Solvent-Free Microwave-Assisted Synthesis of Novel 4-Hetarylpyrazolo[1,5-*a*][1,3,5]triazines

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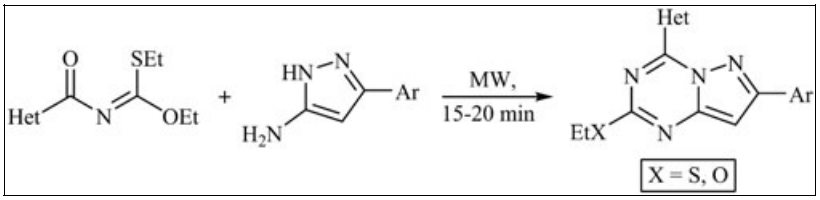

A series of novel 4-hetaryl substituted pyrazolo[1,5-*a*][1,3,5]triazines were synthesized by microwave assisted reaction between *O,S*-diethyl hetaroylimidothiocarbonates and 5-amino-3-aryl-1*H*-pyrazoles under solvent-free conditions. This procedure led to the formation of mixtures of two new pyrazolotriazine derivatives in a 1:4 ratio, which were separated by column chromatography being their corresponding structures unambiguously established by spectroscopic and analytical techniques. Comparison of the reactions mediated by microwave irradiation and by conventional heating in solution of DMF showed that both procedures afforded the same mixtures of products, but the first approach required shorter reaction times and gave higher yields than the second one.

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INTRODUCTION

Pyrazolo[1,5-*a*][1,3,5]triazine derivatives have received considerable attention because of their pharmacological properties, and especially, by their applicability in the treatment of various diseases. Some of them have been evaluated as corticotrophin releasing factor (CRF) antagonists (compound **1**, Fig. 1) [1], for the treatment and prevention of central nervous system disorders [2],[3], and for the treatment of eating disorders, particularly bulimia and obesity associated with excess of the neuropeptide Y (NPY) [2]. Other derivatives have been tested as inhibitors for protein kinase CK2 [4] and cyclic-dependent kinases (CDKs) exhibiting high antiproliferative activity in tumor cell lines [5] and high potential for cancer therapy (compound **2**, Fig. 1) [4],[5]. Some of them were inhibitors of phosphodiesterase type 4 (PDE4) [6], potential therapeutic agents for the control of autoimmune and inflammatory diseases and more recently, the pyrazolo[1,5-*a*][1,3,5] triazine **3** (Fig. 1), was reported as active against the herpes simplex viruses HSV-1 and HSV-2 [7].

In the last years, solvent-free reaction conditions employing the microwave irradiation (MW) as energy source have widely been used for the synthesis of many and diverse organic compounds, mainly because such reactions proceed much faster, with higher yields and sometimes more regioselective than those reactions when conventional heating has been employed [8]. Numerous methods for the synthesis of pyrazolo[1,5-*a*] [1,3,5]triazine derivatives are currently available. The more efficient and commonly used involves the reaction between 5-amino-1*H*-pyrazoles and 1,3-*bis*-electrophilic compounds under conventional heating [3],[4],[7],[9], [10]. Continuing with our current studies on the synthesis of fused heterocycles containing the pyrazole moiety [10],[11], we are describing here the synthesis of novel 4-hetaryl substituted pyrazolo[1,5-*a*][1,3,5]triazine derivatives **7-10** from the reaction of the *O,S*-diethyl hetaroylimidothiocarbonates **4** and **5** with 5-amino-3-aryl-1*H*-pyrazoles **6** by microwave irradiation under solvent-free reaction conditions.

RESULTS AND DISCUSSION

In a first entry, a mixture of equimolar amounts of the *O, S*-diethyl furoylimidothiocarbonate **4** and the 5-amino-3-(4-chlorophenyl)pyrazole **6a** was irradiated for 15 min. at 100°C without using solvent. After reaction finished (TLC control), the plate indicated the formation of two new products, which were separated by column chromatography on silica gel. The new products corresponded to 7-(4-chlorophenyl)-4-(2'-furyl)pyrazolo[1,5-*a*][1,3,5] triazines **7a** and **8a** in ~1:4 ratio, but not to their also possible **11a** and **12a** isomers (Scheme 1). To evaluate the generality of this procedure the *O,S*-diethyl hetaroylimidothiocarbonates **4** and **5** were reacted with the

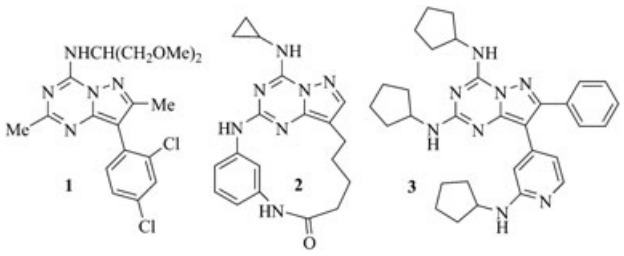


Figure 1. Some pyrazolo[1,5-*a*][1,3,5]triazines of biological interest.

5-aminopyrazoles **6a-c** under similar reaction conditions leading to the formation of their corresponding analogs **(7/8) a-c** and **(9/10)a-c**, respectively, as shown in Scheme 1.

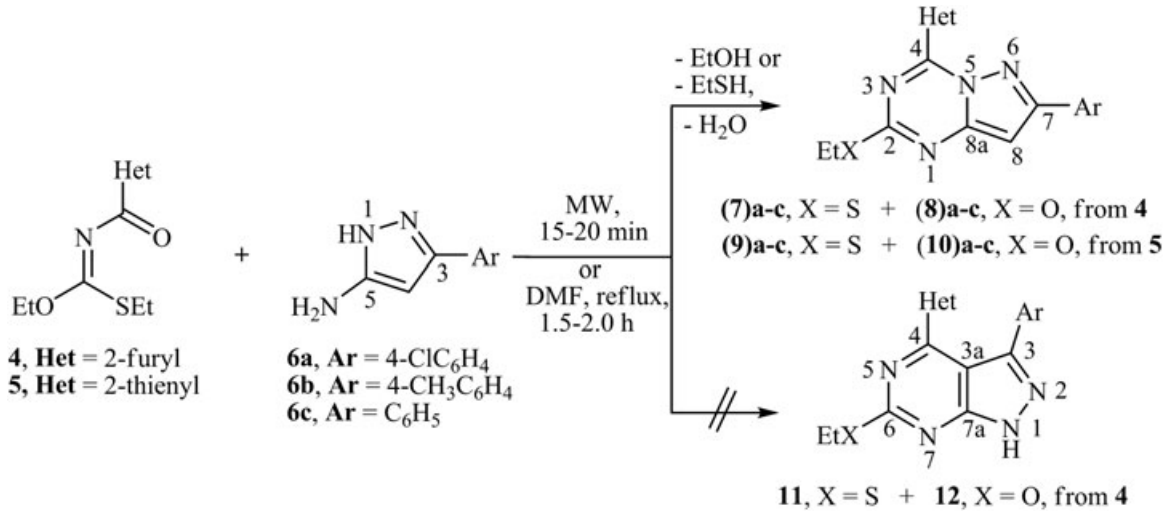
The structures of the obtained compounds **7**, **8**, **9**, and **10** were unambiguously established by spectroscopic and analytical methods. The IR data are consistent with the proposed structures **7**-**10**, and the possible formation of pyrazolo[3,4-*d*]pyrimidines **11** and **12** (Scheme 1), was discarded because the expected absorption band assignable to the N—H stretching was not present in any IR spectra. This finding is also in agreement with the ^{1}H NMR spectra where the more representative signal corresponded to a singlet between 6.60–6.74 ppm assigned to the 8-H protons of the pyrazole ring, confirming that the structures assigned for compounds **7-10** are correct.

The ^{1}H and ^{13}C NMR spectra for each pair of pyrazolotriazines **7**,**8** and **9**,**10** are too similar between them, except for the signal of methylene groups, which, appears around 3.25 ppm and 25.6 ppm (for ^{1}H- and ^{13}C-NMR, respectively) in compounds **7**,**9** and around 4.52 ppm and 64.1 ppm (for ^{1}H- and ^{13}C-NMR, respectively) in compounds **8**,**10** due to the higher electronegativity of the O atom than the S atom, present in the ethoxy and ethylthio fragments, respectively. In Figure 2 it is showed the ^{13}C NMR spectra for the representative compounds **7a** and **8a** confirming the marked differences in chemical shifts between methylenes of the $CH_3\mathbf{CH_2}S$- and $CH_3\mathbf{CH_2}O$- fragments at the high-field region.

The whole carbon atoms of the skeleton of compounds **7-10** were assigned from their ^{13}C NMR spectra combined with the DEPT and ^{1}H, ^{13}C shift correlation HSQC and HMBC experiments. The 2D-NOESY experiment was used to establish the right places of substituents at the triazine ring. Thus, crossed-peaks between the methylene protons of the ethylthio (or ethoxy) substituents and the 8-H protons of the pyrazole moiety, helped us to determine that the ethylthio (or the ethoxy) substituents are located on C-2 and consequently the hetaryl groups are located on C-4 of compounds **7-10** as shown in Figure 3, for the representative compound **7a**, ruling out the formation of its isomer **7a′**.

We consider that the formation of compounds **7-10** resulted from an addition-elimination process. First, the C═N double bond of the starting compounds **4**,**5** suffered a nucleophilic attack from the 5-NH_2 of the pyrazole **6** with subsequent elimination of a molecule of ethanol (or ethanethiol) affording the adducts **13/15** or **14/16,** respectively (Scheme 2). Adduct **14/16** should be the main intermediate because the ethanethiol (pK_a = 10.6) is a better leaving group than the ethanol (pK_a = 15.9). Finally, adducts **13-16** were intramolecularly cyclized after attack of the 1-NH of the pyrazole moiety over the C═O functionality with elimination of a molecule of water affording the isolated pyrazolotriazines **7-10**. Previous reports showing the higher electrophilicity of the C═N double bond than the carbonyl group in compounds type **4**,**5** [12] support the postulated sequence of steps depicted in Scheme 2.

Scheme 1



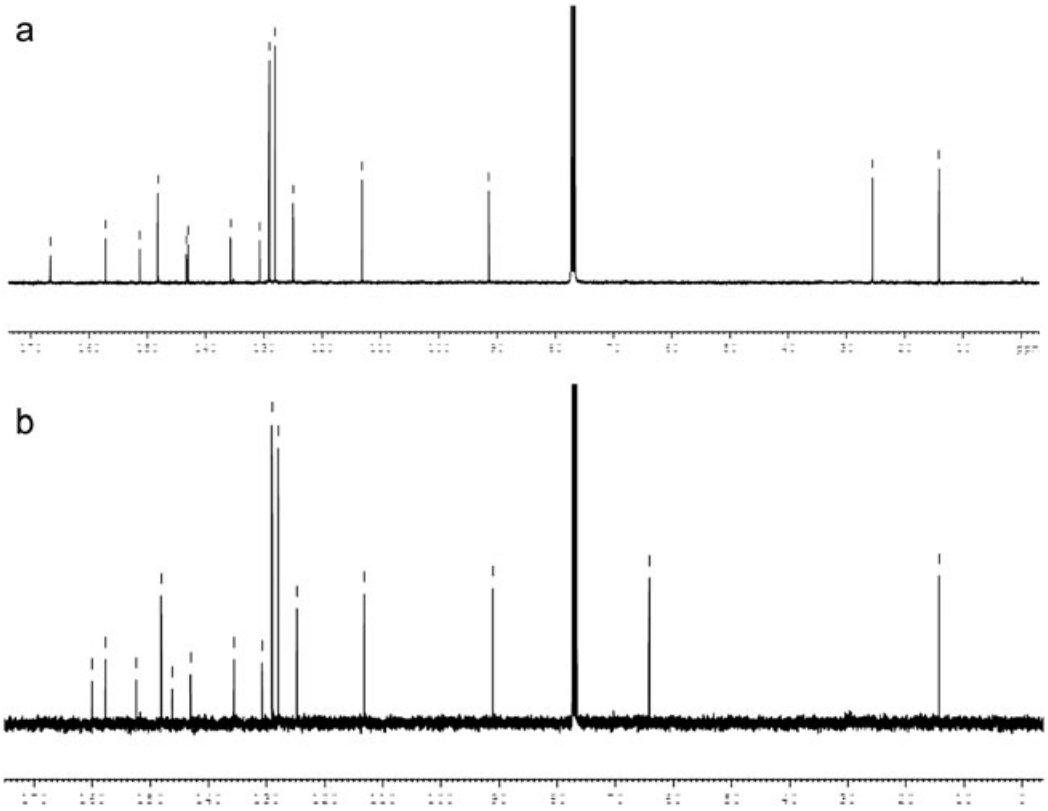


Figure 2. ^{13}C NMR spectra for the new pyrazolotriazines **7a** (a) and **8a** (b).

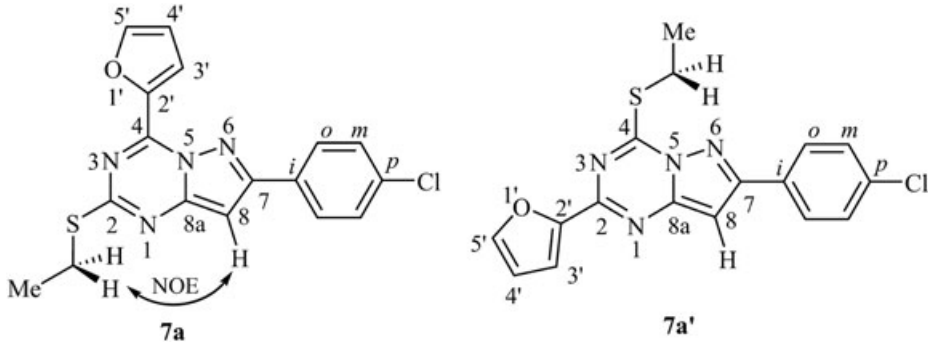


Figure 3. Possible isomeric structures for the pyrazolo[1,5-*a*][1,3,5]triazine systems **7-10**.

Scheme 2

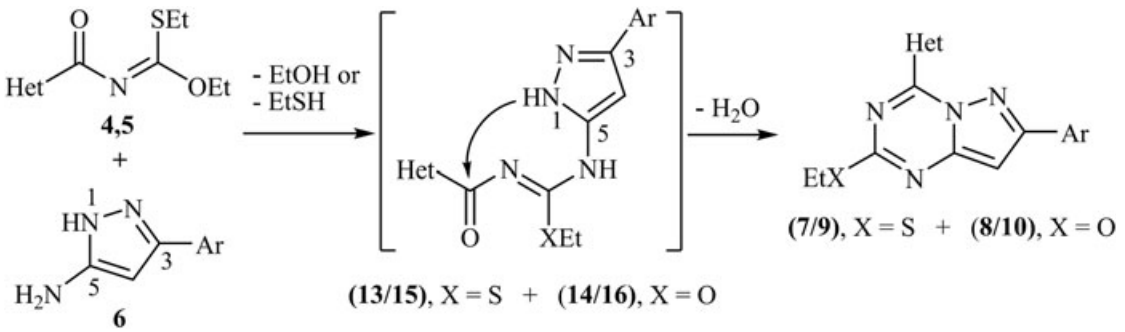


Table 1

Analytical data for the obtained pyrazolo[1,5-*a*][1,3,5]triazines **7–10**.[a,b]

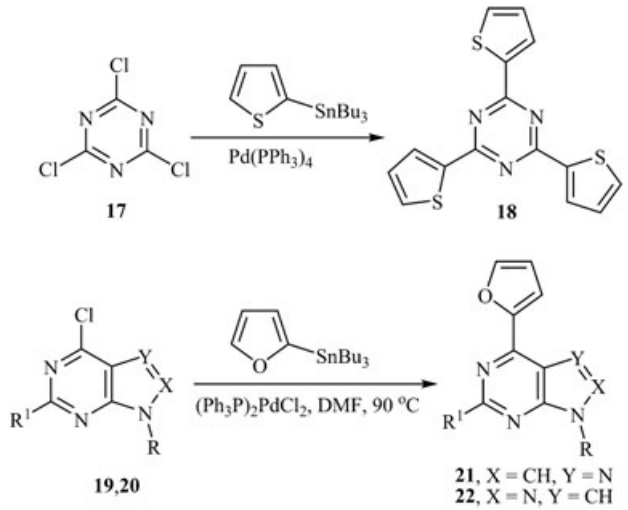
Products	Het	Ar	X	mp (°C)	Yield %[b]	Time (min)
7a	2-furyl	4-ClC_6H_4	S	212	12(9)	15(90)
8a			O	204	52(41)	
7b	2-furyl	4-$CH_3C_6H_4$	S	158	15(10)	16(100)
8b			O	148	63(50)	
7c	2-furyl	C_6H_5	S	144	14(11)	15(95)
8c			O	140	60(53)	
9a	2-thienyl	4-ClC_6H_4	S	146	13(9)	18(105)
10a			O	190	54(42)	
9b	2-thienyl	4-$CH_3C_6H_4$	S	110	16(12)	20(120)
10b			O	139	64(55)	
9c	2-thienyl	C_6H_5	S	112	15(11)	19(110)
10c			O	108	62(51)	

[a]Values in parenthesis are referred to reactions carried out under conventional heating using DMF as solvent.
[b]Isolated yields after column chromatography.

To evaluate the efficacy of the reaction mediated by microwave irradiation, all reactions were repeated under conventional heating using DMF as solvent (see experimental). Table 1 summarizes the comparative results and the evident improved yields and shorter reaction times when reactions were carried out by microwave irradiation than conventional heating.

It is worth mentioning that recently there has been reported the synthesis of the star-shaped triazine derivative **18** of materials science interest [13], the *Micobacterium tuberculosis* inhibitors purine derivatives **21** [14] and the antagonist of the human adenosine receptors A_{2A} pyrazolopyrimidines **22** [15]. All three authors agree that the presence of the thienyl and furyl moieties in structures **18**, **21**, and **22** is determinant for their physical and biological properties displayed. In all cases, the insertion of the 2-thienyl and 2-furyl units into such interesting compounds was mediated by a common C—C coupling process based on the Stille reaction of the corresponding hetarylstannic derivatives and the appropriate starting chloro-compounds **17**, **19**, and **20**, respectively (Scheme 3). In this sense, our protocol described here becomes an alternative procedure to construct fused heterocyclic compounds bearing the important 2-thienyl and 2-furyl units in their structures based on an environmentally friendlier and tin-free methodology.

Scheme 3



In summary, we have implemented a simple, tin-free, and practical method for the synthesis of novel 4-hetaryl substituted pyrazolo[1,5-*a*][1,3,5]triazines **7-10** under solvent-free conditions employing microwave irradiation as the source of heating. Products were obtained in better yields and in shorter times (15–20 min) than when reactions were carried out in solution by conventional heating (90–120 min). In both reaction conditions the new pyrazolotriazines were obtained as separable mixtures of 2-ethylthio- and 2-ethoxy-derivatives (**7/9**)**a-c** and (**8/10**) **a-c**, respectively, depending if an ethanol or an ethanethiol molecule being lost in the first step of the sequence of reaction. Nevertheless structures **9** and **10** were formed as the main components from both reaction conditions.

EXPERIMENTAL

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 discs. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz and 100 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as internal standard. 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 **4** and **5** were obtained according to a procedure previously

described [16]. The starting aminopyrazoles **6** were synthesized following a literature procedure [17]. Reactions under microwave irradiation were performed using a CEM Discover oven, in open glass vessels.

General procedure for the synthesis of pyrazolo[1,5-*a*][1,3,5]triazines 7-10. ***Method A.*** A mixture of the appropriate *O,S*-diethyl hetaroylimidothiocarbonate **4,5** (2.0 mmol) and the corresponding 5-amino-3-aryl-1*H*-pyrazole **6a-c** (2.0 mmol) was subjected to microwave irradiation in absence of solvent (maximum power 300W during 15–20 min. at controlled temperature of 100°C), using a focused microwave reactor (CEM discover). After finished (TLC control), the crude product was dissolved in THF (2.0 mL), and purified by column chromatography on silica gel, using a mixture of hexanes/ethyl acetate (4:1) as eluent. The first chromatographic fraction corresponded to compounds **7/9** and the second one to compounds **8/10**.

Method B. A mixture of the appropriate thiocarbonate **4,5** (2.0 mmol), the corresponding aminopyrazole **6a-c** (2.0 mmol) and DMF (3 mL) was refluxed for 1.5–2.0 h. The solid products were precipitated by adding cold water to the reaction mixture, collected by filtration and purified by column chromatography as described in method A.

7-(4-Chlorophenyl)-2-ethylthio-4-(2′-furyl)pyrazolo[1,5-a][1,3,5] triazine (7a). From 5-amino-3-(4-chlorophenyl)-1*H*-pyrazole **6a** (0.387 g, 2.0 mmol), light yellow solid. IR (KBr): v 2957, 2930, 2870 (CH_3, CH_2), 1604, 1564, 1498 (C═C, C═N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (t, 3H, CH_3), 3.25 (c, 2H, CH_2), 6.70 (s, 1H, H-8), 6.77 (dd, 1H, H-4′), 7.47 (d, 2H, H*m*), 7.86 (br s, 1H, H-5′), 7.96 (d, 2H, H*o*), 8.53 (d, 1H, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3), 25.6 (CH_2), 91.4 (C-8), 113.2 (C-4′), 125.0 (C-3′), 128.1 (C*o*), 129.1 (C*m*), 130.7 (C*i*), 135.7 (C*p*), 143.0 (C-2′), 143.3 (C-4), 148.2 (C-5′), 151.3 (C-8a), 157.1 (C-7), 166.6 (C-2). MS (70 eV) *m/z* (%): 358/356 (7/19, M^+), 341 (10), 323 (13), 235 (10), 111(12), 97 (30), 83 (42), 81 (46), 73 (54), 71 (42), 70 (29), 69 (100), 57 (74), 55 (69), 43 (84), 41 (62), 29 (20). *Anal*. Calcd. for $C_{17}H_{13}ClN_4OS$: C, 57.22; H, 3.67; N, 15.71. Found: C, 57.25; H, 3.88; N, 15.58.

2-Ethylthio-4-(2′-furyl)-7-(4-methylphenyl)pyrazolo[1,5-a][1,3,5] triazine (7b). From 5-amino-3-(4-methylphenyl)-1*H*-pyrazole **6b** (0.346 g, 2.0 mmol), light green solid. IR (KBr): v 2958, 2927, 2860 (CH_3, CH_2), 1607, 1570, 1495 (C═C, C═N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (t, 3H, CH_3), 2.44 (s, 3H, CH_3-Ar), 3.24 (c, 2H, CH_2), 6.71 (s, 1H, H-8), 6.77 (dd, 1H, H-4′), 7.30 (d, 2H, H*m*), 7.85 (br s, 1H, H-5′), 7.93 (d, 2H, H*o*), 8.57 (d, 1H, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3), 21.4 (CH_3-Ar), 25.6 (CH_2), 91.3 (C-8), 113.1 (C-4′), 124.9 (C-3′), 126.8 (C*o*), 129.4 (C*i*), 129.5 (C*m*), 139.9 (C*p*), 143.1 (C-2′), 143.3 (C-4), 148.0 (C-5′), 151.2 (C-8a), 158.5 (C-7), 166.2 (C-2). MS (70 eV) *m/z* (%): 336 (100, M^+), 321 (28), 303 (64), 215 (10), 97 (20), 91 (11), 83 (23), 81 (26), 71 (31), 69 (58), 57 (44), 55 (39), 43 (42), 41 (32), 29 (11). *Anal*. Calcd. for $C_{18}H_{16}N_4OS$: C, 64.27; H, 4.80; N, 16.67. Found: C, 64.25; H, 4.83; N, 16.56.

2-Ethylthio-4-(2′-furyl)-7-phenylpyrazolo[1,5-a][1,3,5]triazine (7c). From 5-amino-3-phenyl-1*H*-pyrazole **6c** (0.318 g, 2.0 mmol), light green solid. IR (KBr): v 2955, 2923, 2859 (CH_3, CH_2), 1609, 1568, 1495 (C═C, C═N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (t, 3H, CH_3), 3.25 (c, 2H, CH_2), 6.74 (s, 1H, H-8), 6.77 (dd, 1H, H-4′), 7.46-7.52 (m, 3H, H*m*, H*p*), 7.86 (br s, 1H, H-5′), 8.00 (d, 2H, H*o*), 8.57 (d, 1H, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3), 25.6 (CH_2), 91.5 (C-8), 113.1 (C-4′), 125.0 (C-3′), 126.9 (C*o*), 128.8 (C*m*), 129.7 (C*p*), 132.2 (C*i*), 143.1 (C-2′), 143.3 (C-4), 148.1 (C-5′), 151.2 (C-8a), 158.3 (C-7), 166.4 (C-2). MS (70 eV) *m/z* (%): 322 (100, M^+), 307 (23), 289 (50), 201 (15), 169 (15), 143 (18), 94 (15), 77 (30), 70 (20), 69 (10), 29 (10). *Anal*. Calcd. for $C_{17}H_{14}N_4OS$: C, 63.34; H, 4.38; N, 17.39. Found: C, 63.01; H, 4.06; N, 17.15.

7-(4-Chlorophenyl)-2-ethoxy-4-(2′-furyl)pyrazolo[1,5-a][1,3,5] triazine (8a). From 5-amino-3-(4-chlorophenyl)-1*H*-pyrazole **6a** (0.387 g, 2.0 mmol), yellow solid. IR (KBr): v 2982, 2926, 2864 (CH_3, CH_2), 1624, 1574, 1534, 1501 (C═C, C═N), 1260, 1021 (C—O—C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (t, 3H, CH_3), 4.51 (c, 2H, CH_2), 6.60 (s, 1H, H-8), 6.76 (dd, 1H, H-4′), 7.46 (d, 2H, H*m*), 7.84 (d, 1H, H-5′), 7.94 (d, 2H, H*o*), 8.52 (d, 1H, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3), 64.1 (CH_2), 91.0 (C-8), 113.1 (C-4′), 124.8 (C-3′), 128.0 (C*o*), 129.0 (C*m*), 130.8 (C*i*), 135.6 (C*p*), 143.1 (C-2′), 146.2 (C-4), 148.1 (C-5′), 152.5 (C-8a), 157.7 (C-7), 160.0 (C-2). MS (70 eV) *m/z* (%): 342/340 (26/73, M^+), 325 (22), 296 (23), 221 (15), 219 (42), 111 (20), 97 (27), 94 (57), 83 (35), 81 (46), 73 (47), 71 (44), 69 (100), 57 (61), 55 (58), 43 (74), 41 (60), 29 (27). *Anal*. Calcd. for $C_{17}H_{13}ClN_4O_2$: C, 59.90; H, 3.85; N, 16.45. Found: C, 59.67; H, 3.94; N, 16.17.

2-Ethoxy-4-(2′-furyl)-7-(4-methylphenyl)pyrazolo[1,5-a][1,3,5] triazine (8b). From 5-amino-3-(4-methylphenyl)-1*H*-pyrazole **6b** (0.346 g, 2.0 mmol), yellow solid. IR (KBr): v 2980, 2955, 2925, 2860 (CH_3, CH_2), 1621, 1574, 1535, 1500 (C═C, C═N), 1256, 1023 (C—O—C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (t, 3H, CH_3), 2.43 (s, 3H, CH_3-Ar), 4.51 (c, 2H, CH_2), 6.62 (s, 1H, H-8), 6.76 (dd, 1H, H-4′), 7.29 (d, 2H, H*m*), 7.83 (d, 1H, H-5′), 7.91 (d, 2H, H*o*), 8.56 (d, 1H, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3 (CH_3), 21.4 (CH_3-Ar), 64.0 (CH_2), 90.9 (C-8), 113.1 (C-4′), 124.7 (C-3′), 126.7 (C*o*), 129.4 (C*i*), 129.5 (C*m*), 139.8 (C*p*), 143.2 (C-2′), 146.2 (C-4), 148.0 (C-5′), 152.3 (C-8a), 159.0 (C-7), 160.0 (C-2). MS (70 eV) *m/z* (%): 320 (100, M^+), 305 (34), 292 (21), 276 (27), 199 (47), 97 (21), 94 (33), 83 (26), 81 (27), 73 (28), 71 (30), 69 (61), 57 (45), 55 (42), 43 (47), 41 (39), 29 (20). *Anal*. Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.47; H, 5.04; N, 17.50. Found: C, 67.19; H, 5.11; N, 17.22.

2-Ethoxy-4-(2′-furyl)-7-phenylpyrazolo[1,5-a][1,3,5]triazine (8c). From 5-amino-3-phenyl-1*H*-pyrazole **6c** (0.318 g, 2.0 mmol), yellow solid. IR (KBr): v 2982, 2926, 2861 (CH_3, CH_2), 1621, 1572, 1531, 1498 (C═C, C═N), 1260, 1019 (C—O—C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.50 (t, 3H, CH_3), 4.53 (c, 2H, CH_2), 6.66 (s, 1H, H-8), 6.77 (dd, 1H, H-4′), 7.45-7.52 (m, 3H, H*m*, H*p*), 7.84 (dd, 1H, H-5′), 8.04 (d, 2H, H*o*), 8.58 (d, 1H, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3 (CH_3), 64.1 (CH_2), 91.1 (C-8), 113.1 (C-4′), 124.8 (C-3′), 126.8 (C*o*), 128.8 (C*m*), 129.6 (C*p*), 132.3 (C*i*), 143.2 (C-2′), 146.3 (C-4), 148.0 (C-5′), 152.3 (C-8a), 159.0 (C-7), 160.0 (C-2). MS (70 eV) *m/z* (%): 306 (100, M^+), 291 (26), 278 (20), 262 (23), 185 (60), 94 (52), 77 (40), 71 (33), 69 (36), 57 (42), 55 (26), 43 (37), 41 (19), 29 (20). *Anal*. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.64; H, 4.61; N, 18.30. Found: C, 66.34; H, 4.72; N, 18.02.

7-(4-Chlorophenyl)-2-ethylthio-4-(2′-thienyl)pyrazolo[1,5-a][1,3,5] triazine (9a). From 5-amino-3-(4-chlorophenyl)-1*H*-pyrazole **6a** (0.387 g, 2.0 mmol), light green solid. IR (KBr): v 2956, 2925, 2858 (CH_3, CH_2), 1601, 1570, 1530, 1490 (C═C, C═N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (t, 3H, CH_3), 3.25 (c, 2H, CH_2), 6.69 (s, 1H, H-8), 7.32 (t, 1H, H-4′), 7.48 (d, 2H, H*m*), 7.86 (d, 1H, H-5′), 7.99 (d, 2H, H*o*), 8.94 (d, 1H, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (CH_3), 25.6 (CH_2), 91.1

(C-8), 128.1 (C*o*), 128.3 (C-4′), 129.1 (C*m*), 130.7 (C*i*), 132.1 (C-2′), 135.7 (C*p*), 136.0 (C-5′), 137.0 (C-3′), 147.6 (C-4), 151.6 (C-8a), 157.1 (C-7), 166.5 (C-2). MS (70 eV) *m/z* (%): 374/372 (36/100, M^+), 357 (22), 339 (33), 235 (27), 111 (39), 109 (28), 97 (59), 95 (42), 85 (44), 83 (55), 81 (42), 71 (69), 69 (63), 57 (70), 55 (62), 43 (50), 41 (28), 29 (10). *Anal*. Calcd. for $C_{17}H_{13}ClN_4S_2$: C, 54.76; H, 3.52; N, 15.04. Found: C, 54.41; H, 3.45; N, 14.90.

2-Ethylthio-7-(4-methylphenyl)-4-(2′-thienyl)pyrazolo[1,5-a][1,3,5]triazine (9b). From 5-amino-3-(4-methylphenyl)-1*H*-pyrazole **6b** (0.346 g, 2.0 mmol), light green solid. IR (KBr): v 2957, 2928, 2860 (CH_3, CH_2), 1602, 1569, 1530, 1492 (C═C, C═N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.51 (t, 3H, CH_3), 2.43 (s, 3H, CH_3-Ar), 3.26 (c, 2H, CH_2), 6.69 (s, 1H, H-8), 7.30-7.33 (m, 3H, H-4′, H*m*), 7.84 (d, 1H, H-5′), 7.96 (d, 2H, H*o*), 8.96 (d, 1H, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (CH_3), 21.4 (CH_3-Ar), 25.6 (CH_2), 91.0 (C-8), 126.8 (C*o*), 128.3 (C-4′), 129.4 (C*i*), 129.5 (C*m*), 132.3 (C-2′), 135.8 (C-5′), 136.9 (C-3′), 139.8 (C*p*), 147.5 (C-4), 151.4 (C-8a), 158.4 (C-7), 166.1 (C-2). MS (70 eV) *m/z* (%): 352 (50, M^+), 337 (12), 319 (36), 215 (53), 186 (41), 183 (43), 115 (34), 110 (40), 109 (19), 91 (27). *Anal*. Calcd. for $C_{18}H_{16}N_4S_2$: C, 61.35; H, 4.58; N, 15.91. Found: C, 61.11; H, 4.67; N, 15.68.

2-Ethylthio-7-phenyl-4-(2′-thienyl)pyrazolo[1,5-a][1,3,5]triazine (9c). From 5-amino-3-phenyl-1*H*-pyrazole **6c** (0.318 g, 2.0 mmol), light green solid. IR (KBr): v 2955, 2929, 2856 (CH_3, CH_2), 1600, 1569, 1529, 1491 (C═C, C═N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (t, 3H, CH_3), 3.26 (c, 2H, CH_2), 6.72 (s, 1H, H-8), 7.32 (t, 1H, H-4′), 7.44-7.54 (m, 3H, H*m*, H*p*), 7.84 (d, 1H, H-5′), 8.07 (d, 2H, H*o*), 8.96 (d, 1H, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (CH_3), 25.6 (CH_2), 91.2 (C-8), 126.9 (C*o*), 128.3 (C-4′), 128.8 (C*m*), 129.7 (C*p*), 132.2 (C*i*), 132.3 (C-2′), 135.9 (C-5′), 137.0 (C-3′), 147.6 (C-4), 151.5 (C-8a), 158.3 (C-7), 166.2 (C-2). MS (70 eV) *m/z* (%): 338 (84, M^+), 323 (15), 305 (51), 201 (62), 169 (67), 143 (85), 110 (77), 109 (51), 77 (100), 70 (68). *Anal*. Calcd. for $C_{17}H_{14}N_4S_2$: C, 60.34; H, 4.17; N, 16.57. Found: C, 60.19; H, 4.08; N, 16.37.

7-(4-Chlorophenyl)-2-ethoxy-4-(2′-thienyl)pyrazolo[1,5-a][1, 3,5]triazine (10a). From 5-amino-3-(4-chlorophenyl)-1*H*-pyrazole **6a** (0.387 g, 2.0 mmol), yellow solid. IR (KBr): v 2982, 2926, 2860 (CH_3, CH_2), 1614, 1572, 1532, 1487 (C═C, C═N), 1256, 1050 (C—O—C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.51 (t, 3H, CH_3), 4.53 (c, 2H, CH_2), 6.60 (s, 1H, H-8), 7.32 (t, 1H, H-4′), 7.46 (d, 2H, H*m*), 7.86 (d, 1H, H-5′), 7.98 (d, 2H, H*o*), 8.96 (d, 1H, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3 (CH_3), 64.2 (CH_2), 90.8 (C-8), 128.1 (C*o*), 128.3 (C-4′), 129.0 (C*m*), 130.8 (C*i*), 131.9 (C-2′), 135.6 (C*p*), 136.2 (C-5′), 137.0 (C-3′), 150.6 (C-4), 152.6 (C-8a), 157.6 (C-7), 160.1 (C-2). MS (70 eV) *m/z* (%): 358/356 (39/100, M^+), 341 (27), 328 (24), 327 (36), 312 (28), 219 (42), 111 (27), 110 (91), 109 (31), 75 (28), 69 (31), 57 (16), 39 (18), 29 (35). *Anal*. Calcd. for $C_{17}H_{13}ClN_4OS$: C, 57.22; H, 3.67; N, 15.71. Found: C, 57.13; H, 3.56; N, 15.54.

2-Ethoxy-7-(4-methylphenyl)-4-(2′-thienyl)pyrazolo[1,5-a][1,3,5]triazine (10b). From 5-amino-3-(4-methylphenyl)-1*H*-pyrazole **6b** (0.346 g, 2.0 mmol), yellow solid. IR (KBr): v 2979, 2953, 2927, 2859 (CH_3, CH_2), 1613, 1567, 1534, 1488 (C═C, C═N), 1253, 1045 (C—O—C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.51 (t, 3H, CH_3), 2.43 (s, 3H, CH_3-Ar), 4.52 (c, 2H, CH_2), 6.60 (s, 1H, H-8), 7.28-7.31 (m, 3H, H-4′, H*m*), 7.84 (d, 1H, H-5′), 7.93 (d, 2H, H*o*), 8.97 (d, 1H, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (CH_3), 21.4 (CH_3-Ar), 64.1 (CH_2), 90.7 (C-8), 126.8 (C*o*), 128.2 (C-4′), 129.4 (C*i*), 129.5 (C*m*), 132.1 (C-2′), 135.9 (C-5′), 137.0 (C-3′), 139.8 (C*p*), 150.5 (C-4), 152.4 (C-8a), 158.9 (C-7), 160.0 (C-2). MS (70 eV) *m/z* (%): 336 (36, M^+), 321 (12), 307 (13), 292 (10), 199 (100), 198 (28), 115 (24), 110 (59), 109 (11), 91 (18). *Anal*. Calcd. for $C_{18}H_{16}N_4OS$: C, 64.27; H, 4.80; N, 16.67. Found: C, 64.09; H, 4.62; N, 16.53.

2-Ethoxy-7-phenyl-4-(2′-thienyl)pyrazolo[1,5-a][1,3,5]triazine (10c). From 5-amino-3-phenyl-1*H*-pyrazole **6c** (0.318 g, 2.0 mmol), yellow solid. IR (KBr): v 2976, 2925, 2860 (CH_3, CH_2), 1611, 1570, 1535, 1487 (C═C, C═N), 1245, 1049 (C—O—C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.51 (t, 3H, CH_3), 4.52 (c, 2H, CH_2), 6.64 (s, 1H, H-8), 7.31 (t, 1H, H-4′), 7.44-7.49 (m, 3H, H*m*, H*p*), 7.84 (d, 1H, H-5′), 8.05 (d, 2H, H*o*), 8.98 (d, 1H, H-3′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (CH_3), 64.1 (CH_2), 90.9 (C-8), 126.9 (C*o*), 128.2 (C-4′), 128.8 (C*m*), 129.6 (C*p*), 132.1 (C-2′), 132.2 (C*i*), 136.0 (C-5′), 137.0 (C-3′), 150.6 (C-4), 152.5 (C-8a), 158.8 (C-7), 160.0 (C-2). MS (70 eV) *m/z* (%): 322 (92, M^+), 307 (10), 293 (38), 278 (14), 185 (87), 110 (100), 109 (35), 102 (36), 77 (76). *Anal*. Calcd. for $C_{17}H_{14}N_4OS$: C, 63.34; H, 4.38; N, 17.39. Found: C, 63.22; H, 4.54; N, 17.18.

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