PERKIN 1

Novel heterocycles containing the pyrazole unit

Jan Světlík *[a] and Tibor Liptaj[b]

[a] *Department of Pharmaceutical Analysis and Nuclear Pharmacy, Faculty of Pharmacy, Comenius University, Odbojarov 10, SK-832 32 Bratislava, Slovak Republic. E-mail: svetlik@fpharm.uniba.sk*

[b] *NMR Laboratory, Slovak Technical University, Radlinskeho 9, SK-812 37 Bratislava, Slovak Republic*

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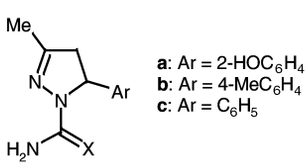
New condensed pyrazolo[1,5-*e*][1,3,5]benzoxadiazocine and bridged 5,11-methano-[1,2,4]triazolo[1,2-*c*]-[1,3,4]benzoxadiazepine heterocyclic ring systems were prepared by cyclizations of 4,5-dihydro-3-methyl-5-(2-hydroxyphenyl)-1*H*-pyrazole-1-carboximidamide with C_1 reagents (triethylorthoformate and 1,1′-carbonyldiimidazole). In contrast, cyclocondensations with C_2 and C_3 reactants occur exclusively at the amidine moiety yielding substituted pyrano[2,3-*d*]pyrimidine, pyrimidine, and imidazole derivatives.

Introduction

In a previous paper[1] we reported an unprecedented ring closure reaction of α,β-unsaturated ketones with aminoguanidine leading to 5-aryl-4,5-dihydro-3-methyl-1*H*-pyrazole-1-carboximidamides **1** and the corresponding carboxamides **2**. Because of our research interests in the chemistry of oxygen-bridged heterocycles, we focused particularly on cyclisations of derivative **1a**. Apparently, the presence of the phenolic hydroxy in pyrazole **1a** lends this compound another reactive centre that could be subsequently coupled to an adjacent carboximidamide moiety by a suitable linker. The aim of the present work is to investigate cyclization reactions of compound **1a** with C_1–C_3 reagents in an effort to explore the synthetic potential for the preparation of fused heterocycles containing the pyrazole ring. Such compounds are of interest because of their inhibiting activity towards nitric oxide synthase, a significant pharmacological aspect addressed also in our previous work.[1]

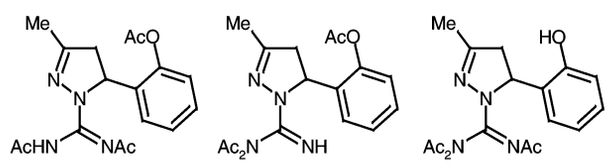


a: Ar = 2-HOC$_6$H$_4$
b: Ar = 4-MeC$_6$H$_4$
c: Ar = C$_6$H$_5$

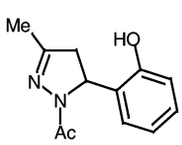
1a-c; X=NH **2b,c**; X=O

Results and discussion

We first attempted to connect both functionalities by using acetic anhydride. However, refluxing amidine **1a** in an excess of acetic anhydride led to a rapid decomposition. When the reaction was carried out at room temperature, the reactant suspension became clear in 6 h and after 1 day we isolated two products. Upon work-up of the reaction mixture, compound **3** (mp 148–150 °C) crystallized from ethyl acetate solution whereas **4** (mp 176–177 °C) was isolated by column chromatography of the mother liquor. The elemental composition of the lower-melting product indicated that a triacetyl derivative of **1a** was produced. Of the three possible isomers, **3a**, **3b** and **3c**, the acetylation product was identified as **3a** by NMR spectra which revealed three distinct ^{1}H and ^{13}C acetyl resonances.



3a **3b** **3c**



4

The molecular formula of the higher-melting product **4**, $C_{12}H_{14}N_2O_2$, showed a loss of a [CH_3N_2] moiety and addition of one acetyl group to the starting pyrazole **1a**, $C_{11}H_{14}N_4O$. The presence of the original heterocyclic skeleton with both substituents in the 3 and 5 positions was proved by NMR spectroscopy. The loss of the afore-mentioned atoms suggested that an amidine group was eliminated from the starting pyrazoline **1a**. This led to the structure of 1,3,5-trisubstituted pyrazole for **4**, which was unambiguously confirmed by independent synthesis from 4-(2-hydroxyphenyl)but-3-en-2-one and hydrazine in refluxing acetic acid adopting a literature method[2] for similar acetylated pyrazoles.

Of particular interest was the reaction of hydroxyphenylpyrazole **1a** with triethyl orthoformate which is a widely used single-carbon cyclizing reagent. Cyclocondensation was accomplished in refluxing orthoformate for 1 h. In another procedure we employed DMF in which the starting material is relatively soluble, but the purity and yield of the obtained product **5a** decreased in this solvent. Besides signals arising from the parent molecule the ^{1}H NMR spectrum of **5a** exhibited an additional sharp low-field singlet (δ_H 9.71) indicating an N–CH=N or O–CH=N moiety. The corresponding tertiary sp^2 carbon was identified in the ^{13}C NMR spectrum (APT technique) at δ_C 165.7. Selective INEPT measurements revealed a long range correlation between the above proton and the quaternary

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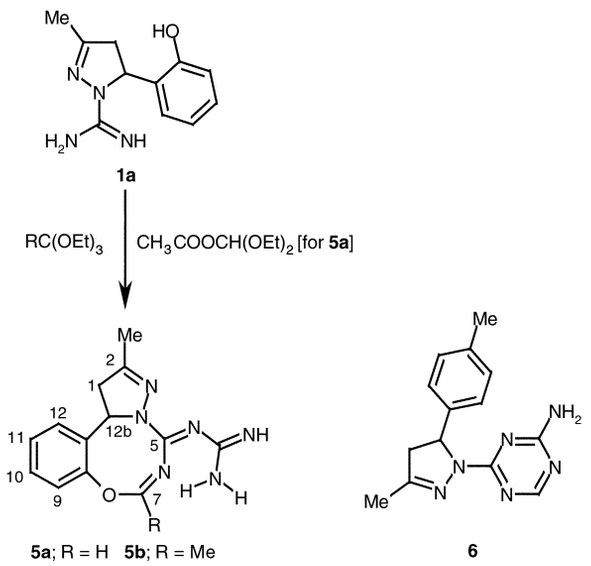
aromatic carbon bearing the oxygen atom. Hence, a =CH–O–C_{ar} connectivity is established which implies a cyclisation mode involving both the phenolic oxygen and a nitrogen atom ("O–N" mode) in the formation of **5a**. Nevertheless, to be consistent with the results from elemental analysis and HR MS, a CN_2H_2 fragment must be added to the expected tricyclic skeleton formed by the condensation. Attachment of the C_1 unit at the exocyclic imine seems logically to lead to guanidine derivative **5a** (Scheme 1). These findings are consistent with the low-field



Scheme 1

quaternary ^{13}C signal whose chemical shift value, δ_C 166.3, closely resembles the published data for amidinohydrazones[3] and substituted guanidines.[4] Furthermore, the spectral pattern of exchangeable amine protons of the =N–C(=NH)NH_2 appendage pointed to the presence of three distinct NH signals that indicated a chemical non-equivalence of primary amine hydrogens; this could be attributed to an intramolecular hydrogen bonding. Accordingly, the terminal NH_2 group may be oriented so as to interact with the near N-6 ring atom whereby an *E* configuration at the exocyclic C=N double bond is expected (see **5**). In this context we deduced that of the three observed NH resonances the relatively narrow, lowest-field peak (δ_H 7.96) corresponds to the signal of the H-bridge proton.

The results of the cyclocondensation studied were further verified by a reaction of **1a** with diethoxymethyl acetate which proves to be a reactive formate equivalent.[5] Under milder conditions (10 min, 80 °C, DMF) compound **5a** was produced but in a low yield (Scheme 1). Moreover, a 7-methyl homologue (**5b**) was prepared similarly from triethyl orthoacetate (Scheme 1). Finally, 1,12b-dihydro-5*H*-pyrazolo[1,5-*e*][1,3,5]benzoxadiazocine derivatives obtained here represent a hitherto unknown ring system in the literature.

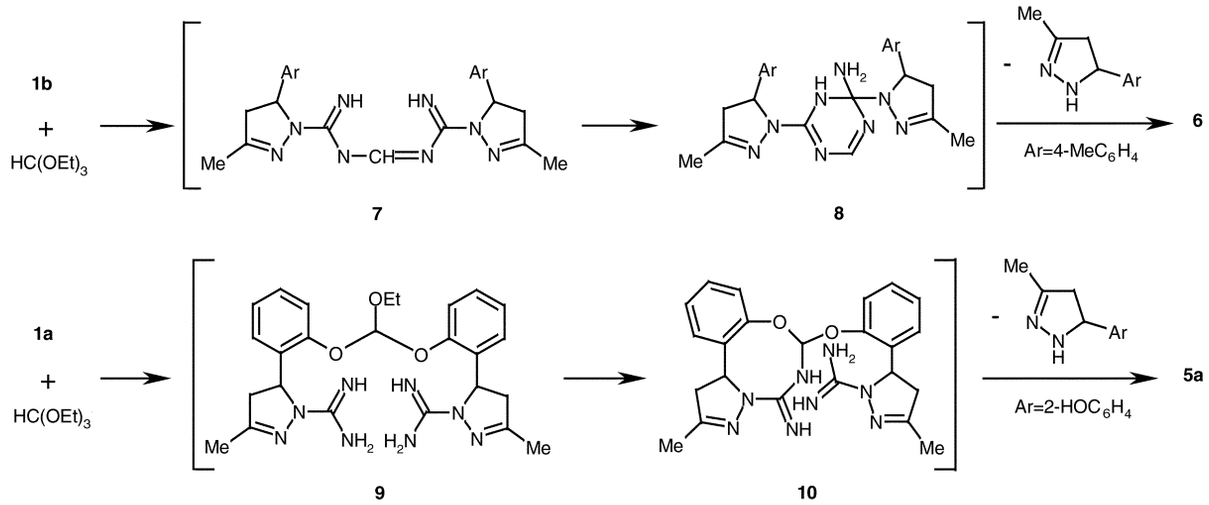
In order to avoid heterocyclization by the phenolic hydroxy group, 5-tolylpyrazole **1b** was allowed to react with triethyl orthoformate. Surprisingly, an unusual transformation occurred again. Taking into account formation of the lateral guanidine function in compound **5**, structure of resulted product **6** was readily established as 2-amino-4-(pyrazol-1-yl)-1,3,5-triazine derivative (Scheme 1). Formation of the product **6** is analogous to the condensations of amidines with carboxylic acid derivatives forming unsymmetrical 1,3,5-triazines,[6,7] although in our case disubstituted pyrazoline is eliminated instead of ammonia (Scheme 2). One could presume that a similar pathway may lead to the compound **5**. Nevertheless, this does not appear to be the case. Formally, tricycle **5** can be derived from an "O–N" ring closure and a transfer of a HNCNH moiety onto the imine function. Such a route seems to be simple but it is not compatible with the fact that we have not observed an analogous transfer of this fragment in the other cyclocondensations. Hence, a different mechanism must be operative. To envisage the formation of guanidine **5**, we postulate the following mechanism (Scheme 2). The reaction is assumed to start with a re-esterification of triethyl orthoformate with phenolic hydroxys of two equivalents of pyrazoline **1a**. The resulting orthoester **9** then undergoes cyclisation with the vicinal amidine moiety, thus producing an oxadiazocine skeleton (structure **10**). Finally, a nucleophilic attack at the carbon atom of the other amidine group by the adjacent exocyclic imine nitrogen allows for C_1-transfer which is followed by elimination of the disubstituted pyrazoline unit to yield the tricyclic derivative **5**.

In contrast, the transformation of hydroxyphenylpyrazole **1a** with 1,1′-carbonyldiimidazole,[8] proceeded in a more conventional fashion, as upon treatment in DMF (100 °C, 1 h) the reaction afforded an oxygen-bridged pyrazolotriazole derivative **11** (Scheme 3). The structure of **11** was easily inferred from the ^{13}C NMR spectrum which lacked the C-3 resonance from the educt **1a**. Instead, a new signal occurred at δ_C 88.5 from the hemiaminal C(O)N atom[9] which indicated a change in the pyrazoline ring 3-position. In addition, the CH_3–C(O)N–CH_2CH–C_6H_4 connectivity pattern was deduced from the INEPT measurements. The presence of the ureido C=O and imine C=N double bonds from the triazoline substructure was confirmed by both IR (ν 1707 and 1668 cm^{-1}, respectively) and the ^{13}C NMR spectra (δ_C 166.1 and 163.8). It is noteworthy that, to the best of our knowledge, 5,11-methano-3*H*,11*H*-[1,2,4]triazolo[1,2-*c*][1,3,4] benzoxadiazepine **11** represents a new tetracyclic bridged system.

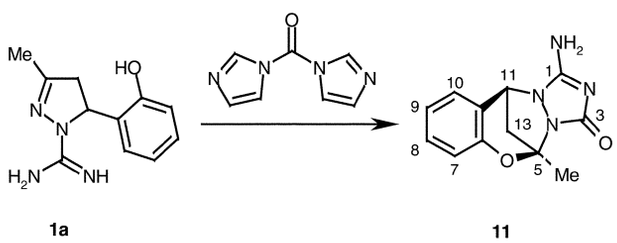
The formation of this novel compound can be rationalized in terms of a [4 + 1] cyclization, involving the formation of two nitrogen–carbonyl bonds, and a subsequent O-bridging process. Presumably, an iminium intermediate **13** is formed from the imidazolide precursor **12** that might play a crucial role in this transformation (Scheme 3). Note that **13** is reminiscent of highly reactive *N*-acyliminium ions.[10] Accordingly, an increased electrophilicity of the iminium carbon in **13** facilitates the intramolecular addition of the phenolic hydroxy. The absence of a direct hydroxy reaction with 1,1′-carbonyldiimidazole is somewhat unexpected, although it is well known that some substituted phenols are inert toward this reagent.[11]

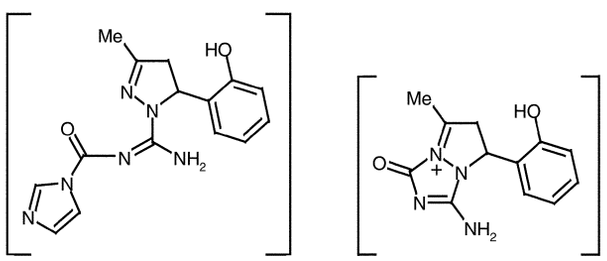
Heterocyclization with diethyl oxalate afforded an expected product. When refluxed with an excess of diethyl oxalate, hydroxyphenylpyrazole **1a** gave rise to imidazoledione derivative **14** as a result of an "N–N" ring closure (Scheme 4) instead of the "O–N" path which would yield a nine-membered oxadiazonine skeleton. Elemental analysis, also indicates a formation of a solvate with 1 mol of dioxane, and absence of any ethoxy signals in the ^1H NMR spectrum confirmed a 1 : 1 condensation stoichiometry. Two additional resonances of quaternary sp^2 carbons between 160–170 ppm were observed by ^{13}C NMR which are attributable to the amide and ester groups.[12] Convincing evidence for structure **14** came from the IR spectrum. In the carbonyl region three absorptions were observed: a medium intense band at 1787 cm^{-1} accompanied by a weaker one at 1740 cm^{-1}, and another strong, broad band at 1618 cm^{-1}. The former two higher wavenumbers belonging to the lactam vibrations are in very good agreement with the data reported by Goerdeler for analogous imidazole-4,5-diones prepared from *N*-substituted benzamidines and oxalyl chloride.[13]

It was also of interest to examine the behaviour of **1a** towards a higher diester homologue, such as diisopropyl malonate. This heterocyclization proved to be a complex process leading to compound **15** with an empirical formula $C_{17}H_{14}N_4O_5$. It followed that two malonate acyls were present in the resulting molecule. This was supported by an EI MS spectrum that displayed a consecutive loss of two ketene molecules from M^+. Although there are a number of theoretical

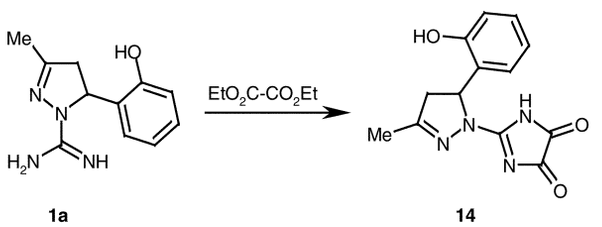


Scheme 2





Scheme 3

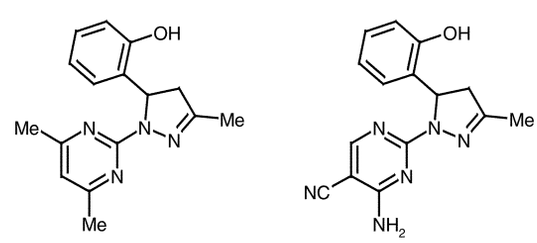


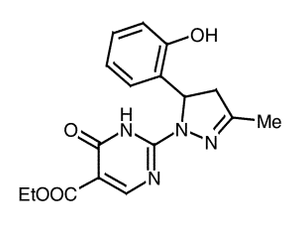
Scheme 4

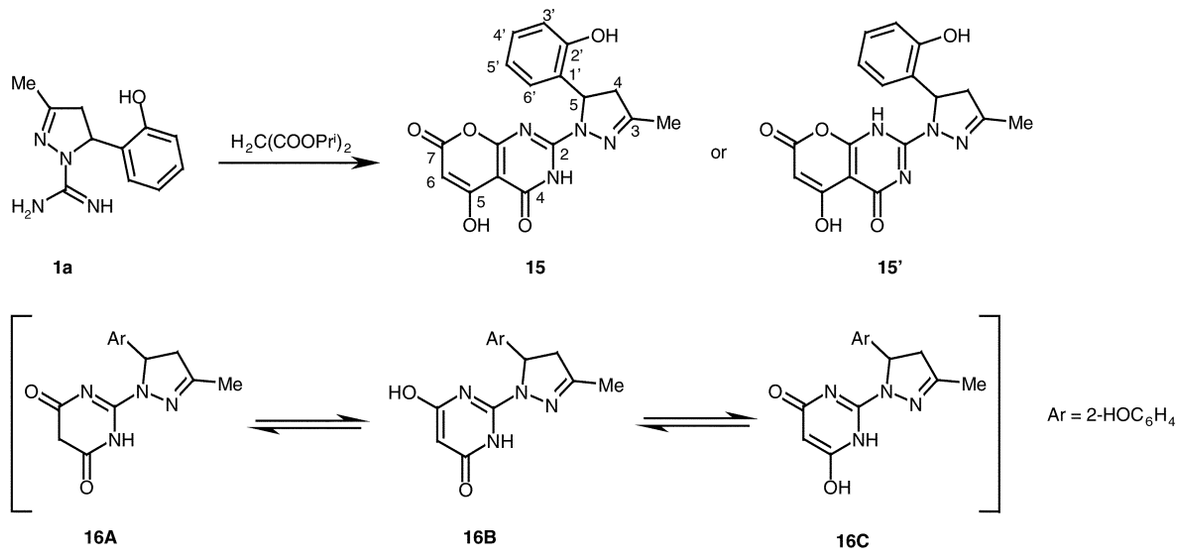
possibilities for the product **15**, we have postulated two isomeric structures **15** and **15′** that are compatible with the spectral data and the proposed reaction mechanism (Scheme 5). The pyranone methine was easily recognized in the NMR spectra at δ_H 5.10 and δ_C 84.0. These chemical shifts closely resemble those reported for the corresponding 3-position in 4-methoxy-6-methyl-2*H*-pyran-2-one (δ_H 5.44 and δ_C 87.3).[14,15] Moreover, the one-bond ^{13}C, ^{1}H-coupling constant of 169.7 Hz parallels the published value[15] $^{1}J_{CH}$ = 172 Hz. A careful comparison of the observed absorption bands in the range of 1500–1750 cm^{-1} with the detailed IR data reported for similar 2-substituted 5-hydroxy-4,5-dihydro-4*H*-pyrano[2,3-*d*]pyrimidine-4,7(3*H*)-diones [16] allowed us to establish tautomer **15** as the most probable reaction product.

Evidently, compound **15** has to originate from precursor **16A** (Scheme 5). This 1 : 1 condensation product may exist in two tautomeric enol forms **16B** and **16C** (when we omit a lactam–lactim tautomerism); either is theoretically capable of a further reaction with the second equivalent of malonate. Such a process which forms the pyranone ring can be visualized as a Claisen type condensation followed by lactonization and proton shift. It should be stressed that our experimental procedure (DMF, reflux) contrasts with the basic conditions generally employed in Claisen condensations.[17] Apparently, the "N–N" ring closure is the decisive factor determining the course of the reaction.

Heterocyclizations of **1a** with pentane-2,4-dione, ethoxymethylenemalononitrile and diethyl ethoxymethylenemalonate were also carried out and the products were identified as substituted pyrazol-2-ylpyrimidines **17**, **18** and **19**, respectively. Consistently, reactions of **1a** with C_3 reagents proceeded exclusively as "N–N" ring closures forming thus functionalized pyrimidine rings. The structures were routinely established from spectral data. The presence of the pyrimidine skeleton in molecules **17** and **18** was also proved by comparison of the one-bond ^{13}C,^{1}H coupling constants with literature values [18] reported for ring positions 4 and 5. In the case of product **19**, we propose the formation of a 6-oxopyrimidine-5-carboxylate rather than a heteroaromatic compound. Indeed, the observed chemical shifts were compatible with structure **19**. Moreover, NMR spectra predicted by the ACD software [19] confirmed this conclusion.







Scheme 5

Experimental

The melting points (uncorrected) were determined with a Kofler hot stage microscope. The IR spectra were recorded on a Nicolet Impact 400 D spectrophotometer. The EI mass spectra were obtained on a JEOL JMS D-100 (operating at 75 eV) for **3a**, **4**, **15**, VG 7070E (70 eV) for **5a**, **5b**, **6**, **11**, **17**–**19**. The FAB mass spectrum of **14** was measured on a Finnigan MAT 95 instrument (Xe, 6 keV, 2 mA). Peak matching with perfluoro-kerosene as the reference was utilized for accurate mass measurements by HRMS. Ion elemental compositions are reported in parentheses with the mass spectra. The NMR spectra were measured on a Bruker AC-400 spectrometer with a dual $^{1}H/^{13}C$ probe (400.136 MHz for ^{1}H and 100.614 MHz for ^{13}C) for **5a**, Bruker Avance-400 for **5b**, **11**, **14**, **15**, **18** and **19** and Varian VXR-300 (299.943/75.429 MHz) for **3a**, **4**, **6** and **17**. *J* values are given in Hz.

Reaction of 4,5-dihydro-3-methyl-5-(2-hydroxyphenyl)-1*H*-pyrazole-1-carboximidamide 1a with acetic anhydride

A suspension of pyrazole **1a** (0.33 g, 1.5 mmol) in acetic anhydride (15 cm^3) was stirred for 24 h at room temperature. The solution was concentrated on a vacuum rotary evaporator, the syrupy residue was dissolved in ethyl acetate (8 cm^3) and allowed to crystallize. The crystalline material was filtered off to obtain triacetate **3a**. The filtrate was chromatographed on silica gel using ethyl acetate as an eluent giving pyrazole **4**.

2-[1-(*N*,*N*′-Diacetylcarbamimidoyl)-4,5-dihydro-3-methyl-1*H*-pyrazol-5-yl]phenyl acetate 3a

This compound was obtained as colourless needles (0.20 g, 39%), mp 148–150 °C (from toluene) (Found: C, 59.5; H, 6.1; N, 16.1. $C_{17}H_{20}N_4O_4$ requires C, 59.3; H, 5.85; N, 16.3%); ν_{max}(KBr)/cm^{-1} 1751 (COO), 1711 (HN–C=O) and 1587 (=NCO/C=N); δ_H [$(CD_3)_2SO$] 1.77 (3 H, s, Me amide), 1.97 (3 H, s, Me amide), 2.02 (3 H, s, Me), 2.32 (3 H, s, Me ester), 2.56 (1 H, dd, *J* 18.5 and 5.9, 4-H_a), 3.49 (1 H, dd, *J* 18.5 and 12.2, 4-H_b), 5.48 (1 H, dd, *J* 12.2 and 5.9, 5-H), 7.11–7.35 (4 H, m, H_{ar}) and 10.27 (1 H, s, NH); δ_C [$(CD_3)_2SO$] 15.5 (Me), 20.7 (Me ester), 23.6 (Me–CONH), 26.3 (Me–CON=), 45.1 (CH_2-4), 55.7 (CH-5), 122.9 (CH_{ar}-3′), 126.1, 126.2 (CH_{ar}-4′/CH_{ar}-5′), 128.2 (CH_{ar}-6′), 133.8 (C_{ar}-1′), 141.5, 147.4, 157.2 (C-3/C_{ar}-2′/N–C=N), 168.3 (CONH), 169.0 (CO ester) and 180.0 (CON=); *m*/*z* 344 (M^+, 0.5%), 329 ($C_{16}H_{17}N_4O_4$, 5), 303 ($C_{15}H_{17}N_3O_4$, 12), 287 (14), 261 (12), 260 ($C_{13}H_{14}N_3O_3$, 12), 218 (33), 202 (13), 186 (11), 175 (40), 145 (43), 135 (23), 125 (13), 83 (59), 43 (100) and 42 (13).

1-Acetyl-4,5-dihydro-3-methyl-5-(2-hydroxyphenyl)-1*H*-pyrazole 4

This compound was obtained as a colourless solid (0.15 g, 46%), mp 176–177 °C (from toluene) (Found: C, 65.7; H, 6.3; N, 12.6. $C_{12}H_{14}N_2O_2$ requires C, 66.0; H, 6.5; N, 12.8%); ν_{max}(KBr)/cm^{-1} 1643 (CO amide) and 1629 (C=N); δ_H ($CDCl_3$) 2.17 (3 H, s, Me), 2.29 (3 H, s, Me amide), 3.00 (1 H, dd, *J* 18.3 and 3.0, 4-H_a), 3.35 (1 H, dd, *J* 18.3 and 11.1, 4-H_b), 5.69 (1 H, dd, *J* 11.1 and 3.0, 5-H), 6.83–6.93 (3 H, m, H_{ar}), 7.10–7.26 (1 H, m, H_{ar}) and 9.35 (1 H, br s, OH); δ_C ($CDCl_3$) 16.1 (Me), 21.4 (Me amide), 43.9 (CH_2-4), 53.3 (CH-5), 118.8 (CH_{ar}-3′), 120.7 (CH_{ar}-5′), 125.5 (CH_{ar}-6′), 127.1 (C_{ar}-1′), 129.6 (CH_{ar}-4′), 155.1 (C_{ar}-2′), 158.6 (C-3) and 169.4 (CON); *m*/*z* 218 ($C_{12}H_{14}N_2O_2$, M^+, 24%), 175 ($C_{10}H_{11}N_2O$, 56), 145 ($C_{10}H_9O$, 41), 94 (11), 91 (16), 83 ($C_4H_7N_2$, 100), 77 (23), 51 (22), 43 (52), 42 (28) and 39 (29).

Preparation of pyrazole derivative 4 – alternative method

To a solution of 4-(2-hydroxyphenyl)but-3-en-2-one (0.81 g, 5 mmol) in acetic acid (10 cm^3) was added hydrazine monohydrate (1.25 cm^3, 25 mmol) and the reaction mixture was refluxed for 1 h. The solvent was evaporated and to the oily residue cold water was added (30 cm^3). The resultant precipitate was filtered, washed with water and dried. Yield (0.70 g, 64%), mp 175–177 °C. This product was identical in all respects with acetylpyrazole **4**.

N-[(5*E*)-1,12b-Dihydro-2-methyl-5*H*-pyrazolo[1,5-*e*][1,3,5]-benzoxadiazocin-5-ylidene]guanidine 5a

A suspension of pyrazole **1a** (0.33 g, 1.5 mmol) in triethyl orthoformate (30 cm^3) was refluxed under stirring for 1 h. After cooling the reaction mixture was diluted with diethyl ether (20 cm^3) and kept standing overnight. The precipitated product was filtered, washed with ether and dried. The title compound was obtained as a white powder (0.15 g, 74%), mp 280–282 °C (from methanol) (Found: C, 57.5; H, 5.0; N, 30.8. $C_{13}H_{14}N_6O$ requires C, 57.8; H, 5.2; N, 31.1%); ν_{max}(KBr)/cm^{-1} 3328 and 3178 (NH_2, NH), 1662 and 1568 (C=N), 1485 and 1459; δ_H [$(CD_3)_2SO$] 1.98 (3 H, s, Me), 2.51 (1 H, dd, *J* 18.0 and 3.4, 1-H_a), 3.44 (1 H, ddd, *J* 18.0, 11.4 and 1.1, 1-H_b), 5.61 (1 H, dd, *J* 11.4 and 3.4, 12b-H), 6.70 (2 H, m, 11-H + 12-H), 6.82 (1 H,

d, *J* 7.9, 9-H), 6.84 (1 H, br s, NH), 7.03 (1 H, ddd, *J* 8.0, 5.7 and 3.2, 10-H), 7.04 (1 H, br s, NH), 7.96 (1 H, br s, NH) and 9.71 (1 H, s, 7-HC=); δ_C [$(CD_3)_2SO$] 15.8 (Me), 44.7 (CH_2), 56.0 (CH), 115.5 (CH-9), 118.8 (CH-1), 124.8 (CH-10), 124.9 (CH-12), 128.4 (C-12a), 153.8 (C-8a), 156.7 (C-2), 161.2 (C-5), 165.7 (O–CH=N) and 166.3 (HN=C–NH_2); *m*/*z* 271 (M^+ + 1, 7%), 270 ($C_{13}H_{14}N_6O$, M^+, 41), 269 (4), 229 (8), 228 ($C_{11}H_{10}N_5O$, 24), 212 (7), 177 ($C_7H_9N_6$, 64), 146 (9), 145 ($C_{10}H_9O$, 100), 126 (9), 118 (6), 111 (17), 109 (11), 96 (10), 91 (11), 83 (14), 77 (9), 68 (16), 65 (7), 63 (6), 51 (7), 43 (32), 42 (16) and 41 (8).

N-[(5*E*)-1,12b-Dihydro-2,7-dimethyl-5*H*-pyrazolo[1,5-*e*][1,3,5]-benzoxadiazocin-5-ylidene]guanidine 5b

This compound was prepared analogously from **1a** and triethyl orthoacetate, as a colourless solid (0.11 g, 52%), mp 312–313 °C (from DMF) (Found: C, 59.4; H, 5.8; N, 29.5. $C_{14}H_{16}N_6O$ requires C, 59.1; H, 5.7; N, 29.6%); ν_{max}(KBr)/cm^{-1} 3490 and 3299 (NH_2, NH), 1642 and 1568 (C=N), 1537 and 1458; δ_H [$(CD_3)_2SO$] 1.99 (3 H, s, Me-2), 2.07 (3 H, s, Me-7), 2.57 (1 H, dd, *J* 17.8 and 3.4, 1-H_a), 3.42 (1 H, dd, *J* 17.8 and 11.2, 1-H_b), 5.62 (1 H, dd, *J* 11.2 and 3.4, 12b-H), 6.68 (1 H, dd, *J* 7.4 and 7.2, 11-H), 6.74 (1 H, d, *J* 7.4, 12-H), 6.83 (1 H, d, *J* 8.0, 9-H), 6.85 (2 H, br s, NH_2), 7.04 (1 H, dd, *J* 8.0 and 7.2, 10-H) and 9.85 (1 H, s, NH); δ_C [$(CD_3)_2SO$] 15.7 (Me-2), 24.8 (Me-7), 44.5 (CH_2), 55.8 (CH), 115.8 (CH-9), 118.9 (CH-11), 125.4 (CH-12), 127.9 (CH-10), 128.4 (C-12a), 154.0 (C-8a), 156.3 (C-2), 161.8 (C-5), 166.6 (HN–C=NH_2) and 174.3 (C-7); accurate mass: 284.1389, $C_{14}H_{16}N_6O$ requires 284.1385.

2-Amino-4-[4,5-dihydro-3-methyl-5-(4-methylphenyl)-1*H*-pyrazol-1-yl]-1,3,5-triazine 6

A suspension of 4,5-dihydro-3-methyl-5-(4-methylphenyl)-1*H*-pyrazole-1-carboximidamide acetate **1b** (0.44 g, 1.6 mmol) in triethyl orthoformate (20 cm^3) was refluxed under stirring for 1 h. Evaporation of the solvent gave an oily residue which was triturated with ether. The solid obtained was collected and recrystallized from ethanol. This compound was obtained as colourless crystals (0.14 g, 65%), mp 241–243 °C (from EtOH) (Found: C, 62.5; H, 6.1; N, 31.2. $C_{14}H_{16}N_6$ requires C, 62.7; H, 6.0; N, 31.3%); ν_{max}(KBr)/cm^{-1} 3365 and 3311 (NH_2, NH), 1644, 1631 and 1587 (C=N), 1558, 1536 and 1463; δ_H [$(CD_3)_2SO$] 2.01 (3 H, s, Me), 2.24 (3 H, s, Me–Tol), 2.59 (1 H, dd, *J* 18.3 and 3.6, 4-H_a), 3.47 (1 H, dd, *J* 18.3 and 11.4, 4-H_b), 5.47 (1 H, dd, *J* 11.4 and 3.6, 5-H), 6.91 (2 H, br s, NH_2), 7.00 (2 H, AA′ part of AA′BB′, *J* 8.1, 3′-H + 5′-H), 7.09 (2 H, BB′ part, *J* 8.1, 2′-H + 6′-H) and 7.94 (1 H, s, triazine 6-H); δ_C [$(CD_3)_2SO$] 15.8 (Me), 20.6 (Me–Tol), 45.8 (CH_2), 59.9 (CH), 125.3 (CH-2′ + CH-6′), 129.1 (CH-3′ + CH-5′), 136.0 (C-4′), 140.1 (C-1′), 155.9 (C-3), 161.3 (triazine C-4), 165.7 (triazine CH-6) and 166.2 (triazine C-2); *m*/*z* 268 (M^+, 11%), 228 (11), 227 (74), 226 (100), 186 (12), 177 (6), 158 (7), 136 (5), 129 (5), 118 (17), 117 (11), 110 (7), 96 (13), 83 (11), 77 (6), 68 (10), 65 (6), 54 (4), 43 (18), 42 (8) and 39 (6).

(5*R**,11*R**)-1-Amino-5-methyl-5,11-methano-3*H*,11*H*- [1,2,4]-triazolo[1,2-*c*][1,3,4]benzoxadiazepin-3-one 11

A solution of pyrazole **1a** (0.66 g, 3.0 mmol) and 1,1′-carbonyldiimidazole (0.56 g, 3.4 mmol) in DMF (40 cm^3) was heated at 100 °C for 1 h with stirring. On cooling precipitated product was filtered and washed with ether. The title compound was obtained as a colourless solid (0.55 g, 75%), mp 259–260 °C (from DMF) (Found: C, 59.3; H, 5.2; N, 23.2. $C_{12}H_{12}N_4O_2$ requires C, 59.0; H, 4.95; N, 22.9%); ν_{max}(KBr)/cm^{-1} 3246 (NH), 1707 (C=O), 1668 (C=N) and 1560; δ_H [$(CD_3)_2SO$] 1.90 (3 H, s, Me), 2.50 (1 H, d, *J* 12.0, 13-H_a), 2.86 (1 H, dd, *J* 12.0 and 4.7, 13-H_b), 5.04 (1 H, d, *J* 4.7 Hz, 11-H), 6.78 (1 H, d, *J* 8.2, 7-H), 6.86 (1 H, dd, *J* 7.3 and 7.2, 9-H), 7.19 (1 H, dd, *J* 8.2 and 7.2, 8-H), 7.26 (2 H, br s, NH_2) and 7.28 (1 H, d, *J* 7.3, 10-H); δ_C [$(CD_3)_2SO$] 21.1 (Me), 40.4 (CH_2), 54.8 (CH), 88.4 (C-5), 114.9 (CH-7), 119.6 (CH-9), 120.6 (C-10a), 127.6, 129.40 (CH-8/CH-10), 152.3 (C-6a), 163.8 and 166.1 (C=N/C=O); *m*/*z* 244 (M^+, 5%), 201 (9), 175 (5), 160 (6), 146 (20), 145 (100), 144 (50), 131 (35), 115 (62), 100 (46), 91 (17), 73 (18), 63 (22), 57 (25), 51 (28) and 43 (67).

2-[4,5-Dihydro-5-(2-hydroxyphenyl)-3-methyl-1*H*-pyrazol-1-yl]-1*H*-imidazole-4,5-dione 14

A suspension of pyrazole **1a** (0.33 g, 1.5 mmol) in diethyl oxalate (50 cm^3) was refluxed under stirring for 1 h. Volatile components were removed on the vacuum rotary evaporator and the oily rest was triturated with dioxane. The crystalline solid was filtered and washed with ether (0.21 g, 39%), mp 170–171 °C (from dioxane) (Found: C, 56.9; H, 5.3; N, 15.8. $C_{13}H_{12}N_4O_3$·dioxane requires C, 56.6; H, 5.6; N, 15.55%); ν_{max}(KBr)/cm^{-1} 3433 (NH), 1787 (COO), 1740 (CO), 1618 (CON) and 1444; δ_H [$(CD_3)_2CO$] 2.28 (3 H, s, Me), 3.25 (1 H, dd, *J* 18.6 and 3.7, 4-H_a), 3.59 (8 H, br s, dioxane), 3.78 (1 H, ddd, *J* 18.6, 11.0 and 1.0, 4-H_b), 5.85 (1 H, dd, *J* 11.0 and 3.7, 5-H), 6.86 (1 H, ddd, *J* 7.8, 7.2 and 1.2, 5′-H), 6.98 (1 H, dd, *J* 8.1 and 1.2, 3′-H), 7.13 (1 H, dd, *J* 7.8 and 1.6, 6′-H), 7.17 (1 H, ddd, *J* 8.1, 7.2 and 1.6, 4′-H), 9.82 (1 H, br s, OH/NH) and 10.93 (1 H, br s, NH/OH); δ_C [$(CD_3)_2CO$] 16.1 (Me), 45.7 (CH_2), 57.8 (CH), 67.7 (CH_2 dioxane), 119.1 (CH-3′), 121.3 (CH-5′), 127.3 (C-1′), 127.8 (CH-6′), 130.6 (CH-4′), 155.9 (C-2′), 162.1, 163.8, 167.8 and 168.6 (C=N/C=N/CO/CO); *m*/*z*(FAB) 273 $(M + H)^+$.

5-Hydroxy-2-[4,5-dihydro-5-(2-hydroxyphenyl)-3-methyl-1*H*-pyrazol-1-yl]-4*H*-pyrano[2,3-*d*]pyrimidine-4,7(3*H*)-dione 15

A suspension of pyrazole **1a** (0.33 g, 1.5 mmol) and diisopropyl malonate (4 cm^3) in DMF (20 cm^3) was refluxed under stirring for 1 h. The solution was concentrated under reduced pressure to give a semisolid. After trituration with ethanol the resultant precipitate was filtered and thoroughly washed with ethanol and then with ether. The title compound was obtained as a colourless powder (0.15 g, 28%), mp 340–341 °C (decomp.) (from DMF) (Found: C, 57.9; H, 4.0; N, 16.0. $C_{17}H_{14}N_4O_5$ requires C, 57.6; H, 4.0; N, 15.8%); ν_{max}(KBr)/cm^{-1} 3273 (OH), 3104 (NH), 1717 (COO), 1667 (CON), 1626 (C=N), 1592 (C=C) and 1556; δ_H [$(CD_3)_2SO$] 2.12 (3 H, s, Me), 2.76 (1 H, dd, *J* 18.6 and 4.2, pyrazole 4-H_a), 3.60 (1 H, dd, *J* 18.6 and 11.3, pyrazole 4-H_b), 5.10 (1 H, s, 6-H), 5.65 (1 H, dd, *J* 11.3 and 4.2, pyrazole 5-H), 6.73 (1 H, t, *J* 7.1, 5′-H), 6.84–6.87 (2 H, m, 3′-H + 6′-H), 7.09 (1 H, t, *J* 8.3, 4′-H), 9.78, 11.93 and 12.33 (3 × 1 H, s, NH/NH/OH); δ_C [$(CD_3)_2SO$] 15.6 (Me), 45.4 (pyrazole CH_2), 57.5 (pyrazole CH), 84.0 (=CH-6, $^1J_{CH}$ 169.7), 87.4 (C-4a), 115.5 (CH-3′), 118.9 (CH-5′), 126.0 (CH-4′), 126.5 (C-1′), 128.4 (CH-6), 153.9 (C-2′), 149.4, 160.7, 162.5, 164.2, 166.2 and 169.5 (pyrazole C=N/C-4/C-5/C-7/C-8a/C-2); *m*/*z* 354 ($C_{17}H_{14}N_4O_5$, M^+, 33%), 312 (8, $C_{15}H_{12}N_4O_4$), 271 (6), 270 (6, $C_{13}H_{10}N_4O_3$), 261 (4), 254 (3), 229 (6), 219 (5), 193 (4), 145 ($C_{10}H_9O$, 100), 118 (14), 94 (4), 91 (13) and 69 (25).

4,6-Dimethyl-2-[4,5-dihydro-5-(2-hydroxyphenyl)-3-methyl-1*H*-pyrazol-1-yl]pyrimidine 17

A suspension of pyrazole **1a** (0.33 g, 1.5 mmol) and pentane-2,4-dione (2 cm^3) in DMF (20 cm^3) was refluxed under stirring for 1 h. After removal of the solvent the oily residue was triturated with ethanol. Crystalline product was filtered off and washed with ether. This compound was obtained as colourless crystals (0.31 g, 73%), mp 281–283 °C (from DMF) (Found: C, 67.9; H, 6.6; N, 20.0. $C_{16}H_{18}N_4O$ requires C, 68.1; H, 6.4; N, 19.8%); ν_{max}(KBr)/cm^{-1} 3245 (OH), 1583 and 1560 (C=N, C=C), 1482, 1458 and 1377; δ_H ($CDCl_3$) 2.28 (3 H, s, Me), 2.40 (6 H, s, Me-2 + Me-4), 3.13 (1 H, dd, *J* 18.5 and 3.7, pyrazole 4-H_a), 3.48 (1 H, ddd, *J* 18.5, 11.7 and 1.3, pyrazole 4-H_b), 5.75

(1 H, dd, *J* 11.7 and 3.7, pyrazole 5-H), 6.39 (1 H, s, pyrimidine 5-H), 6.88 (1 H, ddd, *J* 7.8, 7.1 and 1.4, 5′-H), 6.97 (1 H, dd, *J* 8.2 and 1.3, 3′-H), 7.10 (1 H, dd, *J* 7.8 and 1.7, 6′-H), 7.19 (1 H, ddd, *J* 8.2, 7.1 and 1.7, 4′-H) and 9.95 (1 H, br s, OH); δ_C ($CDCl_3$) 16.3 (Me), 23.7 (Me-4 + Me-6), 44.9 (pyrazole CH_2), 54.3 (pyrazole CH), 110.9 (pyrimidine CH-5, ^1J 163.2), 119.0 (CH-3′), 121.2 (CH-5′), 127.1 (CH-6′), 128.8 (C-1′), 129.6 (CH-4′), 155.2 (C-2′), 155.7 (pyrazole C-3), 156.8 (pyrimidine C-2) and 168.0 (pyrimidine C-4 + C-6); *m/z* 283 (M^+ + 1, 8%), 282 (M^+, 44), 281 (11), 265 (6), 241 (11), 240 (62), 190 (13), 189 (100), 163 (8), 146 (12), 145 (85), 123 (19), 107 (15), 91 (9), 67 (25), 42 (17) and 39 (12).

4-Amino-2-[4,5-dihydro-5-(2-hydroxyphenyl)-3-methyl-1*H*-pyrazol-1-yl]pyrimidine-5-carbonitrile 18

A suspension of pyrazole **1a** (0.33 g, 1.5 mmol) and ethoxymethylenemalononitrile (0.21 g, 1.7 mmol) in DMF (20 cm^3), was refluxed under stirring for 1 h. After evaporation of the solvent the oily residue was dissolved in ethanol (5 cm^3) and allowed to crystallize at room temperature. The resultant precipitate was filtered and washed with ethyl acetate. This compound was obtained as colourless crystals (0.21 g, 40%), mp 314–316 °C (from MeOH) (Found: C, 61.2; H, 4.7; N, 28.3. $C_{15}H_{14}N_6O$ requires C, 61.2; H, 4.8; N, 28.55%); ν_{max}(KBr)/cm^{-1} 3456, 3350, 3238 (OH, NH_2), 2208 (CN), 1631 (C=N), 1587 (C=N, C=C), 1537, 1522 and 1460; δ_H [$(CD_3)_2SO$] 1.99 (3 H, s, Me), 2.54 (1 H, dd, *J* 18.0 and 3.1, pyrazole 4-H_a), 3.46 (1 H, dd, *J* 18.0 and 11.2, pyrazole 4-H_b), 5.68 (1 H, dd, *J* 11.2 and 3.1, pyrazole 5-H), 6.60–6.70 (2 H, m, 5′-H + 6′-H), 6.82 (1 H, d, *J* 8.0, 3′-H), 7.02 (1 H, ddd, *J* 8.0, 6.6 and 1.5, 4′-H), 7.37 (2 H, s, NH_2), 8.18 (1 H, s, pyrimidine 6-H) and 9.64 (1 H, s, OH); δ_C [$(CD_3)_2SO$] 15.7 (Me), 44.8 (pyrazole CH_2), 56.6 (pyrazole CH), 79.6 (pyrimidine C-5), 115.4 (CH-3′), 117.0 (CN), 118.7 (CH-5′), 125.0 (CH-6′), 127.7 (CH-4′), 128.4 (C-1′), 153.8 (C-2′), 157.2 (pyrazole C-3), 157.7 (pyrimidine C-2), 162.9 (pyrimidine C-4, ^3J 5.3) and 161.8 (pyrimidine CH-6, ^1J 182.5); accurate mass: 294.1232, $C_{15}H_{14}N_6O$ requires 294.1229.

Ethyl 1,6-dihydro-2-[4,5-dihydro-5-(2-hydroxyphenyl)-3-methyl-1*H*-pyrazol-1-yl]-6-oxopyrimidine-5-carboxylate 19

A suspension of pyrazole **1a** (0.33 g, 1.5 mmol) and 3 cm^3 diethyl ethoxymethylenemalonate in DMF (20 cm^3) was refluxed under stirring for 1 h. After evaporation of the solvent the syrupy residue was dissolved in ethyl acetate (6 cm^3) and the solution was refrigerated. The precipitate was filtered off and washed with cold ethyl acetate. This compound was obtained as colourless crystals (0.30 g, 58%), mp 240–242 °C (from MeCN) (Found: C, 59.65; H, 5.3; N, 16.2. $C_{17}H_{18}N_4O_4$ requires C, 59.6; H, 5.3; N, 16.4%); ν_{max}(KBr)/cm^{-1} 3248 (OH, NH), 1736 (COO), 1678, 1662 (CON) and 1589 (C=N, C=C); δ_H [$(CD_3)_2SO$] 1.19 (3 H, t, Me ester), 2.08 (3 H, s, Me), 2.71 (1 H, dd, *J* 18.4 and 4.2, pyrazole 4-H_a), 3.58 (1 H, dd, *J* 18.4 and 11.3, pyrazole 4-H_b), 4.11 (2 H, q, CH_2 ester), 5.66 (1 H, dd, *J* 11.3 and 4.2, pyrazole 5-H), 6.71 (1 H, dd, *J* 7.6 and 7.3, 5′-H), 6.79 (1 H, dd, *J* 7.6 and 1.6, 6′-H), 6.84 (1 H, d, *J* 7.9, 3′-H), 7.07 (1 H, ddd, *J* 7.9, 7.3 and 1.6, 4′-H), 8.23 (1 H, s, pyrimidine 4-H), 9.74 (1 H, s, OH) and 10.98 (1 H, s, NH); δ_C [$(CD_3)_2SO$] 14.2 (Me ester), 15.7 (Me), 45.5 (pyrazole CH_2), 56.8 (pyrazole CH), 59.2 (CH_2 ester), 104.9 (pyrimidine C-5), 115.5 (CH-3′), 118.9 (CH-5′), 125.5 (CH-6′), 127.1 (C-1′), 128.2 (CH-4′), 153.8 (C-2′), 152.1, 158.2 (pyrimidine C-2/C-6), 161.3 (pyrazole C-3), 161.8 (pyrimidine CH-4) and 163.8 (COO); accurate mass: 342.1324, $C_{17}H_{18}N_4O_4$ requires 342.1328.

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