# NEW FOUR-COMPONENT UGI-TYPE REACTION. SYNTHESIS OF 3-METHYL-1-OXO-1,3,4,6,11,11*a*-HEXAHYDRO-2*H*-PYRAZINO[1,2-*b*]ISOQUINOLINE-3-CARBOXAMIDES

Alexey P. Ilyn,[a] Andrey S. Trifilenkov,[b] Denis I. Kovrigin,[b] Michail V. Yudin,[b] Alexandre V. Ivachtchenko*[,a]
[b]Department of Organic Chemistry, Chemical Diversity Research Institute, 114401 Khimki, Moscow Reg., Russia, [a]ChemDiv, Inc., San Diego, CA USA
*To whom correspondence should be addressed. Phone: (858) 794-4860. Fax: (858) 794-4931
E-mail: av@chemdiv.com

**Abstract:** A small-sized library of novel 3,4,11,11*a*-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1(6*H*)-ones is synthesized. Key synthetic step is based on a new variant of Ugi four component reaction using bifunctional keto acids, amine and isocyanide as starting materials. The reaction leads to small molecule peptidomimetics with promising pharmacological potential and is readily amenable to high-throughput combinatorial library production.

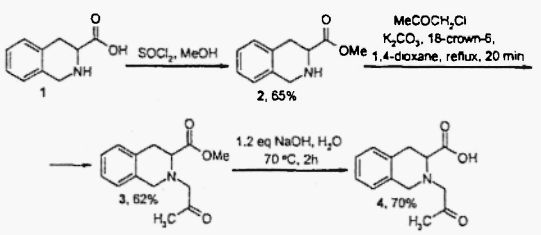
## Introduction

Compounds containing the 3,4,11,11*a*-tetrahydroisoquinoline scaffold constitute an important pharmacophoric moiety present in many drugs acting on various pharmacological targets (1). In particular, compounds containing the 3,4,11,11*a*-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1(6*H*)-one heterocyclic system were described as potential filaricides (2), CNS-active agents (3) and antibiotics (4). These examples illustrate the ongoing interest toward the scaffolds containing pyrazino[1,2-*b*]isoquinolin-1-one fragment. However, the described synthetic strategies approaches to 3,4,11,11*a*-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1(6*H*)-ones (5) have found limitations mainly due to lack of versatility and a limited number of the appropriate initial reactants. In addition, they have not provided a robust method suitable for the production of combinatorial libraries.

Ugi four-component reaction was shown to be an effective synthetic strategy to differently substituted derivatives of piperazinone (6). One of important modifications of the classical four-component Ugi reaction includes the use of bifunctional reagents. Synthetic methods using bifunctional aldehyde or keto acids, amine and isocyanide as starting materials, have been reported (7). Recently, we developed a novel modification of classical four-component Ugi reaction, in which the heterocyclic keto acids were used as the bifunctional coupling partners in the reaction with isonitriles and amines (8,9). Using this method, we efficiently synthesized several series of novel azaheterocyclic scaffolds including pyrrolo[1,2-*a*][1,4]diazepines (8), 3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-ones and 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones (9). In this work, we have focused on broadening the scope of this useful synthetic methodology and developed an efficient synthetic route to novel 3,4,11,11*a*-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1(6*H*)-one heterocycles amenable to high-throughput combinatorial format.

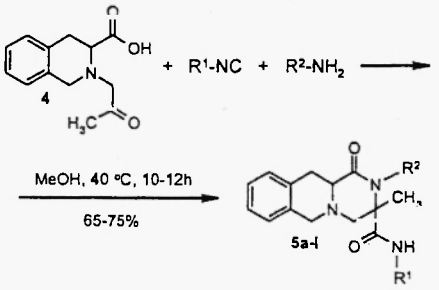
## Results and Discussion

Our synthesis started from 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **1** (Scheme-1), which was prepared as reported (10).




**Scheme-1:** Synthesis of keto acid **4**.

The reaction of carboxylic acid 1 with thionyl chloride in methanol smoothly led to isoquinoline-3-carboxylate **2** in 65% yield. The solution of the carboxylate **2** in 1,4-dioxane was treated with chloroacetone under phase transfer conditions, in the presence of $K_2CO_3$ and 18-crown-6, to afford the desired methyl 2-(2-oxopropyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **3** in good yield (62%). Subsequent mild alkali hydrolysis afforded the desired keto acid **4** (yield 70%). When keto acid **4** was treated with isonitrile and primary amine in methanol at 40 °C, conversion into 3-methyl-1-oxo-1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-3-carboxamides **5a-i** (Scheme-2) proceeded smoothly and without any indication of major side reaction.

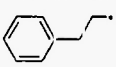
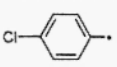
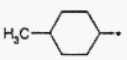
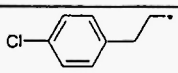
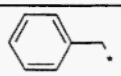


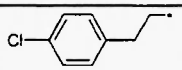
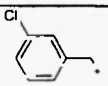

**Scheme-2:** Synthesis of pyrazino[1,2-*b*]isoquinoline-3-carboxamides **5a-i**.

The desired compounds usually precipitated from the reaction media thus allowing their easy separation by filtration of the reaction mixtures. Isolated yields of compounds **5a-i** (Table-1) were generally high (>60%). Their assignment was made on the basis of $^1$H NMR, $^{13}$C NMR and LCMS data. According to LCMS data, all the synthesized compounds have purity >95%. The process is not adversely affected by the presence of halogen or ether residues in the initial reactants. The process does, however, appear to be impeded by steric congestion, with the sterically hindered amines (for example, when $R^2$ = *tert-Bu*) undergoing slow and incomplete conversion to the final products. Electronic effects of electron-withdrawing substituents, such as nitro-substituents on anilines, can significantly decrease the efficacy of condensation. Another restriction is the limited number of commercially or synthetically available isonitriles.

The library synthesized in this work represents a compact set of small molecules containing special biomolecular recognition elements typical of natural peptides. For example, they contain certain characteristic conformationally fixed amino acid fragments, such as dipeptide moieties with *cis* configuration of amide bond and masked phenylalanine fragment. Therefore, these molecules are potentially capable of perturbing many disease-related biological pathways. Biological evaluation of the obtained compounds is currently in progress, and the results of these studies will be reported in due course.

**Table-1:** $R^1/R^2$ Substituents and Yields of Compounds **5a-i**.

| Entry | $R^1$ | $R^2$ | Yield, % |
|---|---|---|---|
| **5a** |  |  | 72 |
| **5b** |  |  | 75 |
| **5c** |  |  | 69 |
| **5d** |  |  | 65 |

| | | | |
|---|---|---|---|
| **5e** |  |  | 75 |
| **5f** |  |  | 65 |
| **5g** |  |  | 77 |
| **5h** |  |  | 71 |
| **5i** |  |  | 70 |

## Experimental

**General procedure for preparation of 3-carboxamide derivatives of 4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-6-carboxamides 5a-i.** The equimolar amounts of keto acids **4** (as an 1:1 mixture of isomers), the corresponding isonitrile and the amine were dissolved in methanol to an approximate concentration of 1M in each component. The reaction mixture was stirred at 40°C for 10-12 h. The reaction was followed by TLC (5% MeOH in $CH_2Cl_2$). On completion, the reaction mixture was cooled to rt, the formed precipitate was filtered off and purified by chromatography on silica gel, eluting with a gradient of 0-10% MeOH in $CH_2Cl_2$.

***N*-cycloheptyl-3-methyl-1-oxo-2-(2-phenylethyl)-1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-3-carboxamide 5a:** Yield 72%, white crystalline solid, mp 203-204 °C. HRMS: m/z [M+H$^+$] calcd for $C_{29}H_{37}N_3O_2$: 460.2959. Found: 460.2953; $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 1.15-1.82 (m, 12H, cyclooctane), 1.42 (s, $CH_3$, 3H), 2.7-2.89 (q, $J$ = 5.4 Hz, 4H, $2CH_2$), 2.9-3.14 (m, 3H, CH, $CH_2$), 3.23-3.31 (d, $J$ = 3.9, 1H, $CH_2$), 3.48-3.5 (d, $J$ = 3.8 Hz, 2H, $CH_2$), 3.72-3.80 (m, 1H, CH), 3.8-3.92 (d, $J$ = 3.9 Hz, 1H, $CH_2$), 6.9-7.28 (m, 9H, ArH), 7.9 (d, $J$ = 7.4 Hz, 1H, NH); $^{13}$C NMR (DMSO-$d_6$): δ 22.66, 24.6, 28.3, 31.5, 34.8, 36.3, 39.7, 40.0, 51.4, 60.1, 62.28, 62.32, 65.4, 99.7, 115.6, 123.0, 126.9, 129.1, 129.2, 129.3, 129.4, 134.2, 140.3, 141.9, 143.9, 169.6, 170.2.

***N*-cycloheptyl-2-cyclopentyl-3-methyl-1-oxo-1,3,4,6,11,11*a*-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-3-carboxamide 5f:** Yield 65%, white crystalline solid, mp 190-191 °C. HRMS: m/z [M+H$^+$] calcd for $C_{26}H_{37}N_3O_2$: 424.2945. Found: 424.2953; $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 1,41 (s, 3H, $CH_3$), 1.20-1.92 (m, 20H, cyclooctane, cyclopentane), 2.2-2.38 (m, 1H, CH), 2.61-2.7 (m, 3H, CH, $CH_2$), 2.73-3.1 (m, 1H, CH), 3.1-3.2 (d, $J$ = 4.0 Hz, 1H, $CH_2$), 3.41-3.48 (m, 1H, $CH_2$), 3.7-3.8 (m, 1H, CH), 3.81-3.90 (d, $J$ = 3.9 Hz, 1H, $CH_2$), 6.9-7.17 (m, 4H, ArH), 7.6 (br s, 1H, NH).

## Conclusions

We have developed a novel synthetic approach to 3,4,11,11*a*-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1(6*H*)-ones based on a novel modification of the Ugi four-component reaction. Through the use of simple complexity-generating reactions conducted under similar, easily reproducible conditions, three simple components are converted efficiently into complex peptidomimetic scaffold with several randomization points. As a synthetic tool for creating diverse compound libraries, the four-component condensation used in this work offers a large number of potential input reactants and resulting products and can be used in combinatorial format.

## Acknowledgements

We thank Dr. Konstantin V. Balakin (ChemDiv, Inc.) for fruitful discussion.

**References**

1. (a) F.A. Romero, S.V. Vodonick, K.R. Criscione, M.J. McLeish, G.L.Grunewald, *J. Med. Chem.* **47**, 4483 (2004). (b) A. Mihalyi, R. Gaspar, Z. Zalan, L. Lazar, F. Fulop, P.A. de Witte, *Anticancer Res.* **24**, 1631 (2004). (c) H. Kubota, A. Kakefuda, T. Watanabe, N. Ishii, K. Wada, N. Masuda, S. Sakamoto, S. Tsukamoto, *J. Med. Chem.* **46**, 4728 (2003).
2. H. Singh, S. Sharma, R.N. Iyer, N. Anand, *Ind. J. Chem.* **1**, 70 (1997).
3. A.K. Saxena, P.C. Jain, N. Anand, *Ind. J. Chem.* **3**, 230 (1975).
4. N. Saito, N. Kawakami, E.Yamada, A. Kubo, *Antibiotics Chem. Pharm. Bull.* **35**, 1493 (1989).
5. (a) A. Hätzelt, S. Laschat, P.G. Jones, J. Grunenberg, *Eur. J. Org. Chem.* **23**, 3936 (2002). (b) C.W. Ona, H.C. Lee, *Austral. J. Chem.* **43**, 773 (1990).
6. (a) K. Illgen, S.Nerdinger, T. Fuchs, C. Friedrich, L. Weber, E. Herdtweck, *Synlett* **1**, 53 (2004). (b) I. Ugi, W. Horl, C. Hanusch, T. Schmid, E. Herdweek, *Heterocycles* **47**, 985 (1998).
7. (a) S. Cho, G. Keum, S.B. Kang, S.Y. Han, Y. Kim, *Mol. Divers.* **6**, 283 (2003). (b) J. Zhang, A. Jacobson, J.R. Rusche, W. Herlihy, *J. Org. Chem.* **64**, 1074 (1999). (c) Y.B. Kim, E.H. Choi, G. Keum, S.B. Kang, D.H. Lee, H.Y. Koh, Y. Kim, *Org. Lett.* **3**, 4149 (2001). (d) B. Beck, G. Larbig, B. Mejat, M. Magnin-Lachaux, A. Picard, E. Herdtweck, A. Domling, *Org. Lett.* **5**, 1047 (2003). (e) J.-F. Cheng, M. Chen, T. Arrhenius, A. Nadzan, *Tetrahedron Lett.* **43**, 6293 (2002).
8. A.P. Ilyn, A.S. Trifilenkov, J.A. Kuzovkova, S.A. Kutepov, A.V. Nikitin, A.V. Ivachtchenko, *J. Org. Chem.* **70**, 1478 (2005).
9. A.P. Ilyn, J.A. Kuzovkova, V.V. Potapov, A.M. Shkirando, D.I. Kovrigin, S.E. Tkachenko, A.V. Ivachtchenko, *Tetrahedron Lett.* **46**, 881 (2005).
10. R. Grigg, J. Idle, P. Mcmeekin, D. Vipond, *J. Chem. Soc. Chem. Comun.* **2**, 49 (1987).

Received on September 15, 2005