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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 2187–2190

# A synthetic approach to new polycyclic ring system of biological interest through domino reaction: indolo[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine

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Received 15 November 2005; revised 19 January 2006; accepted 23 January 2006
Available online 8 February 2006

**Abstract**—The title indolo-triazolo-pyrimidines were obtained from 3-azidoindoles and can be used as models for the design of DNA-interactive compounds. Hetero-domino reaction of azidoindoles/pyrroles and acetonitriles constitutes the synthetic entry to annelated 1,2,3-triazolo[1,5-*a*]pyrimidines.


In previous years we focused our study on synthetic approaches to new heterocyclic ring systems, with potential biological activity, by using domino reactions. A domino reaction is a process involving two or more bond-forming transformations (usually C–C or C–N bonds), which take place under the same reaction conditions without additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step. A substrate with several functionalities, which undergo a transformation individually in the same pot is not a domino reaction. Clearly, the preliminary formation of a reactive intermediate such as a carbocation or a carbanion is not counted as a reaction step.[1]

In this context we explored the synthetic access to angular heterocycles through domino reaction on azido-pyrroles/indoles and reported the preparation[2–4] of the new systems pyrrolo[3,4-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine of type **1** and its rearrangement to pyrrolo[3,4-*d*][1,2,3]-triazolo[1,5-*a*]pyrimidine of type **2**, pyrrolo[2,3-*e*][1,2,3]-triazolo[1,5-*a*]pyrimidine of type **3**, and indolo-[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine of type **4**. All the above systems (Fig. 1) can be related to DNA-interactive drugs such as acridines, anthracyclines, actinomycins, and phenanthridines. These latter compounds are mainly DNA intercalating agents, which possess such a property whose principal driving forces are stacking and charge-transfer interactions as well as hydrogen bonding and electrostatic forces.[5]

Some derivatives belonging to the series **1**–**4** have shown moderate antiproliferative activity against selected tumor cell lines. Previously we have also reported[6,7] the interesting antiproliferative activity of other systems incorporating an indole moiety such as indolo-[3,2-*c*]cinnolines **5**, indolo[1,2-*c*]benzo[1,2,3]triazines **6** (Fig. 2), again related to the above mentioned DNA intercalators.

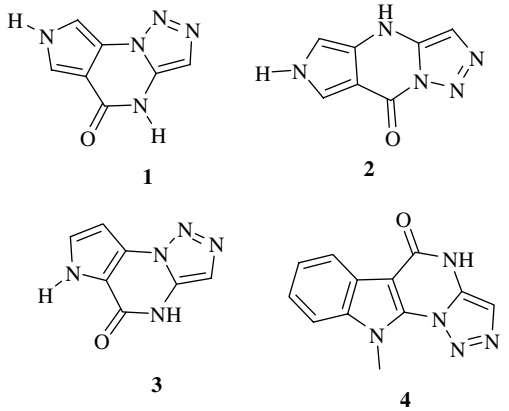


**Figure 1.**

*Keywords*: Domino reaction; Indolo-triazolo-pyrimidine; Docking.
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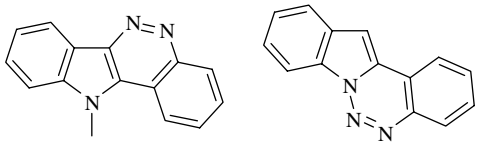
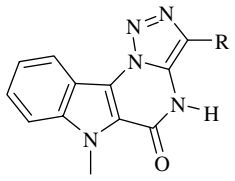
doi:10.1016/j.tetlet.2006.01.112



5 6

**Figure 2.**

Now we became interested in the synthesis of derivatives of the new tetracyclic angular system, namely indolo[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine of type **7**, isomer of polycycle **4**. At the same time we could verify if the domino reaction is of general application also in the azidoindole series. Therefore, in this letter we discuss the synthetic approach to compounds of type **7**, and report the results of preliminary virtual screening tests carried out by using automated docking.



**7**

A route to ring systems **8** can be provided by domino reactions between acetonitriles and azido compound **10** under basic conditions (Scheme 1). The latter through the azido moiety can act as a 1,3-dipolar reagent in cycloaddition reactions with dipolarophiles such as anions of type **9** obtained from methylene active derivatives.

The product resulting from the cycloaddition reaction would be the 3-(triazol-1-yl) compound of type **11**, which bears an amino group, which can undergo further reactions. In the presence of a carboxylate function, it further cyclizes into the pyrimidine ring.

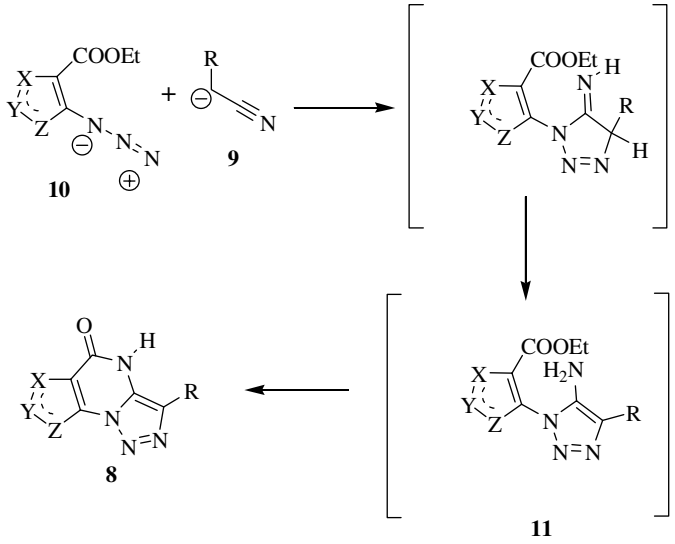
We have already shown that this type of reaction can be used in the pyrrole/indole series,[2–4] and have demonstrated that the nature of the substrate and the reaction conditions can widely influence the nature of the reaction products. The reaction was found to be successful in the case of 3-azidopyrroles and appeared useful with 2-azidoindoles as starting material. Now we investigate its use in combination with 3-azidoindoles.

To this purpose, the 3-aminoindole[8] **12** was diazotized with sodium nitrite in acetic acid. Addition of sodium azide to the intermediate diazonium salt led to the 3-azidoindole **13** in good yield (Scheme 2).

Azide **13** was added at room temperature to the sodium salts of acetonitriles **14a–e** in ethanol, under the experimental conditions used previously.[2–4]

In the reaction starting with acetonitriles **14d**,**e** it was impossible to obtain the corresponding derivatives **7d**,**e**. Moreover after 48 h the reaction mixture showed mainly the presence of amine **12** derived from the decomposition of the azido derivative **13**. This is clearly due to a lower reactivity of the acetonitriles and to the instability of azidoindole **13**.

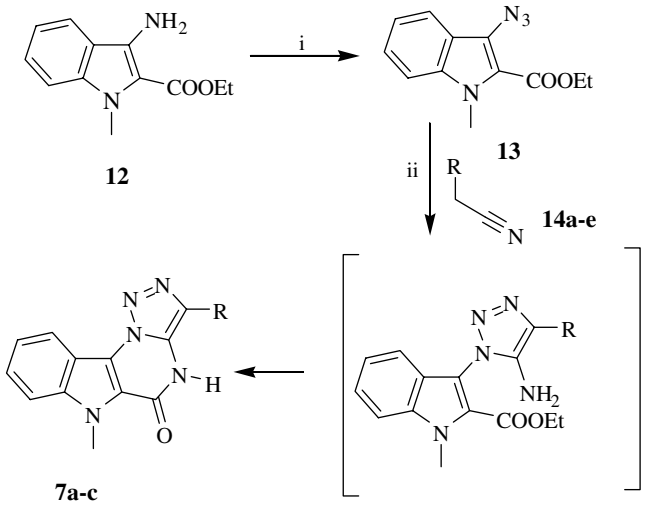
However, the reaction of azide **13** with acetonitriles **14a–c** led to compounds **7a–c**, derivatives containing the new ring system 4*H*-indolo[2,3-*e*][1,2,3]triazolo-[1,5-*a*]pyrimidine, which were generally isolated in high yields (70–80%). Their structure was confirmed by analytical and spectroscopic data;[9] in particular by the presence of a carbonyl signal at 151.2–155.1 ppm in the $^{13}$C NMR, and of the typical absorption bands



**10** **9** **11** **8**

X=NR', Y=CH, Z=CH; X=CH, Y=NR', Z=CH; X=CH, Y=CH, Z=NR';
X-Y=C-(CH)$_4$-C, Z=NR'; X=NR', Y-Z=C-(CH)$_4$-C

**Scheme 1.**




**a** R=Ph; **b** R=CONH$_2$; **c** R=CN
**d** R=COOEt; **e** R=COOMe

**Scheme 2.** Reagents: (i) $NaNO_2$, $NaN_3$, AcOH/$H_2O$; (ii) EtOH/Na.

(at 3419–3150 and 1678–1649 cm$^{-1}$) due to the presence of a cyclic-amide structure in the IR spectra.

For a preliminary evaluation of the ability of the new annelated triazolo-pyrimidines to interact with DNA, we performed a docking calculation by using Autodock software.[10–12] The docking methodology was previously reported by us.[13] The Protein Data Bank[14] was searched for DNA fragments bound with intercalators and the structure 1DSC (an octamer complexed with Actinomycin D) was selected. The original ligand was removed and the DNA sequence was utilized for the docking experiments. The results of these calculations are shown in Table 1.

The change of free energy of binding was found in the range −11.29 to −13.56 kcal/mol and is more negative than the value obtained by us in this study for Actinomycin D (−10.37 kcal/mol). Therefore these indolotriazolo-pyrimidine derivatives are capable of making stable complexes with DNA. Considering that the biological activity of Actinomycin D is related to a very slow dissociation rate of the complex with DNA, our compounds appear to be good candidates as antitumor drugs.

In conclusion, domino reactions between 3-azidoindoles and acetonitriles constitute a versatile entry to indolo[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines. Although in the presence of the same type of complexity (two rings formed in sequence) for this type of domino reaction the bond-forming economy greatly depends on the nature of the starting material (pyrrole/indole) and on the substitution pattern. However, a minor modification of the experimental procedure allows the reaction to become suitable for a general application also in the indole series.

**Table 1.**

| | $\Delta G_{binding}$ (kcal/mol) |
|---|---|
| **7a** | −13.56 |
| **7b** | −11.99 |
| **7c** | −11.29 |
| **7d** | −13.50 |
| **7e** | −12.93 |
| Actinomycin D | −10.37 |

## Acknowledgments

This work was financially supported in part by Ministero dell'Istruzione, dell'Università e della Ricerca.

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9. Experimental data: Melting points (uncorrected) were taken on a Buchi–Tottoli capillary apparatus; IR spectra were determined in bromoform with a Jasco FT/IR 5300 spectrophotometer; $^1$H and $^{13}$C NMR spectra were measured at 200 and 50.3 MHz, respectively, in $(CD_3)_2SO$ solution, unless otherwise specified, using a Bruker AC-E series 200 MHz spectrometer (TMS as internal reference). Column chromatography was performed with a Biotage FLASH40i chromatography module (prepacked cartridge system).
Ethyl 3-azido-1-methyl-1*H*-indole-2-carboxylate (**13**): To a solution of **12** (0.83 g, 3.8 mmol) in acetic acid (30 mL) and water (5 mL), sodium nitrite (0.53 g, 7.6 mmol) in water (4 mL) was added at 0 °C, under vigorous stirring. After 50 min sodium azide (0.98 g, 15 mmol) was added portionwise and the reactants were stirred for further 3 h at rt. The mixture was neutralized with $NaHCO_3$ and extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, and evaporated to dryness. The residue was purified by column chromatography using dichloromethane as eluant to give derivative **13** as a yellow oil: (0.65 g, yield 70%); IR: 2107 ($N_3$), 1700 (CO) cm$^{-1}$; $^1$H NMR $\delta$: 1.36 (3H, t, $J = 7.3$ Hz, $CH_3$), 3.77 (3H, s, $NCH_3$), 4.34 (2H, q, $J = 7.3$ Hz, $CH_2$), 6.94 (1H, t, $J = 7.0$ Hz, H-5), 7.27–7.34 (2H, m, H-6, H-7), 7.86 (1H, d, $J = 7.0$ Hz, H-4); $^{13}$C NMR $\delta$: 14.6 (q), 32.0 (q), 59.2 (t), 106.7 (s), 111.9 (d), 117.6 (d), 118.5 (s), 120.8 (d), 125.9 (d), 136.2 (s), 136.9 (s), 162.6 (s). Anal. Calcd for

$C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.14; H, 6.43; N, 12.74.

General method for the preparation of indolo[2,3-*e*]-[1,2,3]triazolo[1,5-*a*]pyrimidines **7a**–**c**: To a solution of sodium ethoxide in ethanol (5.7 mL, 0.56 M) substituted acetonitriles **14a**–**c** (0.16 mmol) in anhydrous ethanol (10 mL) were added at rt and stirred for 15 min. A solution of azidoindole **13** (0.2 g, 0.8 mmol) in anhydrous ethanol (10 mL) was added and the mixture was stirred for further 24 h at rt. Evaporation of the solvent under reduced pressure gave a solid, which was purified by column chromatography using dichloromethane/ethyl acetate (95:5) as eluant.

6-Methyl-3-phenyl-4*H*-indolo[2,3-*e*][1,2,3]triazolo[1,5-*a*]-pyrimidin-5(6*H*)-one (**7a**): From **13** and benzyl cyanide, white solid (yield 70%) had mp >300 °C; IR: 3183 (NH), 1656 (CO) $cm^{-1}$. $^1H$ NMR $\delta$: 4.22 (3H, s, $CH_3$), 7.37–7.64 (5H, m, H-7, H-8, H-9, H-3′, H-5′), 7.78 (1H, t, $J = 7.4$ Hz, H-4′), 7.94 (2H, d, $J = 7.4$ Hz, H-2′, H-6′), 8.30 (1H, d, $J = 7.3$ Hz, H-10); $^{13}C$ NMR $\delta$: 32.0 (q), 111.4 (d), 113.7 (s), 116.0 (s), 120.1 (s), 121.3 (d), 121.9 (d), 126.5 (d), 127.3 (d), 127.5 (d), 128.5 (d), 129.9 (s), 136.0 (s), 138.5 (s), 143.4 (s), 155.1 (s). Anal. Calcd for $C_{18}H_{13}N_5O$: C, 68.85; H, 5.20; N, 21.79. Found: C, 68.89; H, 5.13; N, 21.88.

6-Methyl-5-oxo-5,6-dihydro-4*H*-indolo[2,3-*e*][1,2,3]tri-azolo[1,5-*a*]pyrimidine-3-carboxamide (**7b**): From **13** and 2-cyanoacetamide, white solid (yield 80%) had mp >300 °C; IR: 3353–3150 ($NH_2$ and NH), 1678 (CO) $cm^{-1}$; $^1H$ NMR (pyridine-$d_5$) $\delta$: 3.27 (2H, s, $NH_2$), 4.22 (3H, s, $CH_3$), 7.23–7.39 (3H, m, H-7, H-8, H-9), 8.02 (1H, d, $J = 7.4$ Hz, H-10); $^{13}C$ NMR (pyridine-$d_5$) $\delta$: 31.5 (q), 111.2 (d), 115.0 (s), 118.5 (s), 121.3 (d), 121.6 (d), 121.7 (s), 127.3 (d), 127.6 (s), 136.9 (s), 139.9 (s), 156.0 (s), 164.0 (s). Anal. Calcd for $C_{13}H_{10}N_6O_2$: C, 55.32; H, 3.57; N, 29.77. Found: C, 55.59; H, 3.59; N, 29.83.

6-Methyl-5-oxo-5,6-dihydro-4*H*-indolo[2,3-*e*][1,2,3]tri-azolo[1,5-*a*]pyrimidine-3-carbo-nitrile (**7c**): From **13** and malononitrile, white solid (yield 80%) had mp >300 °C; IR: 3419–3250 (NH), 2233 (CN), 1649 (CO) $cm^{-1}$; $^1H$ NMR $\delta$: 4.30 (3H, s, $CH_3$), 7.36 (1H, t, $J = 7.3$ Hz, H-9), 7.55 (1H, t, $J = 7.3$ Hz, H-8), 7.73 (1H, d, $J = 7.3$ Hz, H-7), 8.23 (1H, d, $J = 7.3$ Hz, H-10); $^{13}C$ NMR $\delta$: 31.0 (q), 102.5 (s), 111.6 (d), 114.0 (s), 115.8 (s), 118.5 (s), 120.5 (s), 121.1 (d), 121.3 (d), 126.5 (d), 137.1 (s), 143.3 (s), 155.1 (s). Anal. Calcd for $C_{13}H_8N_6O$: C, 59.09; H, 3.05; N, 31.80. Found: C, 59.12; H, 3.11; N, 31.92.

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