Synthesis of 8-Substituted Pyrazolo[1,5-*a*]-1,3,5-triazine Derivatives by Palladium-Catalyzed Cross-Coupling Reactions

Florence Popowycz,[a] Philippe Bernard,[b] Pierre Raboisson,[b] Benoît Joseph*[a]

[a] Laboratoire de Chimie Organique 1, UMR-CNRS 5181, Université Claude Bernard – Lyon 1, CPE – Bâtiment 308, 43 Boulevard du 11 Novembre 1918, 69622 Villeurbanne cedex, France
Fax +33(4)72431214; E-mail: benoit.joseph@univ-lyon1.fr

[b] Greenpharma SA, 3 Allée du Titane, 45100 Orléans, France

Received 5 September 2006; revised 26 October 2006

Abstract: 8-Substituted pyrazolo[1,5-*a*]-1,3,5-triazine derivatives **6** were prepared from the corresponding 8-iodopyrazolo[1,5-*a*]-1,3,5-triazines **5** through palladium-catalyzed cross-coupling reactions. Several bioisosteres of hypoxanthine drugs **2** were then prepared by final nucleophilic aromatic substitution.

Key words: purine, bioisosteres, pyrazolo[1,5-*a*]-1,3,5-triazine, palladium

Pyrazolo[1,5-*a*]-1,3,5-triazines are purine 'carba-bioisosteres' exhibiting pharmaceutical properties such as phosphodiesterase inhibitors,[1] corticotropin-releasing factor antagonists,[2] cyclooxygenase-2 (COX-2) inhibitors,[3] cyclin-dependent kinase (CDK) inhibitors[4] and DNA gyrase inhibitors.[5] Because of their wide range of biological properties, pyrazolo[1,5-*a*]-1,3,5-triazines have attracted considerable interest from the medicinal chemistry community over the past few years, and have prompted the development of novel efficient procedures for the synthesis of functionalized pyrazolo[1,5-*a*]-1,3,5-triazines.

With the aim to overcome some liabilities [e.g. poor drug metabolism and pharmacokinetic (DMPK) properties] of the parent drugs **1**, we synthesized and biologically evaluated novel 8-substituted pyrazolo[1,5-*a*]-1,3,5-triazin-4(1*H*)-one derivatives **2**, as ring equivalent bioisosteres of hypoxanthine-containing drugs **1**, which have been developed for the treatment of neurodegenerative diseases (Figure 1).[6]

Indeed, compound **1a** (AIT-082, Leteprinim potassium, Neotrofin™) causes the production of multiple nerve growth neurotrophic factors, thus it stimulates neuritogenesis, or the sprouting of nerve cells.[7] In animal model, AIT-082 has been used to treat injuries to the central nervous system,[8] and clinical safety and efficacy studies have been performed on patients with Alzheimer's disease.[9] Recently, the therapeutic potential of Neotrofin has been extended to the peripheral nervous system.[10] Compound **1b** (AIT-034) enhances memory and reverses memory deficits in severely impaired animal models providing complementary therapy for Alzheimer's disease. This compound may have applications in treating severe dementia. Finally, compound **1c** (AIT-203) is a dopamine agonist, which was under preclinical investigation for the treatment of Parkinson's disease.[11]

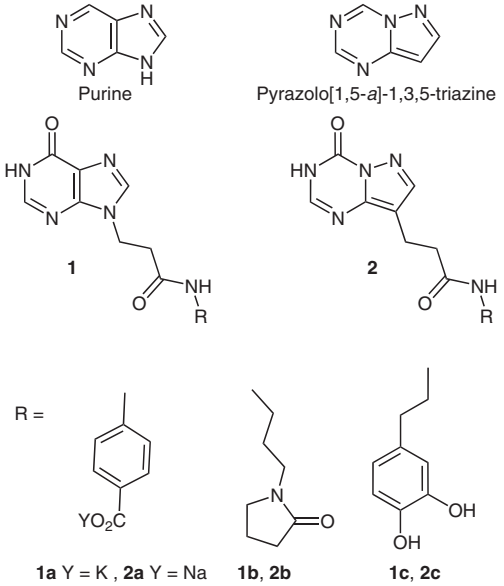
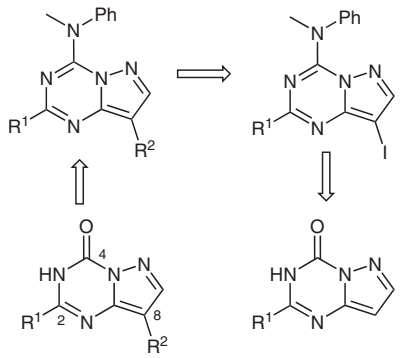


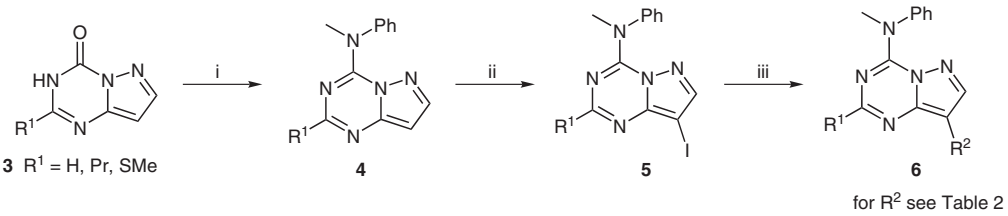
Figure 1 Hypoxanthine derivatives **1** and bioisosteres **2**

We report here an efficient synthetic access to 8-substituted pyrazolo[1,5-*a*]-1,3,5-triazines through a panel of palladium-catalyzed coupling reactions (i.e. Stille, Suzuki, Heck and Sonogashira reactions) as depicted in retrosynthetic Scheme 1. Palladium-mediated cross-coupling reactions with similar substrates have been already reported in the literature.[12,13] In our research project, *N*-methyl-



Scheme 1 Retrosynthetic strategy

SYNTHESIS 2007, No. 3, pp 0367–0374
Advanced online publication: 21.12.2006
DOI: 10.1055/s-2006-958963; Art ID: T13506SS



Scheme 2 *Reagents and conditions*: i. a) $POCl_3$, DMAP, reflux, 2 h; b) *N*-methylaniline, Et_3N, CH_2Cl_2, r.t., overnight; ii. NIS, $CHCl_3$, reflux, 30 min; iii. *Method A*: tributyl(1-ethoxyvinyl)tin, $Pd(PPh_3)_4$, LiCl, DMF, 90 °C, 12 h. *Method B*: phenylboronic acid, $Pd(PPh_3)_4$, $NaHCO_3$, EtOH, toluene, reflux, 12 h. *Method C*: pent-1-yne, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 40 °C, 12 h. *Method D*: *tert*-butyl acrylate, $Pd(OAc)_2$, PPh_3, Et_3N, DMF, 90 °C, 12 h; for yields see Tables 1 and 2.

aniline activating group was introduced on position C-4 in order to increase the solubility of derivatives and allow further introduction of nucleophiles (e.g., amines, thiols) under mild conditions.[13] As example, displacement of this group by hydroxide anion was performed, opening up the access to **2**.

The readily available pyrazolo[1,5-*a*]-1,3,5-triazin-4(1*H*)-ones **3**[14] were first treated with 4-dimethylaminopyridine in refluxing phosphorus oxychloride followed by addition of *N*-methylaniline to afford *N*-methylaniline derivatives **4** in good yields (Scheme 2, Table 1). As already described in the literature for this series, the *N*-methyl-*N*-phenylamino group in position C-4 is a good candidate for nucleophilic addition-elimination displacement.[13,15] Regioselective iodination on position C-8 of **4** was carried out in the presence of *N*-iodosuccinimide to give 8-iodopyrazolo[1,5-*a*]-1,3,5-triazines **5** in 82–93% yields (Scheme 2, Table 1).[12c,13]

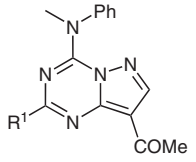
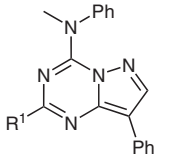
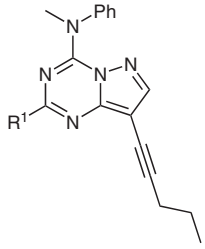
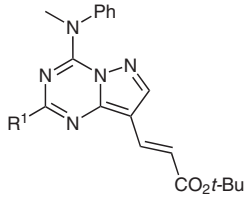
Table 1 Compounds **4** and **5** Prepared

R^1	**4**	Yield (%)	**5**	Yield (%)
H	**4a**	87	**5a**	82
SMe	**4b**	88	**5b**	93
Pr	**4c**	92	**5c**	87

Substituents at position C-8 were introduced in good to excellent yields (Scheme 2 and Table 2) by palladium-catalyzed cross-coupling reactions (Stille reaction: compounds **6a–c**; Suzuki reaction: compounds **6d–f**; Sonogashira reaction: compounds **6g–i** and Heck reaction: compounds **6j–l**) allowing a large diversity of functionalization. Several catalytic palladium systems [$Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$] were used to perform these reactions. As anticipated, the thiomethyl derivative **5b** gave the lowest yield of coupling product.

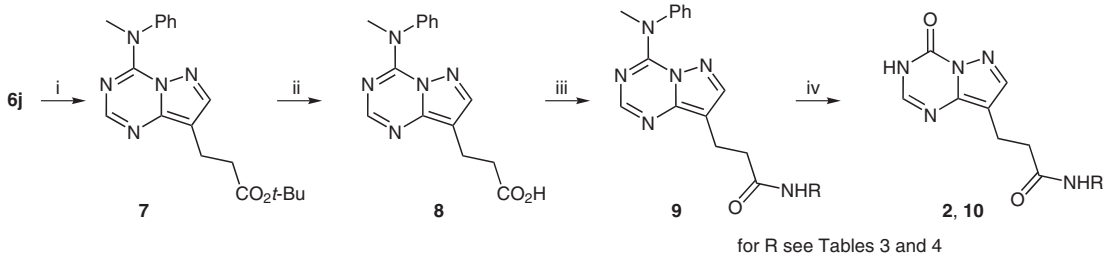
Moreover, the target pyrazolo[1,5-*a*]-1,3,5-triazin-4(1*H*)-ones **2a–c** were prepared in four to five steps from starting material **6j** as depicted in Scheme 3. Catalytic hydrogenation of the exocyclic double bond of compound **6j** in the presence of 10% palladium on charcoal afforded compound **7** in 95% yield. Subsequent hydrolysis of ester **7** was carried out in acidic medium (TFA, toluene) providing the key intermediate **8** in 87% yield. Using classical

Table 2 Compounds **6a–l** Prepared

Method	R^1	**6**		Yield (%)
A	H		**6a**	96
A	SMe		**6b**	84
A	Pr		**6c**	93
B	H		**6d**	85
B	SMe		**6e**	70
B	Pr		**6f**	89
C	H		**6g**	81
C	SMe		**6h**	67
C	Pr		**6i**	70
D	H		**6j**	87
D	SMe		**6k**	68
D	Pr		**6l**	78

peptide coupling conditions, methyl 4-aminobenzoate, *N*-(3-aminopropyl)-2-pyrrolidinone or 2,2-diphenyl-1,3-benzodioxole-5-propanamine[16] were reacted with acid **8** to give the corresponding amides **9** in nearly quantitative yield (Scheme 3, Table 3). The coupling reaction between **8** and dopamine afforded the corresponding amide in 40% yield (not described in experimental part).

To our satisfaction, the displacement of *N*-methyl-*N*-phenyl group of **9** was achieved under mild conditions (5 N aq NaOH at room temperature). Eventually, the target compounds **2a**, **2b** and **10** were obtained in good yield as reported in Table 4. The deprotection of the acetal group of **10** was subsequently performed under acidic conditions, to afford the final product **2c** (Table 4).



Scheme 3 *Reagents and conditions:* i. H_2, 10% Pd/C, 10 bar, THF–EtOAc, r.t., 6 h, 95%; ii. TFA–toluene 1:1, r.t., 4 h, 87%; iii. EDCI, DMAP, RNH_2, CH_2Cl_2, Et_3N, 0 °C to r.t., 24 h; iv. 5 N NaOH, EtOH, 60 °C, 5 h for **9a**; r.t., 5 h for **9b**; r.t., overnight for **9c**; for yields see Tables 3 and 4.

Table 3 Compounds **9** Prepared

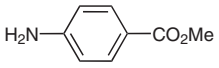
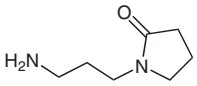
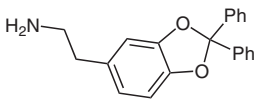
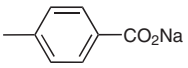
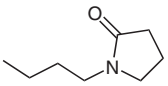
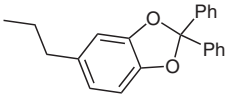
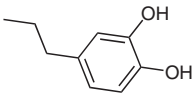
Amine	**9**	Yield (%)
	**9a**	95
	**9b**	93
	**9c**	95

Table 4 Compounds **2** and **10** Prepared

R	**2**, **10**	Yield (%)
	**2a**	82
	**2b**	66
	**10**	87
	**2c**	79[a]

[a] Reagents and conditions: **10**, AcOH–H_2O (8:2), reflux, 6 h

In conclusion, we have disclosed a practical and efficient synthesis of 8-substituted pyrazolo[1,5-*a*]-1,3,5-triazines from readily available starting materials, which can be used for parallel and large-scale applications. This reliable and convenient method opens up the synthesis of numerous 2,8-disubstituted pyrazolo[1,5-*a*]-1,3,5-triazin-4(1*H*)-one derivatives with potential CNS properties.[17] The biological evaluation of these novel hypoxanthine drug bioisosteres will be reported in due course.

Melting points were obtained with a Büchi capillary apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer 681 IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded with a PerkinElmer SCIEX API spectrometer. Elemental analyses were performed on a Thermoquest Flash 1112 series EA analyzer. TLC analyses were conducted on silica gel Merck $60F_{254}$ coated on aluminum sheets. The spots were visualized using an ultraviolet light. Flash chromatography was carried out on silica gel 60 (40–63 μm, Merck) using the indicated solvents [petroleum ether (PE): boiling range 40–60 °C]. All reactions requiring anhydrous conditions were conducted in flame-dried apparatus. All commercially available reagents were used without further purification.

Compounds 4a–c; General Procedure

A solution of **3** (11.5 mmol), DMAP (40.1 mmol, 3.5 equiv) and $POCl_3$ (20 mL) was stirred at reflux for 2 h. After warming up the solution to r.t., the excess of $POCl_3$ was removed in vacuo. The oily residue was dried in vacuum pump for 2 h and dissolved in CH_2Cl_2 (60 mL). *N*-Methylaniline (8 mL) and Et_3N (10 mL) were added dropwise under stirring at 0 °C under argon. After 10 min, the mixture was allowed to warm up to r.t. and stirred overnight. The mixture was washed with H_2O (30 mL) and the organic layer was dried ($MgSO_4$) and concentrated in vacuo. After evaporation of the solvent, the residue was purified by flash chromatography (eluent is indicated below) to afford **4**.

4-(*N*-Methyl-*N*-phenylamino)pyrazolo[1,5-*a*]-1,3,5-triazine (4a)

Chromatography eluent: Et_2O–PE (1:1); yield: 87%; solid; mp 141–142 °C (purified by washing with cyclohexane).

IR (KBr): 1605, 1555, 1460, 1415 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, CH_3), 6.42 (d, *J* = 2.2 Hz, 1 H, H-8), 7.21 (d, *J* = 7.1 Hz, 2 H, ArH), 7.37–7.45 (m, 3 H, ArH), 7.79 (d, *J* = 2.2 Hz, 1 H, H-7), 8.23 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.3 (CH_3), 95.6 (CH), 126.2 (2 CH), 127.4 (CH), 129.2 (2 CH), 144.7 (C), 144.8 (CH), 150.2 (C), 151.1 (C), 152.7 (CH).

MS (ESI): *m*/*z* = 226 $(M + H)^+$.

Anal. Calcd for $C_{12}H_{11}N_5$: C, 63.99; H, 4.92; N, 31.09. Found: C, 64.24; H, 5.17; N, 30.91.

4-(*N*-Methyl-*N*-phenylamino)-2-methylsulfanylpyrazolo[1,5-*a*]-1,3,5-triazine (4b)

Chromatography eluent: Et_2O–PE (1:1); yield: 88%; solid; mp 106–108 °C (EtOAc–PE).

IR (KBr): 1605, 1550 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s, 3 H, CH_3), 3.73 (s, 3 H, CH_3), 6.16 (d, *J* = 2.1 Hz, 1 H, H-8), 7.18 (d, *J* = 7.1 Hz, 2 H, ArH), 7.31–7.42 (m, 3 H, ArH), 7.65 (d, *J* = 2.1 Hz, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 42.3 (CH_3), 93.3 (CH), 126.2 (2 CH), 127.2 (CH), 129.1 (2 CH), 144.7 (C), 145.0 (CH), 148.3 (C), 151.5 (C), 166.8 (C).

MS (ESI): *m*/*z* = 272 $(M + H)^+$.

Anal. Calcd for $C_{13}H_{13}N_5S$: C, 57.54; H, 4.83; N, 25.81. Found: C, 57.33; H, 4.72; N, 25.99.

4-(*N*-Methyl-*N*-phenylamino)-2-propylpyrazolo[1,5-*a*]-1,3,5-triazine (4c)

Chromatography eluent: Et_2O–PE (1:4); yield: 92%; oil.

IR (film): 1590, 1535, 1440, 1405 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.92 (m, 2 H, CH_2), 2.81 (t, *J* = 7.4 Hz, 2 H, CH_2), 3.79 (s, 3 H, CH_3), 6.31 (d, *J* = 2.1 Hz, 1 H, H-8), 7.21 (d, *J* = 7.1 Hz, 2 H, ArH), 7.32–7.45 (m, 3 H, ArH), 7.74 (d, *J* = 2.1 Hz, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 21.4 (CH_3), 40.9 (CH_2), 42.1 (CH_3), 94.3 (CH), 126.1 (2 CH), 126.9 (CH), 129.0 (2 CH), 144.8 (CH), 144.9 (C), 149.4 (C), 151.6 (C), 165.7 (C).

MS (ESI): *m*/*z* = 268 $(M + H)^+$.

Anal. Calcd for $C_{15}H_{17}N_5$: C, 67.39; H, 6.41; N, 26.20. Found: C, 67.55; H, 6.31; N, 26.03.

Iodination of Compounds 4a–c; General Procedure

A solution of **4** (11.0 mmol) and NIS (3.46 g, 15.4 mmol, 1.4 equiv) in anhyd $CHCl_3$ (90 mL) was stirred at reflux for 30 min. The solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with a sat. aq solution of $Na_2S_2O_3$ (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (eluent is indicated below) to afford derivatives **5**.

8-Iodo-4-(*N*-methyl-*N*-phenylamino)pyrazolo[1,5-*a*]-1,3,5-triazine (5a)

Chromatography eluent: EtOAc–PE (2:8); yield: 82%; solid; mp 191–192 °C (EtOH).

IR (KBr): 1590, 1555, 1445, 1405 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3 H, CH_3), 7.18–7.20 (m, 2 H, ArH), 7.34–7.44 (m, 3 H, ArH), 7.76 (s, 1 H, H-7), 8.31 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.6 (CH_3), 48.8 (C), 126.2 (2 CH), 127.7 (CH), 129.2 (2 CH), 144.3 (C), 148.5 (CH), 150.0 (C), 150.6 (C), 153.9 (CH).

MS (ESI): *m*/*z* = 352 $(M + H)^+$.

Anal. Calcd for $C_{12}H_{10}IN_5$: C, 41.05; H, 2.87; N, 19.94. Found: C, 40.85, H, 2.94; N; 20.07.

8-Iodo-4-(*N*-methyl-*N*-phenylamino)-2-methylsulfanylpyrazolo[1,5-*a*]-1,3,5-triazine (5b)

Chromatography eluent: Et_2O–PE (1:9); yield: 93%: solid; mp 162–163 °C (Et_2O–PE).

IR (KBr): 1605, 1585 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.59 (s, 3 H, CH_3), 3.71 (s, 3 H, CH_3), 7.16 (br d, *J* = 7.1 Hz, 2 H, ArH), 7.36–7.39 (m, 3 H, ArH), 7.61 (s, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 42.5 (CH_3), 46.2 (C), 126.2 (2 CH), 127.5 (CH), 129.1 (2 CH), 144.4 (C), 148.1 (C), 148.6 (CH), 150.8 (C), 166.5 (C).

MS (ESI): *m*/*z* = 398 $(M + H)^+$.

Anal. Calcd for $C_{13}H_{12}IN_5S$: C, 39.31; H, 3.04; N, 17.63. Found: C, 38.98; H, 2.86; N, 17.65.

8-Iodo-4-(*N*-methyl-*N*-phenylamino)-2-propylpyrazolo[1,5-*a*]-1,3,5-triazine (5c)

Chromatography eluent: EtOAc–PE (2:8); yield: 87%; solid; mp 100–102 °C (MeOH).

IR (KBr): 1590, 1535, 1440 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.81–1.93 (m, 2 H, CH_2), 2.80 (t, *J* = 7.3 Hz, 2 H, CH_2), 3.73 (s, 3 H, CH_3), 7.13–7.17 (m, 2 H, ArH), 7.30–7.41 (m, 3 H, ArH), 7.67 (s, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 21.3 (CH_2), 40.9 (CH_2), 42.2 (CH_3), 47.1 (C), 126.0 (2 CH), 127.1 (CH), 128.9 (2 CH), 144.5 (C), 148.4 (CH), 149.2 (C), 150.9 (C), 167.2 (C).

MS (ESI): *m*/*z* = 394 $(M + H)^+$.

Anal. Calcd for $C_{15}H_{16}IN_5$: C, 45.82; H, 4.10; N, 17.81. Found: C, 45.66; H, 3.99; N, 17.67.

Stille Reaction with Compounds 5; General Procedure (Method A)

To a stirred mixture of **5** (0.33 mmol), freshly prepared $Pd(PPh_3)_4$ (30 mg, 0.03 mmol, 0.08 equiv) and LiCl (35 mg, 0.82 mmol, 2.5 equiv) in anhyd DMF (3 mL) was added tributyl(1-ethoxyvinyl)tin (160 μL, 0.49 mmol, 1.5 equiv). The mixture was stirred at 90 °C for 12 h and then the solvent was evaporated in vacuo. The crude residue was purified by flash chromatography (eluent indicated below) to give **6a–c**.

8-Acetyl-4-(*N*-methyl-*N*-phenylamino)pyrazolo[1,5-*a*]-1,3,5-triazine (6a)

Chromatography eluent: PE, then EtOAc–PE (1:9, then 2:8); yield: 96%; solid; mp 120–121 °C (MeOH).

IR (KBr): 1655, 1590, 1545 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69 (s, 3 H, CH_3), 3.84 (s, 3 H, CH_3), 7.18–7.21 (m, 2 H, ArH), 7.38–7.43 (m, 3 H, ArH), 8.20 (s, 1 H, H-7), 8.38 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.3 (CH_3), 42.8 (CH_3), 111.3 (C), 126.3 (2 CH), 128.0 (CH), 129.5 (2 CH), 144.3 (C), 145.8 (CH), 150.3 (C), 151.6 (C), 155.5 (CH), 192.3 (C=O).

MS (ESI): *m*/*z* = 268 $(M + H)^+$.

Anal. Calcd for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.73; H, 4.87; N, 26.03.

8-Acetyl-4-(*N*-methyl-*N*-phenylamino)-2-methylsulfanylpyrazolo[1,5-*a*]-1,3,5-triazine (6b)

Chromatography eluent: PE, then CH_2Cl_2–PE–EtOAc (5:6:1); yield: 84%; solid; mp 223–225 °C (MeOH).

IR (KBr): 1670, 1560 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.59 (s, 3 H, CH_3), 2.70 (s, 3 H, CH_3), 3.75 (s, 3 H, CH_3), 7.16–7.19 (m, 2 H, ArH), 7.38–7.45 (m, 3 H, ArH), 8.08 (s, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 29.2 (CH_3), 42.5 (CH_3), 109.4 (C), 126.1 (2 CH), 127.6 (CH), 129.2 (2 CH), 144.1 (C), 145.4 (CH), 148.2 (C), 151.5 (C), 170.9 (C), 192.1 (C=O).

MS (ESI): *m*/*z* = 314 $(M + H)^+$.

Anal. Calcd for $C_{15}H_{15}N_5OS$: C, 57.49; H, 4.82; N, 22.35. Found: C, 57.32; H, 4.73; N, 22.55.

8-Acetyl-4-(*N*-methyl-*N*-phenylamino)-2-propylpyrazolo[1,5-*a*]-1,3,5-triazine (6c)
Chromatography eluent: PE, then Et_2O–PE (1:9), then EtOAc–PE (1:9); yield: 93%; solid; mp 122–123 °C (MeOH).

IR (KBr): 1650, 1590, 1475 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.85–1.93 (m, 2 H, CH_2), 2.71 (s, 3 H, CH_3), 2.82 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.75 (s, 3 H, CH_3), 7.16 (br d, *J* = 6.8 Hz, 2 H, ArH), 7.35–7.42 (m, 3 H, ArH), 8.13 (s, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 21.0 (CH_2), 29.2 (CH_3), 41.0 (CH_2), 42.4 (CH_3), 110.4 (C), 126.2 (2 CH), 127.5 (CH), 129.3 (2 CH), 144.5 (C), 145.7 (CH), 149.6 (C), 152.2 (C), 169.1 (C), 192.6 (C=O).

MS (ESI): *m*/*z* = 310 $(M + H)^+$.

Anal. Calcd for $C_{17}H_{19}N_5O$: C, 66.00; H, 6.19; N, 22.64. Found: C, 66.40; H, 6.27; N, 22.45.

Suzuki Reaction with Compounds 5; General Procedure (Method B)
To a stirred solution of **5** (0.19 mmol) in anhyd toluene (1.5 mL) was added freshly prepared $Pd(PPh_3)_4$ (33 mg, 0.028 mmol, 0.15 equiv). The mixture was stirred for 30 min at r.t. Phenylboronic acid (35 mg, 0.28 mmol, 1.5 equiv) diluted in EtOH (1 mL) was then added, followed immediately by a sat. aq $NaHCO_3$ solution (1 mL). The heterogeneous solution was stirred at reflux for 12 h. The Pd catalyst was removed by filtration. Brine (2 mL) was then added, the layers were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The crude residue was purified by flash chromatography (eluent indicated below) to afford the 8-phenyl derivatives **6d–f**.

4-(*N*-Methyl-*N*-phenylamino)-8-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (6d)
Chromatography eluent: Et_2O–PE (1:9); yield: 85%; solid; mp 147–148 °C (MeOH).

IR (KBr): 1595, 1540, 1490 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, CH_3), 7.22–7.28 (m, 3 H, ArH), 7.38–7.46 (m, 5 H, ArH), 7.94 (d, *J* = 7.2 Hz, 2 H, ArH), 8.11 (s, 1 H, H-7), 8.34 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.5 (CH_3), 109.5 (C), 126.2 (2 CH), 126.5 (2 CH), 127.4 (CH), 128.9 (2 CH), 129.3 (2 CH), 129.6 (CH), 131.6 (C), 143.0 (CH), 144.7 (C), 147.1 (C), 150.3 (C), 152.9 (CH).

MS (ESI): *m*/*z* = 302 $(M + H)^+$.

Anal. Calcd for $C_{18}H_{15}N_5$: C, 71.74; H, 5.02; N, 23.24. Found: C, 71.69; H, 4.90; N, 22.94.

4-(*N*-Methyl-*N*-phenylamino)-2-methylsulfanyl-8-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (6e)
Chromatography eluent: Et_2O–PE (1:9), yield: 70%; solid; mp 128–129 °C (MeOH).

IR (KBr): 1610, 1530, 1455 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.64 (s, 3 H, CH_3), 3.73 (s, 3 H, CH_3), 7.18–7.21 (m, 3 H, ArH), 7.34–7.43 (m, 5 H, ArH), 7.95 (d, *J* = 7.5 Hz, 2 H, ArH), 7.98 (s, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 (CH_3), 42.3 (CH_3), 107.2 (C), 126.0 (2 CH), 126.1 (CH), 126.2 (2 CH), 127.3 (CH), 128.8 (2 CH), 129.2 (2 CH), 131.9 (C), 143.1 (CH), 144.8 (C), 147.4 (C), 148.4 (C), 167.2 (C).

MS (ESI): *m*/*z* = 348 $(M + H)^+$.

Anal. Calcd for $C_{19}H_{17}N_5S$: C, 65.68; H, 4.93; N, 20.16. Found: C, 65.39; H, 5.00; N, 19.99.

4-(*N*-Methyl-*N*-phenylamino)-8-phenyl-2-propylpyrazolo[1,5-*a*]-1,3,5-triazine (6f)
Chromatography eluent: Et_2O–PE (1:9); yield: 89%; solid; mp 100–101 °C (MeOH).

IR (KBr): 1595, 1535, 1410 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.93–2.00 (m, 2 H, CH_2), 2.87 (t, *J* = 7.3 Hz, 2 H, CH_2), 3.77 (s, 3 H, CH_3), 7.20–7.26 (m, 3 H, ArH), 7.35–7.45 (m, 5 H, ArH), 8.00 (d, *J* = 7.5 Hz, 2 H, ArH), 8.05 (s, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 21.2 (CH_2), 41.0 (CH_2), 42.1 (CH_3), 108.0 (C), 126.0 (CH), 126.1 (2 CH), 126.2 (2 CH), 126.9 (CH), 128.8 (2 CH), 129.0 (2 CH), 132.1 (C), 142.9 (CH), 145.0 (C), 147.8 (C), 149.5 (C), 166.0 (C).

MS (ESI): *m*/*z* = 344 $(M + H)^+$.

Anal. Calcd for $C_{21}H_{21}N_5$: C, 73.44; H, 6.16; N, 20.39. Found: C, 73.05; H, 6.18; N, 20.19.

Sonogashira Reaction with Compounds 5; General Procedure (Method C)
To a stirred solution of **5** (0.27 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol, 0.15 equiv) and CuI (7.7 mg, 0.04 mmol, 0.15 equiv) in anhyd DMF (2 mL) were added successively Et_3N (160 μL, 1.13 mmol, 4.2 equiv) and pent-1-yne (132 μL, 1.35 mmol, 5 equiv). The solution was stirred at 40 °C for 12 h. After cooling, the solvent was evaporated in vacuo. The crude residue was purified by flash chromatography (eluent indicated below) to afford the 8-pentynyl derivatives **6g–i**.

4-(*N*-Methyl-*N*-phenylamino)-8-(pentyn-1-yl)pyrazolo[1,5-*a*]-1,3,5-triazine (6g)
Chromatography eluent: EtOAc–PE (1:2); yield: 81%; solid; mp >250 °C (MeOH).

IR (KBr): 1615, 1565, 1485 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.59–1.66 (m, 2 H, CH_2), 2.43 (t, *J* = 7.1 Hz, 2 H, CH_2), 3.80 (s, 3 H, CH_3), 7.16–7.19 (m, 2 H, ArH), 7.35–7.43 (m, 3 H, ArH), 7.78 (s, 1 H, H-7), 8.26 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (CH_3), 21.8 (CH_2), 22.3 (CH_2), 42.5 (CH_3), 69.3 (C), 93.6 (C), 94.4 (C), 126.1 (2 CH), 127.5 (CH), 129.2 (2 CH), 144.4 (C), 146.5 (CH), 150.1 (C), 151.4 (C), 153.4 (C).

MS (ESI): *m*/*z* = 292 $(M + H)^+$.

Anal. Calcd for $C_{17}H_{17}N_5$: C, 70.08; H, 5.88; N, 24.04. Found: C, 69.99; H, 5.98; N, 23.93.

4-(*N*-Methyl-*N*-phenylamino)-2-methylsulfanyl-8-(pentyn-1-yl)pyrazolo[1,5-*a*]-1,3,5-triazine (6h)
Chromatography eluent: Et_2O–PE (1:9); yield: 67%; solid; mp 104–105 °C (MeOH).

IR (KBr): 1610, 1535, 1505 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.59–1.66 (m, 2 H, CH_2), 2.41 (t, *J* = 7.1 Hz, 2 H, CH_2), 2.57 (s, 3 H, CH_3), 3.70 (s, 3 H, CH_3), 7.13–7.16 (m, 2 H, ArH), 7.34–7.38 (m, 3 H, ArH), 7.64 (s, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (CH_3), 14.3 (CH_3), 21.9 (CH_2), 22.3 (CH_2), 42.3 (CH_3), 69.9 (C), 91.2 (C), 93.7 (C), 126.1 (2 CH), 127.3 (CH), 129.1 (2 CH), 144.5 (C), 146.8 (CH), 148.2 (C), 151.7 (C), 168.0 (C).

MS (ESI): *m*/*z* = 338 $(M + H)^+$.

Anal. Calcd for $C_{18}H_{19}N_5S$: C, 64.07; H, 5.68; N, 20.75. Found: C, 63.88; H, 5.65; N, 20.60.

4-(*N*-Methyl-*N*-phenylamino)-8-(pentyn-1-yl)-2-propylpyrazolo[1,5-*a*]-1,3,5-triazine (6i)

Chromatography eluent: EtOAc–PE (2:8); yield: 70%; solid; mp 92–93 °C (MeOH).

IR (KBr): 1605, 1540, 1480, 1405 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.02 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.57–1.69 (m, 2 H, CH_2), 1.80–1.93 (m, 2 H, CH_2), 2.42 (t, *J* = 7.1 Hz, 2 H, CH_2), 2.79 (dd, *J* = 7.1 Hz, 2 H, CH_2), 3.72 (s, 3 H, CH_3), 7.12–7.15 (m, 2 H, ArH), 7.31–7.39 (m, 3 H, ArH), 7.70 (s, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (CH_3), 14.1 (CH_3), 21.4 (CH_2), 22.0 (CH_2), 22.3 (CH_2), 40.9 (CH_3), 42.1 (CH_3), 69.9 (C), 92.1 (C), 93.8 (C), 126.1 (2 CH), 127.1 (CH), 129.0 (2 CH), 144.6 (C), 146.8 (CH), 149.3 (C), 151.7 (C), 166.8 (C).

MS (ESI): *m*/*z* = 334 $(M + H)^+$.

Anal. Calcd for $C_{20}H_{23}N_5$: C, 72.04; H, 6.95; N, 21.00. Found: C, 71.88; H, 7.06; N, 20.75.

Heck Reaction with Compounds 5; General Procedure (Method D)

To a solution of **5** (0.26 mmol), PPh_3 (8.2 mg, 0.031 mmol, 0.12 equiv) and $Pd(OAc)_2$ (4.7 mg, 0.021 mmol, 0.08 equiv) in anhyd DMF (2 mL), were added successively Et_3N (62 μL, 0.44 mmol, 1.7 equiv) and *tert*-butyl acrylate (190 μL, 1.30 mmol, 5 equiv). The resulting mixture was stirred at 90 °C for 12 h. After cooling, the solvent was evaporated in vacuo. The crude residue was purified by flash chromatography (eluent indicated below) to afford alkenes **6j–l**.

***tert*-Butyl 3-[4-(*N*-Methyl-*N*-phenylamino)pyrazolo[1,5-*a*]-1,3,5-triazin-8-yl]prop-2-enoate (6j)**

Chromatography eluent: Et_2O–PE (3:5); yield: 87%; solid; mp 152–153 °C (EtOAc–PE).

IR (KBr): 1700, 1635, 1595, 1555, 1485 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 9 H, 3 CH_3), 3.81 (s, 3 H, CH_3), 6.55 (d, *J* = 15.9 Hz, 1 H, CH=), 7.19–7.22 (m, 2 H, ArH), 7.38–7.45 (m, 3 H, ArH), 7.66 (d, *J* = 15.9 Hz, 1 H, CH=), 7.88 (s, 1 H, H-7), 8.31 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3 (3 CH_3), 42.6 (CH_3), 80.1 (C), 106.0 (C), 118.9 (CH), 126.3 (2 CH), 127.7 (CH), 129.3 (2 CH), 132.0 (CH), 144.4 (CH + C), 149.3 (C), 150.0 (C), 154.0 (CH), 166.9 (C=O).

MS (ESI): *m*/*z* = 352 $(M + H)^+$.

Anal. Calcd for $C_{19}H_{21}N_5O_2$: C, 64.94; H, 6.02; N, 19.93. Found: C, 65.23; H, 5.98; N, 20.12.

***tert*-Butyl 3-[4-(*N*-Methyl-*N*-phenylamino)-2-methylsulfanylpyrazolo[1,5-*a*]-1,3,5-triazin-8-yl]prop-2-enoate (6k)**

Chromatography eluent: Et_2O–PE (1:9, then 1:4); yield: 68%; solid; mp 192–193 °C (MeOH).

IR (KBr): 1695, 1625, 1595 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 9 H, 3 CH_3), 2.59 (s, 3 H, CH_3), 3.71 (s, 3 H, CH_3), 6.48 (d, *J* = 16.0 Hz, 1 H, CH=), 7.15–7.19 (m, 2 H, ArH), 7.34–7.42 (m, 3 H, ArH), 7.63 (d, *J* = 16.0 Hz, 1 H, CH=), 7.74 (s, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 28.4 (3 CH_3), 42.4 (CH_3), 80.0 (C), 104.1 (C), 117.7 (CH), 126.3 (2 CH), 127.6 (CH), 129.2 (2 CH), 132.6 (CH), 144.4 (C), 144.5 (CH), 148.1 (C), 149.6 (C), 167.2 (C), 169.2 (C=O).

MS (ESI): *m*/*z* = 398 $(M + H)^+$.

Anal. Calcd for $C_{20}H_{23}N_5O_2S$: C, 60.43; H, 5.83; N, 17.62. Found: C, 60.65; H, 5.91; N, 17.49.

***tert*-Butyl 3-[4-(*N*-Methyl-*N*-phenylamino)-2-propylpyrazolo[1,5-*a*]-1,3,5-triazin-8-yl]prop-2-enoate (6l)**

Chromatography eluent: Et_2O–PE (1:4); yield: 78%; solid, mp 149–150 °C (MeOH).

IR (KBr): 1695, 1635, 1550, 1415 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.52 (s, 9 H, 3 CH_3), 1.82–1.93 (m, 2 H, CH_2), 2.80 (t, *J* = 7.3 Hz, 2 H, CH_2), 3.73 (s, 3 H, CH_3), 6.52 (d, *J* = 15.8 Hz, 1 H, CH=), 7.15–7.20 (m, 2 H, ArH), 7.34–7.42 (m, 3 H, ArH), 7.67 (d, *J* = 15.9 Hz, 1 H, CH=), 7.80 (s, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 21.2 (CH_2), 28.4 (3 CH_3), 41.0 (CH_2), 42.2 (CH_3), 80.0 (C), 104.9 (C), 117.9 (CH), 126.2 (2 CH), 127.3 (CH), 129.1 (2 CH), 132.7 (CH), 144.5 (CH), 144.7 (C), 149.3 (C), 150.0 (C), 167.2 (C), 167.7 (C=O).

MS (ESI): *m*/*z* = 394 $(M + H)^+$.

Anal. Calcd for $C_{22}H_{27}N_5O_2$: C, 67.15; H, 6.92; N, 17.80. Found: C, 66.80; H, 6.81; N, 17.60.

***tert*-Butyl 3-[4-(*N*-Methyl-*N*-phenylamino)pyrazolo[1,5-*a*]-1,3,5-triazin-8-yl]propanoate (7)**

A suspension of **6j** (1.50 g, 4.27 mmol) and 10% Pd/C (500 mg) in THF–EtOAc (30 mL, 1:1) was stirred in a stainless steel reactor under 10 bar of H_2 for 6 h at r.t. The catalyst was removed by filtration over Celite and the filtrate was concentrated in vacuo. The crude solid was recrystallized from EtOH to give **7** (1.43 g, 95%); solid; mp 84–85 °C (EtOH).

IR (KBr): 1695, 1635, 1555, 1485 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, CH_3), 2.57 (t, *J* = 7.5 Hz, 2 H, CH_2), 2.97 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.81 (s, 3 H, CH_3), 7.17–7.20 (m, 2 H, ArH), 7.32–7.43 (m, 3 H, ArH), 7.68 (s, 1 H, H-7), 8.19 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4 (CH_2), 28.2 (3 CH_3), 35.9 (CH_2), 42.3 (CH_3), 80.3 (C), 107.9 (C), 126.1 (2 CH), 127.3 (CH), 129.2 (2 CH), 144.7 (C), 144.8 (CH), 147.9 (C), 150.1 (C), 151.6 (CH), 172.2 (C=O).

MS (ESI): *m*/*z* = 354 $(M + H)^+$.

Anal. Calcd for $C_{19}H_{23}N_5O_2$: C, 64.57; H, 6.56; N, 19.82. Found: C, 64.92; H, 6.68; N, 20.00.

3-[4-(*N*-Methyl-*N*-phenylamino)pyrazolo[1,5-*a*]-1,3,5-triazin-8-yl]propionic Acid (8)

A solution of **7** (1.00 g, 2.83 mmol) in TFA–anhyd toluene (22 mL, 1:10) was stirred for 4 h at r.t. The solvent was evaporated in vacuo. The crude residue was purified by flash chromatography (EtOAc) to give **8** (732 mg, 87%); solid; mp 161–163 °C (MeOH).

^1H NMR (300 MHz, DMSO-d_6): δ = 2.56 (t, *J* = 7.5 Hz, 2 H, CH_2), 2.81 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.72 (s, 3 H, CH_3), 7.27–7.41 (m, 5 H, ArH), 7.82 (s, 1 H, H-7), 8.16 (s, 1 H, H-2), 12.13 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 17.9 (CH_2), 33.9 (CH_2), 41.9 (CH_3), 107.1 (C), 126.2 (2 CH), 126.8 (CH), 128.8 (2 CH), 144.3 (CH), 144.7 (C), 147.5 (C), 149.5 (C), 151.4 (CH), 173.8 (C=O).

MS (ESI): *m*/*z* = 298 $(M + H)^+$.

Anal. Calcd for $C_{15}H_{15}N_5O_2$: C, 60.60; H, 5.09; N, 23.55. Found: C, 60.45; H, 4.93; N, 23.56.

Coupling Reaction of 8, General Procedure

To a solution of the appropriate amine (11 mmol, 1.1 equiv, Table 3) in anhyd CH_2Cl_2 (100 mL), were successively added at

0 °C, a catalytic amount of DMAP, **8** (2.87 g, 10 mmol) and EDCI (2.10 g, 11 mmol, 1.1 equiv). The mixture was stirred for 24 h at r.t. and the solvent was evaporated. The residue was taken up in EtOAc (50 mL) and 10% HCl (20 mL), and stirred for 10 min. The two phases were separated, the aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic layers were successively washed with 1 M NaOH (25 mL) and brine (25 mL). After drying ($MgSO_4$), the organic phase was evaporated in vacuo. The crude residue was purified by flash chromatography (eluent indicated below) to give **9**.

N′-(4-Ethoxycarbonylphenyl)-3′-[4-(N-methyl-N-phenylamino)pyrazolo[1,5-*a*]-1,3,5-triazin-8-yl]propionamide (9a)

Amine used: methyl 4-aminobenzoate; chromatography eluent: PE–EtOAc (1:1); yield: 95%; solid; mp 184–186 °C (MeOH).

IR (KBr): 3310, 1715, 1665, 1615, 1530, 1480 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.81 (t, *J* = 7.0 Hz, 2 H, CH_2), 3.12 (t, *J* = 7.0 Hz, 2 H, CH_2), 3.84 (s, 3 H, CH_3), 3.89 (s, 3 H, CH_3), 7.17–7.21 (m, 2 H, ArH), 7.37–7.45 (m, 3 H, ArH), 7.61 (d, *J* = 8.7 Hz, 2 H, ArH), 7.71 (s, 1 H, H-7), 7.97 (d, *J* = 8.7 Hz, 2 H, ArH), 8.22 (s, 1 H, H-2), 8.40 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (CH_2), 37.7 (CH_2), 42.5 (CH_3), 52.1 (CH_3), 107.3 (C), 118.8 (2 CH), 125.3 (C), 126.3 (2 CH), 127.6 (CH), 129.3 (2 CH), 130.8 (2 CH), 142.5 (C), 144.5 (C), 145.2 (CH), 147.6 (C), 150.1 (C), 151.7 (CH), 166.8 (C=O), 171.1 (C=O).

MS (ESI): *m*/*z* = 431 $(M + H)^+$.

Anal. Calcd for $C_{23}H_{22}N_6O_3$: C, 64.17; H, 5.15; N, 19.52. Found: C, 64.33; H, 5.09; N, 19.44.

N′-[3-(2-Oxopyrrolidin-1-yl)propyl]-4-({1-oxo-3-[4-(N-methyl-N-phenylamino)pyrazolo[1,5-*a*]-1,3,5-triazin-8-yl]propyl}amino)propionamide (9b)

Amine used: *N*-(3-aminopropyl)-2-pyrrolidinone; chromatography eluent: CH_2Cl_2–MeOH (98:2); yield: 93%; oil.

IR (film): 3310, 1670, 1615, 1545, 1480 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.58–1.67 (m, 2 H, CH_2), 1.97–2.07 (m, 2 H, CH_2), 2.38 (t, *J* = 7.9 Hz, 2 H,CH_2), 2.54 (t, *J* = 7.9 Hz, 2 H, CH_2), 3.01 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.15 (br q, *J* = 6.3 Hz, 2 H, CH_2), 3.26 (t, *J* = 6.3 Hz, 2 H, CH_2), 3.36 (t, *J* = 7.1 Hz, 2 H, CH_2), 3.79 (s, 3 H, CH_3), 6.73 (br t, *J* = 6.3 Hz, 1 H, NH), 7.16–7.19 (m, 2 H, ArH), 7.30–7.41 (m, 3 H, ArH), 7.67 (s, 1 H, H-7), 8.16 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7 (CH_2), 18.8 (CH_2), 26.4 (CH_2), 30.7 (CH_2), 35.6 (CH_2), 36.7 (CH_2), 39.4 (CH_2), 42.1 (CH_3), 47.1 (CH_2), 107.7 (C), 126.0 (2 CH), 127.0 (CH), 128.9 (2 CH), 144.5 (C), 144.6 (CH), 147.7 (C), 149.9 (C), 151.4 (CH), 172.1 (C=O), 175.5 (C=O).

MS (ESI): *m*/*z* = 422 $(M + H)^+$.

Anal. Calcd for $C_{22}H_{27}N_7O_2$: C, 62.69; H, 6.46; N, 23.26. Found: C, 62.90; H, 6.58; N, 23.35.

N-[2-(2,2-Diphenyl-1,3-benzodioxol-5-yl)ethyl]-3-[4-(N-methyl-N-phenylamino)pyrazolo[1,5-*a*]-1,3,5-triazin-8-yl]propionamide (9c)

Amine used: 2,2-diphenyl-1,3-benzodioxole-5-propanamine; chromatography eluent: PE–EtOAc (8:2); yield: 95%; oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.49 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.63 (t, *J* = 6.9 Hz, 2 H, CH_2), 2.99 (t, *J* = 7.3 Hz, 2 H, CH_2), 3.40 (br q, *J* = 6.8 Hz, 2 H, CH_2), 3.80 (s, 3 H, CH_3), 6.53 (dd, *J* = 1.5, 7.9 Hz, 1 H, ArH), 6.66 (d, *J* = 1.5 Hz, 1 H, ArH), 6.76 (d, *J* = 7.9 Hz, 1 H, ArH), 7.16–7.19 (m, 2 H, ArH), 7.34–7.42 (m, 9 H, ArH), 7.55–7.58 (m, 4 H, ArH), 7.67 (s, 1 H, H-7), 8.14 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8 (CH_2), 35.4 (CH_2), 36.6 (CH_2), 40.8 (CH_2), 42.2 (CH_3), 107.6 (C), 108.3 (CH), 109.0 (CH), 116.6 (C), 121.5 (CH), 126.1 (2 CH), 126.2 (4 CH), 127.2 (CH), 128.2 (4 CH), 129.0 (2 CH), 129.1 (2 CH), 132.7 (C), 140.3 (2 C), 144.5 (C), 144.9 (CH), 145.7 (C), 147.3 (C), 147.8 (C), 149.9 (C), 151.5 (CH), 172.0 (C=O).

MS (ESI): *m*/*z* = 597 $(M + H)^+$.

Anal. Calcd for $C_{36}H_{32}N_6O_3$: C, 72.47; H, 5.41; N, 14.08. Found: C, 72.40; H, 5.33; N, 13.97.

Sodium 4-{[3-(1,4-Dihydro-4-oxopyrazolo[1,5-*a*]-1,3,5-triazin-8-yl)-1-oxopropyl]amino}benzoate (2a)

To a solution of **9a** (120 mg, 0.28 mmol) in EtOH (10 mL) was added a 5 N aq solution of NaOH (0.28 mL) at 0 °C. The mixture was stirred at 60 °C for 5 h. After cooling, the precipitate obtained was filtered and washed with cold EtOH to afford **2a** (80 mg, 82%); solid; mp >210 °C (MeOH).

IR (KBr): 3460, 1670, 1605, 1530, 1470 cm^{-1}.

NMR (300 MHz, D_2O): δ = 2.70 (t, *J* = 7.0 Hz, 2 H, CH_2), 3.01 (t, *J* = 7.0 Hz, 2 H, CH_2), 7.31 (d, *J* = 8.5 Hz, 2 H, ArH), 7.79 (d, *J* = 8.5 Hz, 2 H, ArH), 7.84 (s, 1 H, H-7), 7.88 (s, 1 H, H-2).

^{13}C NMR (75 MHz, D_2O): δ = 19.4 (CH_2), 37.9 (CH_2), 107.3 (C), 121.3 (2 CH), 130.4 (2 CH), 133.3 (C), 139.9 (C), 144.5 (CH), 148.3 (C), 155.0 (C), 156.0 (CH), 175.1 (C=O), 175.6 (C=O).

MS (ESI): *m*/*z* = 328 $(M + H)^+$.

HRMS (LSIMS): *m*/*z* $(M + H)^+$ calcd for $C_{15}H_{14}N_5O_4$: 328.1046; found: 328.1044.

N-[3-(2-Oxo-1-pyrrolidinyl)propyl]-4-{[1-oxo-3-(4-oxopyrazolo[1,5-*a*]-1,3,5-triazin-8-yl)propyl]amino}propionamide (2b)

To a solution of **9b** (120 mg, 0.28 mmol) in EtOH (10 mL) was added a 5 N aq solution of NaOH (0.28 mL) at 0 °C. The mixture was stirred for 5 h at r.t. The solvent was evaporated in vacuo and the residue was partitioned between CH_2Cl_2 (10 mL) and 10% HCl (until pH 7–8). The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The crude residue was purified by flash chromatography (eluent: CH_2Cl_2–MeOH, 85:15) to afford **2b** (62 mg, 66%); solid; mp 180–181 °C (MeOH).

IR (KBr): 3265, 1760, 1725, 1655, 1620, 1560, 1460 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6 + D_2O): δ = 1.44–1.53 (m, 2 H, CH_2), 1.82–1.92 (m, 2 H, CH_2), 2.20 (t, *J* = 8.0 Hz, 2 H, CH_2), 2.38 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.77 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.95 (t, *J* = 7.1 Hz, 2 H, CH_2), 3.04 (t, *J* = 7.1 Hz, 2 H, CH_2), 3.26 (t, *J* = 7.1 Hz, 2 H, CH_2), 7.88 (s, 1 H, H-7), 7.89 (s, 1 H, H-2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 17.5 (CH_2), 18.5 (CH_2), 26.9 (CH_2), 30.4 (CH_2), 35.7 (CH_2), 36.2 (CH_2), 39.5 (CH_2), 46.3 (CH_2), 111.3 (C), 145.1 (C), 145.9 (2 CH), 171.1 (2 C=O), 173.8 (C=O).

MS (ESI): *m*/*z* = 333 $(M + H)^+$.

HRMS (LSIMS): *m*/*z* $(M + H)^+$ calcd for $C_{15}H_{21}N_6O_3$: 333.1675; found: 333.1676.

N-[2-(2,2-Diphenyl-1,3-benzodioxol-5-yl)ethyl]-3-(4-oxopyrazolo[1,5-*a*]-1,3,5-triazin-8-yl)propionamide (10)

To a solution of **9c** (175 mg, 0.29 mmol) in EtOH (10 mL) was added a 5 N aq solution of NaOH (0.29 mL) at 0 °C. The mixture was stirred overnight at r.t. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% HCl (until pH 7–8). The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The solid obtained was taken up in Et_2O and filtered to afford **10** (130 mg, 87%); solid; mp 142–143 °C (purified by washing with Et_2O).

^{1}H NMR (300 MHz, CD_3OD + D_2O): δ = 2.44 (t, *J* = 7.3 Hz, 2 H, CH_2), 2.63 (t, *J* = 6.9 Hz, 2 H, CH_2), 2.89 (t, *J* = 7.3 Hz, 2 H, CH_2), 3.31 (t, *J* = 6.9 Hz, 2 H, CH_2), 6.58 (dd, *J* = 1.3, 7.9 Hz, 1 H, ArH), 6.72 (d, *J* = 1.3 Hz, 1 H, ArH), 6.76 (d, *J* = 7.9 Hz, 1 H, ArH), 7.33–7.37 (m, 6 H, ArH), 7.50–7.53 (m, 4 H, ArH), 7.80 (s, 1 H, H-7), 7.90 (s, 1 H, H-2).

MS (ESI): *m*/*z* = 508 $(M + H)^+$.

Anal. Calcd for $C_{29}H_{25}N_5O_4$: C, 68.63; H, 4.96; N, 13.80. Found: C, 68.45; H, 5.05; N, 13.90.

_N_-[2-(3,4-Dihydroxyphenyl)ethyl]3-(4-oxopyrazolo[1,5-*a*]-1,3,5-triazin-8-yl)propionamide (2c)

Compound **10** (130 mg, 0.26 mmol) was placed in a mixture of AcOH–H_2O (10 mL, 4:1). The mixture was heated at reflux for 6 h. Then, EtOAc (15 mL) and a sat aq $NaHCO_3$ solution (until pH 7–8) were added. The organic phase was separated and washed with a sat aq $NaHCO_3$ solution (10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The solid obtained was taken up in Et_2O (2 × 10 mL) and filtered to afford **2c** (70 mg, 79%); solid; mp 236–238 °C (purified by washing Et_2O).

IR (KBr): 3400–2500, 3282, 1770, 1620 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD + D_2O): δ = 2.50 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.57 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.93 (t, *J* = 7.4 Hz, 2 H, CH_2), 3.30 (t, *J* = 7.4 Hz, 2 H, CH_2), 6.45 (dd, *J* = 1.7, 7.9 Hz, 1 H, ArH), 6.60 (d, *J* = 1.7 Hz, 1 H, ArH), 6.65 (d, *J* = 7.9 Hz, 1 H, ArH), 7.85 (s, 1 H, H-7), 7.91 (s, 1 H, H-2).

^{13}C NMR (75 MHz, CD_3OD): δ = 19.9 (CH_2), 35.7 (CH_2), 37.3 (CH_2), 42.1 (CH_2), 112.2 (C), 116.4 (CH), 116.9 (CH), 121.1 (CH), 132.1 (C), 144.5 (C), 146.0 (C), 146.4 (CH), 147.5 (C), 148.0 (CH), 175.1 (2 C=O).

MS (ESI): *m*/*z* = 342 $(M - H)^-$.

HRMS (LSIMS): *m*/*z* $(M - H)^-$ calcd for $C_{16}H_{16}N_5O_4$: 342.1202; found: 342.1208.

References

(1) Senga, K.; O'Brien, D. E.; Scholten, M. B.; Novinson, T.; Miller, J. P.; Robins, R. K. *J. Med. Chem.* **1982**, *25*, 243.

(2) (a) Gilligan, P. J.; Folmer, B. K.; Hartz, R. A.; Koch, S.; Nanda, K. K.; Andreuski, S.; Fitzgerald, L.; Miller, K.; Marshall, W. J. *Bioorg. Med. Chem.* **2003**, *11*, 4093. (b) He, L.; Gilligan, P. J.; Zaczek, R.; Fitzgerald, L. W.; McElroy, J.; Shen, H.-S. L.; Saye, J. A.; Kalin, N. H.; Shelton, S.; Christ, D.; Trainor, G.; Hartig, P. *J. Med. Chem.* **2000**, *43*, 449.

(3) Almansa, C.; de Arriba, A. F.; Cavalcanti, F. L.; Gómez, L. A.; Miralles, A.; Merlos, M.; García-Rafanell, J.; Forn, J. *J. Med. Chem.* **2001**, *44*, 350.

(4) (a) Prevost, G.; Lonchampt, M.-O.; Kim, S.; Morgan, B.; Ulibarri, G.; Thurieau, C. PCT Int. Appl. WO 2002050079, *Chem. Abstr.* **2002**, *137*, 47234. (b) Guzi, T. J.; Paruch, K. US Patent US 2005187219, *Chem. Abstr.* **2005**, *143*, 248417.

(5) Lübbers, T.; Angehrn, P.; Gmünder, H.; Herzig, S.; Kulhanek, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 821.

(6) Subramanyam, C.; Ault, B.; Sawutz, D.; Bacon, E. R.; Singh, B.; Pennock, P. O.; Kelly, M. D.; Kraynak, M.; Krafte, D.; Treasurywala, A. *J. Med. Chem.* **1995**, *38*, 587.

(7) Glasky, A. J.; Glasky, M. S.; Ritzmann, R. F.; Rathbone, M. P. *Exp. Opin. Invest. Drugs* **1997**, *6*, 1413.

(8) Rathbone, M. P.; Middlemiss, P. J.; Crocker, C. E.; Glasky, M. S.; Juurlink, B. H. J.; Ramirez, J. J.; Cicarelli, R.; Di Ioro, P.; Caciagli, F. *Exp. Opin. Invest. Drugs* **1999**, *8*, 1255.

(9) Grundman, M.; Caparelli, E.; Kim, H. T.; Morris, J. C.; Farlow, M.; Rubin, E. H.; Heidebrink, J.; Hake, A.; Ho, G.; Schultz, A. N.; Schafer, K.; Houston, W.; Thomas, R.; Thal, L. J. *Life Sci.* **2003**, *73*, 539.

(10) Holmes, M.; Maysinger, D.; Foerster, D.; Pertens, E.; Barlas, C.; Diamond, J. *Mol. Cell. Neurosci.* **2003**, *24*, 568.

(11) Glasky, A. J. PCT Int. Appl. WO 9957119, *Chem. Abstr.* **1999**, *131*, 322486.

(12) (a) Zhang, H.-C.; Brakta, M.; Daves, G. D. Jr. *Tetrahedron Lett.* **1993**, *34*, 1571. (b) Zhang, H.-C.; Daves, G. D. Jr. *Organometallics* **1993**, *12*, 1499. (c) Zhang, H.-C.; Brakta, M.; Daves, G. D. Jr. *Nucleosides Nucleotides* **1995**, *14*, 105.

(13) Raboisson, P.; Baurand, A.; Cazenave, J.-P.; Gachet, C.; Schultz, D.; Spiess, B.; Bourguignon, J.-J. *J. Org. Chem.* **2002**, *67*, 8063.

(14) (a) Kobe, J.; Robins, R. K.; O'Brien, D. E. *J. Heterocycl. Chem.* **1974**, 199. (b) Tam, S. Y.-K.; Klein, R. S.; Wempen, I.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 4547. (c) Vogel, A.; Troxler, F. *Helv. Chim. Acta* **1975**, *58*, 761.

(15) (a) Raboisson, P.; Schultz, D.; Lugnier, C.; Bourguignon, J.-J. *Tetrahedron Lett.* **2002**, *43*, 9501. (b) Raboisson, P.; Schultz, D.; Lugnier, C.; Mathieu, R.; Bourguignon, J.-J. *Tetrahedron Lett.* **2003**, *44*, 703.

(16) Liu, Y.; Li, K. *Macromol. Rapid Commun.* **2002**, *23*, 739.

(17) Bernard, P.; Raboisson, P.; Joseph, B. PCT Int. Appl. WO 2004011464, *Chem. Abstr.* **2004**, *140*, 146171.