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The chameleon-like behaviour of 3-amino-1,2,4-triazole in the Biginelli reaction: unexpected formation of a novel spiroheterocyclic system

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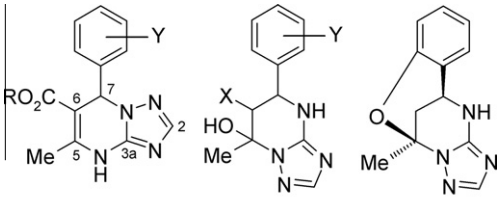
ABSTRACT

A novel Biginelli-like assembly of 3-amino-1,2,4-triazole with methyl acetoacetate and salicylaldehyde has been developed to enable easy access to spiro{[1]benzopyran-2,7′-[1,2,4]triazolo[1,5-*a*]pyrimidine} compounds as representatives of a new class of spiro-fused heterocycles. A three-component condensation mechanism is proposed and discussed.

There are only a few reports describing regioselectivity in the Biginelli-like condensation between 3-amino-1,2,4-triazole (**1**), aromatic aldehydes **2** and alkyl acetoacetates **3**. Although 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines **4** are the commonly accepted products of this three-component process, the formation of a related but oppositely oriented fused heterocycle of type **5**, formally being the regioisomeric precursor of **4**, has been demonstrated independently by two research groups.[1,2] Van der Eycken and coworkers[2] chose substituted salicylaldehydes and various active methylene components for their study. They prepared triazolopyrimidine **5a** under mild conditions (EtOH, HCl catalyst, 40 °C, 16 h); however, when acetone was used for the heterocyclization, two different products were formed, depending on the reaction conditions. The expected bicyclic derivative **6** was formed under the usual reaction conditions, while 5,11-methano[1,2,4]triazolo[1,5-*c*][1,3,5]benzoxadiazocine (**7**) was formed under microwave irradiation in EtOH, in the presence of HCl as the catalyst, at 150 °C for 30 min (Fig. 1).

As we have reported aminoazoles in the Biginelli-like reaction,[3] and since conformationally restricted oxygen-bridged pyridines and pyrimidines also fall into our research area,[4,5] the above article[2] attracted our attention. We present herein our interesting and unexpected results which arose from a re-examination of the above-mentioned three-component cyclization.

The Biginelli-like reaction of 3-aminotriazole (**1**), salicylaldehyde (**2a**) and methyl acetoacetate (**3**) was conducted under slightly modified conditions. Thus, an equimolar mixture of reactants in EtOH was heated at reflux for 20 h with a catalytic amount of 35% aqueous HCl.[6] Surprisingly, the mass spectrum of the isolated product (*m*/*z* 390) was not consistent with the expected derivative **5b** (*m*/*z* 304). This was also corroborated by the ^{1}H and ^{13}C NMR spectra which indicated two salicylaldehyde molecules in the product. Accordingly, upon doubling the equivalents of salicylaldehyde the yield of the new product **8** improved considerably. Applying 2D NMR homo- (COSY, NOESY) and heteronuclear correlation (HSQC, HMBC and the hybrid inverse experiment HSQC-TOCSY) spectroscopy allowed us to determine the structure of the product. Based on these spectra, we postulated two reasonable structures, **8a** and **8′a** (Scheme 1) where the former is a spiroheterocyclic system and the latter an oxygen-bridged triazolopyrimidine. These candidates were resolved by careful analysis



4 **5a**: X = COOEt, Y = 2-OH **7**
5b: X = COOMe, Y = 2-OH
6: X = H, Y = 2-OH

Figure 1. Known products of the Biginelli-like reaction with 3-amino-1,2,4-triazole.

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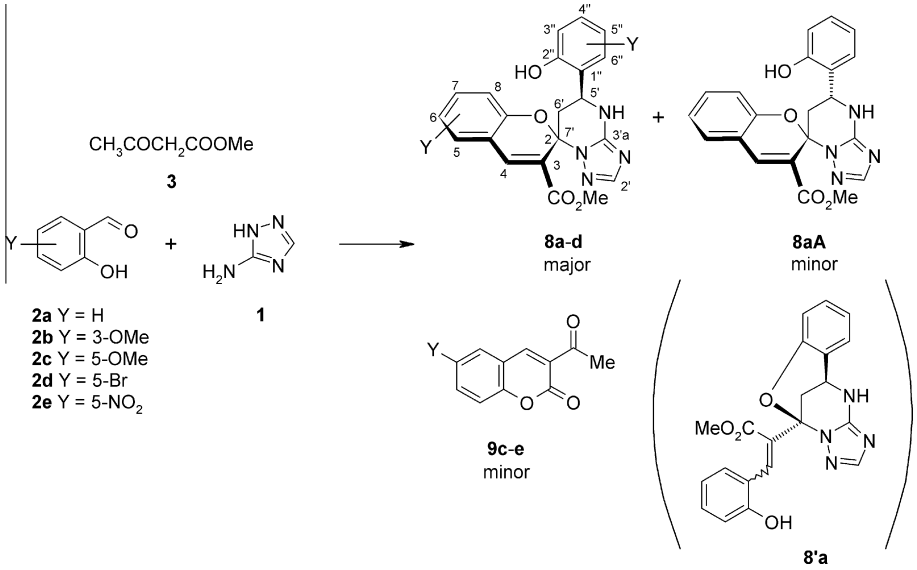


Scheme 1. Biginelli-like condensation of salicylaldehydes with 3-amino-1,2,4-triazole.

of the HMBC measurements. Firstly, the ^{1}H spin–spin connectivities in both aromatic rings were mapped by COSY and then the location of the CH_2CH unit was determined. In addition, the HMBC data revealed that the NH functionality (δ_H 7.82) was attached to the benzylic methine, indicating a reversed orientation. Finally, having recognized the 'benzylic' phenylene fragment, other crucial correlations, observed between the OH proton (δ_H 9.69) and three aromatic carbons of the benzylic unit (i.e., CH *ortho* to C–O and both quaternary ^{13}C atoms), clearly established **8a** as the reaction product. Additional proof of the spiro compound was acquired from NOESY experiments which revealed the close proximity of the OH and adjacent *ortho* aromatic proton belonging to the above phenylene moiety.

Moreover, two additional stereochemical features could be deduced from the ^{1}H NMR spectrum. Firstly, the large vicinal coupling ($^{3}J \approx 12$ Hz) for the CH_2CH segment indicates a *trans*-coplanar relationship between the interacting protons implying that the 2-hydroxyphenyl adopts an equatorial position on the pyrimidine ring. Secondly, of the two methylene protons, the equatorial one resonating at lower field (δ_H 2.59) was identified easily due to its planar 'W' coupling with NH.[6]

In order to confirm the structure of **8a** and to determine its relative stereochemistry, a single-crystal X-ray analysis was undertaken.[7] A perspective view of the molecular conformation is shown in Fig. 2a. As expected, the partially saturated pyrimidine ring adopts a flat envelope conformation and the 2-hydroxyphenyl group occupies the equatorial position and is almost coplanar with the mean plane of the pyrimidine ring. The molecule as a whole consists of two nearly planar segments oriented, due to the spiro fusion, perpendicular to one another. In the crystal, there are two independent molecules differing in the conformation of the methoxycarbonyl substituent bonded to the benzopyran heterocycle.

It is noteworthy that 5′,6′-dihydro-4′*H*-spiro{[1]benzopyran-2,7′-[1,2,4]triazolo[1,5-*a*]pyrimidine}-3-carboxylate (**8a**) repre-

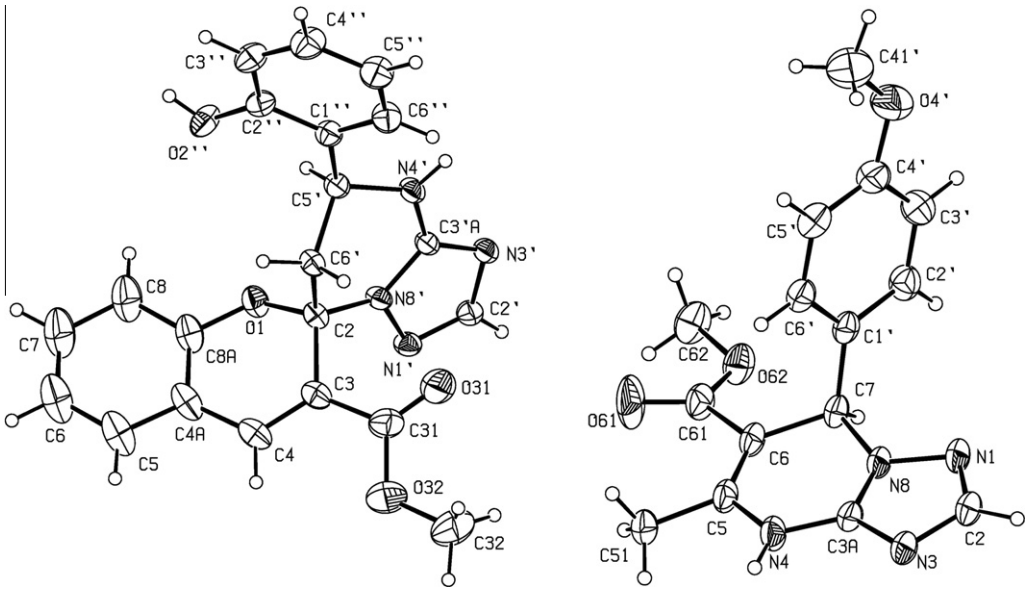
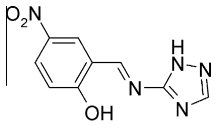


Figure 2. ORTEP views of (a) spiro derivative **8a** (left), and (b) pyrimidine **4a** (right).



10

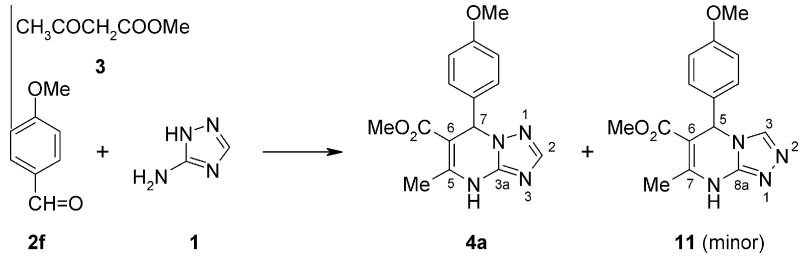
Figure 3. Isolated by-product **10**.

sents a novel polyheterocyclic monospiro system not previously described in the literature.

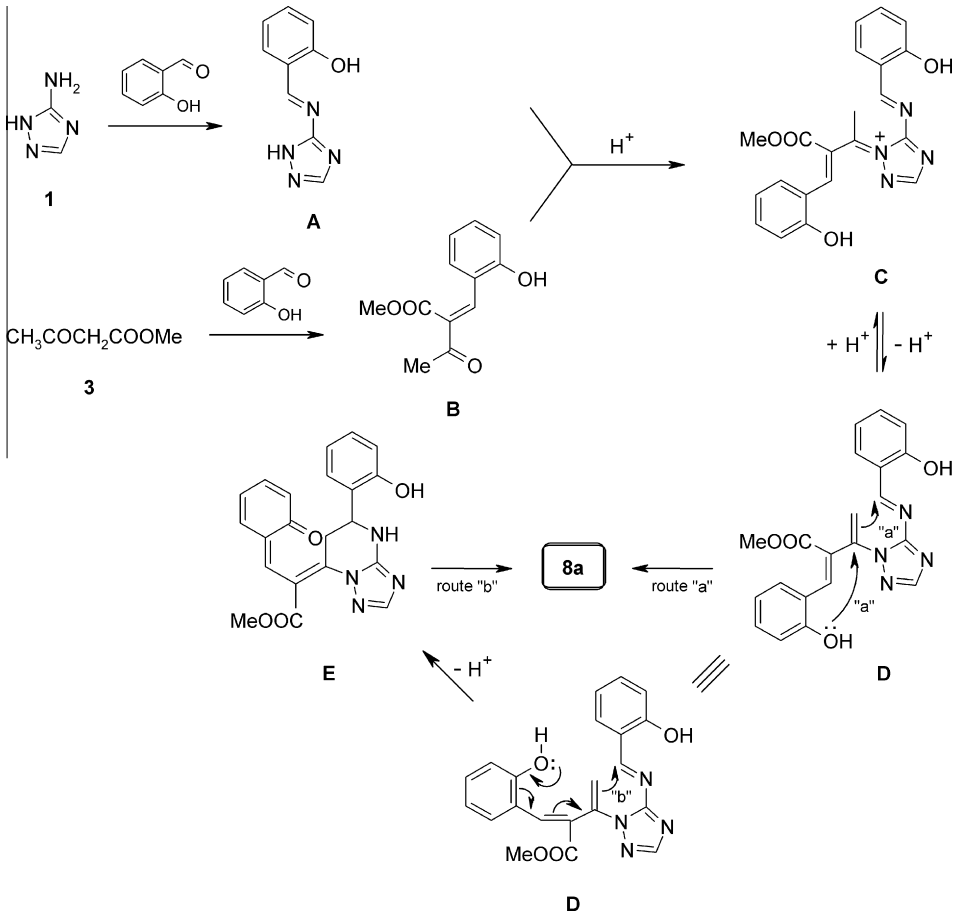
The results of this work provide the first example of the Biginelli reaction with salicylaldehyde where the aldehyde component forms the oxaspiro framework instead of an oxygen-bridged heterocycle,[4,5] or a fused benzopyranone skeleton.[3] In addition, the involvement of the terminal acetoacetate methyl group was also unexpected.

In the search for a by-product or isomer of **8a**, we analysed thoroughly the ^{1}H and ^{13}C NMR spectra of the crude reaction product. While the major fraction of the product precipitated in a pure form, the second crop showed additional low intensity signals which were most likely due to the diastereoisomer, **8aA**. Since both isomers were produced in a 91:9 ratio, this three-component domino reaction evidently proceeds in a highly diastereoselective manner. Attempts to induce isomerization or ring-opening on standing the product **8a** in dimethylsulfoxide for five days (monitored by NMR) failed.

2-Hydroxybenzaldehydes **2b–d** reacted similarly to give the corresponding spiro-fused heterocycles **8b–d**. We did not observe the appearance of any additional diastereoisomer in these cases. In particular, cyclization of 3-methoxysalicylaldehyde (**2b**) proceeded very cleanly. In addition to spiro derivatives **8c** and **8d**, minor by-products identified by ^{1}H NMR as 6-substituted 3-acetylcoumarins **9c** and **9d** were also obtained (Scheme 1). These benz-



Scheme 2. Synthesis of triazolopyrimidine derivatives **4a** and **11**.



Scheme 3. Plausible spirocyclization mechanisms leading to **8a**.

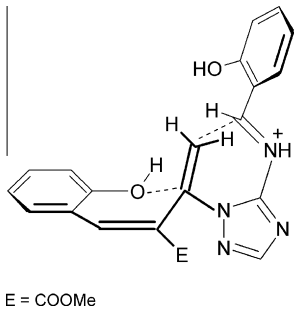


Figure 4. Transition state conformation leading to product **8a**.

opyran-2-ones, formed by condensation of the salicylaldehydes and acetoacetate, crystallized prior to the spiro compounds and hence the target heterocycles **8c** and **8d** could be readily separated. In contrast, 5-nitrosalicylaldehyde **2e** afforded only the corresponding coumarin **9e** along with the azomethine derivative **10** (Fig. 3) which arose from simple condensation of **2e** with aminotriazole **1**.

The spiro-pyrimidines **8a–d**, obtained from electron-rich salicylaldehydes, were isolated by precipitation as stable crystalline compounds in yields ranging from 48% to 64%. From these results, we conclude that the electronic nature of the substituents on the salicylaldehydes has a significant effect on the reaction outcome.

Next, the three-component cyclization was repeated using the related benzaldehyde **2f**, in order to assess the effect of the aldehyde component on the product distribution. Thus, treatment of 4-methoxybenzaldehyde (**2f**) with triazole **1** and methyl acetoacetate (**3**) provided, under identical conditions, the 'normal' Biginelli triazolo[1,5-*a*]pyrimidine (**4a**) accompanied by traces of isomer **11** (8:1 ratio as determined by ^{1}H NMR spectroscopy) (Scheme 2). Although the spectral data[8] offered ample proof of the structure of **4a**, its identity was verified by X-ray diffraction[7] (Fig. 2b). The differences in chemical shift values found for the benzylic proton in **4a** and the isomers of type **5**, **7** and **8** ($\Delta\delta \approx 1$ ppm) are high enough to distinguish between them.

A plausible mechanism for the formation of spiro derivatives **8** is shown in Scheme 3. Thus, the initially produced precursors, aldimine **A** and Knoevenagel adduct **B**, combine in a condensation step to yield iminium species **C**. Intermediate **C** may exist in equilibrium with key enamine **D** which subsequently undergoes a cationic domino process.[9] The postulated ring closure involves intramolecular C–O and C–C bond formation. Consequently, the crucial spirocyclization occurs via a geometrically favoured 6-*exo*-trig/6-*endo*-trig sequence, while the final step providing the product **8** can be formally classified as a Mannich-type reaction. Nevertheless, due to the acidic conditions, it is quite possible that another iminium ion, arising from protonation of the azomethine or triazole nitrogen in structure **D**, may participate in the domino reaction. This could parallel the known mechanism of the Biginelli reaction.[10] Another possible mechanistic pathway from enamine **D** to product **8** can be envisioned which involves the formation of a pyrimidine scaffold bearing a conjugated 1-oxatriene moiety (**E**) which then undergoes stereoselective spiroannelation via a 6π disrotatory electrocyclic ring closure, furnishing the target benzopyran skeleton. We are currently pursuing further experimental work to elucidate the detailed reaction mechanism.

As reported by Royer,[11] formation of six-membered rings via iminium ion cyclization usually occurs through highly-ordered transition states and thereby delivers substituted heterocycles in a stereocontrolled manner. Accordingly, the above-mentioned domino process may allow effective stereocontrol. A tentative model incorporating a sofa–sofa transition state structure has been proposed to rationalize the stereochemical outcome (Fig. 4). In this case, the s-*cis* conformation of the diene unit should ensure a sterically favourable arrangement for attack by the phenolic oxygen, unlike the s-*trans* form in which the corresponding benzene nucleus and the triazole ring would come closer and generate a destabilizing contact.

Finally, our findings demonstrate, in accordance with the above-mentioned article,[2] that in the case of salicylaldehydes, the *ortho*-phenolic hydroxy directs the three-component condensation towards the 'reversed' triazolopyrimidine Biginelli products. By contrast, the reaction employing a substituted benzaldehyde which lacked this functionality follows a pathway leading to the 'normal' isomer. However, Yang and co-workers reported[1] that various benzaldehydes and β-ketoesters often gave rise to a mixture of both regioisomers in an analogous Biginelli cyclization catalysed by *p*-TsOH in aqueous solution. In this respect 4-aminotriazole (**1**) behaves as a chemical chameleon in the Biginelli reaction in the sense that its reactivity depends upon the reactants and conditions used.

In conclusion, the acid-catalysed, three-component condensation of 3-amino-1,2,4-triazole and methyl acetoacetate with various substituted salicylaldehydes represents a synthetically useful route to a new class of spiroheterocycles. The regio- and stereoselective cyclization described herein leads to the spiro{[1]benzopyran-2,7′-[1,2,4]triazolo[1,5-*a*]pyrimidine} system and represents an attractive supplement to the classical Biginelli reaction in terms of constructing a structurally novel type of product. Further application of the reported methodology is currently being investigated.

Acknowledgements

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6. *Typical procedure*. To a solution of 3-amino-1,2,4-triazole (**1**) (0.35 g, 4.0 mmol) in EtOH (20 mL) were added aldehyde **2** (8.0 mmol) and methyl acetoacetate (**3**) (0.44 mL, 4.0 mmol). The mixture containing four drops of concd HCl was refluxed for 20 h. After cooling, the solution was left to crystallize. The crude product was recrystallized: **8a** from MeCN, and **8b–d** from MeOH. In the case of aldehyde **2d**, pure coumarin **9d** precipitated first whereas aldehyde **2c** afforded a mixture of **9c** and **8c** in the first crop. *Methyl 5′-(2-hydroxyphenyl)-5′,6′-dihydro-4′H-spiro{[1]benzopyran-2,7′-[1,2,4]triazolo[1,5-a]pyrimidine}-3-carboxylate* (**8a**): mp 238–239 °C, isolated yield 51%; IR (KBr) ν_{max} 3422, 1715, 1635, 1539, 1458, 1294, 1264, 1217, 1121, 1038, 754 cm^{-1}; ^{1}H NMR (DMSO-d_6, 600 MHz) δ 2.53 (dd, 1H, J = 12.2 and 12.0 Hz, H-6′ax), 2.59 (dd, 1H, J = 12.2 and 1.2 Hz, H-6′eq), 3.63 (s, 3H, OMe), 5.23 (dd, 1H, J = 12.0 and 3.0 Hz, H-5′), 6.82 (dd, 1H, J = 8.4 and 1.2 Hz, H-3″), 6.86 (dt, 1H, J = 7.8 and 1.2 Hz, H-5″), 6.97 (d, 1H, J = 7.8 Hz, H-8), 7.05 (dt, 1H, J = 7.8 and 1.2 Hz, H-6), 7.12 (dt, 1H, J = 7.8 and 1.2 Hz, H-4″), 7.38 (dt, 1H, J = 7.8 and 1.2 Hz, H-7), 7.42 (dd, 1H, J = 7.8 and 1.8 Hz, H-6″), 7.43 (s, 1H, H-2′), 7.50 (dd, 1H, J = 7.8 and 1.8 Hz, H-5), 7.82 (s, 1H, NH), 7.86 (s, 1H, H-4), 9.69 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 38.5 (CH_2), 44.4 (CH), 51.9 (OMe), 85.6 (C-2 spiro), 115.1 (CH-3″), 115.9 (CH-8), 118.3 (C-4a), 119.3 (CH-5″), 122.3 (C-3), 122.4 (CH-6), 126.6 (C-1″), 126.7 (CH-6″), 128.4 (CH-4″), 129.4 (CH-5), 132.9 (CH-7), 136.2 (CH-4), 149.7 (CH-2′), 151.5 (C-8a), 154.3 (C-2″), 154.6 (C-3′a), 163.5 (COO); EI MS (*m*/*z*, %) 390 (M^+, 22), 331 (10), 307 (18), 247 (28), 203 (17), 202 (100), 201 (16), 189 (18), 188 (20), 171 (48), 145 (24), 144 (81), 115 (40), 91 (23), 77 (52), 65 (20). Anal. Calcd for $C_{21}H_{18}N_4O_4$ (390.39): C, 64.61; H, 4.65; N, 14.35%. Found: C, 64.38; H, 4.30; N, 14.51%. Product **8b**: mp 221–223 °C, yield 64%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.53 (d, 2H, J = 7.8 Hz, H-6′), 3.63 (s, 3H, ester-OMe), 3.78 (s, 3H, OMe), 3.80 (s, 3H, OMe), 5.30 (t, 1H, J = 7.8 Hz, H-5′), 6.81–7.13 (m, 6H, H_{arom}), 7.42 (s, 1H, H-2′), 7.81 (s, 1H, NH), 7.84 (s, 1H, H-4), 8.83 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 38.4 (CH_2), 44.4 (CH), 51.9 (ester-OMe), 55.9 (OMe), 56.2 (OMe), 85.5 (C-2 spiro), 110.9 (CH_{arom}), 116.6 (CH_{arom}), 118.4

(CH_{arom}), 118.9 (C_{arom}), 119.1 (CH_{arom}), 121.1 (CH_{arom}), 122.0 (CH_{arom}), 122.2 (C-3), 127.0 (C_{arom}), 136.4 (CH-4), 140.7 (C_{arom}), 143.4 (C_{arom}), 147.3 (C_{arom}), 147.4 (C_{arom}), 149.7 (CH-2′), 154.4 (C-3′a), 163.5 (COO). Anal. Calcd for $C_{23}H_{22}N_4O_6$ (450.45): C, 61.33; H, 4.92; N, 12.44%. Found: C, 61.58; H, 5.09; N, 12.51%. Compound **8c**: mp 231–232 °C, yield 48%; ^{1}H NMR (DMSO-d_6) δ 2.43 (t, 1H, J = 12.0 Hz, H-6′ax), 2.60 (br d, 1H, J = 12.0 Hz, H-6′eq), 3.62 (s, 3H, ester-OMe), 3.70 (s, 3H, OMe), 3.73 (s, 3H, OMe), 5.16 (dd, 1H, J = 12.0 and 2.7 Hz, H-5′), 6.69–6.76 (m, 2H, H_{arom}), 6.89–6.98 (m, 3H, H_{arom}), 7.13 (d, 1H, J = 2.7 Hz, H_{arom}), 7.42 (s, 1H, H-2′), 7.82 (s, 1H, H-4), 7.83 (s, 1H, NH), 9.21 (s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ 37.9 (CH_2), 44.7 (CH), 51.9 (ester-OMe), 55.4 (OMe), 55.6 (OMe), 85.6 (C-2 spiro), 112.0 (CH_{arom}), 113.3 (CH_{arom}), 113.4 (CH_{arom}), 115.7 (CH_{arom}), 116.8 (CH_{arom}), 118.7 (CH_{arom}), 119.0 (C_{arom}), 123.1 (C-3), 127.4 (C_{arom}), 136.2 (CH-4), 145.4 (C_{arom}), 147.9 (C_{arom}), 149.6 (CH-2′), 152.3 (C_{arom}), 154.2 (C_{arom}), 154.5 (C-3′a), 163.5 (COO). Anal. Calcd for $C_{23}H_{22}N_4O_6$ (450.45): C, 61.33; H, 4.92; N, 12.44%. Found: C, 61.08; H, 4.81; N, 12.61%. Compound **8d**: mp 239–241 °C, yield 51%; ^{1}H NMR (DMSO-d_6) δ 2.49 (t, 1H, J = 12.0 Hz, H-6′ax), 2.61 (d, 1H, J = 12.0 Hz, H-6′eq), 3.63 (s, 3H, ester-OMe), 5.14 (dd, 1H, J = 12.0 and 2.7 Hz, H-5′), 6.79 (d, 1H, J = 8.7 Hz, H_{arom}), 6.96 (d, 1H, J = 8.7 Hz, H_{arom}), 7.29 (dd, 1H, J = 8.7 and 2.4 Hz, H_{arom}), 7.45 (s, 1H, H-2′), 7.50–7.54 (m, 2H, H_{arom}), 7.77 (d, 1H, J = 2.4 Hz, H_{arom}), 7.86 (s, 1H, H-4), 7.94 (s, 1H, NH), 10.10 (s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ 38.0 (CH_2), 44.4 (CH), 52.1 (ester-OMe), 85.6 (C-2 spiro), 110.3 (C_{arom}), 113.6 (C_{arom}), 117.3 (CH_{arom}), 118.3 (CH_{arom}), 120.5 (C_{arom}), 123.4 (C-3), 129.0 (C_{arom}), 129.1 (CH_{arom}), 131.0 (CH_{arom}), 131.3 (CH_{arom}), 134.9 (CH_{arom}), 135.0 (CH-4), 149.9 (CH-2′), 150.6 (C_{arom}), 153.7 (C_{arom}), 154.4 (C-3′a), 163.2 (COO). Anal. Calcd for $C_{21}H_{16}Br_2N_4O_4$ (548.19): C, 46.01; H, 2.94; N, 10.22%. Found: C, 45.88; H, 3.09; N, 10.41%. Compound **9c**: Yield 5% (determined from the ^{1}H NMR spectrum of the crude product): Yuan, H. J.; Wang, M.; Liu Y. J.; Liu, Q. *Adv. Synth. Catal.* **2009**, *351*, 112; compound **9d**: mp 217–219 °C (EtOH), yield 10%; mp 217 °C: Linch, F. W. *J. Chem. Soc., Trans.* **1912**, *101*, 1758; compound **9e**: mp 195–197 °C (EtOH), yield 10%; mp 194–195 °C: Wahlberg, E. *Chem. Ber.* **1932**, *65*, 1857.

7. Crystallographic data (excluding structures factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 795123 for **8a** and 795122 for **4a**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
8. *Methyl 7-(4-methoxyphenyl)-5-methyl-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (**4a**):* mp 234–236 °C (MeOH), yield 46%; IR (KBr) ν_{max} 3440, 1700, 1591, 1535, 1256, 1192 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.41 (s, 3H, Me), 3.51 (s, 3H, ester-OMe), 3.70 (s, 3H, OMe), 6.22 (s, 1H, H-7), 6.85 (d, 2H, J = 8.7 Hz, H-3′ and H-5′), 7.13 (d, 2H, J = 8.7 Hz, H-2′ and H-6′), 7.64 (s, 1H, H-2), 10.79 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 18.5 (Me), 50.9 (ester-OMe), 55.0 (OMe), 58.8 (CH-7), 97.3 (C-6), 113.7 (CH-3′ and CH-5′), 128.1 (CH-2′ and CH-6′), 134.2 (C-1′), 146.6 (C-5), 147.0 (C-3a), 150.0 (CH-2), 158.9 (C-4′), 165.7 (COO). Anal. Calcd for $C_{15}H_{16}N_4O_3$ (300.32): C, 59.99; H, 5.37; N, 18.66%. Found: C, 60.22; H, 5.11; N, 18.43%. Isomer **11a**: ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H, Me), 3.50 (s, 3H, ester-OMe), 3.71 (s, 3H, OMe), 6.31 (s, 1H, H-5), 6.87 (d, 2H, J = 8.7 Hz, H-3′ and H-5′), 7.20 (d, 2H, J = 8.7 Hz, H-2′ and H-6′), 8.15 (s, 1H, H-3), 10.78 (s, 1H, NH).
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