Synthesis of pyrazole and pyrimidine Tröger's-base analogues

Rodrigo Abonia,*[a] Andrea Albornoz,[a] Hector Larrahondo,[a] Jairo Quiroga,[a] Braulio Insuasty,[a] Henry Insuasty,[a] Angelina Hormaza,[b] Adolfo Sánchez[c] and Manuel Nogueras[c]

[a] *Department of Chemistry, Universidad del Valle, A.A. 25360, Cali, Colombia*
[b] *Department of Chemistry, Universidad Nacional, A.A. 3840, Medellín, Colombia*
[c] *Departamento de Quimica Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, Spain*

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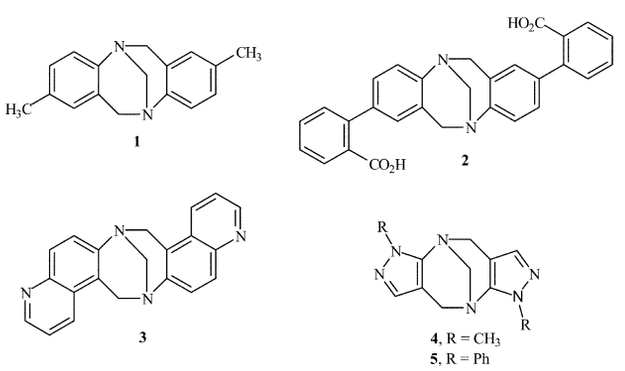
Tröger's-base analogues bearing fused pyrazolic or pyrimidinic rings were prepared in acceptable to good yields through the reaction of 3-alkyl-5-amino-1-arylpyrazoles and 6-aminopyrimidin-4(3*H*)-ones with formaldehyde under mild conditions (*i.e.*, in ethanol at 50 °C in the presence of catalytic amounts of acetic acid). Two key intermediates were isolated from the reaction mixtures, which helped us to suggest a sequence of steps for the formation of the Tröger's bases obtained. The structures of the products were assigned by ^{1}H and ^{13}C NMR, mass spectra and elemental analysis and confirmed by X-ray diffraction for one of the obtained compounds.

Introduction

Although the first Tröger's base **1** was obtained more than a century ago from the reaction of *p*-toluidine and formaldehyde,[1] recently the study of these compounds has gained importance due to their potential applications. They possess a relatively rigid chiral structure which makes them suitable for the development of possible synthetic enzyme and artificial receptor systems,[2] chelating and biomimetic systems,[3] and transition metal complexes for regio- and stereoselective catalytic reactions.[4] For these reasons, numerous Tröger's-base derivatives have been prepared bearing different types of substituents and structures (*i.e.*, **2**–**5** Scheme 1), with the purpose of



Scheme 1 The original Tröger's base **1** and some interesting derivatives and analogues.

increasing their potential applications.[2,3,5] However, some of the above methodologies possess tedious work-up procedures or include relatively strong reaction conditions, such as treatment of the starting materials for several hours with an ethanolic solution of conc. hydrochloric acid or TFA solution, with poor to moderate yields, as is the case for analogues **4** and **5**.[5e]

Considering these potential applications, we now report a simple synthetic method for the preparation of 5,12-dialkyl-3,10-diaryl-1,3,4,8,10,11-hexaazatetracyclo[6.6.1.0^{2,6}.0^{9,13}]-pentadeca-2(6),4,9(13),11-tetraenes **8a**–**e** and 4,12-dimethoxy-1,3,5,9,11,13-hexaazatetracyclo[7.7.1.0^{2,7}.0^{10,15}]heptadeca-2(7),3,10(15),11-tetraene-6,14-diones **10a**,**b** based on the reaction of 3-alkyl-5-amino-1-arylpyrazoles **6** and 6-aminopyrimidin-4(3*H*)-ones **9** with formaldehyde in ethanol and catalytic amounts of acetic acid. Compounds **8** and **10** are new Tröger's-base analogues bearing heterocyclic rings instead of the usual phenyl rings in their aromatic parts.

Results and discussion

In an attempt to prepare the benzotriazolyl derivative **7a**, which could be used as an intermediate in the synthesis of new hydroquinoline analogues of interest,[6] a mixture of 5-amino-3-methyl-1-phenylpyrazole **6a**, formaldehyde and benzotriazole in 10 mL of ethanol, with catalytic amounts of acetic acid, was heated at 50 °C for 5 minutes. A solid precipitated from the solution while it was still hot. However, no consumption of benzotriazole was observed by TLC.

The reaction conditions were modified and the same product was obtained when the reaction was carried out without using benzotriazole, as shown in Chart 1. On the basis of NMR and mass spectra and X-ray crystallographic analysis we established that the structure of this compound is 5,12-dimethyl-3,10-diphenyl-1,3,4,8,10,11-hexaazatetracyclo[6.6.1.0^{2,6}.0^{9,13}]pentadeca-2(6),4,9(13),11-tetraene **8a**, a new pentagonal Tröger's-

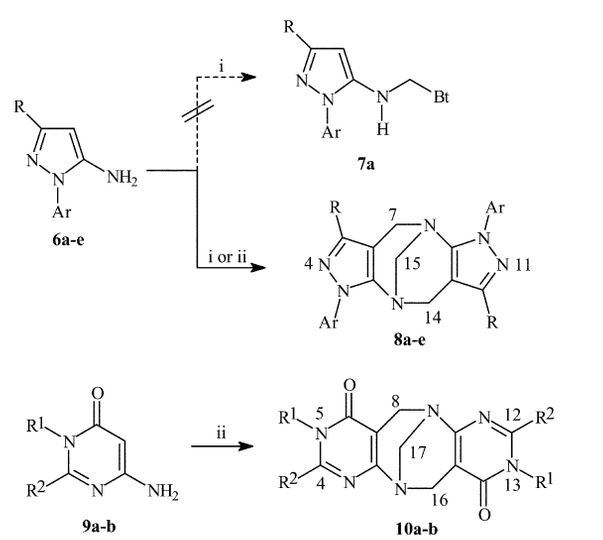


Chart 1 Reaction of 5-aminopyrazoles **6** and 6-aminopyrimidin-4(3*H*)-ones **9** with formaldehyde. *Reagents:* i = CH_2O, BtH, EtOH, HOAc; ii = CH_2O, EtOH, HOAc; BtH = Benzotriazole.

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Table 1 Tröger's-base analogues

Entry	Product	R	Ar	R^1	R^2	Mp/°C (EtOH)	Yield (%)
1	**8a**	CH_3	C_6H_5			278	73
2	**8b**	$C(CH_3)_3$	C_6H_5			211	76
3	**8c**	CH_3	C_6H_4Cl-*p*			364	60
4	**8d**	$C(CH_3)_3$	C_6H_4Cl-*p*			297	65
5	**8e**	$C(CH_3)_3$	$C_6H_4NO_2$-*p*			324	67
6	**10a**			CH_3	OCH_3	248	42
7	**10b**			H	OCH_3	267	50

base analogue.[7] This result prompted us to explore other aminopyrazoles **6b–e** and aminopyrimidinones **9a**,**b**, which have now shown similar chemical reactivity, yielding the corresponding products **8b–e** and **10a**,**b** in acceptable to good yields and in relatively short reaction times, as shown in Table 1 and the Experimental section.

In the preparation of **8e**, a yellow and sparingly soluble precipitate was initially obtained under the above conditions, and which corresponded to the partially cyclized intermediate **11e** (Chart 2). Heating of **11e** for one hour with more formaldehyde

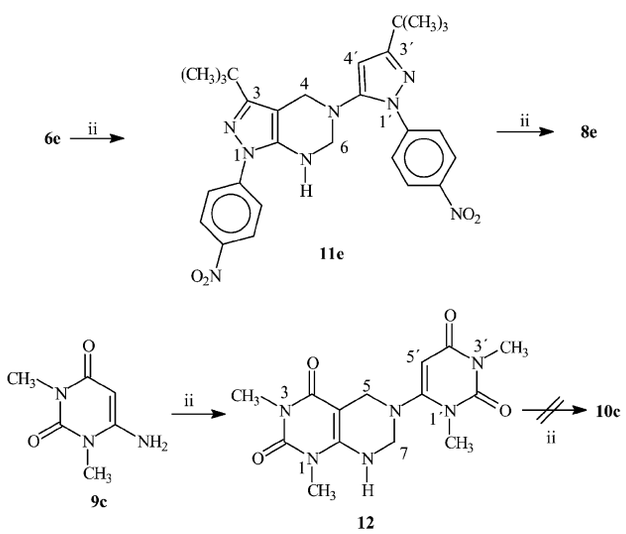
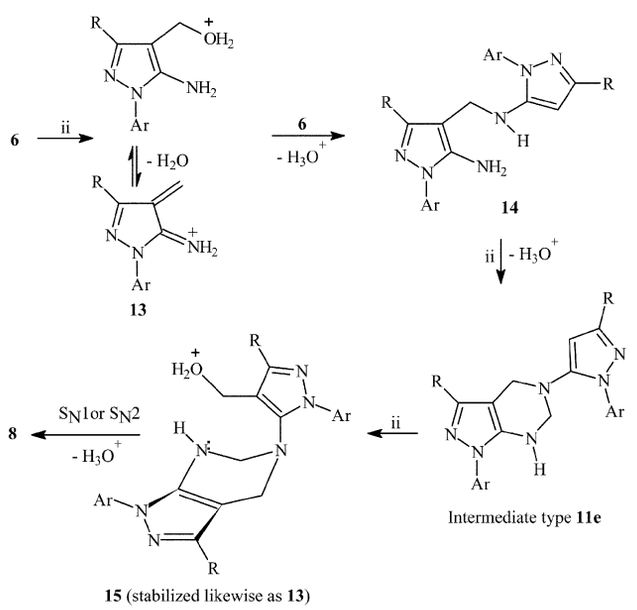


Chart 2 Formation of the intermediates **11e** and **12**.

(1.5 equivalents) in ethanol (≈ 20 mL), until complete dissolution, yielded the expected product **8e** in 70% yield. Compound **8e** was directly obtained in 67% yield, by heating of the starting materials in 20–30 mL of ethanol without precipitation of **11e**. A similar result was obtained from the reaction of the aminopyrimidine **9c** with formaldehyde, but in this case it was impossible to cyclize the intermediate **12** to **10c** under our experimental conditions, due to its poor solubility (Chart 2). Some compounds of type **11**(**12**) have previously been obtained from similar reactions.[8]

All compounds were extensively characterized by ^1H and ^{13}C NMR spectra (including DEPT, COSY and HMBC techniques)[9] and by mass spectra and elemental analysis. All signals in the ^1H NMR spectrum are consistent with the structures proposed for compounds **8** and **10**, where the most relevant feature is the non-equivalence of the geminal protons 7-/14-CH_2 and 8-/16-CH_2 respectively, each showing a geminally coupled doublet with reference to H-*endo* and H-*exo* in the framework. The bridging 15-/17-CH_2 protons appear as singlets, in agreement with what has previously been observed for similar systems.[5] The main feature observed in the ^{13}C NMR spectra to both compounds **8** and **10** is the regular sequence 7-/14-C, 15-C, 6-/13-C, 2-/9-C and 8-/16-C, 17-C, 7-/15-C, 2-/10-C from high field to low field respectively, corresponding to the four carbon atoms of their concavities. The other aliphatic and aromatic carbon atoms were also assigned to both structures. The structures of compounds **11e** and **12** were also supported by the appearance of N–H stretchings at ν = 3295 and ν = 3400, respectively, in the IR spectra and by a singlet at δ = 5.82 in the ^1H NMR spectrum of compound **11e**. This signal corresponds to the free pyrazolic proton, which commonly appears at a higher field than a normal aromatic proton.[10] Mass spectra and elemental analysis were also consistent with structures **11e** and **12**.

According to these results, compounds **8a–e** and **10a**,**b** could be formed through intermediates of type **11** and **12**, respectively, by an intramolecular cyclization from protonated alcohol **15** (in the case of compounds **8**) as shown in Scheme 2.



Scheme 2 General stepwise sequence to formation of compounds **8a–e** and **10a**,**b**.

C-Alkylation as the first step (forming protonated alcohol **13**) is well supported for aminopyrazoles and aminopyrimidines.[11] The presence of a 5 (or 6)-amino group increases the reactivity of position 4 or 5, respectively, toward condensation reactions. Then water is displaced by a second molecule of **6** through intermediate **14** (not isolated) which reacts with another molecule of **6** to afford the isolated intermediate type **11e**. The last step (conversion of **15** to **8**) could occur under an S_N1 or S_N2 reaction. However, it seems more likely that an S_N1 reaction occurred, according to the reaction conditions used. This proposed sequence is also supported by the lack of formation of compound **7a** (Chart 1). In fact, if N-alkylation had been the first step instead of C-alkylation, compound **7a** would have certainly been the only product obtained from this reaction, as is usually the case.[6]

In conclusion, we have adapted milder and more efficient reaction conditions (in comparison with the previous report)[5e] for the synthesis of five new pyrazole and two new pyrimidine Tröger's-base analogues. This methodology could be extended to other starting monoamines for Tröger's bases, and the newly

obtained compounds offer further possibilities for potential applications, considering that only a few examples of Tröger's bases bearing heterocyclic rings instead of the usual phenyl group in their aromatic part have previously been reported.[5e] Also, we have reported the isolation of two key intermediates from the reaction mixtures (*i.e.*, compounds **11e** and **12**), which helped us to suggest a sequence of steps for the formation of the Tröger's bases obtained. Similar findings previously reported support this proposal.[8] Finally, owing to the high content of nitrogen atoms in compounds **8**–**10**, we are planning to try some of them as possible mono- or bidentate ligands in the synthesis of interesting transition metal clusters of some of the group eight metals (*i.e.*, Fe, Ru and Os), as recently has been reported for other homo- and heterocyclic organic molecules.[12]

Experimental

General methods

All melting points were determined on a Büchi melting-point apparatus and are uncorrected. NMR spectra were recorded on a Bruker DPX 300 (300 MHz and 75.5 MHz, for ^{1}H and ^{13}C, respectively), $CDCl_3$ and DMSO-d_6 (δ_H = 2.5; δ_C = 39.5) as solvents, TMS as internal standard. IR spectra were recorded on an ATI-MATTSON FT spectrophotometer for samples in KBr discs. Mass spectra were run on a Hewlett Packard 5989-B spectrometer (EI, 70 eV). Microanalyses were performed with a LECO CHNS-900 elemental analyzer. The starting aminopyrazoles **6** were prepared from 3-aminocrotononitrile and the appropriate phenylhydrazine following a general procedure described in ref. 13. For *tert*-butyl derivatives 4,4-dimethyl-3-oxopentanonitrile was used instead of the 3-aminocrotononitrile. Aminopyrimidines **9a**–**c** were prepared following the procedure described in ref. 14.

General procedure for preparing the compounds 8a–e and 10a,b

A solution of a 5-amino-3-alkyl-1-arylpyrazole **6** (2.89 mmol), formaldehyde (10.0 mmol; 37% solution) and acetic acid (0.2–0.5 mL) in 10–30 mL of ethanol was heated to 50 °C for 30–90 minutes and monitored by TLC. After cooling, the precipitate was filtered off, and recrystallized from ethanol or alternatively purified by column chromatography on silica gel with chloroform as eluent. The same procedure was followed for compounds **10a**,**b** by using 50 mL of ethanol and heating the mixtures for two hours.

5,12-Dimethyl-3,10-diphenyl-1,3,4,8,10,11-hexaazatetracyclo-[6.6.1.0^{2,6}.0^{9,13}]pentadeca-2(6),4,9(13),11-tetraene 8a. White solid (Found: C, 72.1; H, 5.9; N, 22.1. $C_{23}H_{22}N_6$ requires C, 72.2; H, 5.8; N, 22.0%); ν_{max}(disc)/cm^{-1} 1593br and 1498br; δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.92 (6 H, s, 5-/12-Me), 3.56 (2 H, d, J_{gem} 15.7, 7-/14-H$_{endo}$), 4.26 (2 H, d, J_{gem} 15.7, 7-/14-H$_{exo}$), 4.31 (2 H, s, 15-H$_2$), 7.29 (2 H, t, J 7.4, Ph–H$_{para}$), 7.50 (4 H, br t, J 7.9, Ph–H$_{meta}$) and 7.96 (4 H, d, J 8.7, Ph–H$_{ortho}$); δ_C(75 MHz; DMSO-d_6; Me_4Si) 12.1 (5-/12-Me), 47.4 (7-/14-C), 67.5 (15-C), 104.3 (6-/13-C), 119.7 (Ph–C$_{meta}$), 125.5 (Ph–C$_{para}$), 129.3 (Ph–C$_{ortho}$), 139.2 (Ph–C$_{ipso}$), 144.7 (2-/9-C) and 144.9 (5-/12-C); *m*/*z* (EI) 382 (M$^+$, 100%), 354 (23), 198 (53), 77 (30).

5,12-Di-(*tert*-butyl)-3,10-diphenyl-1,3,4,8,10,11-hexaaza-tetracyclo[6.6.1.0^{2,6}.0^{9,13}]pentadeca-2(6),4,9(13),11-tetraene 8b. White solid (Found: C, 74.7; H, 7.25; N, 18.15. $C_{29}H_{34}N_6$ requires C, 74.65; H, 7.3; N, 18.0%); ν_{max}(disc)/cm^{-1} 1598br and 1500br; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.15 (18 H, s, 5-/12-Bu^t), 3.82 (2 H, d, J_{gem} 15.6, 7-/14-H$_{endo}$), 4.23 (2 H, s, 15-H$_2$), 4.25 (2 H, d, J_{gem} 15.6, 7-/14-H$_{exo}$), 7.24 (2 H, t, J 7.3, Ph–H$_{para}$), 7.43 (4 H, t, J 7.5, Ph–H$_{meta}$) and 7.95 (4 H, d, J 8.3, Ph–H$_{ortho}$); δ_C(75 MHz; $CDCl_3$; Me_4Si) 29.4 (5-/12-Bu^t- × 6C), 33.2 (5-/12-Bu^t- × 2C), 49.6 (7-/14-C), 68.1 (15-C), 102.4 (6-/13-C), 121.3 (Ph–C$_{meta}$), 125.8 (Ph–C$_{para}$), 129.1 (Ph–C$_{ortho}$), 139.8 (Ph–C$_{ipso}$), 145.3 (2-/9-C) and 157.0 (5-/12-C); *m*/*z* (EI) 466 (M$^+$, 100%), 438 (18), 240 (60), 77 (26).

3,10-Bis-(*p*-chlorophenyl)-5,12-dimethyl-1,3,4,8,10,11-hexa-azatetracyclo[6.6.1.0^{2,6}.0^{9,13}]pentadeca-2(6),4,9(13),11-tetraene 8c. Pale yellow solid (Found: C, 61.1; H, 4.55; N, 18.7. $C_{23}H_{20}Cl_2N_6$ requires C, 61.2; H, 4.5; N, 18.6%); ν_{max}(disc)/cm^{-1} 1602br and 1493br; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.02 (6 H, s, 5-/12-Me), 3.58 (2 H, d, J_{gem} 15.6, 7-/14-H$_{endo}$), 4.14 (2 H, d, J_{gem} 16.1, 7-/14-H$_{exo}$), 4.21 (2 H, s, 15-H$_2$), 7.39 (4 H, d, J 8.3, Ar–H$_{meta}$) and 7.92 (4 H, d, J 8.3, Ar–H$_{ortho}$); δ_C(75 MHz; $CDCl_3$; Me_4Si) 13.3 (5-/12-Me), 49.2 (7-/14-C), 69.5 (15-C), 105.6 (6-/13-C), 123.2 (Ar–C$_{meta}$), 130.8 (Ar–C$_{ortho}$), 132.6 (Ar–C$_{para}$), 139.4 (Ar–C$_{ipso}$), 146.4 (2-/9-C) and 147.3 (5-/12-C); *m*/*z* (EI) 454/452/450 (M$^+$, Cl$_2$ pattern, 100%), 422 (31), 232 (48), 111 (17).

5,12-Di-(*tert*-butyl)-3,10-bis-(*p*-chlorophenyl)-1,3,4,8,10,11-hexaazatetracyclo[6.6.1.0^{2,6}.0^{9,13}]pentadeca-2(6),4,9(13),11-tetraene 8d. Light pink solid (Found: C, 65.15; H, 5.9; N, 13.2. $C_{29}H_{32}Cl_2N_6$ requires C, 65.0; H, 6.0; N, 13.2%); ν_{max}(disc)/cm^{-1} 1590br and 1502br; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.15 (18 H, s, 5-/12-Bu^t), 3.78 (2 H, d, J_{gem} 16.1, 7-/14-H$_{endo}$), 4.20 (2 H, s, 15-H$_2$), 4.26 (2 H, d, J_{gem} 15.6, 7-/14-H$_{exo}$), 7.38 (4 H, d, J 8.8, Ar–H$_{meta}$) and 7.93 (4 H, d, J 8.8, Ar–H$_{ortho}$); δ_C(75 MHz; $CDCl_3$; Me_4Si) 29.3 (5-/12-Bu^t- × 6C), 33.3 (5-/12-Bu^t- × 2C), 49.6 (7-/14-C), 69.9 (15-C), 102.6 (6-/13-C), 122.0 (Ar–C$_{meta}$), 129.3 (Ar–C$_{ortho}$), 131.1 (Ar–C$_{para}$), 133.3 (Ar–C$_{ipso}$), 145.3 (2-/9-C) and 157.4 (5-/12-C); *m*/*z* (EI) 538/536/534 (M$^+$, Cl$_2$ pattern, 100%), 506 (28), 274 (45), 111 (18).

5,12-Di-(*tert*-butyl)-3,10-bis-(*p*-nitrophenyl)-1,3,4,8,10,11-hexaazatetracyclo[6.6.1.0^{2,6}.0^{9,13}]pentadeca-2(6),4,9(13),11-tetraene 8e. Pale yellow solid (Found: C, 62.7; H, 5.8; N, 20.0. $C_{29}H_{32}N_8O_4$ requires C, 62.6; H, 5.8; N, 20.1%); ν_{max}(disc)/cm^{-1} 1604br, 1511 and 1308br (NO_2); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.20 (18 H, s, 5-/12-Bu^t-), 3.86 (2 H, d, J_{gem} 15.3, 7-/14-H$_{endo}$), 4.31 (2 H, s, 15-H$_2$), 4.45 (2 H, d, J_{gem} 16.0, 7-/14-H$_{exo}$) and 8.35 (8 H, br s, Ar–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) 30.6 (5-/12-Bu^t- × 6C), 34.9 (5-/12-Bu^t- × 2C), 51.2 (7-/14-C), 69.2 (15-C), 105.4 (6-/13-C), 120.9 (Ar–C$_{meta}$), 126.8 (Ar–C$_{ortho}$), 146.1 (Ar–C$_{ipso}$), 146.3 (Ar–C$_{para}$), 147.8 (2-/9-C) and 160.6 (5-/12-C); *m*/*z* (EI) 556 (M$^+$, 100%), 528 (28), 285 (45), 122 (12).

4,12-Dimethoxy-5,13-dimethyl-1,3,5,9,11,13-hexaazatetra-cyclo[7.7.1.0^{2,7}.0^{10,15}]heptadeca-2(7),3,10(15),11-tetraene-6,14-dione 10a. Pale yellow solid (Found: C, 52.1; H, 5.2; N, 24.2. $C_{15}H_{18}N_6O_4$ requires C, 52.0; H, 5.2; N, 24.3%); ν_{max}(disc)/cm^{-1} 1668br (C=O) and 1213 (OMe); δ_H(300 MHz; DMSO-d_6; Me_4Si) 3.25 (6 H, s, 5-/13-Me), 3.47 (2 H, d, J_{gem} 15.5, 8-/16-H$_{endo}$), 3.90 (2 H, s, 17-H$_2$), 3.93 (6 H, s, 4-/12-OMe) and 4.82 (2 H, d, J_{gem} 15.7, 8-/16-H$_{exo}$); δ_C(75 MHz; DMSO-d_6; Me_4Si) 27.2 (5-/13-Me), 55.3 (4-/12-OMe), 62.4 (8-/16-C), 71.0 (17-C), 91.1 (7-/15-C), 154.5 (2-/10-C), 158.3 (4-/12-C) and 163.9 (6-/14-C=O); *m*/*z* (EI) 346 (M$^+$, 1.5%), 334 (34), 322 (100), 157 (2).

4,12-Dimethoxy-1,3,5,9,11,13-hexaazatetracyclo-[7.7.1.0^{2,7}.0^{10,15}]heptadeca-2(7),3,10(15),11-tetraene-6,14-dione 10b. Pale yellow solid (Found: C, 49.0; H, 4.5; N, 26.4. $C_{13}H_{14}N_6O_4$ requires C, 49.1; H, 4.4; N, 26.4%); ν_{max}(disc)/cm^{-1} 3418 (NH), 1658br (C=O) and 1215 (OMe); δ_H(300 MHz; DMSO-d_6; Me_4Si) 3.20 (2 H, d, J_{gem} 15.7, 8-/16-H$_{endo}$), 3.74 (6 H, s, 4-/12-OMe), 3.82 (2 H, d, J_{gem} 15.7, 8-/16-H$_{exo}$), 4.78 (2 H, s, 17-H$_2$), and 11.6 (2 H, br s, 5-/13-H); δ_C(75 MHz; DMSO-d_6; Me_4Si) 54.2 (4-/12-OMe), 64.1 (8-/16-C), 69.0 (17-C), 89.5 (7-/15-C), 155.5 (2-/10-C), 161.8 (4-/12-C) and 164.6 (6-/14-C=O); *m*/*z* (EI) 318 (M$^+$, 1.0%), 308 (18), 294 (100), 280 (12).

3-*Tert*-butyl-5-[3-*tert*-butyl-1-(4-nitrophenyl)-1*H*-pyrazol-5-yl]-1-(4-nitrophenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*d*]-pyrimidine 11e. Yellow solid (0.51 g, 65%); mp 216 °C (from EtOH) (Found: C, 61.9; H, 5.8; N, 20.5. $C_{28}H_{32}N_8O_4$ requires C, 61.75; H, 5.9; N, 20.6%); ν_{max}(disc)/cm^{-1} 3295 (NH), 1509 and 1305 (NO_2); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.26 (9 H, s, 3- or 3′-Bu^t-), 1.32 (9 H, s, 3′- or 3-Bu^t-), 3.90 (1 H, t, *J* 6.8, 7-NH), 4.19 (2 H, d, *J* 6.8, 6-H_2), 4.34 (2 H, s, 4-H_2) 5.82 (1-H, s, 4′-H), 8.00 (2 H, d, *J* 8.8, Ar–H), 8.13 (2 H, d, *J* 9.3, Ar–H), 8.22 (2 H, d, *J* 9.3, Ar–H) and 8.27 (2 H, d, *J* 9.3, Ar–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) 29.1, 30.0, 32.6, 33.5, 48.8 (4-C), 62.8 (6-C), 95.9 (4′-C), 101.0 (4a-C), 119.9, 121.7, 124.8, 125.0, 142.2, 144.6, 144.9, 145.2, 149.2, 159.0 and 163.6.

6-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl)]-1,3-dimethyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione 12. White solid (0.23 g, 48%); mp 347 °C (Found: C, 50.4; H, 5.5; N, 25.1. $C_{14}H_{18}N_6O_4$ requires C, 50.3; H, 5.4; N, 25.1%); ν_{max}(disc)/cm^{-1} 3400 (NH) 1665br (C=O) and 1624br (C=O); *m*/*z* (EI) 334 (M^+, 1.7%), 322 (100), 294 (100), 156 (25).

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