 (65), 74 (33). Anal. Calcd for $C_{13}H_{10}N_4O_2S_2$: C, 49.04; H, 3.17; N, 17.60. Found: C, 49.12; H, 3.28; N, 17.51.

*4.5.4. 1-(3-(2-Furyl)pyrazol-5-yl)-3-(2-thenoyl)thiourea (**15d**).* White solid, mp 218–219 °C. IR (KBr): ν 3287 (NH), 1675 (C=O), 1584, 1528 (C=C, C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.64 (dd, J=1.5, 3.3 Hz, 1H, H_B-4), 6.90 (d, J=2.8 Hz, 1H, H_B-5), 7.26 (t, J=4.3 Hz, 1H, H_A-4), 7.36 (s, 1H, H-4), 7.79 (br s, 1H, H_B-3), 8.07 (d, J=4.8 Hz, 1H, H_A-5), 8.42 (d, J=3.5 Hz, 1H, H_A-3), 11.72 (s, 1H, exocyclic NH-1), 13.06 (s, 1H, endocyclic NH-1), 13.36 (s, 1H, NH-3). ^{13}C NMR (DMSO-d_6): δ 94.8 (C-4), 107.1 (C_B-3), 111.8 (C_B-5), 128.7 (C_B-4), 132.9 (C_A-4), 133.6 (C_A-3), 135.5 (C_A-2), 136.4 (C_A-5), 143.2 (C_B-2), 144.3 (C-5), 147.5 (C-3), 162.5 (C=S), 176.8 (C=O). MS (70 eV) m/z (%): 318 (100, M^+), 176 (38), 192 (28), 129 (28), 111 (72), 74 (45). Anal. Calcd for $C_{13}H_{10}N_4O_2S_2$: C, 49.04; H, 3.17; N, 17.60. Found: C, 49.13; H, 3.13; N, 17.53.

4.6. Procedure for the synthesis of 2-ethyl-1-(3-(2-furyl) pyrazol-5-yl)-3-(2-thenoyl)isothiourea 16d

A slight excess of sodium hydride (60% suspension in oil, 0.003 mol) was added to a solution of the 1-(3-(2-furyl)pyrazol-5-yl)-3-(2-thenoyl)thiourea **15d** (0.002 mol) in DMF (5 mL). The mixture was stirred for 10 min at room temperature and then ethyl bromide (0.004 mol) was dropped slowly and the stirring was continued for a further 30 min to afford compound **16d**. After dilution of the reaction mixture with cold water, the resulting solid was collected by filtration, washed with *n*-hexane, and dried at room temperature. White solid, 75% yield. IR (KBr): ν 1633 (C=O), 1571, 1502 (C=C, C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.32 (t, 3H, CH_3), 3.10 (q, 2H, CH_2), 6.43 (s, 1H, H-4), 6.63 (d, J=3.3 Hz, 1H, H_B-4), 6.88 (d, J=3.7 Hz, 1H, H_A-4), 7.25 (d, J=2.4 Hz, 1H, H_B-5), 7.79 (br s, 2H, H_A-5 and H_B-3), 8.04 (d, J=3.7 Hz, 1H, H_A-3), 12.01 (s, 1H, endocyclic NH), 13.42 (s, 1H, exocyclic NH). MS (70 eV) m/z (%): 346 (100, M^+), 317 (32), 206 (18), 134 (25), 111 (54). Anal. Calcd for $C_{15}H_{14}N_4O_2S_2$: C, 52.01; H, 4.07; N, 16.17. Found: $C_{15}H_{14}N_4O_2S_2$: C, 52.13; H, 4.15; N, 16.12.

4.7. Procedure for the synthesis of 2-ethyl-1-(2-thenoyl)-3-(3-(2-thienyl)pyrazol-5-yl)isothiourea 16b and 2-ethyl-1-(2-thenoyl)-3-(3-(2-thienyl)pyrazol-5-yl)isourea 17b

A mixture of *O*,*S*-diethyl 2-thenoylimidothiocarbonate **10b** (0.015 mol) and 5-amino-3-(2-thienyl)-1*H*-pyrazole **12b** (0.015 mol) was submitted to microwave irradiation in absence of

solvent (maximum power 300 W for 3 min at 160 °C). When finished (TLC control), the crude product was dissolved in chloroform (3 mL) and purified by column chromatography on silica gel, using a mixture of hexanes/ethyl acetate (3:1) as eluent. The first chromatographic fraction corresponded to compound **16b** and the second one to compound **17b**.

*4.7.1. 2-Ethyl-1-(2-thenoyl)-3-(3-(2-thienyl)pyrazol-5-yl)isothiourea (**16b**).* White solid. IR (KBr): ν 1623 (C=O), 1570, 1497 (C=C, C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.33 (t, 3H, CH_3), 3.18 (q, 2H, CH_2), 6.43 (s, 1H, H-4), 7.19 (t, J=4,3 Hz, 2H, H_B-4 and H_A-4), 7.50 (d, J=4.5 Hz, 1H, H_B-5), 7.63 (d, J=2.8 Hz, 1H, H_B-3), 7.79 (d, J=5.0 Hz, 1H, H_A-5), 7.85 (d, J=3.3 Hz, 1H, H_A-3), 11.95 (s, 1H, endocyclic NH), 13.32 (s, 1H, exocyclic NH). MS (70 eV) m/z (%): 362 (58, M^+), 317 (34), 235 (27), 111 (100), 45 (19). Anal. Calcd for $C_{15}H_{14}N_4OS_3$: C, 49.70; H, 3.89; N, 15.46. Found: C, 49.75; H, 3.81; N, 15.40.

*4.7.2. 2-Ethyl-1-(2-thenoyl)-3-(3-(2-thienyl)pyrazol-5-yl)isourea (**17b**).* White solid. IR (KBr): ν 1622 (C=O), 1564, 1490 (C=C, C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.43 (t, 3H, CH_3), 4.60 (q, 2H, CH_2), 6.51 (s, 1H, H-4), 7.19 (t, J=4.0 Hz, 2H, H_B-4 and H_A-4), 7.49 (br s, 1H, H_B-5), 7.61 (d, J=3.7 Hz, 1H, H_B-3), 7.83 (br s, 2H, H_A-5 and H_A-3), 11.81 (s, 1H, endocyclic NH), 13.17 (s, 1H, exocyclic NH). ^{13}C NMR (DMSO-d_6): δ 14.7 (CH_3), 65.1 (CH_2), 95.5 (C-4), 125.5 (C_B-3), 126.8 (C_B-5), 128.5 (C_B-4), 128.7 (C_A-4), 131.3 (C_A-3), 132.3 (C_A-5), 133.4 (C_A-2), 137.9 (C_B-2), 143.2 (C-5), 145.8 (C-3), 159.4 (C-2), 172.1 (C=O). MS (70 eV) m/z (%): 346 (100, M^+), 328 (27), 313 (18), 191 (19), 111 (25). Anal. Calcd for $C_{15}H_{14}N_4O_2S_2$: C, 52.01; H, 4.07; N, 16.17. Found: C, 52.12; H, 3.93; N, 16.21.

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