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Regioselective synthesis of fused pyrazolo[1,5-*a*]pyrimidines by reaction of 5-amino-1*H*-pyrazoles and β-dicarbonyl compounds containing five-membered rings

Jaime Portilla [a,*], Jairo Quiroga [b], Manuel Nogueras [c], Justo Cobo [c]

[a] *Bioorganic Compounds Research Group, Department of Chemistry, Universidad de los Andes, Carrera 1 N° 18A 10, Bogotá, Colombia*
[b] *Heterocyclic Compounds Research Group, Department of Chemistry, Universidad del Valle, A.A. 25360 Cali, Colombia*
[c] *Department of Inorganic and Organic Chemistry, Universidad de Jaén, 23071 Jaén, Spain*

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ABSTRACT

Reactions of 3-substituted-5-amino-1*H*-pyrazoles with 2-acetylcyclopentanone or 2-ethoxycarbonylcyclopentanone lead to the regioselective formation of a new series of cyclopentapyrazolo[1,5-*a*]pyrimidines in good yields. When 2-acetylbutyrolactone was used, the reaction provided 6-(2-hydroxyethyl)pyrazolo[1,5-*a*]pyrimidinone and/or the intermediate (3*Z*)-3-{1-[(5-*R*-1*H*-pyrazol-3-yl)amino]ethylidene}-4,5-dihydrofuranone. This indicates that the cyclization proceeds with butyrolactone ring opening as the last step. Several aspects of this regioselective reaction, including mechanistic and structural studies, are considered.

1. Introduction

Pyrazolo[1,5-*a*]pyrimidine is a fused heterocyclic system of interest for drug development because of its analogy to purines.[1] Some derivatives have therefore been studied as analogues for purine nucleoside antimetabolites.[2–4] Others display antitrypanosomal or antischistosomal activities,[5,6] and some derivatives show potential activity against respiratory diseases.[7] These interesting biological properties have considerably stimulated the search for new and efficient procedures of wide generality for building this ring system.[7,8] Compounds with these ring systems can also be used as scaffolds in the dyestuff industry.[9] Recently, Okun and colleagues have reported the synthesis of sulfonylsubstituted cyclopentapyrazolo[1,5-*a*]pyrimidines and their evaluation as 5-HT_6 receptor antagonists. They found that these compounds are highly selective antagonists with sub-nanomolar affinities (K_i<1 nM, Fig. 1).[10]

The drive towards clean technology has also encouraged the application of solvent-free conditions in organic synthesis.[11] This has led in some cases to improved results and more benign synthetic procedures for these compounds.[12] In particular, the possibility of using solvent-free conditions for cyclocondensation reactions has received much attention.[13]

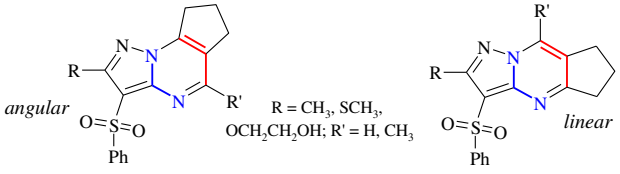

Fig. 1. 3-Phenylsulfonylcyclopentapyrazolo[1,5-*a*]pyrimidines as 5-HT_6 receptor antagonists.

Several methods have been described in the literature for the synthesis of pyrazolo[1,5-*a*]pyrimidines in the last 20 years. Most of them involve the reaction between 5-amino-1*H*-pyrazoles with 1,3-bis-electrophilic reagents, such as β-dicarbonyl, α,β-unsaturedcarbonyl, alkoxymethylene-β-dicarbonyl and β-enaminone compounds.[1,14–16]

Recently, we have reported several studies on solvent-free methods for the preparation of pyrazolo[1,5-*a*]pyrimidines in the reaction between 5-amino-1*H*-pyrazoles **1** and some alkoxymethylene-β-dicarbonyl compounds **2** or **3** (Scheme 1) or β-triketones **6** or **7** (Scheme 2).

The use of cyclic reagents such as **2**, **3**, **6** and **7** allows the introduction of polyfunctionality into the pyrazolo[1,5-*a*]pyrimidine

* Corresponding author. Tel.: +57 13554935; fax: +57 13324366; e-mail addresses: jportill@uniandes.edu.co, jantopos@gmail.com (J. Portilla).

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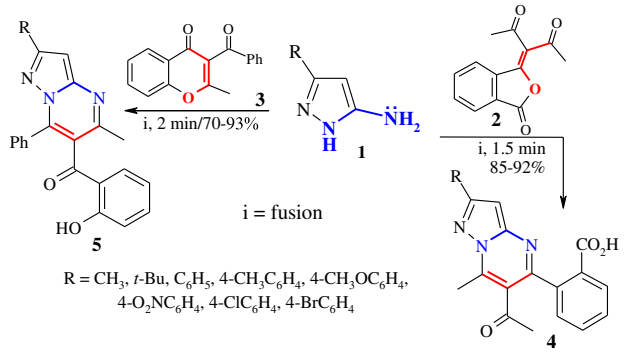
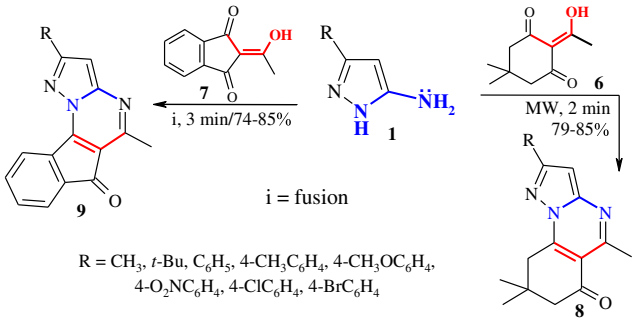


Scheme 1. Reaction of 5-amino-1*H*-pyrazoles **1** with alkoxymethylene-β-dicarbonyl compounds.[16a,b]



Scheme 2. Reaction of 5-amino-1*H*-pyrazoles **1** with cyclic β-triketones.[16c]

system, such as the benzoic acid **4**[16a] or phenol **5**[16b] residues (Scheme 1). Alternatively, fused pyrazolo[1,5-*a*]pyrimidines **8** or **9**[16c] also can be obtained (Scheme 2).

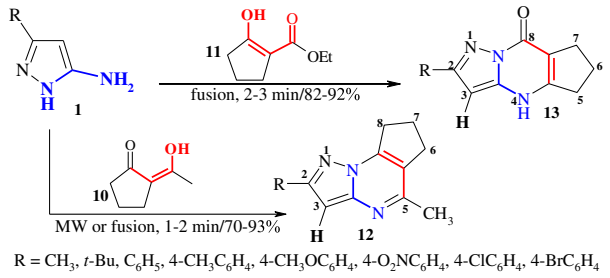
All of these reactions are highly regioselective, being initially controlled by a Michael type addition of exocyclic amino group in the aminopyrazole to the alkoxymethylene-β-dicarbonyl compounds **2** or **3** and in a similar fashion by an initial condensation with carbonyl moiety with higher enolic contribution in the case of **6** or **7**.[16]

We report herein an extension of this study to now include reactions involving diverse β-dicarbonyl compounds containing five-membered rings, which react with aminopyrazoles **1** in a highly regioselective fashion and provide good yields of isolated products. Moreover, it is noteworthy that these reactions were carried out in a highly regioselective manner via an efficient and environmentally friendly method as compared to the synthesis of similar systems.[1a,10,17] Although the bioactivities of these compound are not reported in this article, we emphasize that the introduction of structural variations, such the cyclopenta-fused moiety, is potentially useful for the development of new biologically active compounds, because it has been found in potential drugs for the treatment of various diseases of the central nervous system.[10,17]

2. Results and discussion

2.1. Synthesis of cyclopentapyrazolo[1,5-*a*]pyrimidines

Continuing our current studies on the application of free-solvent cyclocondensation procedures[16,18] and particularly in the synthesis of fused pyrazoles,[16,18,19] we have now synthesized a new series of cyclopenta-fused pyrazolo[1,5-*a*]pyrimidines **12** or **13** via a cyclocondensation reaction of 3-substituted-5-amino-1*H*-pyrazoles **1** with 2-acetylcyclopentanone **10** or 2-ethoxycarbonylcyclopentanone **11** (Scheme 3).



Scheme 3. Synthesis of cyclopentapyrazolo[1,5-*a*]pyrimidines **12** and **13**.

In order to achieve this, we have investigated the synthesis of cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidines **12** and cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidones **13** under solvent-free conditions (Scheme 3), using both fusion and microwave irradiation methods and have compared our results with traditional reflux methods in ethanol in order to demonstrate the advantages of the former methods. Heating of an equimolar amount of the precursors **1** and **10** in refluxing ethanol for 17–20 h rendered the compounds **12** in 17–26% yields, whereas compound **13** was obtained in 19–27% yields from precursors **1** and **11** by heating for 15–20 h. It is clear that both of these solvent-free methods (fusion and MW) are preferred because of their short reaction times (few minutes) and high yields (see Scheme 3).

These results suggest that the reaction is highly regioselective and the nature of the β-dicarbonyl compounds is crucial in controlling the regiochemistry, in order to permit the preparation of cyclopentapyrazolo[1,5-*a*]pyrimidines **12** or **13** (angular or linear isomers, respectively). This is the main disadvantage in the work reported by Okun and colleagues.[10] All structures were fully characterized by standard spectroscopic and analytical methods.

The NMR data are consistent with structures **12** and **13** and rules out the possible formation of regioisomeric structures such cyclopentapyrazolo[3,4-*b*]pyridines **14** and **15** as the cyclopentapyrazolo [3,4-*b*]pyridones **16** and **17**, respectively (Fig. 2). These involve pyrazolic carbon (]CH-pyrazolic) instead of the nitrogen in the final cyclization step.

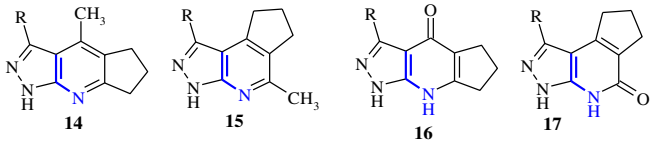
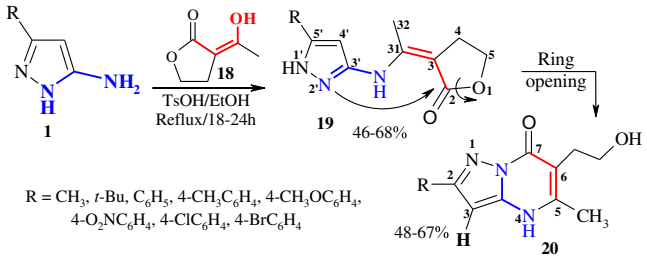


Fig. 2. Discarded cyclopentapyrazolo[3,4-*b*]pyridines **14**–**17**.

Compounds **12a** and **13a** exhibit a ^{1}H NMR spectrum (see Experimental) with one sharp singlet at 6.30 and 5.89 ppm, respectively, which correspond to the]CH-pyrazolic proton at position 3. The entire carbon skeleton was assigned using ^{13}C NMR spectra combined with DEPT, and two dimensional ^{1}H, ^{13}C shift correlation HMQC and HMBC experiments. Solid-state studies unambiguously corroborate these features, and, for example, in the case of structure **12**, the isolation of unique crystals for some derivatives permitted the determination of their crystal structure from X-ray diffraction analysis.[20a,b]

2.2. Synthesis of 6-hydroxyethylpyrazolo[1,5-*a*]pyrimidines

We also employed 2-acetylbutyrolactone **18**, which contains a lactone moiety instead of a cyclic carbonyl group (Scheme 4). In this case, we obtained 6-(2-hydroxyethyl)pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-ones (Scheme 4). Unfortunately, the reaction between aminopyrazoles **1** and **18** under free-solvent conditions (fusion or MW) did not afford satisfactory results.



Scheme 4. Synthesis of 6-(2-hydroxyethyl)pyrazolo[1,5-*a*]pyrimidinone **20**.

Aminopyrazoles **1** were reacted with 2-acetylbutyrolactone **18** in the presence of a catalytic amount of *p*-TsOH (Scheme 4). This reaction required long times under conventional heating and the isolation of the products was problematic. 6-(2-Hydroxyethyl) pyrazolo[1,5-*a*]pyrimidinone **20** and, in some cases, its precursor (3*Z*)-3-{1-[(5-*R*-1*H*-pyrazol-3-yl)amino]ethylidene}-4,5-dihydrofuranone **19** were obtained, evidencing that the cyclization proceeds with the butyrolactone ring opening as the last step after the initial condensation between the exocyclic amino group in **1** and the carbonyl group in **18**.

In the case of 1a (R=CH_3) we isolated a solid that the ^{1}H NMR analysis showed to be a mixture of two products. Recrystallization of this mixture from DMF yielded colourless crystals, which were suitable for single crystal X-ray diffraction. The structure of this solid is a stoichiometric adduct 3-{1-[(5-methyl-1*H*-pyrazol-3-yl) amino]ethylidene}-4,5-dihydrofuran-2-one/6-(2-hydroxyethyl)-2,5-dimethylpyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one **19a**/**20a** (1:1).[20c]

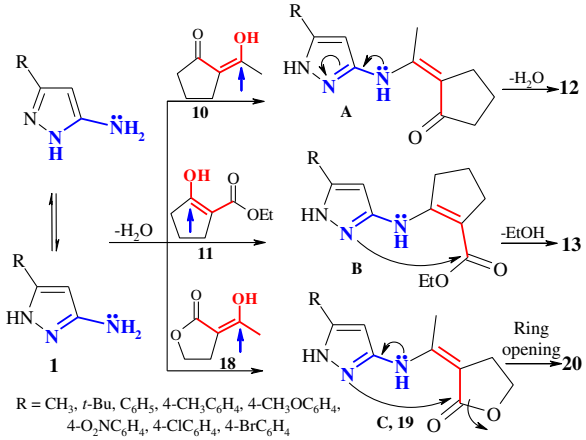
Compounds **19** and **20** were fully characterized by standard spectroscopic and analytical methods. As in the previous reactions, the reaction is highly regioselective and the nature of the β-dicarbonyl compounds controls the course of reaction. In this reaction, the NMR data were also used to rule out the possible formation of regioisomeric structures such pyrazolo[3,4-*b*]pyridones **21** and **22** (Fig. 3).

Fig. 3. Discarded pyrazolo[3,4-*b*]pyridones **21** and **22**.

The heterocyclic nucleus in this product, see, for example, compound **20b**, exhibits a ^{1}H NMR spectrum (see Experimental) that contains one sharp singlet at 5.87 ppm, which correspond to the]CH-pyrazolic proton at position 3 and the spectrum agrees with the proposed regiochemistry. Moreover, the isolation of intermediates **19** supports, as previously mentioned, the proposed reaction route. Compound **19c**, exhibits, for example, a ^{1}H NMR spectrum with one sharp singlet at 6.52 ppm, corresponding to the]CH-pyrazolic proton at positions 4′; two additional broad singlets appear around 12.89 and 10.05 ppm, which correspond to the NH-pyrazolic proton at position 1′ and the NH-group at position 3′, respectively. In addition, a pair of coupled triplets is found around 2.86 and 4.26 ppm, corresponding to the ethylene moiety of the lactone ring. These results suggest that the reaction first proceeds with the condensation of the NH_2-group at aminopyrazole **1** with the exocyclic C]O (the most enolic one) of compound **18** (Schemes 3 and 4). The entire carbon skeleton could be assigned using ^{13}C NMR spectra combining with DEPT and two dimensional experiments.

2.3. Effect of modification in the β-dicarbonyl compounds

Scheme 5 shows the sequence step for the cyclocondensation reaction of 3-substituted-5-amino-1*H*-pyrazoles **1** with the three dicarbonylic derivatives **10**, **11** and **18**.



Scheme 5. Mechanism for the formation of compounds **12**, **13** and **20**.

As an initial stage, we assume an initial condensation between the NH_2-group of the aminopyrazole **1** and the carbonyl group in **10**, **11** or **18** with a high contribution of the enolic form (see Scheme 5). This can be considered as being a Michael type nucleophilic addition–elimination to yield the intermediates **A**, **B** or **C** (**19**), respectively, which can then evolve cyclocondensation by via attack of the nucleophilic nitrogen at the pyrazole to the other carbonyl group (endocyclic on **A**, **C** and exocyclic on **B**) followed by the subsequent loss of a second molecule (water, **A** or ethanol, **B**) and the butyrolactone ring opening (for **C**) to form the final pyrazolo [1,5-*a*]pyrimidines **12**, **13** and **20**, respectively.

3. Conclusions

We report in this article a highly regioselective one-step synthesis of cyclopentapyrazolo[1,5-*a*]pyrimidines starting from aminopyrazoles **1** and cyclic dicarbonylic derivatives, which was carried out in solvent-free conditions, both under heating in fusion and MW irradiation. This provides a high-throughput methodology because of its ease in execution, rapid access, and good yields. The use of 2-acetylbutyrolactone in the reaction with 5-aminopyrazoles served to establish the proposed reaction pathway, due to the isolation of an intermediate **19**, which indicates that the reaction starts with a condensation between the exocyclic amino group and the carbonyl moiety with higher enolic contribution. In addition, the introduction of structural variations in these biologically active scaffolds is potentially useful for the improvement of their biological effects.

4. Experimental section

4.1. General

3-Substituted 5-aminopyrazoles **1a**–**h** were synthesized following a literature procedure.[21] The starting 2-acetylcyclopentanone **10**, 2-ethoxycarbonylcyclopentanone **11** and 2-acetylbutyrolactone **18** were purchased from Aldrich, Fluka and Merck (analytical reagent grades) and were used without further purification. Solvents and other chemicals commercially available were used as shipped. Silica gel aluminium plates (Merck 60 F_{254}) were used for analytical TLC. Microwave experiments were carried out on a focused microwave

reactor (300 W CEM Discover™). Melting points were taken on Stuart SMP10 meeting point apparatus and were uncorrected. IR spectra were recorded on a Shimadzu FTIR 8400 spectrophotometer in KBr disks. The ^{1}H and ^{13}C NMR spectra were run on a *BRUKER UltraShield* spectrometer operating at 400 MHz and 100 MHz, respectively, and other at 500 MHz and 125 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra were recorded on a Shimadzu GC–MS-QP 2010 spectrometer (equipped with a direct inlet probe) operating at 70 eV. The elemental analyses were performed with a Thermo Finnigan Flash EA1112 CHN (STIUJA) instrument.

4.2. General procedure for the synthesis of 2-substituted-5-methyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*] pyrimidines 12a–h

Method A. A mixture of equimolar amounts of 3-substituted-5-amino-1*H*-pyrazoles **1a**–**h** (1 mmol) and 2-acetycyclopentanone **10** (1 mmol) was thoroughly mixed at room temperature, and heated in an oil-bath at 160 °C for 2 min. After the reaction mixture was cooled down to room temperature, the solid material was treated with ethanol (4 mL) the solvent was removed, and the products were recrystallized from DMF. *Method B*. The initial mixture was subjected to microwave irradiation at 150 °C with a maximum power of 150 W for 1–2 min (see Scheme 3). Then the reaction mixture was treated with ethanol and the deposited solid was collected by filtration and recrystallized from DMF to give compounds **12**.

*4.2.1. 2,5-Dimethyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (**12a**).* This compound was isolated as colourless crystals in 90% yield; mp 168–169 °C. FTIR: ν=1605 (C]N) cm^{-1}. ^{1}H NMR (400 MHz, 27 °C): δ=2.17 (m, 2H, 7-CH$_2$), 2.37 (s, 3H, 2-CH$_3$), 2.38 (s, 3H, 5-CH$_3$), 2.87 (t, J=7.3 Hz, 2H, 6-CH$_2$), 3.18 (t, J=7.3 Hz, 2H, 8-CH$_2$), 6.30 (s, 1H, 3-H) ppm. ^{13}C NMR (100 MHz, 27 °C): δ=14.2 (2-CH$_3$), 21.5 (7-CH$_2$), 22.2 (5-CH$_3$), 28.8 (6-CH$_2$), 29.3 (8-CH$_2$), 93.8 (C-3), 120.8 (C-5a), 147.5 (C-8a), 148.9 (C-3a), 153.3 (C-2), 155.2 (C-5) ppm. MS: (70 eV, EI): m/z (%)=187 (100) [M$^+$], 172 (6) [M−15], 104 (25) [M−83], 65 (17) [C$_5$H$_5$], 39 (20) [C$_3$H$_3$]. Elemental analysis calcd for C$_{11}$H$_{13}$N$_3$ (187.24): C, 70.56; H, 7.00; N, 22.44. Found: C, 70.61; H, 7.04; N, 22.50.

*4.2.2. 2-(tert-Butyl)-5-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (**12b**).* This compound was isolated as colourless crystals in 85% yield; mp 186–188 °C. FTIR: ν=1600 (C]N) cm^{-1}. ^{1}H NMR (400 MHz, 27 °C): δ=1.36 (s, 9H, *t*-Bu), 2.22 (m, 2H, 7-CH$_2$), 2.41 (s, 3H, 5-CH$_3$), 2.94 (t, J=7.4 Hz, 2H, 6-CH$_2$), 3.24 (t, J=7.4 Hz, 2H, 8-CH$_2$), 6.32 (s, 1H, 3-H) ppm. ^{13}C NMR (100 MHz, 27 °C): δ=21.7 (7-CH$_2$), 22.0 (5-CH$_3$), 29.0 (6-CH$_2$), 30.4 (8-CH$_2$), 30.5 (C–(CH$_3$)$_3$), 32.5 (*C*–(CH$_3$)$_3$), 90.5 (C-3), 120.9 (C-5a), 147.8 (C-3a), 149.2 (C-8a), 155.3 (C-5), 166.8 (C-2) ppm. MS: (70 eV, EI): m/z (%)=229 (64) [M$^+$], 214 (100) [M−15], 187 (87) [M−42], 65 (25) [C$_5$H$_5$], 39 (40) [C$_3$H$_3$]. Elemental analysis calcd for C$_{14}$H$_{19}$N$_3$ (229.32): C, 73.33; H, 8.35; N, 18.32. Found: C, 73.37; H, 8.40; N, 18.35.

*4.2.3. 5-Methyl-2-phenyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (**12c**).* This compound was isolated as colourless crystals in 78% fusion/80% MW yield; mp 233–234 °C. FTIR: ν=1625 (C]N) cm^{-1}. ^{1}H NMR (500 MHz, 110 °C): δ=2.29 (m, 2H, 7-CH$_2$), 2.48 (s, 3H, 5-CH$_3$), 3.01 (t, J=7.4 Hz, 2H, 6-CH$_2$), 3.35 (t, J=7.4 Hz, 2H, 8-CH$_2$), 6.93 (s, 1H, 3-H), 7.38 (t, J=7.4 Hz, 1H, *p*-Ph), 7.48 (t, J=7.4 Hz, 2H, *m*-Ph), 8.00 (d, J=7.3 Hz, 2H, *o*-Ph) ppm. ^{13}C NMR (125 MHz, 110 °C): δ=22.6 (5-CH$_3$), 22.9 (7-CH$_2$), 29.6 (6-CH$_2$), 29.9 (8-CH$_2$), 92.1 (C-3), 120.5 (C-5a), 126.7 (C-*o*), 128.9 (C-*p*), 129.1 (C-*m*), 133.9 (C-*i*), 148.4 (C-8a), 150.2 (C-3a), 155.3 (C-5), 156.3 (C-2) ppm. MS: (70 eV, EI): m/z (%)=249 (100) [M$^+$], 234 (4) [M−15], 65 (35) [C$_5$H$_5$], 39 (30) [C$_3$H$_3$]. Elemental analysis calcd for C$_{16}$H$_{15}$N$_3$ (249.31): C, 77.08; H, 6.06; N, 16.85. Found: C, 77.14; H, 6.10; N, 16.91.

*4.2.4. 5-Methyl-2-(4-methylphenyl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (**12d**).* This compound was isolated as colourless crystals in 80% yield; mp 239–240 °C. FTIR: ν=1623 (C]N) cm^{-1}. ^{1}H NMR (500 MHz, 120 °C): δ=2.27 (m, 2H, 7-CH$_2$), 2.36 (s, 3H, CH$_3$–Ar), 2.46 (s, 3H, 5-CH$_3$), 2.98 (t, J=7.3 Hz, 2H, 6-CH$_2$), 3.32 (t, J=7.3 Hz, 2H, 8-CH$_2$), 6.85 (s, 1H, 3-H), 7.26 (d, J=8.3 Hz, 2H, *m*-Ar), 7.86 (d, J=8.2 Hz, 2H, *o*-Ar) ppm. ^{13}C NMR (125 MHz, 120 °C): δ=20.0 (CH$_3$–Ar), 21.0 (7-CH$_2$), 21.4 (5-CH$_3$), 28.4 (6-CH$_2$), 28.8 (8-CH$_2$), 90.6 (C-3), 121.4 (C-5a), 125.4 (C*o*-Ar), 128.5 (C*m*-Ar), 130.0 (C*i*-Ar), 137.3 (C*p*-Ar), 147.2 (C-8a), 149.0 (C-3a), 154.2 (C-2), 155.0 (C-5) ppm. MS: (70 eV, EI): m/z (%)=263 (100) [M$^+$], 248 (4) [M−15], 65 (28) [C$_5$H$_5$], 39 (40) [C$_3$H$_3$]. Elemental analysis calcd for C$_{17}$H$_{17}$N$_3$ (263.34): C, 77.54; H, 6.51; N, 15.96. Found: C, 77.60; H, 6.54; N, 16.12.

*4.2.5. 2-(4-Methoxyphenyl)-5-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (**12e**).* This compound was isolated as colourless crystals in 85% yield; mp 224–225 °C. FTIR: ν=1618 (C]N), 1251 (C–OCH$_3$) cm^{-1}. ^{1}H NMR (500 MHz, 110 °C): δ=2.26 (m, 2H, 7-CH$_2$), 2.45 (s, 3H, 5-CH$_3$), 2.98 (t, J=7.3 Hz, 2H, 6-CH$_2$), 3.31 (t, J=7.3 Hz, 2H, 8-CH$_2$), 3.83 (s, 3H, OCH$_3$), 6.81 (s, 1H, 3-H), 7.01 (d, J=8.2 Hz, 2H, *m*-Ar), 7.90 (d, J=8.2 Hz, 2H, *o*-Ar) ppm. ^{13}C NMR (125 MHz, 110 °C): δ=21.0 (7-CH$_2$), 21.5 (5-CH$_3$), 28.5 (6-CH$_2$), 28.8 (8-CH$_2$), 54.8 (OCH$_3$), 90.3 (C-3), 113.8 (C*m*-Ar), 121.0 (C-5a), 125.4 (C*i*-Ar), 126.9 (C*o*-Ar), 147.2 (C-8a), 149.1 (C-3a), 154.1 (C-2), 155.0 (C-5), 159.4 (C*p*-Ar) ppm. MS: (70 eV, EI) m/z (%)=279 (100) [M$^+$], 264 (27) [M−15], 65 (22) [C$_5$H$_5$], 39 (42) [C$_3$H$_3$]. Elemental analysis calcd for C$_{17}$H$_{17}$N$_3$O (279.34): C, 73.10; H, 6.13; N, 15.04. Found: C, 73.14; H, 6.16; N, 15.11.

*4.2.6. 2-(4-Chlorophenyl)-5-methyl-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (**12f**).* This compound was isolated as colourless crystals in 91% (method A)/83% (method B) yields; mp 223–224 °C. FTIR: ν=1620 (C]N) cm^{-1}. ^{1}H NMR (500 MHz, 100 °C): δ=2.26 (m, 2H, 7-CH$_2$), 2.46 (s, 3H, 5-CH$_3$), 2.98 (t, J=7.3 Hz, 2H, 6-CH$_2$), 3.32 (t, J=7.4 Hz, 2H, 8-CH$_2$), 6.94 (s, 1H, 3-H), 7.48 (d, J=8.2 Hz, 2H, *m*-Ar), 7.98 (d, J=8.2 Hz, 2H, *o*-Ar) ppm. ^{13}C NMR (125 MHz, 100 °C): δ=21.3 (C-7), 21.6 (CH$_3$), 28.6 (C-6), 28.9 (C-8), 91.3 (C-3), 121.2 (C-5a), 127.1 (C*m*-Ar), 128.1 (C*o*-Ar), 131.6 (C*i*-Ar), 132.7 (C*p*-Ar), 147.4 (C-8a), 149.1 (C-3a), 152.3 (C-2), 156.0 (C-5) ppm. MS: (70 eV, EI) m/z (%)=285/283 (35/100) [M$^+$], 270/268 (3/8) [M−15], 65 (23) [C$_5$H$_5$], 39 (41) [C$_3$H$_3$]. Elemental analysis calcd for C$_{16}$H$_{14}$ClN$_3$ (283.76): C, 67.72; H, 4.97; N, 14.81. Found: C, 67.75; H, 5.01; N, 14.82.

*4.2.7. 2-(4-Bromophenyl)-5-methyl-7,8-dihydro-6H-cyclopenta[g]pyrazolo[1,5-a]pyrimidine (**12g**).* This compound was isolated as colourless crystals in 83% yields; mp 223–224 °C. FTIR: ν=1605 (C]N) cm^{-1}. ^{1}H NMR (500 MHz, 110 °C): δ=2.27 (m, 2H, 7-CH$_2$), 2.47 (s, 3H, 5-CH$_3$), 3.00 (t, J=7.3 Hz, 2H, 6-CH$_2$), 3.33 (t, J=7.3 Hz, 2H, 8-CH$_2$), 6.94 (s, 1H, 3-H), 7.62 (d, J=8.2 Hz, 2H, *m*-Ar), 7.92 (d, J=8.2 Hz, 2H, *o*-Ar) ppm. ^{13}C NMR (125 MHz, 110 °C): δ=21.0 (C-7), 21.5 (CH$_3$), 28.5 (C-6), 28.8 (C-8), 91.2 (C-3), 121.1 (C*i*-Ar), 121.8 (C-5a), 127.4 (C*o*-Ar), 131.0 (C*m*-Ar), 132.0 (C*p*-Ar), 147.4 (C-8a), 149.1 (C-3a), 152.9 (C-2), 155.5 (C-5) ppm. MS: (70 eV, EI) m/z (%)=329/327 (97/100) [M$^+$], 312 (5) [M−15], 65 (32) [C$_5$H$_5$], 39 (31) [C$_3$H$_3$]. Elemental analysis calcd for C$_{16}$H$_{14}$BrN$_3$ (328.21): C, 58.55; H, 4.30; N, 12.80. Found: C, 58.57; H, 4.34; N, 12.82.

*4.2.8. 5-Methyl-2-(4-nitrophenyl)-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (**12h**).* This compound was isolated as yellow crystals in 70% yield; mp 258–259 °C. FTIR: 1615 cm^{-1} (C]N);

^{1}H NMR (500 MHz, 110 °C): δ=2.29 (m, 2H, 7-CH_2), 2.49 (s, 3H, CH_3), 3.02 (t, J=7.3 Hz, 2H, 6-CH_2), 3.36 (t, J=7.3 Hz, 2H, 8-CH_2), 7.11 (s, 1H, 3-H), 8.23 (d, J=9.2 Hz, 2H, *o*-Ar), 8.27 (d, J=9.2 Hz, 2H, *m*-Ar) ppm. ^{13}C NMR (125 MHz, 110 °C): δ=21.0 (C-7), 21.6 (CH_3), 28.6 (C-6), 28.8 (C-8), 92.6 (C-3), 122.5 (C-5a), 123.2 (C*m*-Ar), 126.4 (C*o*-Ar), 139.0 (C*i*-Ar), 147.0 (C*p*-Ar), 147.5 (C-8a), 149.1 (C-3a), 151.7 (C-2), 156.0 (C-5) ppm. MS: (70 eV, EI) *m*/*z* (%)=294 (100) [M^+], 248 (12) [M−46], 65 (18) [C_5H_5], 39 (32) [C_3H_3]. Elemental analysis calcd for $C_{16}H_{14}N_4O_2$ (294.31): C, 65.30; H, 4.79; N, 19.04. Found: C, 65.33; H, 4.85; N, 19.06.

4.3. General procedure for the synthesis of 2-substituted-4,5,6,7-tetrahydro-8*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-ones 13a–h

A mixture of equimolar amounts of 3-substituted-5-amino-1*H*-pyrazoles **1a**–**h** (1 mmol) and 2-ethoxycarbonylcyclopentanone **11** (1 mmol) was thoroughly mixed at room temperature. The mixture was heated in an oil-bath at 160 °C for 2–3 min (see Scheme 3), then cooled down to room temperature and the solid material treated with ethanol (8 mL). The solvent was removed and the products were recrystallized from ethanol to give compounds **13**.

*4.3.1. 2-Methyl-4,5,6,7-tetrahydro-8H-cyclopenta[d]pyrazolo[1,5-a]pyrimidin-8-one (**13a**).* This compound was isolated as white solid in 92% yield; mp 286–288 °C. FTIR: ν=1580 (C]N), 1667 (C]O), 3125 (N–H) cm^{-1}. ^{1}H NMR (400 MHz, 27 °C): δ=2.04 (m, 2H, 6-CH_2), 2.25 (s, 3H, 2-CH_3), 2.64 (t, J=7.3 Hz, 2H, 7-CH_2), 3.06 (t, J=7.3 Hz, 2H, 5-CH_2), 5.89 (s, 1H, 3-H), 12.29 (s, 1H, 4-NH) ppm. ^{13}C NMR (100 MHz, 27 °C): δ=14.6 (2-CH_3), 22.2 (6-CH_2), 27.9 (7-CH_2), 30.0 (5-CH_2), 88.0 (C-3), 106.7 (C-7a), 143.2 (C-3a), 151.8 (C-4a), 153.8 (C-2), 155.3 (C-8, C]O) ppm. MS: (70 eV, EI): *m*/*z* (%)=189 (100) [M^+], 174 (6) [M−15], 65 (43) [C_5H_5], 39 (51) [C_3H_3]. Elemental analysis calcd for $C_{10}H_{11}N_3O$ (189.21): C, 63.48; H, 5.86; N, 22.21. Found: C, 63.51; H, 5.91; N, 22.23.

*4.3.2. 2-(tert-Butyl)-4,5,6,7-tetrahydro-8H-cyclopenta[d]pyrazolo[1,5-a]pyrimidin-8-one (**13b**).* This compound was isolated as white solid in 83% yield; mp >330 °C. FTIR: ν=1587 (C]N), 1678 (C]O), 3120 (N–H) cm^{-1}. ^{1}H NMR (400 MHz, 120 °C): δ=1.30 (s, 9H, *t*-Bu), 2.07 (m, 2H, 6-CH_2), 2.67 (t, J=7.3 Hz, 2H, 7-CH_2), 2.87 (t, J=7.3 Hz, 2H, 5-CH_2), 5.87 (s, 1H, 3-H), 11.69 (s, 1H, 4-NH) ppm. ^{13}C NMR (100 MHz, 120 °C): δ=21.9 (6-CH_2), 27.0 (7-CH_2), 31.3 (5-CH_2), 30.1 (C(CH_3)$_3$), 32.3 (*C*(CH_3)$_3$), 84.1 (C-3), 106.6 (C-7a), 142.8 (C-3a), 153.0 (C-4a), 155.1 (C-8, C]O), 164.2 (C-2) ppm. MS: (70 eV, EI): *m*/*z* (%)=231 (70) [M^+], 216 (100) [M−15], 189 (46) [M−42], 65 (18) [C_5H_5], 39 (20) [C_3H_3]. Elemental analysis calcd for $C_{13}H_{17}N_3O$ (231.29): C, 67.51; H, 7.41; N, 18.17. Found: C, 67.55; H, 7.46; N, 18.16.

*4.3.3. 2-Phenyl-4,5,6,7-tetrahydro-8H-cyclopenta[d]pyrazolo[1,5-a]pyrimidin-8-one (**13c**).* This compound was isolated as white solid in 92% yield; mp >330 °C. FTIR: ν=1591 (C]N), 1668 (C]O), 3130 (N–H) cm^{-1}. ^{1}H NMR (400 MHz, 120 °C): δ=2.12 (m, 2H, 6-CH_2), 2.75 (t, J=7.3 Hz, 2H, 7-CH_2), 2.93 (t, J=7.3 Hz, 2H, 5-CH_2), 6.43 (s, 1H, 3-H), 7.38 (t, J=7.5 Hz, 1H, *p*-Ph), 7.44 (t, J=7.5 Hz, 2H, *m*-Ph), 7.93 (d, J=7.4 Hz, 2H, *o*-Ph), 11.94 (s, 1H, 4-NH) ppm. ^{13}C NMR (125 MHz, 120 °C): δ=21.2 (6-CH_2), 26.3 (7-CH_2), 30.7 (5-CH_2), 84.4 (C-3), 106.4 (C-7a), 126.6 (C-*o*), 128.8 (C-*p*), 128.9 (C-*m*), 132.6 (C-*i*), 143.0 (C-3a), 152.3 (C-2), 152.9 (C-4a), 154.2 (C(8)]O) ppm. MS: (70 eV, EI): *m*/*z* (%)=251 (100) [M^+], 222 (46) [M−29], 65 (41) [C_5H_5], 39 (31) [C_3H_3]. Elemental analysis calcd for $C_{15}H_{13}N_3O$ (251.28): C, 71.70; H, 5.21; N, 16.72. Found: C, 71.69; H, 5.23; N, 16.73.

*4.3.4. 2-(4-Methylphenyl)-4,5,6,7-tetrahydro-8H-cyclopenta[d]pyrazolo[1,5-a]pyrimidin-8-one (**13d**).* This compound was isolated as white solid in 85% yield; mp >300 °C. FTIR: ν=1590 (C]N), 1664 (C]O), 3119 (N–H) cm^{-1}. ^{1}H NMR (400 MHz, 120 °C): δ=2.09 (m, 2H, 6-CH_2), 2.35 (s, 3H, CH_3–Ar), 2.70 (t, J=7.3 Hz, 2H, 7-CH_2), 2.92 (t, J=7.3 Hz, 2H, 8-CH_2), 6.53 (s, 1H, 3-H), 7.24 (d, J=8.0 Hz, 2H, *m*-Ar), 7.85 (d, J=8.0 Hz, 2H, *o*-Ar), 12.52 (s, 1H, 4-NH) ppm. ^{13}C NMR (100 MHz, 120 °C): δ=21.1 (CH_3–Ar), 22.4 (6-CH_2), 27.5 (7-CH_2), 31.9 (5-CH_2), 85.3 (C-3), 106.3 (C-7a), 126.5 (C*o*-Ar), 129.6 (C*m*-Ar), 129.8 (C*i*-Ar), 137.3 (C*p*-Ar), 143.1 (C-3a), 152.3 (C-4a), 152.9 (C-2), 154.3 (C(8)]O) ppm. MS: (70 e, EI): *m*/*z* (%)=265 (100) [M^+], 65 (21) [C_5H_5], 39 (14) [C_3H_3]. Elemental analysis calcd for $C_{16}H_{15}N_3O$ (265.31): C, 72.43; H, 5.70; N, 15.84. Found: C, 72.45; H, 5.74; N, 15.88.

*4.3.5. 2-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-8H-cyclopenta[d]pyrazolo[1,5-a]pyrimidin-8-one (**13e**).* This compound was isolated as white solid in 92% yield; mp >300 °C. FTIR: ν=1262 (C–OCH_3), 1599 (C]N), 1665 (C]O), 3120 (N–H) cm^{-1}. ^{1}H NMR (400 MHz, 120 °C): δ=2.12 (m, 2H, 6-CH_2), 2.73 (t, J=7.4 Hz, 2H, 7-CH_2), 2.92 (t, J=7.4 Hz, 2H, 5-CH_2), 3.83 (s, 3H, OCH_3), 6.34 (s, 1H, 3-H), 7.00 (d, J=8.2 Hz, 2H, *m*-Ar), 7.84 (d, J=8.2 Hz, 2H, *o*-Ar), 11.86 (s, 1H, 4-NH) ppm. ^{13}C NMR (100 MHz, 120 °C): δ=21.2 (6-CH_2), 26.3 (7-CH_2), 30.7 (5-CH_2), 54.7 (OCH_3), 83.9 (C-3), 106.3 (C-7a), 113.7 (C*m*-Ar), 125.2 (C*i*-Ar), 126.8 (C*o*-Ar), 143.0 (C-3a), 152.2 (C-2), 152.7 (C-4a), 154.3 (C(8)]O), 159.4 (C*p*-Ar) ppm. MS: (70 eV, EI) *m*/*z* (%)=281 (100) [M^+], 266 (9) [M−15], 252 (15) [M−29], 238 (24) [M−29], 65 (16) [C_5H_5], 39 (12) [C_3H_3]. Elemental analysis calcd for $C_{16}H_{15}N_3O_2$ (281.31): C, 68.31; H, 5.37; N, 14.94. Found: C, 68.34; H, 5.41; N, 14.95.

*4.3.6. 2-(4-Chlorophenyl)-4,5,6,7-tetrahydro-8H-cyclopenta[d]pyrazolo[1,5-a]pyrimidin-8-one (**13f**).* This compound was isolated as white solid in 82% yield; mp >330 °C. FTIR: ν=1594 (C]N), 1664 (C]O), 3121 (N–H) cm^{-1}. ^{1}H NMR (400 MHz, 120 °C): δ=2.11 (m, 2H, 6-CH_2), 2.73 (t, J=7.3 Hz, 2H, 7-CH_2), 2.92 (t, J=7.3 Hz, 2H, 5-CH_2), 6.43 (s, 1H, 3H), 7.46 (d, J=8.3 Hz, 2H, *m*-Ar), 7.92 (d, J=8.3 Hz, 2H, *o*-Ar), 12.18 (s, 1H, 4-NH) ppm. ^{13}C NMR (100 MHz, 120 °C): δ=21.2 (C-6), 26.3 (C-7), 30.8 (C-5), 84.6 (C-3), 106.4 (C-7a), 127.2 (C*m*-Ar), 127.9 (C*o*-Ar), 131.5 (C*i*-Ar), 132.7 (C*p*-Ar), 143.5 (C-3a), 151.1 (C-2), 153.4 (C-4a), 154.2 (C-8, C]O) ppm. MS: (70 eV, EI) *m*/*z* (%)=287/285 (41/100) [M^+], 258/256 (14/60) [M−29], 65 (25) [C_5H_5], 39 (19) [C_3H_3]. Elemental analysis calcd for $C_{15}H_{12}ClN_3O$ (285.73): C, 63.05; H, 4.23; N, 14.71. Found: C, 63.09; H, 4.25; N, 14.75.

*4.3.7. 2-(4-Bromophenyl)-4,5,6,7-tetrahydro-8H-cyclopenta[d]pyrazolo[1,5-a]pyrimidin-8-one (**13g**).* This compound was isolated as white solid in 90% yield; mp >300 °C. FTIR: ν=1591 (C]N), 1665 (C]O), 3123 (N–H) cm^{-1}. ^{1}H NMR (400 MHz,, 120 °C): δ=2.12 (m, 2H, 6-CH_2), 2.74 (t, J=7.3 Hz, 2H, 7-CH_2), 2.93 (t, J=7.3 Hz, 2H, 5-CH_2), 6.45 (s, 1H, 3H), 7.61 (d, J=8.5 Hz, 2H, *m*-Ar), 7.87 (d, J=8.5 Hz, 2H, *o*-Ar), 12.02 (s, 1H, 4-NH) ppm. ^{13}C NMR (100 MHz, 120 °C): δ=21.2 (C-6), 26.3 (C-7), 30.7 (C-5), 84.5 (C-3), 106.5 (C-7a), 121.1 (C*i*-Ar), 127.4 (C*o*-Ar), 130.8 (C*m*-Ar), 131.8 (C*p*-Ar), 143.1 (C-3a), 151.2 (C-2), 153.1 (C-4a), 154.2 (C-8, C]O) ppm. MS: (70 eV, EI) *m*/*z* (%)=331/329 (99/100) [M^+], 302/300 (29/28) [M−29], 65 (45) [C_5H_5], 39 (28) [C_3H_3]. Elemental analysis calcd for $C_{15}H_{12}BrN_3O$ (330.18): C, 54.56; H, 3.66; N, 12.73. Found: C, 54.60; H, 3.72; N, 12.75.

*4.3.8. 2-(4-Nitrophenyl)-4,5,6,7-tetrahydro-8H-cyclopenta[d]pyrazolo[1,5-a]pyrimidin-8-one (**13h**).* This compound was isolated as pale yellow solid in 86% yield; mp >330 °C. FTIR: ν=1587 (C]N), 1662 (C]O), 3117 (N–H) cm^{-1}; ^{1}H NMR (400 MHz,, 100 °C): δ=2.11 (m, 2H, 6-CH_2), 2.73 (t, J=7.3 Hz, 2H, 7-CH_2), 2.94 (t, J=7.3 Hz, 2H, 5-CH_2), 6.61 (s, 1H, 3H), 8.18 (d, J=8.2 Hz, 2H, *o*-Ar), 8.25 (d, J=8.2 Hz, 2H, *m*-Ar), 11.90 (s, 1H, 4-NH) ppm. ^{13}C NMR (100 MHz, 100 °C): δ=21.8 (C-6), 26.9 (C-7), 31.5 (C-5), 94.2 (C-3), 107.1 (C-7a), 123.7 (C*m*-Ar), 125.9 (C*o*-Ar), 138.9 (C*i*-Ar), 144.2 (C-3a), 147.6 (C*p*-Ar),

150.6 (C-2), 154.6 (C-4a), 154.8 (C-8, C]O) ppm. MS: (70 eV, EI) *m*/*z* (%)=296 (100) [M^+], 268 (19) [M−28], 65 (26) [C_5H_5], 39 (22) [C_3H_3]. Elemental analysis calcd for $C_{15}H_{12}N_4O_3$ (296.28): C, 60.81; H, 4.08; N, 18.91. Found: C, 60.84; H, 4.14; N, 18.95.

4.4. General procedure for the synthesis of 6-(2-hydroxyethyl)-5-methyl-2-substituted-pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one 20 and/or (3*Z*)-3-{1-[(5-substituted-1*H*-pyrazol-3-yl)amino]ethylidene}-4,5-dihydrofuranone 19

A mixture of 3-substituted-5-amino-1*H*-pyrazoles **1a**–**h** (1 mmol), 2-acetylbutyrolactone **18** (1 mmol) and 4-toluensulfonic acid (~0.01 mmol) in ethanol (15 mL) was heated under reflux with magnetic stirring until TLC showed the absence of the starting material (18–24 h). After the reaction mixture was cooled down to room temperature, the solvent was removed under reduced pressure, and the resulting solid was purified by recrystallization from DMF to give compounds **19** and/or **20** (see Scheme 4).

*4.4.1. (3Z)-3-{1-[(5-Methyl-1H-pyrazol-3-yl)amino]ethylidene}-4,5-dihydrofuran-2(3H)-one/6-(2-hydroxyethyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7(4H)-one (1:1) (**19a**/**20a**).* This mixture was isolated as colourless crystals in 48% yield; mp 220–221 °C, and analysed by single crystal X-ray diffraction.[20c]

*4.4.2. 2-(tert-Butyl)-6-(2-hydroxyethyl)-5-methylpyrazolo[1,5-a]pyrimidin-7(4H)-one (**20b**).* This compound was isolated white solid in 67% yield; mp 265–266 °C. FTIR: ν=1598 (C]N), 1681 (C]O), 3201 (N–H) cm^{-1}. ^1H NMR (400 MHz, 28 °C): δ=1.64 (s, 9H, *t*-Bu), 2.29 (s, 3H, 5-CH_3), 2.58 (t, *J*=6.7 Hz, 2H, CH_2), 4.39 (m, 2H, CH_2O), 4.55 (s, 1H, OH), 5.87 (s, 1H, 3-H), 12.20 (s, 1H, 4-NH) ppm. ^{13}C NMR (100 MHz, 28 °C): δ=17.7 (5-CH_3), 29.2 (CH_2), 30.5 (C(CH_3)$_3$), 32.8 (*C*(CH_3)$_3$), 60.3 (CH_2O), 84.2 (C-3), 102.7 (C-6), 141.7 (C-5), 146.8 (C-3a), 157.3 (C(7)]O), 164.8 (C-2) ppm. MS: (70 eV, EI): *m*/*z* (%)=249 (37) [M^+], 234 (40) [M−15], 220 (54) [M−29], 218 (100) [M−31], 134 (22) [M−115], 48 (8), 41 (10). Elemental analysis calcd for $C_{13}H_{19}N_3O_2$ (249.31): C, 62.63; H, 7.68; N, 16.85. Found: C, 62.65; H, 7.71; N, 16.88.

*4.4.3. (3Z)-3-{1-[(5-Phenyl-1H-pyrazol-3-yl)amino]ethylidene}-4,5-dihydrofuran-2(3H)-one (**19c**).* This compound was isolated as colourless crystals in 63% yield; mp 322–323 °C. FTIR: ν=1603 (C]N), 1668 (C]O), 3174 (N–H) cm^{-1}. ^1H NMR (400 MHz, 35 °C): δ=2.18 (s, 3H, CH_3), 2.86 (t, *J*=7.3 Hz, 2H, 4-CH_2), 4.26 (t, *J*=7.34 Hz, 2H, 5-CH_2), 6.52 (s, 1H, 4′-H), 7.33 (t, *J*=8.1 Hz, 1H, *p*-Ph), 7.43 (t, *J*=8.1 Hz, 2H, *m*-Ph), 7.73 (d, *J*=8.1 Hz, 2H, *o*-Ph), 10.05 (s, 1H, NH-amino), 12.89 (s, 1H, 1′-NH) ppm. ^{13}C NMR (100 MHz, 35 °C): δ=18.3 (CH_3), 26.0 (4-CH_2), 65.5 (5-CH_2), 94.9 (C-4′), 100.0 (C-3), 125.5 (C-*o*), 128.7 (C-*p*), 129.3 (C-*m*), 133.1 (C-*i*), 142.5 (C-31), 147.4 (C-3′), 155.3 (C-5′), 173.6 (C(2)]O) ppm. MS: (70 eV, EI): *m*/*z* (%)=269 (100) [M^+], 254 (40) [M−15], 224 (41) [M−45], 210 (26) [M−59], 77 (19) [C_5H_5]. Elemental analysis calcd for $C_{15}H_{15}N_3O_2$ (269.30): C, 66.90; H, 5.61; N, 15.60. Found: C, 66.91; H, 5.65; N, 15.63.

*4.4.4. 6-(2-Hydroxyethyl)-5-methyl-2-(4-methylphenyl)pyrazolo[1,5-a]pyrimidin-7(4H)-one (**19d**).* This compound was isolated as light yellow solid in 59% yield; mp 223–225 °C. FTIR: ν=1601 (C]N), 1678 (C]O), 3197 (N–H) cm^{-1}. ^1H NMR (400 MHz, 28 °C): δ=2.28 (s, 3H, 5-CH_3), 2.30 (s, 3H, CH_3-Ar), 2.64 (t, *J*=6.7 Hz, 2H, CH_2), 3.42 (s, 1H, OH), 3.49 (m, 2H, CH_2O), 6.42 (s, 1H, 3-H), 7.24 (d, *J*=8.3 Hz, 2H, *m*-Ar), 7.83 (d, *J*=8.3 Hz, 2H, *o*-Ar), 12.10 (s, 1H, 4-NH) ppm. ^{13}C NMR (100 MHz, 28 °C): δ=17.8 (5-CH_3), 21.3 (CH_3–Ar), 29.3 (CH_2), 60.3 (CH_2O), 84.7 (C-3), 103.3 (C-6), 126.5 (C*o*-Ar), 129.7 (C*m*-Ar), 130.3 (C*i*-Ar), 138.7 (C*p*-Ar) 142.4 (C-5), 147.3 (C-3a), 153.4 (C-2), 157.2 (C(7)]O) ppm. MS: (70 eV, EI): *m*/*z* (%)=283 (50) [M^+], 254 (80) [M−29], 252 (100) [M−29], 224 (31) [M−59], 198 (17) [M−85], 53 (18), 42 (15), 41 (9). Elemental analysis calcd for $C_{16}H_{17}N_3O_2$ (283.33): C, 67.83; H, 6.05; N, 14.83. Found: C, 67.85; H, 6.10; N, 14.83.

*4.4.5. (3Z)-3-{1-[(5-(4-Methoxyphenyl)-1H-pyrazol-3-yl)amino]ethylidene}-4,5-dihydrofuran-2(3H)-one (**19e**).* This compound was isolated as light yellow solid in 65% yield; mp 188–190 °C. FTIR: ν=1611 (C]N), 1679 (C]O), 3201 (N–H) cm^{-1}. ^1H NMR (400 MHz, 33 °C): δ=2.17 (s, 3H, CH_3), 2.85 (t, *J*=7.8 Hz, 2H, 4-CH_2), 3.77 (s, 3H, OCH_3–Ar), 4.24 (t, *J*=7.8 Hz, 2H, 5-CH_2), 6.40 (s, 1H, 4′-H), 7.00 (d, *J*=8.6 Hz, 2H, *o*-Ph), 7.67 (d, *J*=8.6 Hz, 2H, *m*-Ph), 10.03 (s, 1H, NH-amino), 12.76 (s, 1H, 1′-NH) ppm. ^{13}C NMR (100 MHz, 33 °C): δ=18.3 (CH_3), 26.0 (4-CH_2), 55.7 (OCH_3–Ar), 65.4 (5-CH_2), 94.1 (C-4′), 97.8 (C-3), 114.8 (C-*m*), 126.9 (C-*o*), 128.0 (C-*i*), 142.4 (C-31), 147.1 (C-3′), 153.3 (C-5′), 159.7 (C-*p*), 173.6 (C-2, C]O) ppm. MS: (70 eV, EI): *m*/*z* (%)=299 (65) [M^+], 270 (83) [M−29], 268 (100) [M−31], 240 (26) [M−59], 53 (17), 42 (10). Elemental analysis calcd for $C_{16}H_{17}N_3O_3$ (299.33): C, 64.20; H, 5.72; N, 14.04. Found: C, 64.23; H, 5.78; N, 14.09.

*4.4.6. (3Z)-3-{1-[(5-(4-Chlorophenyl)-1H-pyrazol-3-yl)amino]ethylidene}-4,5-dihydrofuran-2(3H)-one (**19f**).* This compound was isolated as light yellow solid in 68% yield; mp 167–169 °C. FTIR: ν=1604 (C]N), 1668 (C]O), 3189 (N–H) cm^{-1}. ^1H NMR (400 MHz, 33 °C): δ=2.16 (s, 3H, CH_3), 2.85 (t, *J*=7.8 Hz, 2H, 4-CH_2), 4.26 (t, *J*=7.8 Hz, 2H, 5-CH_2), 6.54 (s, 1H, 4′-H), 7.48 (d, *J*=8.1 Hz, 2H, *m*-Ph), 7.74 (d, *J*=8.1 Hz, 2H, *o*-Ph), 10.05 (s, 1H, NH-amino), 12.95 (s, 1H, 1′-NH) ppm. ^{13}C NMR (100 MHz, 33 °C): δ=18.2 (CH_3), 25.9 (4-CH_2), 65.7 (5-CH_2), 95.2 (C-4′), 100.1 (C-3), 127.28 (C-*m*), 128.4 (C-*o*), 132.0 (C-*i*), 133.1 (C-*p*), 142.5 (C-31), 147.5 (C-3′), 157.1 (C-5′), 173.6 (C-2, C]O) ppm. MS: (70 eV, EI): *m*/*z* (%)=303/305 (100/35) [M^+], 288/290 (45/13) [M−15], 258/260 (53/20) [M−45], 244/246 (45/15) [M−59], 41 (20). Elemental analysis calcd for $C_{15}H_{14}ClN_3O_2$ (303.75): C, 59.31; H, 4.65; N, 13.83. Found: C, 59.33; H, 4.68; N, 13.85.

*4.4.7. 2-(4-Bromophenyl)-6-(2-hydroxyethyl)-5-methylpyrazolo[1,5-a]pyrimidin-7(4H)-one (**20g**).* This compound was isolated as white solid in 65% yield; mp 242–244 °C. FTIR: ν=1611 (C]N), 1681 (C]O), 3194 (N–H) cm^{-1}. ^1H NMR (400 MHz, 32 °C): δ=2.34 (s, 3H, 5-CH_3), 2.62 (t, *J*=6.5 Hz, 2H, CH_2), 3.49 (m, 2H, CH_2O), 4.56 (s, 1H, OH), 6.49 (s, 1H, 3-H), 7.62 (d, *J*=8.2 Hz, 2H, *m*-Ar), 7.90 (d, *J*=8.2 Hz, 2H, *o*-Ar), 12.13 (s, 1H, 4-NH) ppm. ^{13}C NMR (100 MHz, 32 °C): δ=18.4 (5-CH_3), 29.6 (CH_2), 58.3 (CH_2O), 94.6 (C-3), 100.0 (C-6), 117.1 (C*i*-Ar), 127.1 (C*o*-Ar), 129.3 (C*m*-Ar), 130.0 (C*p*-Ar) 139.4 (C-5), 148.1 (C-3a), 154.9 (C-2), 162.6 (C-7, C]O) ppm. MS: (70 eV, EI): *m*/*z* (%)=347/349 (25/26) [M^+], 318/320 (100/97) [M−29], 288/290 (17/18) [M−59], 96 (29), 42 (24). Elemental analysis calcd for $C_{15}H_{14}BrN_3O_2$ (348.20): C, 51.74; H, 4.05; N, 12.07. Found: C, 51.75; H, 4.09; N, 12.10.

*4.4.8. (3Z)-3-{1-[(5-(4-Nitrophenyl)-1H-pyrazol-3-yl)amino]ethylidene}-4,5-dihydrofuran-2(3H)-one (**19h**).* This compound was isolated as light yellow solid in 46% yield; mp 222–224 °C. FTIR: ν=1598 (C]N), 1671 (C]O), 3194 (N–H) cm^{-1}. ^1H NMR (400 MHz, 34 °C): δ=2.18 (s, 3H, CH_3), 2.88 (t, *J*=7.8 Hz, 2H, 4-CH_2), 4.28 (t, *J*=7.8 Hz, 2H, 5-CH_2), 6.76 (s, 1H, 4′-H), 8.01 (d, *J*=8.6 Hz, 2H, *m*-Ph), 8.28 (d, *J*=8.6 Hz, 2H, *o*-Ph), 10.08 (s, 1H, NH-amino), 13.23 (s, 1H, 1′-NH) ppm. ^{13}C NMR (100 MHz, 34 °C): δ=18.2 (CH_3), 25.9 (4-CH_2), 65.7 (5-CH_2), 94.4 (C-4′), 100.0 (C-3), 124.7 (C-*m*), 126.3 (C-*o*), 138.6 (C-*i*), 142.5 (C-31), 146.1 (C-*p*), 147.1 (C-3′), 152.9 (C-5′), 173.6 (C-2, C]O) ppm. MS: (70 eV, EI): *m*/*z* (%)=314 (100) [M^+], 299 (26) [M−15], 269 (32) [M−45], 255 (21) [M−59], 67 (20), 42 (20), 41 (29). Elemental analysis calcd for $C_{15}H_{14}N_4O_4$ (314.30): C, 57.32; H, 4.49; N, 17.83. Found: C, 57.35; H, 4.51; N, 17.84.

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