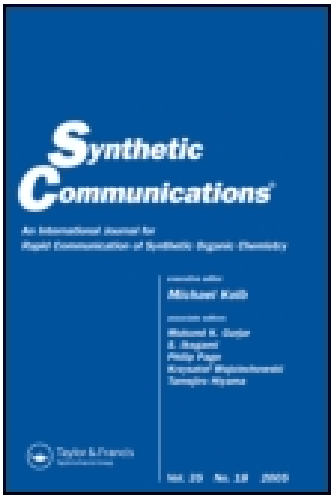


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# Synthesis of New Pyrazolo[1,5-α]quinazoline Derivatives

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# SYNTHESIS OF NEW PYRAZOLO[1,5-α]QUINAZOLINE DERIVATIVES

**Dániel Kovács, Judit Molnár-Tóth, Gábor Blaskó, Imre Fejes, and Miklós Nyerges**
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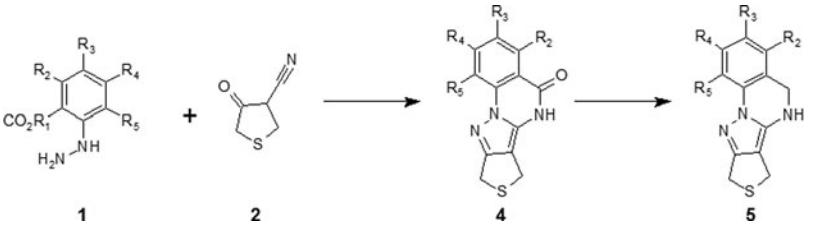
## GRAPHICAL ABSTRACT




1 2 4 5

**Abstract** *The reaction of various anthranilic acid derivatives or their esters with 4-oxotetrahydrothiophene-3-carbonitrile 2, 2-oxocyclopentanecarbonitrile (9, n = 1) or 2-oxocyclohexanecarbonitrile (9, n = 2) in ethanol under reflux conditions giving rise the formation of single products isolated in each case after simple filtration. The products were characterized as pyrazolo[1,5-a]quinazolin-5-ones* ***4*** *instead of the expected pyrazol-3-amines* ***3****. These cascade condensation–intramolecular acylation processes generated in one-step reactions from simple starting materials novel heterocyclic scaffolds ready for further functionalization. The present synthetic protocol provides acceptable yields of new tetracyclic products in high purity.*

**Keywords** Cascade reactions; heterocycles; pyrazoles

## INTRODUCTION

During one of our ongoing medicinal chemistry programs, we intended to prepare a small library of 2-aryl-4,6-dihydrothieno[3,4-*c*]pyrazol-3-amine derivatives (**3**) using the known nucleophilic addition: cyclization domino reaction between the appropriate aryl-hydrazine derivatives (**1**) and 4-oxotetrahydrothiophene-3-carbonitrile (**2**) (Scheme 1).[1] A large number of derivatives of this heterocycle are well described in the patent literature because of their interesting pharmacological

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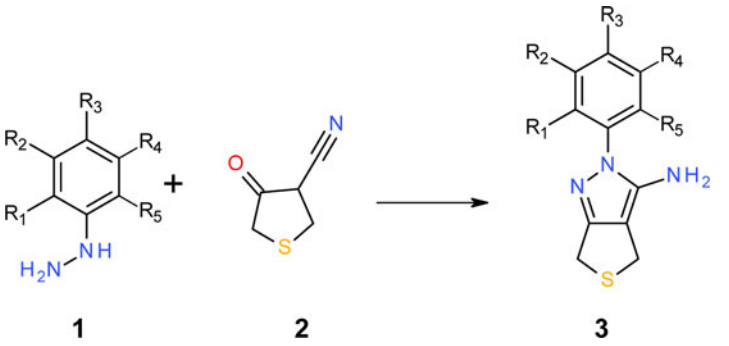
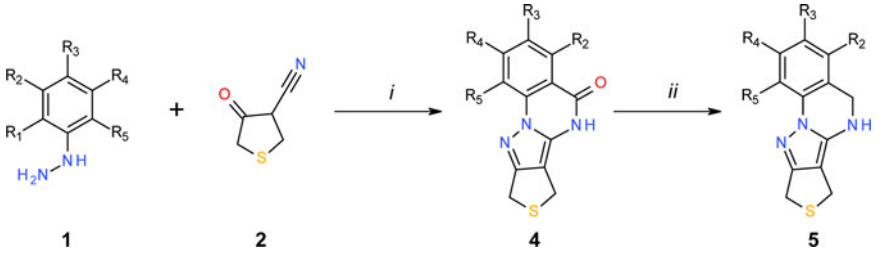



**Scheme 1.** General synthesis of pyrazole amines.

properties that allow them to function as P2X7 receptor antagonists,[2] inhibitors of PDE4[3] or the TrkA kinase,[4] antivirials,[5] or modulators of nicotinic acetylcholine receptors.[6] However, to date there is no example described for the reaction of 2-hydrazino-benzoic acids (**1**, R1=COOH), or their esters (**1**, R1=COOR) and 4-oxotetrahydrothiophene-3-carbonitrile **2** in such processes.

## RESULTS AND DISCUSSION

The starting 2-hydrazino-benzoic acids or their esters **1** are commercially available; however, because of their relatively high price all of them were prepared in house from the corresponding anthranilic acid derivatives according to the procedures described in the literature.[7,8] These acids or their esters were reacted with 4-oxotetrahydrothiophene-3-carbonitrile **2** in ethanol under reflux. After 3 h heating a single product was isolated (via **6, 7** and **8**) in each case after simple filtration. These products were characterized as 6,7-dihydro-5*H*,9*H*-thieno[3′4′:3,4]pyrazolo[1,5-*a*] quinazolin-5-ones **4** instead of the expected thieno[3,4-*c*]pyrazol-3-amines **3** on the basis of their elemental analysis as well as infrared (IR), $^{1}$H NMR, $^{13}$C NMR, and mass spectral (MS) analysis. The IR spectrum of **4** revealed the presence of a carbonyl stretching vibration band around 1680 cm$^{-1}$, for the lactam carbonyl group, and in the NMR spectra a newly formed amide was visible instead of the amine. This lactam **4** was later reduced to the corresponding amine **5,** which become the key compound for further diversification of this small compound library in our medicinal




**Scheme 2.** Reagents and conditions: (i) ethanol, reflux; (ii) $BH_3$, THF.

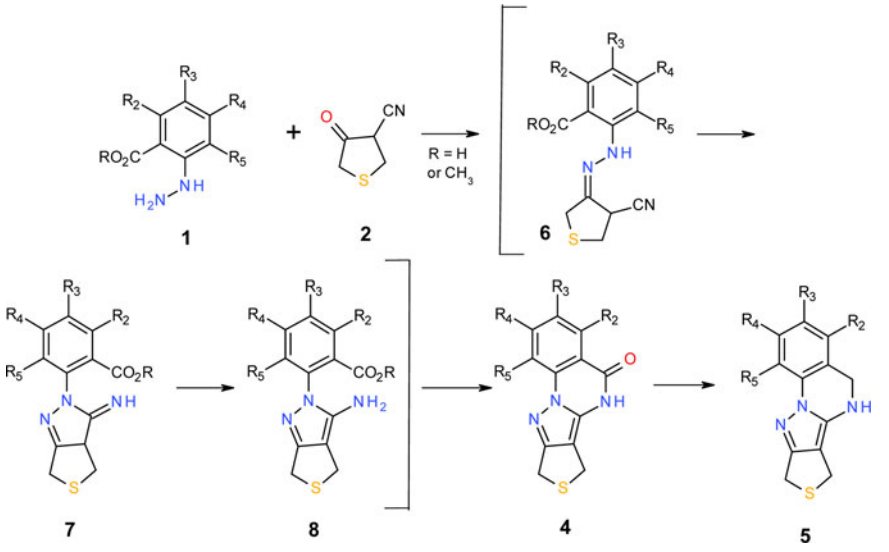
**Table 1.** The synthesized thieno[3′,4′.3,4]pyrazolo[1,5-*a*]quinazoline derivatives

| Entry | Hydrazine | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Product | Yield (%) | Product | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | **1a** | $CO_2H$ | H | H | H | H | **4a** | 74 | **5a** | 51 |
| **2** | **1b** | $CO_2H$ | H | H | H | $CH_3$ | **4b** | 9 | **5b** | — |
| **3** | **1c** | $CO_2H$ | H | $CH_3$ | H | H | **4c** | 43 | **5c** | 95 |
| **4** | **1d** | $CO_2H$ | H | H | $CH_3$ | H | **4d** | 49 | **5d** | — |
| **5** | **1e** | $CO_2CH_3$ | $CH_3$ | H | H | H | **4e** | 15 | **5e** | — |
| **6** | **1f** | $CO_2CH_3$ | H | $OCH_3$ | H | H | **4f** | 56 | **5f** | 85 |
| **7** | **1 g** | $CO_2CH_3$ | Br | H | H | H | **4 g** | 9 | **5 g** | — |

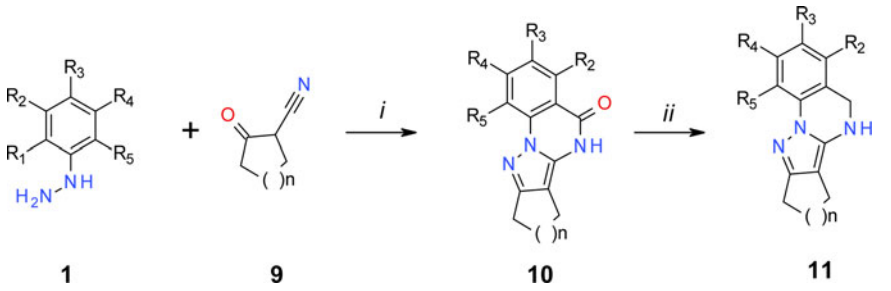
chemistry program (Scheme 2, Table 1). Among the products **5a, 5c**, and **5f** were successfully prepared. In other cases, a complex mixture was observed during the reduction that lacked the desired products (**5b, 5d**, **5e**, and **5g**).

The formation of the pyrazole ring in the reaction of a keto-cyanide **1** and arylhydrazine **2** is well documented in the literature. However, the intramolecular acylation of the pyrazolamine **8** usually requires more activated acid derivatives such as chloride in the presence of base (Scheme 3).

In the same way, refluxing a solution of 2-oxocyclopentanecarbonitrile (**9**, n = 1) or 2-oxocyclohexanecarbonitrile (**9**, n = 2) in ethanol with arylhydrazines **1** afforded a series of novel tetracyclic pyrazolo[1,5-*a*]quinazoline **10** derivatives in a single step (Scheme 4, Table 2). Then the lactam **10** was reduced to the corresponding amine **11** under the same conditions described previously. Besides the successful reactions of **11a–c, 11e,** and **11f** (Table 2), the products **11d, 11 g,** and **11 h** were not observed, probably due to the decomposition of the proper lactams under the applied reaction conditions.




**Scheme 3.** Proposed reaction mechanism of the formation of the new thieno[3′,4′.3,4]pyrazolo[1,5-*a*] quinazoline derivatives.




**Scheme 4.** Reagents and conditions: (i) ethanol, reflux; (ii) $BH_3$, THF.

In conclusion, we report a cascade condensation–intramolecular acylation process generated in the reaction of cyclic ketocyanides **2** and 2-hydrazino-benzoic acids or their esters **1** ($R^1 = CO_2H$ or $CO_2Me$ accordingly) to afford novel heterocycles. The present synthetic protocol provides acceptable yields of new tetracyclic products in good purity. The bioactivity of the newly synthesized compounds will be published elsewhere.

## EXPERIMENTAL

### Preparation of 2-Hydrazino-benzoic Acids

The corresponding anthranilic acid (1 mmol) was suspended in hydrochloric acid (6 M, 2.4 ml) and cooled to −5°C. Sodium nitrite (1.1 mmol) was dissolved in water (0.4 ml) and added dropwise. The reaction mixture was stirred for 1 h at −5°C and then $SnCl_2 \cdot 2H_2O$ was added (0.451 g, 2 mmol dissolved in 0.6 ml of 6 M aqueous HCl). The product was precipitated, filtered, washed with water, and dried in vacuo. The product was used without any further purification (yield 64–100%).

### Reaction of Hydrazines with α-Oxo-cyanides

The corresponding 2-hydrazino-benzoic acid or methyl-2-hydrazino-benzoate (1.1 mmol) and the α -oxo-cyano compound (1 mmol) were suspended in dry ethanol (5.5 ml) and refluxed for 3 h. After cooling, the product was precipitated, filtered, and dried in vacuo to yield (51–85%) the title products.

**Table 2.** The synthesized novel tetracyclic pyrazolo[1,5-*a*]quinazolines

| Entry | Hydrazine | n | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Product | Yield (%) | Product | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | **1a** | 1 | $CO_2H$ | H | H | H | H | **10a** | 54 | **11a** | 87 |
| **2** | **1c** | 1 | $CO_2H$ | H | $CH_3$ | H | H | **10b** | 44 | **11b** | 87 |
| **3** | **1f** | 1 | $CO_2CH_3$ | H | $OCH_3$ | H | H | **10c** | 30 | **11c** | 57 |
| **4** | **1 g** | 1 | $CO_2CH_3$ | Br | H | H | H | **10d** | 8 | **11d** | — |
| **5** | **1a** | 2 | $CO_2H$ | H | H | H | H | **10e** | 55 | **11e** | 26 |
| **6** | **1c** | 2 | $CO_2H$ | H | $CH_3$ | H | H | **10f** | 47 | **11f** | 44 |
| **7** | **1f** | 2 | $CO_2CH_3$ | H | $OCH_3$ | H | H | **10 g** | 52 | **11 g** | — |
| **8** | **1 g** | 2 | $CO_2CH_3$ | Br | H | H | H | **10 h** | 3 | **11 h** | — |

### 6,7-Dihydro-*5H,9H*-thieno[3′,4′.3,4]pyrazolo[1,5-a]quinazoline-5-one (4a)

White powder, 0.180 g (74%); $^1$H NMR (500 MHz, DMSO-$d_6$): 12.28 (s, 1H, NH), 8.11 (d, 1H, $J$ = 7.5 Hz, Ar-4′H), 7.97 (d, 1H, $J$ = 8.0 Hz, Ar-1′H), 7.84 (t, 1H, $J$ = 8.4 Hz, Ar-2′H), 7.45 (t, 1H, $J$ = 7.5 Hz, Ar-3′H), 4.02 (s, 2H, H-9), 3.83 (s, 2H, H-7); $^{13}$C NMR (125 MHz, DMSO-$d_6$): 161.3 (q), 158.8 (q), 138.5 (q), 135.6 (CH), 132.7 (q), 128.6 (CH), 125.5 (CH), 116.2 (q), 114.6 (CH), 104.7 (q), 28.9 ($CH_2$), 26.8 ($CH_2$); IR (KBr, cm$^{-1}$): 2820, 1667. HRMS $m/z$ calcd. for $C_{12}H_9N_3OS$ $(M + H)^+$ 244.0546; found 244.0541.

### Lactam Reduction

The corresponding indazolo[2,3-*a*]qinazoline-5(6*H*)-one or pyrazolo[1,5-*a*] quinazoline-5-one (1 mmol) was dissolved in dry tetrahydrofurane (30 ml) and at −5°C under a nitrogen atmosphere. $BH_3 \cdot THF$ solution (1 M, 7 ml) was added dropwise. The mixture was stirred at room temperature for 4 h, and then aqueous hydrochloric acid solution (6 M, until no more gas evolved) was added. The pH was adjusted to 13 with 2 M sodium hydroxide solution, and the mixture was extracted with dichloromethane (2 × 200 ml), dried over sodium sulfate, and evaporated. The crude product was purified by column chromatography over silica (eluent: heptane–ethyl acetate 3:1) to yield (26–87%) the product.

### 6,7-Dihydro-*5H,9H*-thieno[3′,4′.3,4]pyrazolo[1,5-α]quinazoline (5a)

Yield 0.117 g (51%); white powder; $^1$H NMR (500 MHz, DMSO-$d_6$): 7.45 (dm, 1H, $J$ = 8.0 Hz, Ar-1′H), 7.29 (m, 1H, Ar-2′H), 7.23 (dm, 1H, $J$ = 7.3 Hz, Ar-4′H), 7.09 (m, 1H, Ar-3′H), 6.75 (brs, 1H, NH), 4.34 (brs, 2H, H-5), 3.85 (brt, 2H, H-9), 3.68 (brt, 2H, H-7); $^{13}$C NMR (125 MHz, DMSO-$d_6$): 160.3 (q), 140.8 (q), 135.9 (q), 128.7 (CH), 126.8 (CH), 124.6 (CH), 121.5 (q), 113.7 (CH), 102.5 (q), 42.8 ($CH_2$), 28.9 ($CH_2$), 26.7 ($CH_2$). IR (KBr, cm$^{-1}$): 3280, 2916. HRMS $m/z$ calcd. for $C_{12}H_{11}N_3S$ $(M + H)^+$ 230.0754; found 230.0741.

## SUPPLEMENTAL MATERIAL

Full experimental details, assignment, the $^1$H and $^{13}$C NMR spectra, IR spectra, and HRMS details for this article can be accessed on the publisher's website.

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