Tetrahedron Letters 54 (2013) 454–458

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Divergent ionic liquid supported synthesis of isolable guanidine linked quinoxalinone and benzodiamine

Li-Hsun Chen [a], Zhan-Hui Xu [a], Chun-Chung Lin [b], Chung-Ming Sun [a,*]

[a] Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300-50, Taiwan, ROC
[b] Department of Chemistry, National Tsing Hua University, Hsinchu 300-13, Taiwan, ROC

ARTICLE INFO

Article history:
Received 22 September 2012
Revised 23 October 2012
Accepted 2 November 2012
Available online 20 November 2012

Keywords:
Ionic liquid support
Microwave synthesis
One-Bead-Two-Compound
Quinoxalinones

ABSTRACT

Ionic liquid supported synthesis of guanidine linked piperazine, diazepane, and aminomethylpiperidine to difluoroquinoxalinones and difluoro benzodiamine was achieved by two regioisomeric products. They were isolated from one pot reduction and intramolecular cyclization to afford quinoxalinone ring system with traceless cleavage of ionic liquid support. Besides, the ionic-supported other isomer was further cleaved in methanol. All the reactions were carried out on an ionic liquid support under various conditions to deliver biologically relevant scaffolds with high purity and excellent yields.

Introduction

Diversity oriented synthesis (DOS) has significantly revolutionized the drug discovery process and also has an impact on material science, catalysts, polymers, and pesticides.[1] In recent years, the design and synthesis of pharmacologically relevant heterocyclic molecules by DOS techniques has proven to be a promising strategy in the preparation of privileged-substructure-based libraries.[2] Integration of advanced technologies such as microwave, ionic liquid (IL), and polymer supported synthesis in the combinatorial synthesis of numerous multi-functionalized molecules is the key to speed up initial drug discovery.[3] Microwave-assisted IL supported organic synthesis is more popular in recent years because of the advanced instrumentation to provide reproducible results in homogeneous conditions.[4] Focusing on the synthesis of drug-like molecules, substituted heterocyclic compounds with a high degree of structural diversity are useful as potentially therapeutic agents.[5] Furthermore, compounds that contain heterocyclic moieties often exhibit improved solubility and can facilitate salt formation properties, which are important for oral absorption and bioavailability.[6] In chemical genetics, development of synthetic libraries in privileged scaffolds is specifically utilized to explore biological pathway in cells or organisms. The design and synthesis of small molecules with structural, substituent, and chiral diversity from easily available building block through a short and efficient approach is important to access a wide variety of structurally complex small molecules.[7,8]

Our interest is to develop the regioselective nucleophilic method for IL-fluorinated nitrobenzene. We choose 2,3,4,5-tetrafluoronitrobenzene (TFNB) for our studies where two activated fluorine atoms (2 and 4 positions) for regioselective nucleophilic substitution and two non-active fluorine atoms (3 and 5 positions) could present in target compound to attempt to increase its potential pharmacodynamic utilities. In the solution phase synthesis, generally nucleophilic aromatic substitution follows the sequence of C-2 ≈ C-4 > C-5 > C-3 order according to MNDO semi-empirical calculation for nucleophilic reactivity on TFNB as shown in Figure 1. Based on these differences in calculations of reactivity in activated fluoro group as well as analysis of the nature of nucleophile, we contemplate that the modification in the reaction conditions could provide the selective nucleophilic substitution. According to our assumption, we designed a synthetic route that allowed sequential nucleophilic aromatic substitution and provide the controlled synthetic route for multi-substituted TFNB system. For a succession of two nucleophilic substitution steps, where N1 is the first nucleophile and N2 is the second nucleophile, the order of substitution presents the opportunity of obtaining heterocyclic scaffolds and was shown in Figure 1.[9]

Our approach based on sequential S_NAr reactions on TFNB was planned to apply for the synthesis of guanidine linked to quinoxalinone moiety by heterocyclic core such as piperazine, azepane, and aminomethylpiperidine. Quinoxalinones represent a privileged moiety in medicinal chemistry and are ubiquitous substructures in material science and pharmaceuticals.[9] Some of the quinoxalinone derivatives act as psychotropic, hypnotic, cardiotonic, antihistamine agents, and possess cardiovascular activity, antiinflammatory activity as well as are HIV-1 reverse transcriptase

* Corresponding author. Tel.: +886 3 513 1511; fax: +886 3 573 6007.
E-mail address: cmsun@mail.nctu.edu.tw (C.-M. Sun).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.11.012

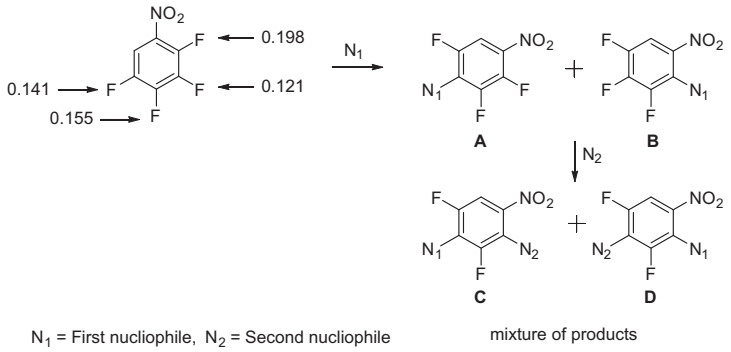


Figure 1. MNDO semi-empirical calculation for TFNB.

inhibitor (I).[10] The incorporation of piperazine or related heteroaromatic sub-units on the quinoxalinone ring system has been the focus of much attention which has exhibited a wide range of biological activities, for example, Carta et al. recently reported the synthesis and antimicrobial activities of over 150 quinoxalinones (II).[11] Moreover, the synthesis of such systems bearing bioactive guanidine unit that are attached to heterocyclic systems are of much interest due to the often unusual chemical, physical, and biological properties that such systems exhibit.[12] The introduction of a guanidyl type group improves the in vivo pharmacokinetic properties of thrombin and FXa inhibitors (III)[13] (Fig. 2).

Here we report the efficient traceless synthesis of guanidine linked piperazinyl, azepanyl, and aminomethylpiperidinyl quinoxalinones with substitutional diversity from versatile building blocks which include chiral amino acids, secondary amine derivatives such as piperidines, piperazines, and homopiperazines, and their stepwise regio-selective reaction with TFNB. The method describe in this Letter is a part of our continuing effort to explore traceless synthetic methodology to construct new heterocycles libraries. An IL-supported approach gives the advantage to employ the inexpensive asymmetric scaffold TFNB for the straightforward construction of complicated, fused heterocycles.

The synthetic strategy commenced with anchoring of amino acids to IL by the esterification method developed by our group.[8] Various aliphatic, aromatic, and hetero-aromatic chiral amino acids were immobilized on an ionic liquid support to produce the IL-supported amino acid conjugates **1** with built-in structural diversity. The main task of this synthetic pathway was the regioselective nucleophilic aromatic substitution reaction with tetra-fluoro-nitrobenzene (TFNB) by IL anchored chiral amino acid **1**. The TFNB has two active sites (2-fluoro and 4-fluoro) for nucleophilic substitution. Previously, Hardcastle and co-workers tried the similar nucleophilic substitution with penta-fluoro-nitrobenzene and ended up with the mixture of 2-substituted and 4-substituted nitrobenzene products.[9] Similarly, Ji et al also obtained the mixture of *ortho* and *para* substituted compounds in a similar substitution in dimethyl formamide at room temperature.

We reported here the efficient traceless synthesis of 5,7-difluoro-2-oxo-1,2,3,4-tetrahydro-quinoxalin-piperazines with three points of diversity. These versatile building blocks which include chiral amino acids, secondary amine derivatives such as piperidines, piperazines, and homopiperazines, and their regio-selective reaction appear to occur at either 2- or 4-position of 2,3,4,5-tetrafluoronitrobenzene (TFNB) to provide two isomeric products. For the purpose of library generation, the multi-step synthesis is conveniently carried out on the ionic liquid support to facilitate purification by precipitation. The fluoro displacement reaction of **1** with an excess of TFNB inside the microwave cavity proceeds to completion in 30 min with the formation of IL-bound tri-fluoronitrobenzoamines **3** and **4**. It takes 10 h to finish the same coupling reaction by conventional reflux heating or 1 h by sealed tube or 24 h to complete the coupling reaction at room temperature (Scheme 1).

When IL-bound amines **1** react with TFNB **2** in acetonitrile, two IL-bound region-isomers **3** and **4** are formed to display a 'one-bead-two-compound' feature. Just as expected, the reaction appears to occur at either 2- or 4-position to provide two isomeric products from each IL support. This was theoretically predicted by the MNDO semi-empirical calculation method and other organic synthesis reports.[9] So in a subsequent step, the displacement of the second active fluorine at 2- or 4-position with piperazines, homopiperazines, and 4-(aminomethyl)piperidines in the presence of triethylamine was introduced to this basic structure to give the products **5** and **6**, though there is a primary amine group in the 4-(aminomethyl)piperidine. Next we tried to introduce the guanidinyl group into **5** and **6** with *N,N′*-di-*tert*-butoxycarbonyl 1*H*-benzotriazole-1-carboxamidine derivatives **7** in ACN in the presence of TEA which took place for 18 h to give products **8** and **9**. All the IL bound intermediates and final compounds are purified by precipitation with the addition of ether (Scheme 2).

Reduction mixtures of IL bound intermediates **8** and **9** with Zn/$HCOONH_4$ gave the anticipated compounds **10** because the cyclization had taken place at the same time. The reduction and cyclization of **8** were operated simultaneously in situ, this is also accompanied by the cleavage of the ionic liquid support by an

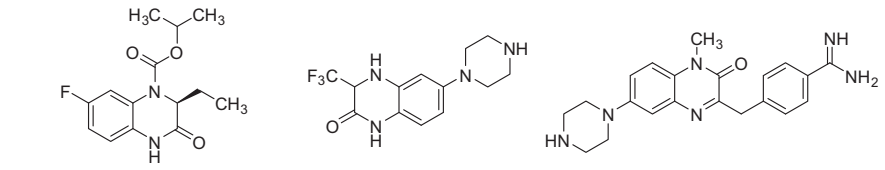
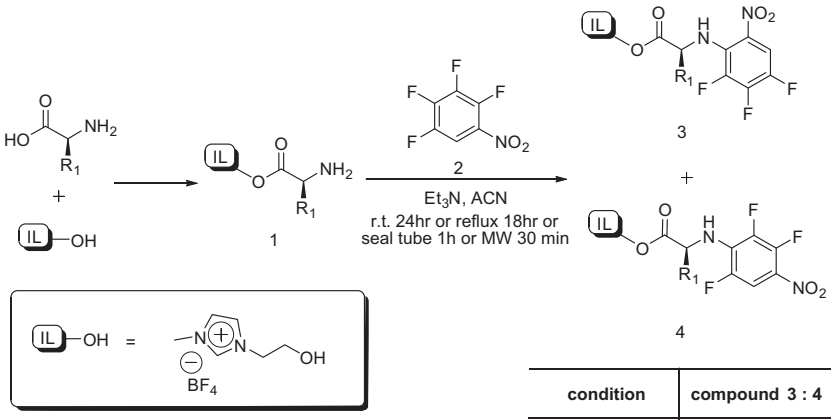
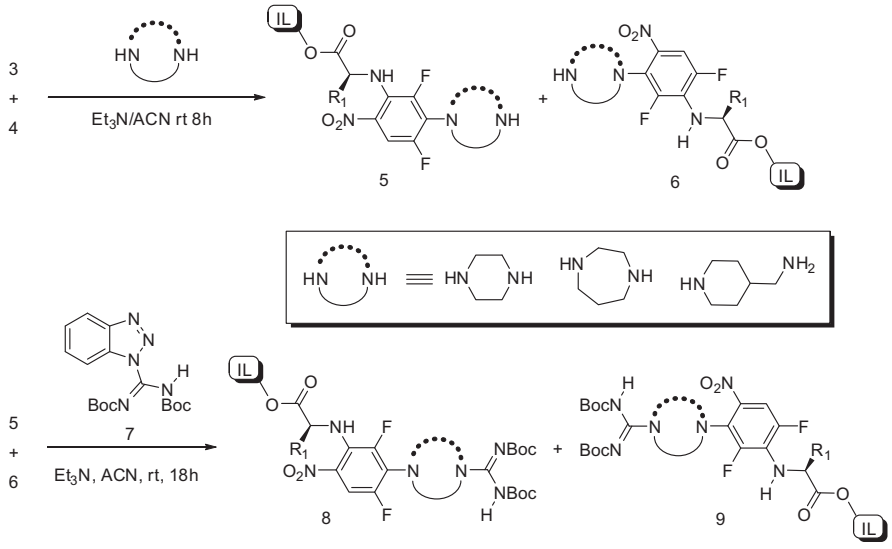


Figure 2. Biologically active relevant heterocyclic scaffolds.

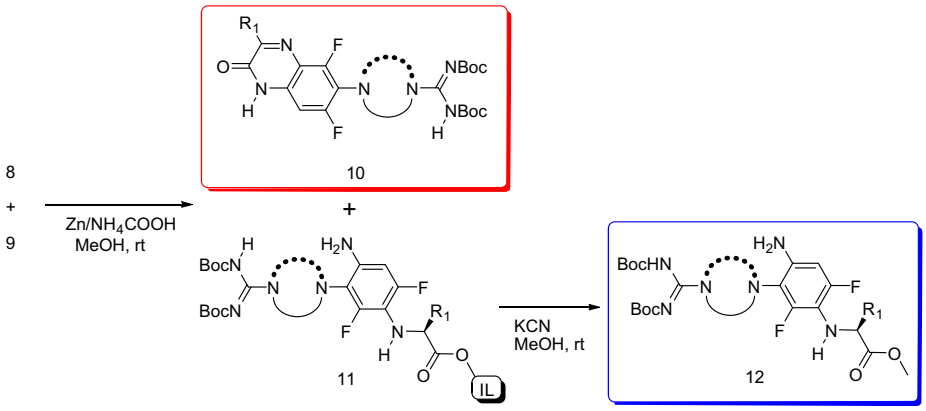


condition	compound 3 : 4
room temperature	2 : 1
reflux	3 : 1
seal tube	4 : 1
micro wave	1 : 1

Scheme 1. Regioselective S_NAr reaction at *ortho*-position of TFNB.

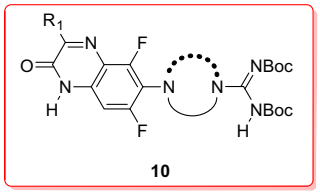


Scheme 2. Second S_NAr reaction to incorporate heterocyclic unit and guanidinylation.

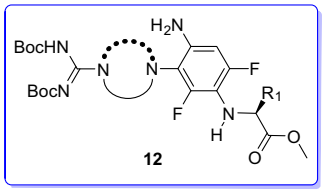


Scheme 3. Traceless synthesis of difluoro-dihydro-quinoxalinones.

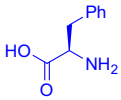
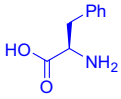
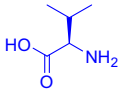
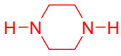
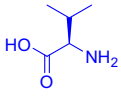
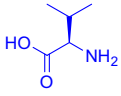
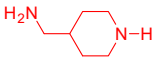
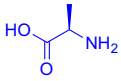
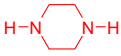
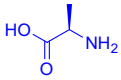
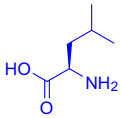
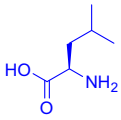
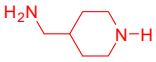
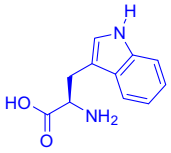
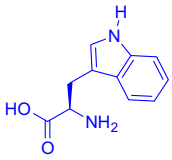
Table 1
Scope of methodology



10



12

Entry	Amino acids	Diamines	Yields[a] (**10**/**12**)
a			86(2/1)
b			82(4/1)
c			80(2/1)
d			83(1:1)
e			92(4:1)
f			85(3/1)
g			86(1/1)
h			88(3/1)
i			86(4/1)
j			88(1/1)
k			90(1/1)

[a] Isolated yield: in parentheses ratio of **10**–**12**.

intra-molecular nucleophilic attack on the IL attached site and no more cleavage step is required. Traceless cleavage compounds **10** and IL-supported compounds **11** are separated easily by addition of ether to precipitate **11** selectively. Acyclic aniline **11** will need further to split in the presence of KCN to give *trans*-esterified moiety **12** (Scheme 3).[14]

We successfully acquired the drug-like skeletons difluorobenzodiamines **12** and difluoro-2-quinoxalinones **10**, upon completion of the reduction of **8**, subsequent intra-molecular cyclization reaction to give traceless compounds **10** and IL immobilized **9** was obtained through filtration after precipitation in ether. The versatility of sequential regioselective nucleophilic reaction was determined

by employing various aliphatic, aromatic, and hetero-aromatic amino acids. In all the amino acids the regioselectivity was achieved in nucleophilic substitution reaction. The chiral elements were introduced into the difluorobenzodiamines **12** by using the chiral amino acids. Furthermore the different diamino-heterocycles namely piperazine, diazepine, and 4-aminomethylpiperidines were used in combination with the above amino acid to construct the scaffold diversity. All the substrates reacted efficiently to deliver the final cyclized products with no substantial difference in the yields. Table 1 describes the scope of developed methodology and the diversity elements of the scaffold.

We have successfully developed a rapid and efficient solution synthesis of benzimidazole linked pyrrolo[1,2-*a*]benzimidazolones, pyrido[1,2-*a*]benzimidazolones, and isoindo[1,2-*a*]benzimidazoles with three sets of diversity on ionic liquid support. A cascade reaction was systematically applied to furnish diverse heterocyclic molecular libraries with IL-supported synthesis from an IL-fluoro scaffold (TFNB) moiety which was indispensable for the method in view of its double reactive sites. Guanidine linked difluoro-2-quinoxalinones **10** were directly obtained by concomitant intramolecular cyclization after reduction, whereas the stable difluorobenzodiamines **12** was further released from the ionic liquid support after precipitation.

This approach provides a high speed path for the rapid synthesis of bis-heterocyclic libraries with a high degree of structural diversity. The powerful potential of multidisciplinary synthetic approach, integrating ionic liquid support, and microwave synthesis with multistep synthesis has great potential to produce biologically interesting molecules for drug discovery.

Acknowledgments

The authors thank the National Science Council of Taiwan for the financial assistance. This work is particularly supported by 'Center for Bioinformatics Research of Aiming for the Top University Program' of the National Chiao Tung University and Ministry of Education, Taiwan, ROC.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.012.

References and notes

1. Mnyusiwalla, A.; Daar, A. S.; Singer, P. A. *Nanotechnology* **2003**, *14*, R9–R13.
2. (a) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Salvino, J. M.; Zhang, W. *J. Comb. Chem.* **2007**, 9, 855–902; (b) Cironi, A.; Alvarez, M.; Albericio, F. *Mini-Rev. Med. Chem.* **2006**, *6*, 11–25; (c) Kennedy, J. P.; Williams, L.; Bridges, T. M.; Daniels, R. N.; Weaver, D.; Lindsley, C. W. *J. Comb. Chem.* **2008**, *10*, 345–354; (d) Boger, D. L.; Desharnais, J.; Capps, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4138–4176.
3. (a) Hsiao, Y. S.; Yellol, G. S.; Chen, L. H.; Sun, C. M. *J. Comb. Chem.* **2010**, *12*, 723–732; (b) Bai, L.; Wang, J. X. *Adv. Synth. Catal.* **2008**, *350*, 315–320; (c) Zhang, W.; Chen, C. H.; Lu, Y.; Nagashima, T. *Org. Lett.* **2004**, *6*, 1473–1476; (d) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205–1208.
4. DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473–494.
5. Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Disc.* **2007**, *6*, 881–890.
6. (a) Jung, N.; Wiehn, M.; Bräse, S. *Comb. Chem. Solid Support.* **2007**, *278*, 1–88; (b) Ganesan, A. *Mini-Rev. Med. Chem.* **2006**, *6*, 3–10; (c) Bräse, S. *Acc. Chem. Res.* **2004**, *37*, 805–816.
7. (a) Holland, R. J.; Hardcastle, I. R.; Dick, A. G.; Nutley, B. P.; Hayes, A.; Jarman, M. *Tetrahedron Lett.* **2002**, *43*, 719–721; (b) Ji, Y. F.; Pan, X. D.; Wei, X. Y. *Synlett* **2004**, 1607–1609; (c) Ji, Y. F.; Wei, X. Y. *Org. Prep. Proced. Int.* **2007**, *39*, 591–602.
8. Thummanagoti, S.; Yellol, G. S.; Sun, C. M. *Tetrahedron Lett.* **2011**, *52*, 2818–2822.
9. Gierczyk, B.; Eitner, K.; Schroeder, G.; Przybylski, P.; Brzezinski, B. *J. Mol. Struct.* **2003**, *655*, 259–267.
10. Kleim, J. P.; Bender, R.; Billhard, U. M.; Meischner, C.; Reiss, G.; Rosner, M.; Winkler, I.; Paessens, A. *Antimicrob. Agents Chemother.* **1993**, *37*, 1659.
11. (a) Carta, A.; Loriga, M.; Zanetti, S.; Sechi, L. *Farmaco* **2003**, *58*, 1251; (b) Carta, A.; Sanna, P.; Loriga, M.; Setzu, M. G.; La Colla, P.; Loddo, R. *Farmaco* **2002**, *57*, 19; (c) Sanna, P.; Carta, A.; Loriga, M.; Zanetti, S.; Sechi, L. *Farmaco* **1999**, *54*, 169.
12. (a) Bucknall, R. A.; Swallow, D. L.; Moores, H.; Harrad, J. *Nature* **1973**, *246*, 144–145; (b) Wang, Q.; Loennberg, H. *J. Am. Chem. Soc.* **2006**, *128*, 10716–10728; (c) Medina-Molner, A.; Blacque, O.; Spingler, B. *Org. Lett.* **2007**, *9*, 4829–4831; (d) Suhs, T.; Konig, B. *Mini-Rev. Org. Chem.* **2006**, *3*, 315–331; (e) Ganesan, A. *Mini-Rev. Med. Chem.* **2006**, *6*, 3–10.
13. (a) Ries, U. J.; Priepke, H. W. M.; Hauel, N. H.; Handschuh, S.; Mihm, G.; Stassen, J. M.; Wienen, W.; Nar, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2297; (b) Willardssen, J. A.; Dudley, D. A.; Cody, W. L.; Chi, L.; McClanahan, T. B.; Mertz, T. E.; Potoczak, R. E.; Narasimhan, L. S.; Holland, D. R.; Rapundalo, S. T.; Edmunds, J. *J. Med. Chem.* **2004**, *47*, 4089.
14. *General procedure for the synthesis of **10** and **12***: IL-supported compound **1** (1 g) was added to a 50 ml flask with 0.11 g of TFNB **2** (3 equiv, 0.59 mmol) and TEA 0.16 mL (6 equiv, 1.15 mmol) in 10 ml acetonitrile. The reaction mixture was heated for 30 min under microwave in open vessel condition. After the completion of reaction, ether was added to the reaction mixture to precipitate the two isomers of the IL-supported compounds **3** and **4** and washed with ether (30 mL × 2). IL-supported compounds **3** and **4** dissolved in acetonitrile (10 mL), piperazine or homopiperazine or aminomethylpiperidine (3 equiv, 0.57 mmol), and 0.18 ml TEA (6 equiv, 1.18 mmol) were stirred at room temperature for 8 h, then ether was added to the reaction mixture to precipitate the IL-supported compounds **5** and **6**. IL-supported compounds **5** and **6** dissolved in acetonitrile (10 mL) with 0.20 g of *N,N′*-di-*tert*-butoxycarbonyl-1*H*-benzotriazole-1-carbox-amidine **7** (3 equiv, 0.56 mmol) and 0.16 ml TEA (6 equiv, 1.15 mmol) were stirred at room temperature for 18 h. The ether (50 mL) was added after the reaction was completed. The precipitation was filtered, and dried under high vacuum to give guanidinyl compounds **8** and **9**. IL-supported compounds **8** and **9** dissolved in methanol (10 mL) with 233 mg of powder Zn and 112 mg of NH_4COOH (10 equiv, 1.79 mmol) were stirred at room temperature for 1 h. Monitoring the reaction progress by TLC showed that compound **10** was released from ionic liquid support. The filtrate was concentrated after precipitation, dried well and submitted to spectrum analysis. Further purification by column chromatography furnished the pure guanidinyl heterocyclic linked quinaxolinones **10** as a liquid. *Compound **10a***: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.18 (s, –NH), 8.95 (s, 1H), 7.39–7.35 (m, 2H), 7.32–7.30 (m, 1H), 7.20–7.17 (m, 2H), 6.40 (d, J = 11.2 Hz, 1H), 4.05–3.91 (m, 2H), 3.71 (m, 4H), 3.19 (m, 4H), 2.86–2.78 (dd, J = 13.3, 10.8 Hz, 1H), 1.50 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 164.7, 160.4, 159.2, 155.9, 152.8, 149.3, 136.1, 135.9, 129.2, 128.9, 128.6, 127.1, 126.7, 120.2, 118.0, 99.9, 97.8, 50.8, 44.5, 39.9, 31.1, 29.6, 28.0; IR (cm^{-1}, neat): 3275, 2924, 2852, 1678; MS (ESI-MS) m/z: 601 $[M+H]^+$; HRMS Calcd for $C_{30}H_{38}F_2N_6O_5$: m/z 600.2872; Found 601.2948 $[M+H]^+$. The IL-supported compound **11** was cleaved in methanol (10 mL) and 26 mg KCN (3 equiv, 0.40 mmol) for 18 h. Ether (50 mL) was added to precipitate IL-**1** and the filtrate was concentrated to give compounds **12** as a liquid. *Compound **12a***: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.22 (m, 3H), 7.17–7.15 (m, 2H), 6.25–6.20 (dd, J = 12.3, 2.0 Hz, 1H), 4.31 (t, J = 6.1 Hz, 1H), 3.63 (s, 3H), 3.38–3.20 (m, 4H), 3.07 (d, J = 6.5 Hz, 2H), 2.81–2.76 (m, 4H), 1.50 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 167.7, 148.9, 145.6, 143.8, 142.6, 136.4, 132.4, 128.7, 128.4, 126.8, 114.8, 114.5, 110.2, 97.5, 83.3, 52.8, 51.8, 49.9, 46.2, 38.6; IR (cm^{-1}, neat): 2871, 1737; MS (ESI-MS) m/z: 633 $[M+H^+]$; HRMS Calcd for $C_{31}H_{42}F_2N_6O_6$: m/z 632.3134; Found 633.3211 $[M+H^+]$.