Published in final edited form as:

Tetrahedron Lett. 2013 August 14; 54(33): 4467–4470. doi:10.1016/j.tetlet.2013.06.042.

Construction of functionalized tricyclic dihydropyrazino-quinazolinedione chemotypes via an Ugi/*N*-acyliminium ion cyclization cascade

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Abstract

Dihydropyrazino-quinazolinedione chemotypes are complex and structurally challenging structures of biological interest, being found in the marine alkaloids such as brevianamide M-N and fumiquinazolines A-C. Herein we report the synthesis of this tricyclic system in three synthetic operations by means of an Ugi multi-component reaction (MCR) followed by a tandem *N*-acyliminium ion cyclization-intramolecular nucleophilic addition reaction sequence. Additional structural diversification for further library enrichment was also accomplished via sequential *N*-alkylation and *N*-acylation/sulfonation.

Keywords

Peptidomimetics; Ugi reaction; multi-component reaction; *N*-acyliminium ion; heterocycles

The compelling quest to discover novel small molecules that modulate protein function has enabled access to ever-growing regions of chemical space.¹ Over the past 20 years, isocyanide-based MCRs (IMCRs) have proven to be a convenient and versatile approach toward expeditious molecular diversity generation, allowing the generation of numerous unique, drug-like small molecules for biological evaluation.² In particular, the Ugi IMCR (Scheme 1), which proceeds through reaction of an aldehyde or ketone, amines, isocyanides and carboxylic acids to produce the dipeptide-like adduct **1**, has undergone many post-condensation modifications, accessing numerous new scaffolds. To cite a few examples, these post-MCR transformations comprise Ugi/deprotection/cyclization (UDC),³ Ugi/Heck,⁴ Ugi/Pictet-Spengler,⁵ Ugi/RCM,⁶ Ugi/Knoevenagel,⁷ Ugi/cycloaddition,⁸ Ugi/Diels-Alder,⁹ Ugi/Pd-catalyzed arylation,¹⁰ Ugi/Mitsunobu¹¹ and, most recently, elegant Ugi/Aldol methodologies.¹² In this context, Ugi/*N*-acyliminium ion sequences used to expand our toolbox of heterocyclic chemotypes are relatively underexploited, and only one article has been published that describes the synthesis of Δ^5 -2-oxopiperazines **3** (Scheme 2) using aminoacetaldehyde diethylacetal **2** as the carbonyl surrogate.¹³ However, reports do exist of *N*-acyliminium ion strategies being employed with other MCRs.¹⁴ Herein, post-

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condensation modifications of the Ugi adduct driven by *N*-acyliminium ion cascade reactions are reported to prepare ketopiperazine containing tricyclic chemotypes **7** (Scheme 3) whose unusual core structure is found in the marine alkaloids brevianamide M-N¹⁵ **8** and **9** and fumiquinazolines A-C¹⁶ **10**, **11** and **12** possessing insecticidal and antineoplastic activity, respectively (Figure 1).

Thus, studies began with evaluation of reagent compatibility for the Ugi MCR (Scheme 4). Specifically, mixing an aldehyde, 2-fluoro-5-nitro-benzoic acid **4**, the ammonia surrogate 2,4-dimethoxybenzylamine **5**¹⁷ and 1,1-diethoxy-2-isocyanoethane **6**¹⁸ rendered Ugi products **13** upon overnight stirring at ambient temperature in moderate to good yields (43–82%, Table 1). It is worth noting that isocyanide **6** can be readily synthesized in two steps and has also been reported to be an extremely valuable building block for the preparation of several families of heterocycles that include imidazoles¹⁹ and thiazoles.²⁰ Subsequent displacement of the fluorine group in **13** by a primary amine was achieved under mild conditions in DCE and afforded **14**, which was subjected without purification to an acid-mediated double cyclization generating tricyclic system **7** (Table 1). Mechanistically, this pathway is presumably initiated by the generation of an oxonium ion and concomitant removal of the acid labile 2,4-dimethoxybenzyl moiety **15** (Scheme 4). Closure of the amidic nitrogen onto the oxonium ion thus leads to the formation of hemiaminal **16**, which under the acidic reaction conditions affords *N*-acyliminium ion **18** with the associated loss of a molecule of ethanol. The sequence concludes through nucleophilic attack of the anilinic amine onto the newly formed *N*-acyliminium ion **18** to give the desired dihydropyrazinoquinazolinone **7**.

Scaffold **7** is likely to exist as an *anti*-diastereomer in which the two hydrogens of the two chiral centers, 'a' and 'b', are predicted to be in a pseudo-*trans* relationship (Figure 2). Molecular dynamics studies reveal that both enantiomers of **7a** exist in a lower energy state than the corresponding pair of enantiomers (**20** and **22**) of the alternate diastereomer, thus suggesting preferential formation of **7a**.²¹ Observed stereoselectivity may be explained by the steric hindrance between the propyl group and the approaching anilinic nitrogen of intermediate **19** (*R*-enantiomer) at the *si*-face that negates formation of **20** (*R,R*), affording **7a** (*R,S*) as the strongly preferred product (Figure 2). In analogous fashion, *si*-attack on the intermediate **21** (*S*-enantiomer) affording **7a** (*S,R*) (Figure 2) is suggested to be favored [Note that comparison of the relative energies of two diastereomers is only justified when assuming reversibility of reactions going through either 19 or 21, with product **7** preferred over **20** under thermodynamic control]. This configuration is in accordance with a report by Patek et al. describing the assembly of 1-acyl-3-oxopiperazines via a multi-step solid-phase synthesis.²² Unequivocal structural confirmation of **7a** was also provided by X-ray crystallography (Figure 3).

With **7a** in hand as the 'model study' molecule, a small collection of compounds was prepared to demonstrate the generality of the reaction sequence utilizing different aldehydes and primary amines (Table 1). Concurrently, further functionalization of **7** was also enabled via *N*-alkylation on the amidic nitrogen and by *N*-acylation and/or sulfonation upon reduction of the nitro group, leading to the addition of two further diversity points (Scheme 5). Tables 2 and 3 summarize selected alkyl bromides and acyl/sulfonyl chlorides employed to attain **23** and **24**, respectively, in high overall yields.

In summary, a concise three-step synthesis of a collection of tricyclic dihydropyrazinoquinazolinones **7** has been successfully established with only one diastereomer formed utilizing an Ugi/*N*-acyliminium ion cyclization-intramolecular nucleophilic addition reaction cascade. Moreover, this scaffold can be readily diversified via sequential *N*-alkylation and *N*-acylation and/or sulfonation, adding two further variety points by means of commercially

available alkyl bromides and acyl and/or sulfonyl chlorides. Due to the uniqueness of the chemotypes produced, their favorable drug-like properties, and the potential for structural diversification, this procedure represents a practical and enticing approach for the enrichment of small molecules libraries in a high-throughput and operationally friendly manner.

Acknowledgments

The authors thank Dr. Sue Roberts for X-ray crystallography work, Drs. Fabio De Moliner and David M. Bishop for proofreading, and the National Institutes of Health (P41GM086190) for financial support.

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20. Molecular dynamics calculations were performed on ChemBio3D Ultra 12.0. MMF94 was performed on each molecule with maximum number of iterations of 5,000 and minimum RMS gradient of 0.100, followed by energy and gradient calculations. Finally, MMF94 molecular dynamics were performed at 2 fs (step interval), 1,000 fs (frame interval), 100,000 steps (number of iterations), 1 kcal/atom/ps (heating/cooling rate) and 300K (target temperature). Upon completion, MMF94 energy minimizations were reiterated and provided the numbers displayed in Figure 2.
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Figure 1.
Brevianamide M-N (8 and 9) and fumiquinazolines A-C (10–12).

Figure 2.
Stereoselectivity and calculated energy for each diastereomer.

Figure 3.
Definitive structural confirmation by X-ray crystallography of **11a**.

Scheme 1.
The Ugi MCR.

Scheme 2.
Synthesis of Δ^5 -2-oxopiperazines **3**

Scheme 3.
General Ugi/*N*-acyliminium ion cyclization sequences.

Scheme 4.
Synthesis of dihydropyrazino-quinazolidinedione **7**.

Scheme 5.
Synthesis of dihydropyrazino-quinazolidinedione **7**.

Table 1

Tricyclic analogs **7a–f**.

Entry	Ugi product	R ₁	Yield (%)	7	R ₂	Yield (%) [*]
1	13a	propyl	67	7a	isobutyl	67
2	13b	phenyl	78	7b	isobutyl	79
3	13c	3-(methylthio)ethyl	43	7c	isobutyl	41
4	13d	cyclopropyl	82	7d	2-methoxyethyl	41

^{*} two-step yield for fluoride displacement and acid treatment

Table 2Functionalized tricyclic chemotype **23**.

Entry	7	R₃	23	Yield (%)
1	7a	3-methoxybenzyl	23a	94
2	7a	4-fluorophenethyl	23b	87
3	7a	cyclobutylmethyl	23c	87
4	7b	3-methoxybenzyl	23d	71
5	7b	4-fluorophenethyl	23e	46

Table 3Functionalized tricyclic chemotype **24**.

Entry	23	R ₄	24	Yield (%) [*]
1	23a	CO-Ph	24a	85
2	23b	SO ₂ Me	24b	83
3	23b	CO-Ph	24c	75
4	23c	SO ₂ Me	24d	80
5	23c	CO-Ph	24e	89

^{*} two-step yield for hydrogenation and *N*-acylation