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Solvent-Free Synthesis of Fused Pyrazolo[1,5-*a*]pyrimidines by Reaction of 5-Amino-1*H*-pyrazoles and β-Triketones

Jairo Quiroga*[,a], Jaime Portilla*[,b], Silvia Cruz[c], Rodrigo Abonía[a], Braulio Insuasty[a], Manuel Nogueras[d], Justo Cobo[d] and Mike Hursthouse[e]

[a]*Grupo de Investigación de Compuestos Heterocíclicos, Departamento de Química, Universidad del Valle, A. A. 25360, Cali, Colombia*

[b]*Grupo de Investigación en Compuestos Bio-orgánicos, Departamento de Química, Universidad de los Andes, Carrera 1 No. 18A 10, Bogotá, Colombia*

[c]*Departamento de Química, Universidad de Nariño, A. A. 1175, Pasto-Colombia*

[d]*Departamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, Spain*

[e]*School of Chemistry, University of Southampton, Highfield, Southampton. SO17 1BJ, UK*

Abstract: The solvent-free reaction between 5-amino-1*H*-pyrazoles and β-triketones (2-acetyldimedone and 2-acetylindandione) leads to the formation of new fused pyrazolo[1,5-*a*]pyrimidines in good yields. A possible mechanistic route is postulated on the basis of the isolation of the cyclization intermediate. The structures and regiospecificity of the reaction were determined on the basis of nmr measurements and X-ray diffraction.

Keywords: 5-Amino-1*H*-pyrazole, β-triketones, trimethyl *ortho*-acetate, fused pyrazolo[1,5-*a*]pyrimidine, solvent-free reaction.

INTRODUCTION

Among the organic structures, heterocycles are of particular interest in combinatorial synthesis due their analogies with many natural and synthetic molecules with known biological activity [1]. In general, among fused heterocyclic compounds, the pyrazolo[1,5-*a*]pyrimidines and their derivatives are known to possess pharmacological activity, i.e. anxiolytic properties [2]. Some pharmacophores containing the quinazoline skeleton [3], such pyrazoloquinazolines have exhibited multiple pharmaceutical applications, such as antifungal properties [4] or as potential antimetabolite agents [5-10], being even potent amino acid antagonist [8] or showing anti-inflammatory, antiasthmatic, antiallergenic and immunosuppressant activities [9]. Several methods for the synthesis of fused pyrazolo[1,5-*a*]pyrimidines have been reported, several starting from fused aminopyrazoles [10], but few from non-fused aminopyrazoles [11]; although there has been reported the 3-amino-1*H*-pyrazoles reacting with bidentate electrophiles for the synthesis of non-fused pyrazolo[1,5-*a*]pyrimidines [12].

The cyclic β-triketones are part of the skeleton of many biologically active natural products and also are precursors suitable for a wide variety of compounds with valuable and diverse biological and pharmacological properties [13]. These ketones, acting as bidentate electrophiles have been used in the synthesis of fused heterocyclic compounds through regioselective cyclocondensations, which would depend on the major tautomer of these compounds [14].

Industrial chemistry in the new millennium is widely adopting the concept of "Green Chemistry" [15] to meet the fundamental scientific challenges for protecting the human health and environment while maintaining commercial viability. For example, the possibility of performing reactions under solvent-free conditions to enhance the reaction efficiency from both economic and ecological points of view has given to these kinds of procedures a remarkable synthetic value and received a great attention [16]. The potential application of microwave technology in organic synthesis [17], particularly in solvent-free conditions, is increasing rapidly because of its reaction simplicity, less pollution, and minimum reaction time providing rapid access to large libraries of diverse molecules.

As part of our interest in novel biologically active nitrogen-containing heterocyclic scaffolds [18] and continuing our studies on the application of solvent-free cyclocondensation procedures [19], we are here describing the solvent-free reaction between 5-amino-1*H*-pyrazoles **3** and β-triketones (2-acetyldimedone **4** and 2-acetylindandione **5**), in order to obtain the fused pyrazolo[1,5-*a*]pirimidines **1** and **2** (Fig. **1**).

RESULTS AND DISCUSSION

In order to prepare the target pyrazolo[1,5-*a*]quinazolin-6-ones **1** we have carried out the reaction of a series of 5-amino-3-R-1*H*-pyrazoles **3a-h** with equimolecular amounts

*Address correspondence to these authors at the Grupo de Investigación de Compuestos Heterocíclicos, Departamento de Química, Universidad del Valle, A.A. 25360, Cali, Colombia and Grupo de Investigación en Compuestos Bio-orgánicos, Departamento de Química, Universidad de los Andes, Carrera 1 N° 18A 10, Bogotá, Colombia; Tel: +57(1) 3394949 Ext. 2080; Fax: +57(1) 3324366,
E-mails: jaiquir@.univalle.edu.co; jportill@uniandes.edu.co

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of 2-acetyldimedone **4** under solvent-free conditions heated in an oil-bath at 180 ºC for 1.5 minutes in an air open Pyrex-tube. The reaction proceeded regioselectively as expected rendering the compounds **1** in good isolated yields (Scheme **1**).

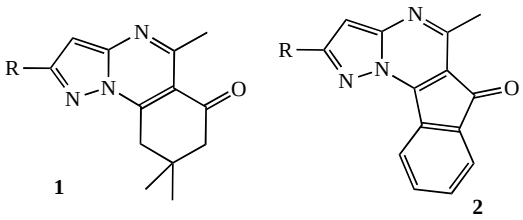


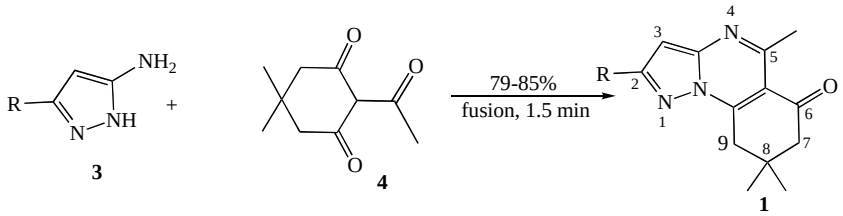
Fig. (1). Target pyrazolo[1,5-*a*]pyrimidines.

The structures of the new synthesized pyrazolo[1,5-*a*]quinazolines **1** have been determined by analytical and spectroscopic data, mainly by nmr analysis, and by X-ray diffraction. The nmr data are consistent with structures **1**. Taking as example compound **1a,** the heterocyclic nucleus exhibits a ^{1}H-nmr spectrum (see experimental) with one sharp singlet at 6.97 ppm, corresponding to the =CH-pyrazole proton at position 3, what is the key for the proposed reaction route, discarding the possible formation of pyrazoloquinolines **1'** (Fig. **2**); another two singlets appear around 2.56 and 3.39 ppm corresponding to the diastereotopic CH_2-groups at position 9 and 7 respectively.

The whole carbon skeleton was assigned using ^{13}C-nmr spectra, combining with dept, and two-dimensional ^{1}H, ^{13}C shift correlation HMQC and HMBC experiments and noesy. Compound **1a** shows in its ^{13}C-nmr spectrum the signals for C2 and C5 at higher δ values 153.5 and 158.1 ppm respectively, than that for carbon atom C5a at δ values 112.5 ppm, which is due to the influence of the linked nitrogen and the carbonyl group (C=O, δ=195.1 ppm). The isolation of single crystals for several compounds **1** permitted the unambiguous determination of their crystal structure from X-ray diffraction analysis [20]. All those crystal structures present similar crystal features. Regarding the mass spectra, all products **1** exhibit similar behavior in their fragmentation, showing the molecular peak as the base peak with a typical loss of the methyl group.

In order to verify the versatility of above described method, we have carried out, under the same conditions (direct fusion of equimolar amount of precursors **3** and **5** in an oil-bath at 180 ºC for 3 minutes), the reaction between the aminopyrazoles **3** with 2-acetylindandione **5**. In this case, the indeno[2,1-*e*]pyrazolo[1,5-*a*]-pyrimidin-6-ones **2** were obtained, also in a regioselectivite manner, in good isolated yields (Scheme **2**).

It has to be remarked that when the reaction was carried out with 5-amino-3-*tert*-butyl-1*H*-pyrazole **3b** under the same conditions but with shorter reaction time (1.5 min) a new compound was formed, which appears mixed with **2b**. The reaction mixture was treated with ethanol. After the solvent was removed, this new compound was separated by column chromatography on silica gel, using dichloromethane-ethanol (±40:1 v/v) as eluent. The first fraction eluted contained the compound **2b** and the second fraction



Entry	R	Yield., %
1a	CH_3	85
1b	$(CH_3)_3C$	85
1c	C_6H_5	82
1d	4-CH_3-C_6H_4	82
1e	4-CH_3O-C_6H_4	80
1f	4-O_2N-C_6H_4	79
1g	4-Cl-C_6H_4	83
1h	4-Br-C6H_4	82

Scheme 1. Synthesis of pyrazolo[1,5-*a*]quinazolines **1**.

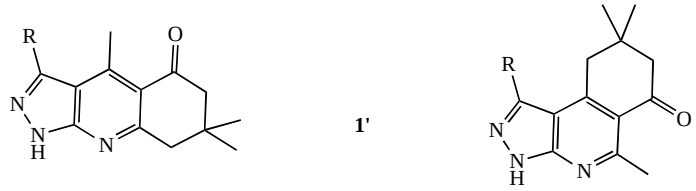
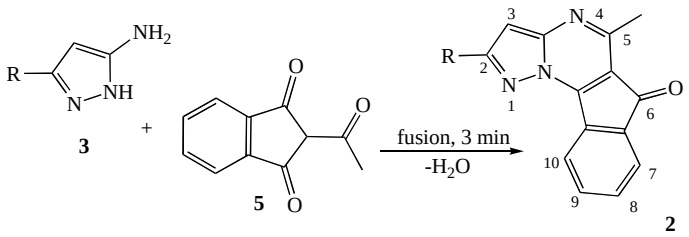


Fig. (2). Regioisomeric pyrazoloquinolines **1'.**



Entry	R	Yield., %
2a	CH_3	85
2b	$(CH_3)_3C$	85
2c	C_6H_5	80
2d	4-CH_3-C_6H_4	75
2e	4-CH_3O-C_6H_4	77
2f	4-O_2N-C_6H_4	78
2g	4-Cl-C_6H_4	80
2h	4-Br-C6H_4	74

Scheme 2. Synthesis of indeno[2,1-*e*]pyrazolo[1,5-*a*]pyrimidin-6-ones **2**.

contained the new compound 2-{1-[(5-*tert*-butyl-1*H*-pyrazol-3-yl)amino]ethylidene}-1*H*-indane-1,3(2*H*)-dione **6b** (Fig. **3**).

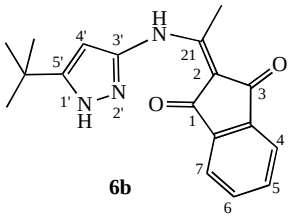


Fig. (3). Intermediate isolated in the reaction.

The subsequent heating at 180 °C of intermediate **6b** for 1.5 minutes additionally leads to the formation of the expected compound **2b.** This experimental fact confirmed that the reaction proceeds through the intermediate type **6**, with subsequent loss of a second water molecule.

The structures of all compounds (**2a-h** and **6b**) have been determined by analytical and spectroscopic data. In addition, the structure of the intermediate isolated **6b** was confirmed by X-Ray diffraction analysis [21].

In general, there is a great similarity in the nmr spectra of indenopyrazolo[1,5-*a*]quinazolines **2** and the pyrazolo[1,5-*a*]quinazolines **1**. For example, compound **2b** exhibits a ^{1}H-nmr spectrum (see experimental) with one sharp singlet at 6.52 ppm, corresponding to the =CH-pyrazolic proton at positions 3, which allowed to discard the possible formation of indenopyrazolopyridines **2'** (Fig. **4**).

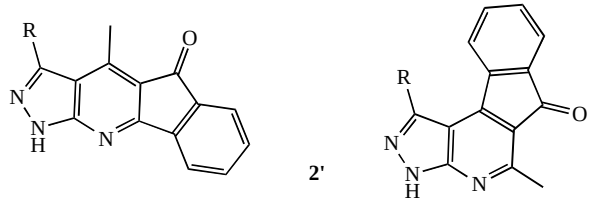


Fig. (4). Regioisomeric indenopyrazolopyridines **2'**.

On the other hand, the intermediate **6b** exhibits a ^{1}H-nmr spectrum (see experimental) with one sharp singlet at 6.13 ppm, corresponding to the =CH-pyrazolic proton at positions 4', supporting the proposed reaction route; another two wide singlets appear around 12.35 and 12.71 ppm corresponding to the NH-pyrazolic proton at positions 1' and the NH-group at position 3'. This compound shows in its ^{13}C-nmr spectrum the signals for C1 and C3 (C=O) at higher δ values 190.1 and 193.7 ppm respectively, than those for carbon atom C2 and C21 at δ values 100.0 and 103.3 ppm, which is due to the influence of the enamine group (C=CNH). Regarding the mass spectra, the intermediate **6b** exhibits a molecular peak as the base peak. Solid state gives unambiguous proof of the above features, and the isolation of single crystals for the intermediate isolated **6b** permitted the determination of its crystal structure from X-ray diffraction analysis (Fig. **5**) [21].

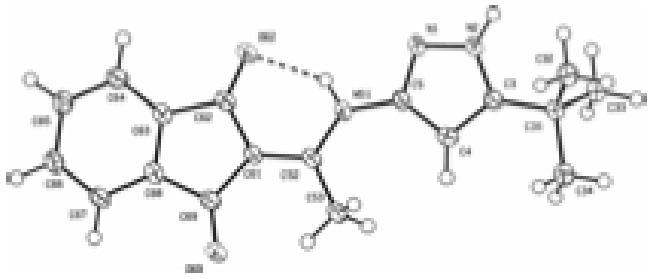


Fig. (5). Molecular structure of intermediate isolated **6b** showing 30% of probability ellipsoid.

We believe that the high regioselectivity of our reaction can be explained on the basis of the existence of different tautomeric forms of β-triketones. It is known that for studied cyclic β-triketones the predominant tautomeric form corresponds to exocyclic enol form **4b** and **5b** [14] (Fig. **6**).

According to our results, we have postulated a route for the formation of compounds **1** and **2**. As initial stage, we assume a Michael type nucleophilic addition of NH_2-group of aminopyrazole **3** to C=C bond of compounds **4** and **5** with

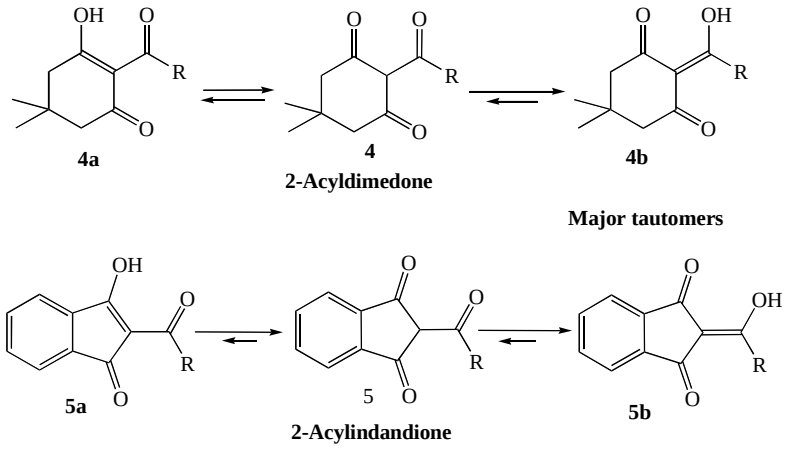
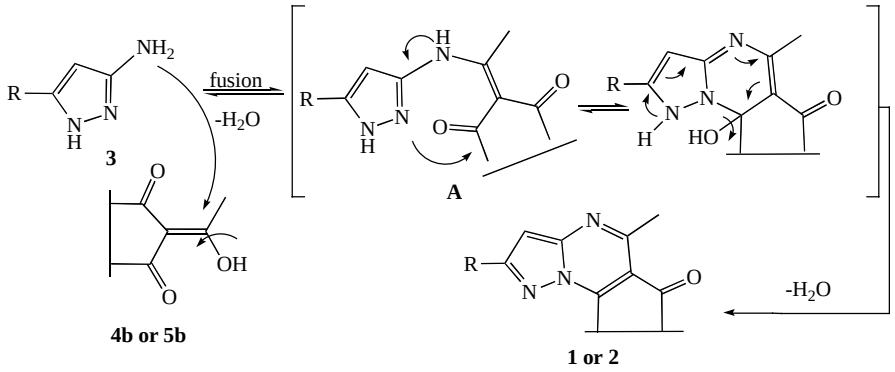


Fig. (6). Some possible tautomers of 2-acyldimedone and 2-acylindandione.



Scheme 3. Postulated route for the formation of compounds **1** and **2**.

loss of a water molecule to give the intermediate **A** (intermediate type **6**), which can then evolve by cyclocondensation *via* attack of the nucleophilic nitrogen at the pyrazole to a carbonyl group and subsequent loss of a second water molecule to form the isolated compounds **1** and **2** respectively. In this reaction, the β-triketones **4** and **5** behave like alkoxymethylene-β-dicarbonyl system of large reactivity [14,19f] (Scheme **3**).

An additional evidence to support the proposed mechanistic route is the fact that the three-component reaction between aminopyrazole **3**, dimedone **7** and ethyl *ortho*-acetate **8** in an air-open Pyrex-erlenmeyer, irradiated in a multimode microwave oven during 1-2 minutes (at 600 watts) leads to the formation of the same compounds **1** but in acceptable isolated yields (40-65%). We consider that the reaction occurred through of the intermediate **9**, which is an alkoxymethylene-β-dicarbonyl system (Scheme **4**).

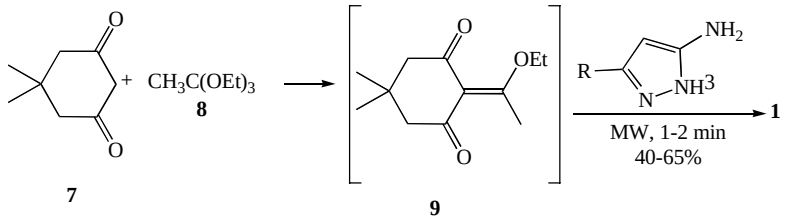
CONCLUSIONS

In summary, we have developed a simple, convenient and rapid method for the synthesis of pyrazolo[1,5-*a*]quinazolin-6-ones **1** and indeno[2,1-*e*]pyrazolo[1,5-*a*]pyrimidin-6-ones **2** by reaction between aminopyrazole **3** with β-triketones **4** or **5** under solvent-free conditions in a regiochemical manner. This method avoids the use of toxic and flammable organic solvents and extended reaction times, which makes it a versatile and friendly environmentally methodology.

EXPERIMENTAL SECTION

General Information

Melting points were determined in a Stuart SMP3 Melting Point Apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu Prestige 21 spectrophotometer and only partial spectral data are listed. NMR spec-



Scheme 4. Three-component synthesis of pyrazolo[1,5-*a*]-quinazolines **1**.

tra were run on a Bruker Avance at 400 MHz (9.4 Tesla, 400.13 MHz for 1H, 100.62 MHz for ^{13}C) using TMS as internal reference; chemical shift (δ in ppm) are given from internal solvent, $CDCl_3$ 7.26 for ^1H and 77.0 for ^{13}C, DMSO-d_6 2.49 for ^1H and 39.5 for ^{13}C. The mass spectra were recorded on a Hewlett Packard HP Engine-5989 spectrometer (equiped with a direct inlet probe) and operating at 70 eV, High Resolution Mass Spectra (HRMS) by electron impact were recorded on a Micromass AutoSpec-Ultima, magnetic sector mass spectrometer at 70 eV. The elemental analyses have been obtained using a LECO CHNS-900 elemental analyzer. Analytical thin-layer chromatography (TLC) was carried out with silica gel 60 F_{254} pre-coated aluminum sheets (Merck). Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh).

General Procedure for the Preparation of the Substituted 5,8,8-trimethyl-8,9-dihydropyrazolo[1,5-*a*]quinazolin-6(7*H*)-ones (1a-h)

Method A

A mixture of equimolar amounts of 5-amino-1-*H*-pyrazole **3** and 2-acetyldimedone **4** was heated in an oil-bath at 180 ºC for 1.5 minutes. It was then stirred and allowed to cool to room temperature till it solidified. The solid material was treated with ethanol. After the solvent was removed and the products formed were recrystallized from absolute ethanol.

Method B

A mixture of **3** with equimolecular amounts of dimedone **7** and an excess of trimethyl-*ortho*-acetate **8** was placed in an air open Pyrex-erlenmeyer irradiated in a multimode microwave oven during 1-2 minutes (at 600 watts). The product was treated with ethanol and recristallized from absolute ethanol.

Yields are given in order method A/method B.

2,5,8,8-Tetramethyl-8,9-dihydropyrazolo[1,5-a]quinazolin-6(7H)-one (1a)

This compound was obtained according to the general procedures as a white solid in 85%/58% yields, mp = 198-199 ºC; IR (KBr): 1725 cm^{-1} (C=O), 1620 cm^{-1} (C=N); δ_H (DMSO-d_6): 1.16 (s, 6H, 8-CH_3), 2.37 (s, 3H, 2-CH_3), 2.56 (s, 2H, H9), 2.71 (s, 3H, 5-CH_3), 3.39 (s, 2H, H7), 6.97 (s, 1H, H3); δ_C (DMSO-d_6): 14.9 (2-CH_3), 24.6 (5-CH_3), 26.9 (8-CH_3), 31.1 (C8), 36.8 (C9), 51.9 (C7), 92.8 (C3), 112.5 (C5a), 148.1 (C9a), 151.9 (C3a), 153.5 (C2), 158.1 (C5), 195.1 (C=O); MS: (70 eV) m/z (%) = 243 (100, M^+), 228 (17). HRMS: calcd for $C_{14}H_{17}N_3O$: *m/z* = 243.1372; found, 243.1369.

2-tert-Butyl-5,8,8-trimethyl-8,9-dihydropyrazolo[1,5-a]quinazolin-6(7H)-one (1b)

This compound was obtained according to the general procedures as a white solid in 85%/62% yield, mp = 187-189 ºC; IR (KBr): 1715 cm^{-1} (C=O), 1623 cm^{-1} (C=N); δ_H (DMSO-d_6): 1.15 (s, 6H, 8-CH_3), 1.39 (s, 9H, $(CH_3)_3$), 2.55 (s, 2H, H9), 2.70 (s, 3H, 5-CH_3), 3.38 (s, 2H, H7), 6.96 (s, 1H, H3); δ_C (DMSO-d_6): 24.5 (5-CH_3), 26.7 (8-CH_3), 29.9 ($(CH_3)_3$), 31.0 (C8), 32.0 (C*t*), 36.7 (C9), 51.8 (C7), 92.6 (C3), 112.3 (C5a), 148.0 (C9a), 151.7 (C3a), 158.0 (C5), 165.9 (C2), 195.3 (C=O); MS: (70 eV) m/z (%) = 285 (100, M^+), 270 (15). HRMS: calcd for $C_{17}H_{23}N_3O$: *m/z* = 285.1841; found, 285.1839.

5,8,8-Trimethyl-2-phenyl-8,9-dihydropyrazolo[1,5-a]quinazolin-6(7H)-one (1c)

This compound was obtained according to the general procedures as a yellow solid in 82%/62% yield, mp = 219-220 ºC; IR (KBr): 1721 cm^{-1} (C=O), 1610 cm^{-1} (C=N); δ_H (DMSO-d_6): 1.18 (s, 6H, 8-CH_3), 2.57 (s, 2H, H9), 2.72 (s, 3H, 5-CH_3), 3.40 (s, 2H, H7), 6.98 (s, 1H, H3), 7.37 (t, 1H, H*p*, *J* = 7.72 Hz), 7.43 (t, 2H, H*m*, *J* = 7.49 and 7.72 Hz), 7.95 (d, 2H, H*o*, *J* = 7.49); δ_C (DMSO-d_6): 24.7 (5-CH_3), 26.9 (8-CH_3), 31.2 (C8), 36.9 (C9), 52.0 (C7), 92.8 (C3), 112.5 (C5a), 125.9 (C*o*), 127.8 (C*p*), 128.2 (C*m*), 147.5 (C*i*), 148.2 (C9a), 151.9 (C3a), 157.6 (C2), 158.1 (C5), 195.0 (C=O); MS: (70 eV) m/z (%) = 305 (100, M^+), 290 (12). HRMS: calcd for $C_{19}H_{19}N_3O$: *m/z* = 305.1528; found, 305.1531.

5,8,8-Trimethyl-2-(4-methylphenyl)-8,9-dihydropyrazolo [1,5-a]quinazolin-6(7H)-one (1d)

This compound was obtained according to the general procedures as yellow crystals in 82%/60% yield, mp = 235-237 ºC; IR (KBr): 1702 cm^{-1} (C=O), 1607 cm^{-1} (C=N); δ_H (DMSO-d_6): 1.17 (s, 6H, 8-CH_3), 2.58 (s, 2H, H9), 2.77 (s, 3H, 5-CH_3), 2.94 (s, 3H, *p*-CH_3), 3.43 (s, 2H, H7), 7.01 (s, 1H, H3), 7.30 (d, 2H, H*m*, *J* = 8.50 Hz), 7.93 (d, 2H, H*o*, *J* = 8.50 Hz); δ_C (DMSO-d_6): 20.1 (*p*-CH_3), 24.9 (5-CH_3), 27.2 (8-CH_3), 31.0 (C8), 37.2 (C9), 51.8 (C7), 93.0 (C3), 112.2 (C5a), 128.7 (C*m*), 128.8 (C*i*), 125.8 (C*o*), 138.4 (C*p*), 147.9 (C9a), 152.1 (C3a), 157.3 (C2), 157.4 (C5), 194.8 (C=O); MS: (70 eV) m/z (%) = 319 (100, M^+), 304 (9). HRMS: calcd for $C_{20}H_{21}N_3O$: *m/z* = 319.1685; found, 319.1688.

2-(4-Methoxyphenyl)-5,8,8-trimethyl-8,9-dihydropyrazolo [1,5-a]quinazolin-6(7H)-one (1e)

This compound was obtained according to the general procedures as yellow crystals in 80%/65% yield, mp = 204-206 ºC; IR (KBr): 1698 cm^{-1} (C=O), 1605 cm^{-1} (C=N); δ_H (DMSO-d_6): 1.18 (s, 6H, 8-CH_3), 2.59 (s, 2H, H9), 2.78 (s, 3H, 5-CH_3), 3.43 (s. 2H, H7), 3.85 (s, 3H, OCH_3), 6.98 (s. 1H, H3), 7.06 (d, 2H, H*m*, *J* = 8.00 Hz), 7.98 (d, 2H, H*o*, *J* = 8.00 Hz); δ_C (DMSO-d_6): 25.0 (5-CH_3), 27.4 (8-CH_3), 31.1 (C8), 37.2 (C9), 51.8 (C7), 54.9 (OCH_3), 92.8 (C3), 112.1 (C5a), 114.0 (C*m*), 124.4 (C*i*), 127.5 (C*o*), 148.0 (C9a), 152.1 (C3a), 157.3 (C2), 157.4 (C5), 160.2 (C*p*), 194.9 (C=O); MS: (70 eV) m/z (%) = 335 (100, M^+), 320 (5), 279 (20). HRMS: calcd for $C_{20}H_{21}N_3O_2$: *m/z* = 335.1634; found, 335.1629.

5,8,8-Trimethyl-2-(4-nitrophenyl)-8,9-dihydropyrazolo[1,5-a]quinazolin-6(7H)-one (1f)

This compound was obtained according to the general procedure as an orange solid in 79%/40% yield, mp = 298-300 ºC; IR (KBr): 1712 cm^{-1} (C=O), 1612 cm^{-1} (C=N); δ_H (DMSO-d_6): 1.20 (s, 6H, 8-CH_3), 2.62 (s, 2H, H9), 2.75 (s, 3H, 5-CH_3), 3.42 (s, 2H, H7), 7.24 (s, 1H, H3), 7.56 (d, 2H, H*o*, *J* = 7.67 Hz), 8.09 (d, 2H, H*m*, *J* = 7.67 Hz); δ_C (DMSO-d_6): 26.2 (5-CH_3), 27.8 (8-CH_3), 31.7 (C8), 39.0 (C9), 51.9 (C7), 94.1 (C3), 112.1 (C5a), 128.1 (C*m*), 129.0 (C*o*), 139.2 (C*i*), 146.6 (C*p*), 147.9 (C9a), 152.2 (C3a), 157.1 (C2),

157.5 (C5), 195.8 (C=O); MS: (70 eV) m/z (%) = 335 (100, M^+), 320 (5), 279 (20). HRMS: calcd for $C_{19}H_{18}N_4O_3$: *m/z* = 350.1379; found, 350.1382.

2-(4-Chlorophenyl)-5,8,8-trimethyl-8,9-dihydropyrazolo[1, 5-a]quinazolin-6(7H)-one (1g)

This compound was obtained according to the general procedure as a yellow solid in 83%/60% yield, mp = 219-220 ºC; IR (KBr): 1711 cm^{-1} (C=O), 1605 cm^{-1} (C=N); δ_H (DMSO-d_6): 1.18 (s, 6H, 8-CH_3), 2.57 (s, 2H, H9), 2.79 (s, 3H, 5-CH_3), 3.42 (s, 2H, H7), 7.00 (s, 1H, H3), 7.42 (d, 2H, H*m*, *J* = 8.05 Hz), 7.91 (d, 2H, H*o*, *J* = 8.07 Hz); δ_C (DMSO-d_6): 24.7 (5-CH_3), 27.3 (8-CH_3), 31.1 (C8), 37.1 (C9), 51.6 (C7), 93.1 (C3), 112.3 (C5a), 127.3 (C*m*), 131.2 (C*i*), 128.0 (C*o*), 132.8 (C*p*), 147.8 (C9a), 152.0 (C3a), 157.2 (C2), 157.3 (C5), 194.9 (C=O); MS: (70 eV) m/z (%) = 341/339 (34/100, M^+), 324 (8). HRMS: calcd for $C_{19}H_{18}ClN_3O$: *m/z* = 341.1109/339.1138 (32/100); found, 341.1112/339.1140 (33/100).

2-(4-Bromophenyl)-5,8,8-trimethyl-8,9-dihydropyrazolo[1, 5-a]quinazolin-6(7H)-one (1h)

This compound was obtained according to the general procedure as a yellow solid in 82%/57% yield, mp = 215-217 ºC; IR (KBr): 1700 cm^{-1} (C=O), 1610 cm^{-1} (C=N); δ_H (DMSO-d_6): 1.17 (s, 6H, 8-CH_3), 2.55 (s, 2H, H9), 2.77 (s, 3H, 5-CH_3), 3.41 (s, 2H, H7), 7.02 (s, 1H, H3), 7.62 (d, 2H, H*m*, *J* = 8.45 Hz), 7.93 (d, 2H, H*o*, *J* = 8.45 Hz); δ_C (DMSO-d_6): 24.5 (5-CH_3), 27.4 (8-CH_3), 31.2 (C8), 37.0 (C9), 51.5 (C7), 92.5 (C3), 112.1 (C5a), 121.2 (C*i*), 127.6 (C*o*), 131.3 (C*m*), 132.1 (C*p*), 147.5 (C9a), 152.1 (C3a), 156.9 (C2), 157.5 (C5), 195.3 (C=O); MS: (70 eV) m/z (%) = 385/383 (98/100, M^+), 370/368 (11/12). HRMS: calcd for $C_{19}H_{18}BrN_3O$: *m/z* = 385.0613/383.0633 (97.3/100); found, 385.0615/383.0631 (98/100).

General Procedure for the Preparation of the Substituted 5-methy-6*H*-indeno[2,1-*e*]pyrazolo[1,5-*a*]pyrimidin-6-one (2a-h)

A mixture of equimolar amounts of 5-amino-1-*H*-pyrazole **3** and 2-acetylindandione **5** was heated in an oil-bath at 180 ºC for 3 minutes. It was then stirred and allowed to cool to room temperature till it solidified. The solid material was treated with ethanol. After the solvent was removed and the products formed were recrystallized from absolute ethanol.

2,5-Dimethy-6H-indeno[2,1-e]pyrazolo[1,5-a]pyrimidin-6-one (2a)

This compound was obtained according to the general procedure as an orange solid in 85% yield, mp = 220-221 ºC; IR (KBr): 1711 cm^{-1} (C=O), 1623 cm^{-1} (C=N); δ_H (DMSO-d_6): 2.49 (s, 3H, 2-CH_3), 2.80 (s, 3H, 5-CH_3), 6.51 (s, 1H, 3H), 7.55 (t, 1H, H9, *J* = 7.11 and 7.83), 7.61 (t, 1H, H8, *J* = 7.14 and 7.82), 7.68 (d, 1H, H7, *J* = 7.12), 8.42 (d, 1H, H10, *J* = 7.40); δ_C (DMSO-d_6): 14.7 (2-CH_3), 21.6 (5-CH_3), 95.6 (C3), 110.2 (C5a), 123.4 (C7), 126.2 (C10), 133.3 (C9), 133.8 (C8), 134.2 (C6a), 134.3 (C10a), 151.5 (C3a), 153.1 (C10b), 155.4 (C2), 155.6 (C5), 190.1 (C=O); MS: (70 eV) m/z (%) = 249 (100, M^+), 234 (17), 221 (11). HRMS: calcd for $C_{15}H_{11}N_3O$: *m/z* = 249.0902; found, 249.0901.

2-tert-Butyl-5-methy-6H-indeno[2,1-e]pyrazolo[1,5-a]pyrimidin-6-one (2b)

This compound was obtained according to the general procedure as an orange solid in 85% yield, mp = 231-232ºC; IR (KBr): 1709 cm^{-1} (C=O), 1622 cm^{-1} (C=N); δ_H (DMSO-d_6): 1.48 (s, 9H, $(CH_3)_3$), 2.81 (s, 3H, 5-CH_3), 6.52 (s, 1H, 3H), 7.54 (t, 1H, H9, *J* = 6.96 and 7.80), 7.61 (t, 1H, H8, *J* = 7.04 and 7.76), 7.68 (d, 1H, H7, *J* = 7.00), 8.41 (d, 1H, H10, *J* = 7.28); δ_C (DMSO-d_6): 21.5 (5-CH_3), (30.1 ($(CH_3)_3$), 33.3 (C*t*), 93.8 (C3), 110.0 (C5a), 123.5 (C7), 126.3 (C10), 133.1 (C9), 133.8 (C8), 134.3 (C6a), 134.4 (C10a), 151.6 (C3a), 153.0 (C10b), 155.6 (C5), 173.7 (C2), 189.5 (C=O); MS: (70 eV) m/z (%) = 291 (M^+, 100), 276 (35). HRMS: calcd for $C_{18}H_{17}N_3O$: *m/z* = 291.1372; found, 291.1375.

5-Methy-2-phenyl-6H-indeno[2,1-e]pyrazolo[1,5-a]pyrimidin-6-one (2c)

This compound was obtained according to the general procedure as an orange solid in 80% yield, mp = 273-274 ºC; IR (KBr): 1708 cm^{-1} (C=O), 1618 cm^{-1} (C=N); δ_H (DMSO-d_6): 2.82 (s, 3H, 5-CH_3), 7.29 (s, 1H, 3H), 7.45 (t, 1H, H*p*, *J* = 7.67 Hz), 7.53-755 (m, 3H, H9-H*m*), 7.62-7.67 (m, 2H, H8-H7), 8.09 (d, 2H, H*o*, *J* = 7.45 Hz), 8.44 (d, 1H, H10, *J* = 7.33); δ_C (DMSO-d_6): 21.7 (5-CH_3), 94.1 (C3), 109.9 (C5a), 123.6 (C7), 126.3 (C10), 126.5 (C*o*), 128.7 (C*m*), 129.1 (C*p*), 132.4 (C*i*), 133.1 (C9), 133.8 (C8), 134.3 (C6a), 134.4 (C10a), 151.6 (C3a), 153.0 (C10b), 155.6 (C5), 156.2 (C2), 189.9 (C=O); MS: (70 eV) m/z (%) = 311 (M^+, 100), 296 (5), 77 (25). HRMS: calcd for $C_{20}H_{13}N_3O$: *m/z* = 311.1059; found, 311.1063.

5-Methy-2-(4-methylphenyl)-6H-indeno[2,1-e]pyrazolo[1, 5-a]pyrimidin-6-one (2d)

This compound was obtained according to the general procedure as an orange solid in 75% yield, mp = 270-271 ºC; IR (KBr): 1709 cm^{-1} (C=O), 1624 cm^{-1} (C=N); δ_H (DMSO-d_6): 2.37 (s, 3H, *p*-CH_3), 2.80 (s, 3H, 5-CH_3), 7.22 (s, 1H, 3H), 7.30 (d, 2H, H*m*, *J* = 8.55 Hz), 7.53 (t, 1H, H9, *J* = 7.08 and 7.81), 7.62-765 (m, 2H, H8-H7), 7.92 (d, 2H, H*o*, *J* = 8.55 Hz) 8.43 (d, 1H, H10, *J* = 7.29); δ_C (DMSO-d_6): 20.9 (*p*-CH_3), 21.4 (5-CH_3), 93.7 (C3), 110.1 (C5a), 123.4 (C7), 126.2 (C*o*), 126.5 (C10), 129.5 (C*m*), 129.6 (C*i*), 133.2 (C9), 133.9 (C8), 134.5 (C6a), 134.5 (C10a), 138.8 (C*p*), 151.3 (C3a), 153.2 (C10b), 155.8 (C5), 156.3 (C2), 190.0 (C=O); MS: (70 eV) m/z (%) = 325 (M^+, 100), 310 (10). HRMS: calcd for $C_{21}H_{15}N_3O$: *m/z* = 325.1215; found, 325.1219.

2-(4-Methoxyphenyl)-5-methy-6H-indeno[2,1-e]pyrazolo [1,5-a]pyrimidin-6-one (2e)

This compound was obtained according to the general procedure as an orange solid in 75% yield, mp = 262-263 ºC; IR (KBr): 1704 cm^{-1} (C=O), 1596 cm^{-1} (C=N); δ_H (DMSO-d_6): 2.83 (s, 3H, 5-CH_3), 3.84 (s, 3H, OCH_3), 7.03 (d, 2H, H*m*, *J* = 7.52 Hz), 7.19 (s, 1H, 3H), 7.56-759 (m, 2H, H9-H8), 7.67 (d, 1H, H7, *J* = 7.08), 8.03 (d, 2H, H*o*, *J* = 7.52 Hz), 8.45 (d, 1H, H10, *J* = 7.19); δ_C (DMSO-d_6): 21.3 (5-CH_3), 55.4 (OCH_3), 93.3 (C3), 109.9 (C5a), 112.7 (C*m*), 124.1 (C7), 125.2 (C*i*), 126.4 (C10), 126.8 (C*o*), 133.2 (C9), 134.1 (C8), 134.6 (C6a), 134.7 (C10a), 151.8 (C3a), 153.2 (C10b), 155.4 (C5), 156.1 (C2), 159.5 (C*p*), 190.0 (C=O); MS: (70 eV) m/z (%) = 341 (M^+, 100), 326 (6). HRMS: calcd for $C_{21}H_{15}N_3O_2$: *m/z* = 341.1164; found, 341.1167.

5-Methy-2-(4-nitrophenyl)-6H-indeno[2,1-e]pyrazolo[1,5-a]pyrimidin-6-one (2f)

This compound was obtained according to the general procedure as an orange solid in 78% yield, mp >300 ºC; IR (KBr): 1710 cm^{-1} (C=O), 1616 cm^{-1} (C=N); δ_H (DMSO-d_6): 2.81 (s, 3H, 5-CH_3), 6.52 (s, 1H, 3H), 7.55-765 (m, 3H, H9-H8-H7), 8.34 (dd, 4H H*o*/*m*, *J* = 7.82 Hz), 8.41 (d, 1H, H10, *J* = 7.23); δ_C (DMSO-d_6): 21.5 (5-CH_3), 93.8 (C3), 110.0 (C5a), 123.5 (C7), 124.5 (C*m*), 126.3 (C10), 127.4 (C*o*), 133.1 (C9), 133.8 (C8), 134.3 (C6a), 134.4 (C10a), 138.0 (C*i*), 146.1 (C*p*), 151.6 (C3a), 153.0 (C10b), 153.7 (C2), 155.5 (C5), 189.9 (C=O); MS: (70 eV) m/z (%) = 356 (M^+, 100), 329 (35), 300 (27), 270 (70). HRMS: calcd for $C_{20}H_{12}N_4O_3$: *m/z* = 356.0909; found, 356.0912.

2-(4-Chlorophenyl)-5-methy-6H-indeno[2,1-e]pyrazolo-[1,5-a]pyrimidin-6-one (2g)

This compound was obtained according to the general procedure as an orange solid in 80% yield, mp = 235-236 ºC; IR (KBr): 1707cm^{-1} (C=O), 1622 cm^{-1} (C=N); δ_H (DMSO-d_6): 2.80 (s, 3H, 5-CH_3), 7.33 (s, 1H, 3H), 7.55-7.58 (m, 3H, H9-H*m*) 7.62-7.65 (m, 2H, H8-H7), 8.15 (d, 2H, H*o*, *J* = 8.47 Hz), 8.41 (d, 1H, H10, *J* = 7.25); δ_C (DMSO-d_6): 21.4 (5-CH_3), 94.3 (C3), 110.1 (5a), 123.6 (C7), 126.4 (C10), 128.1 (C*m*), 129.3 (C*o*), 131.0 (C*i*), 133.2 (C9), 133.9 (C8), 134.1 (C*p*), 134.5 (C6a), 134.6 (C10a), 151.7 (C3a), 153.1 (C10b), 155.5 (C5), 156.3 (C2), 190.1 (C=O); MS: (70 eV) m/z (%) = 347/345 (M^+, 35/100), 330 (7). HRMS: calcd for $C_{20}H_{12}ClN_3O$: *m/z* = 347.0639/345.0669 (32/100); found, 347.0642/345.0670 (33/100).

2-(4-Bromophenyl)-5-methy-6H-indeno[2,1-e]pyrazolo-[1,5-a]pyrimidin-6-one (2h)

This compound was obtained according to the general procedure as an orange solid in 74% yield, mp = 255-256 ºC; IR (KBr): 1707cm^{-1} (C=O), 1620 cm^{-1} (C=N); δ_H (DMSO-d_6): 2.81 (s, 3H, 5-CH_3), 7.35 (s, 1H, 3H), 7.54-763 (m, 3H, H9-H8-H7), 7.74 (d, 2H, H*m*, *J* = 8.48 Hz), 8.08 (d, 2H, H*o*, *J* = 8.48 Hz), 8.42 (d, 1H, H10, *J* = 7.31); δ_C (DMSO-d_6): 21.6 (5-CH_3), 94.1 (C3), 110.1 (C5a), 122.5 (C*i*), 123.5 (C7), 126.3 (C10), 128.2 (C*o*), 131.3 (C*m*), 132.3 (C*p*), 133.2 (C9), 133.8 (C8), 134.3 (C6a), 134.4 (C10a), 151.7 (C3a), 153.0 (C10b), 155.5 (C5), 156.1 (C2), 190.0 (C=O); MS: (70 eV) m/z (%) = 391/389 (M^+, 100/99), 296 (8/9). HRMS: calcd for $C_{20}H_{12}BrN_3O$: *m/z* = 391.0143/389.0164 (97.3/100); found, 391.0139/389.0167 (98/100).

*2-{1-[(5-*tert*-Butyl-1*H*-pyrazol-3-yl)amino]ethylidene}-1*H*-indane-1,3(2*H*)-dione (6)*

Equimolar amounts of 5-*tert*-butyl-3-amino-2*H*-pyrazole **1** (2.0 mmol) and 2-acetylindan-1,3-dione **2** (2.0 mmol) were placed in open Pyrex glass vessels and was heated in an oil-bath at 180 ºC for 1.5 min. The reaction mixtures were treated with ethanol and, after removal of the solvent; the products were separated by column chromatography on silica gel, using DCM-EtOH (40:1 v/v) as eluant. The first fraction eluted contained the compound **2** (56%). The second fraction contained the compound **6** (30%). This intermediate **6** was obtained as green crystals in 30% yield, mp = 221-222 ºC. IR (KBr): 3217, 3110 cm^{-1} (NH), 1670 cm^{-1} (C=O), 1611 cm^{-1} (C=N); δ_H (DMSO-d_6): 1.27 (s, 9H, $(CH_3)_3$), 2.74 (s, 3H, CH_3), 6.13 (s, 1H, H4'), 7.64 (m, 4H, H4-7), a 12.35 (s, 1H, NH-1'), 12.71 (s, 1H, NH); δ_C (DMSO-d_6): 15.95 (CH_3), 30.3 ((CH_3)$_3$), 31.3 (C*t*), 95.4 (C4'), 100.0 (C2), 103.3 (C21), 121.4 (C4), 121.6 (C7), 134.0 (C6), 134.2 (C5), 138.5 (C3a), 139.8 (C7a), 154.8 (C3'), 165.4 (C5'), 190.1 (C1), 193.7 (C3); MS: (70 eV) m/z (%) = 309 (100, M^+), 294 (15), 280 (25), 266 (15), 252 (20). HRMS: calcd for $C_{20}H_{12}N_4O_3$: *m/z* = 309.1477; found, 309.1481.

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