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SI - SCS-09

Scaffold-directed and traceless synthesis of tricyclic quinoxalinone imidazoles under microwave irradiation

For SCS-09 special issue-combinatorial approaches to drug discovery

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Abstract Traceless synthesis of 2-aminoimidazoquinoxalinones has been performed on soluble polymer support under open-vessel microwave dielectric heating. The reaction progression is monitored directly by the conventional proton NMR which indicated no release of the substrate from the support. Fmoc-deprotected amino acid polymer conjugates react with 1,5-difluoro-2,4-dinitro benzene to yield polymer bound dinitro fluoro amines, which are further substituted by various primary amines to yield PEG-immobilized dinitrodiamines. Simultaneous reduction of aromatic *meta*-dinitro group leads to the traceless release of 2-quinoxalinones, followed by N-hetero cyclization with various isothiocyanates in the presence of mercury(II)chloride to furnish 2-aminoimidazoquinolinone rings with three points of diversity at rapid pace.

Keywords Traceless liquid-phase strategy · Tricyclicquinoxalinoneimidazole · Open-vessel microwave irradiation

Introduction

Heterocyclic derivatives with polycyclic skeletons such as tricyclic quinoxalinones (**I** and **III**) play an important role in the arsenal of clinically useful therapeutic agents (Fig. 1) [1–6]. These compounds constitute an interesting chemical space of drug-like derivatives since a small variation of the structure can lead to a profound change in the receptor binding profile or clinical activity [7–9]. Imidazo[4,5-g]quinoxaline (I) comprises an imidazoquinoxaline scaffold with a variable moiety at the second position to inhibit the phosphorylation activity of Akt/PKB isoforms selectively [10]. Diaminobenzobisthiazoles (**II**) containing bis-tertiary amino side chain show good in vivo anti-swelling effect when administered orally in the paw prophylactic adjuvant arthritis model [11]. Imidazol[4,5-g]quinoxaline (**III**) has been identified as inhibitors against testis-specific serine/threonine kinase1 [12]. The design of the present library originated from the observation of the extensive biological activities of the quinoxalin-2(1H)-one and 1H-benzo[d]-imidazol-2-amine moieties which are attractive privileged scaffolds. The creation of a hybrid quinoxaline-related tricycle scaffold composed of quinoxalinone and 2-amino-benzimidazoles, thus has a substantial intellectual appeal resembling drug-like molecules. Therefore, combination of these two privileged pharmacophores may provide additional opportunities to discover new lead compounds.

Drug discovery is a time-consuming and expensive process. The bottleneck lies in the generation of compound libraries with diversity of various chemical spaces. Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. As a result, an increasing range and number of pharmaceutically interesting heterocyclic compounds have been prepared rapidly using combinatorial chemistry to keep pace of high throughput biological screening [13,14]. Application of solid phase combinatorial synthesis for the rapid generation of small molecules continues to be an area of great interest [15,16].

In providing a viable alternative to the solid support reaction, liquid phase synthesis has been signifying the usefulness of employing a soluble macromolecular support as

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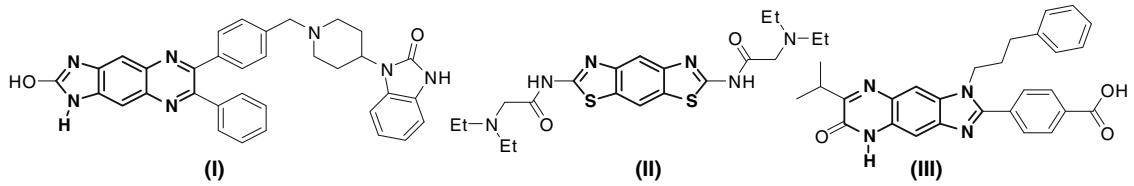


Fig. 1 Some pharmacologically active tricyclic imidazoquinolinones

a carrier such as polyethylene glycol (PEG). Polyethylene glycol is inexpensive than that of other soluble polymer supports such as polyethylene oxide and polyoxyethylene. The significant differences in physical properties between PEG_{4000}, PEG_{6000}, and PEG_{5000} are their loading capacity and contained hydroxyl functionalities. PEG_{5000} contains one hydroxyl group and its loading capacity is 0.2 mmol/g, whereas PEG_{4000} and PEG_{6000} have two hydroxyl groups and their loading capacities are 0.5 and 0.33 mmol/g, respectively. Soluble polymer supported synthesis of small molecules benefits the advantages of both solution phase and solid phase syntheses. Various synthetic steps are conducted under homogeneous conditions with favorable reaction kinetics, whereas purifications are performed just by filtration and polymer precipitation. This alternative strategy, known as liquid-phase combinatorial synthesis, has been investigated to synthesize various heterocyclic combinatorial libraries [17–20]. Soluble polymer supported molecules are directly amenable to standard spectroscopic methods such as nuclear magnetic resonance spectroscopy and mass spectrometry which allow to perform in situ reaction monitoring without the need to cleave the compound from the polymeric support [21,22].

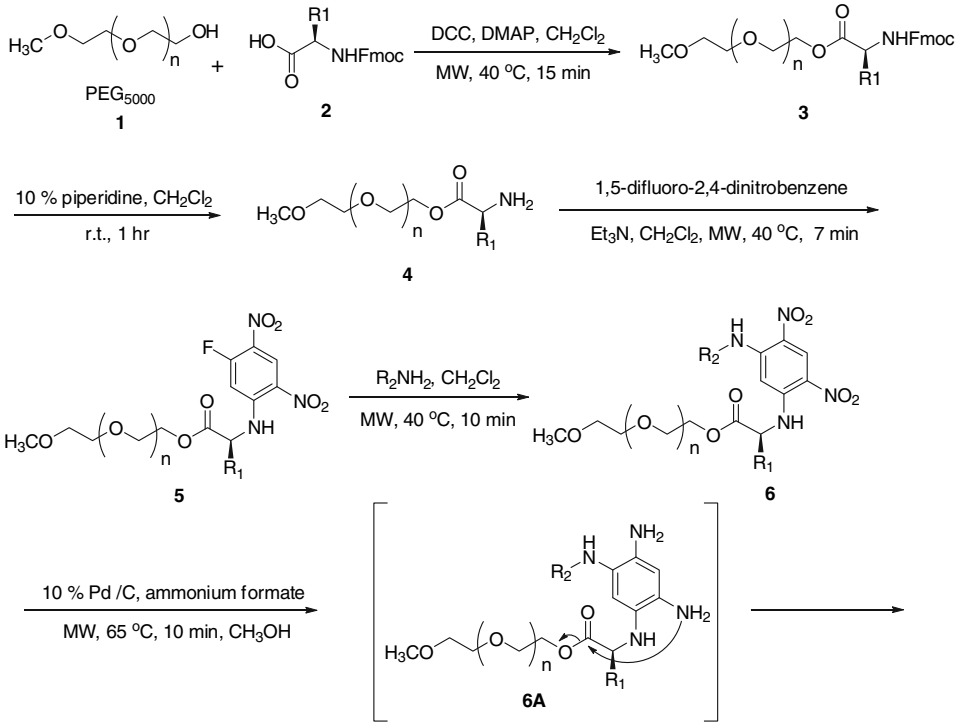
Liquid phase organic synthesis on a soluble support can decrease the time of library generation by simplifying the purification procedure. The optimization of reaction condition is still a time-consuming process. During last two decades, microwave assisted organic synthesis has been demonstrated in drastically accelerating a variety of synthetic transformations. Microwave assisted chemical synthesis attributes to the application of electromagnetic radiation within the microwave frequencies to convey the energy to start, force or promote some chemical reactions. The main benefits of performing reactions under microwave irradiation are the significant rate enhancement and the higher product yields that can frequently be observed [23,24]. Given the current demand for novel compounds in drug discovery, the combination of microwave assisted organic synthesis and traceless liquid phase synthetic strategy improve the efficiency of library generation importantly.

In this report, we described a scaffold-directed approach to prepare benzofused chemical libraries using 1,5-difluoro-2,4-dinitrobenzene (DFDNB) as a multifunctional building block [25–28]. To extend the scope of our recent studies, we report herein an efficient cyclization-cleavage (i.e., traceless) method to simplify the synthetic strategy as well as to reduce the synthetic steps. After being released from the support, the desired products are easily recovered, ignoring the requirement of post cleavage workup. Hence heterocyclic compounds of interest can be generated in free of any trace of the linker used to tether the starting building block to the polymer support. In view of our ongoing program for the development of novel synthetic strategy toward heterocyclic compounds, we herein report the microwave-assisted traceless synthesis of tricyclic quinoxalinone imidazole libraries with three points of structural diversity.

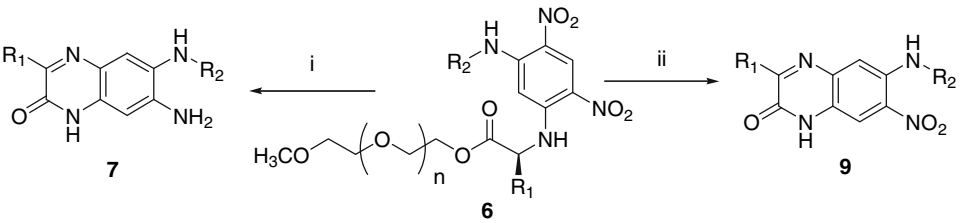
Results and discussion

Polyethylene glycol **1** (MW∼5000, 200 μmoles of free OH groups/g) is used as the soluble polymer support for the microwave-assisted synthesis of imidazoquinoxalinones. The PEG_{5000} has been proven to be a versatile and useful polymer support for the rapid synthesis of small heterocyclic molecules [29] and oligonucleotides [30,31]. The PEG_{5000} has also applied in drug delivery system of cancer therapy [32]. PEG_{5000} is easy to form gelatinous precipitation when the polymer-tethered building blocks are growing up after several synthetic transformations. In the beginning, PEG_{5000} **1** was reacted with Fmoc protected amino acid **2** under carbodiimide-mediated coupling condition (Scheme 1). This coupling reaction achieved under opened-vessel microwave conditions (150 W) for 15 min to afford the Fmoc-protected amino ester conjugates **3** and the first diversity was established by the side chain of Fmoc protected amino acid. Using the same stoichiometry of reagents, the coupling reaction was complete in 8 h by conventional reflux heating. The emergence of the free amino group was induced by treating **3** with 10 % piperidine in dichloromethane at room temperature which left the polymer support intact and led to the polymer-bound amines **4**. One of the two fluorines of the 1,5-difluoro-2,4-dinitrobenzene was substituted by the nucleophilic polymer-bound aminoester **4** in the presence of triethylamine. This *ipso*-fluoro displacement reaction was achieved in 7 min under microwave irradiation condition. It should be mentioned that no di-substituted species were observed under harsh microwave dielectric heating. The evidence is based on the relative integration ratio of aromatic protons of the 1,5-difluoro-2,4-dinitrobenzene with amino

Scheme 1 The traceless synthetic route to the targeted molecules by multistep microwave irradiation



Scheme 2 Reduction study of PEG-immobilized dinitro diamines **6**



Reaction condition of reduction (i) Pd-C/$HCOONH_4$/MW, MeOH. (ii) a : Pd-C/H_2/MeOH/rt; or b : $SnCl_2.7H_2O$/MeOH/reflux or MW; or c : Zn/ $HCOONH_4$/MeOH/reflux or MW

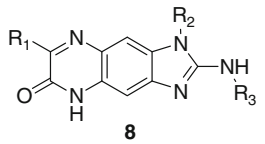
group protons. The immobilized polymer conjugated **5** may be too bulky to proceed second *ipso*-fluoro displacement with polymer-bound aminoester **4**. Furthermore, compound **5** became less reactive than difluoronitrobenzene once one fluorine atom is replaced by polymer bound amino esters **4**.

After nucleophilic aromatic substitution reaction (S_NAr), the new signals in the aromatic region were merged due to protons from fluoronitrobenzene ring. Displacement of the remaining fluorine atom by various primary amines introduced the second point of diversity to give **6** in high yield. The reactions went smoothly under open vessel MW conditions (150 W) for 10 min, and no side reactions such as cleavage of the polymer support were observed. Comparison of proton NMR spectrums of compound 5 with compound 6 indicate that, the peak (doublet) due to aromatic proton ortho-to fluoro-group is shifted to upfield region and appeared at 5.55 ppm (singlet) which implied the weak electron donating fluoro atom was transformed into strong electron donating amine functionality. (See Fig. 1 in supplementary information for detailed proton NMR monitoring synthesis of imidazoquinoxalinones on the support).

To completely reduce the aromatic *m*-dinitro group of PEG-immobilized dinitro diamines **6** to the corresponding *o*-phenylenediamine derivative **7**, various reduction conditions (Scheme 2) were investigated systemically including H_2-Pd/C [33], $SnCl_2{\cdot}7H_2O$ [34,35], and Zn/$HCOONH_4$ [36]. All the above-mentioned methods delivered directly 2-quinoxalinone analogues **9**, an *o*-nitroaniline intermediate

without further reduction of another nitro group. It is also not possible to convert intermediate **9** to aniline **7** using the same reduction conditions. This is implied that the resulting polymer bound triaminobenzene **6A** was cyclized spontaneously after reduction and aromatized to give the compound **9**. It cannot be further reduced to di-amino compound **7** either by refluxing or microwave irradiation. These results may indicate the difficulty to reduce di-nitro groups because of double resonance effect of the electron donating amino groups in the *ortho* and *para* positions. However, simultaneous

Table 1 One-pot cyclization toward 2-aminoimidazoquinoxalines **8**



8

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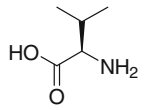
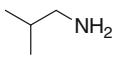
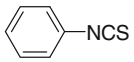
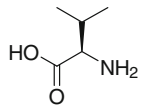
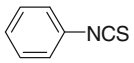
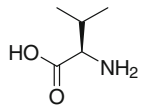
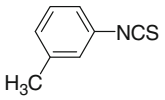
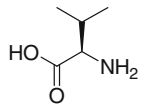
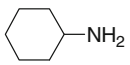
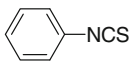
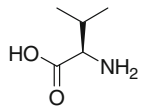
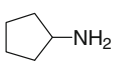
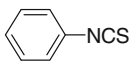
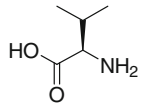
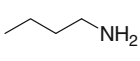
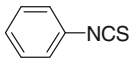
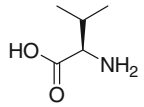
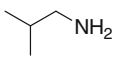
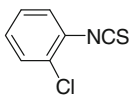
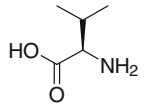
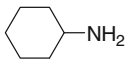
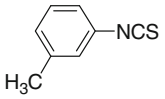
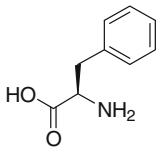
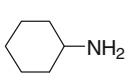
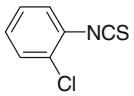
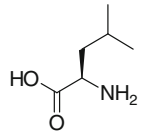
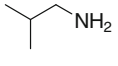
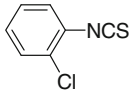
a				375	92%
b				361	94%
c				375	90%
d				401	88%
e				387	90%
f				375	85%
g				409	84%
h				415	86%
i				483	82%
j				423	84%

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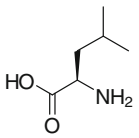
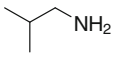
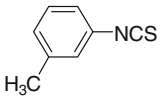
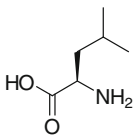
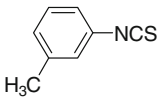
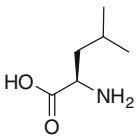
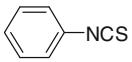
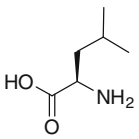
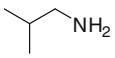
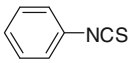
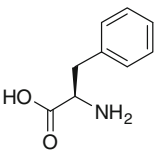
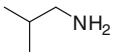
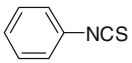
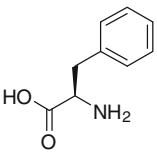
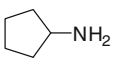
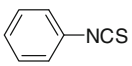
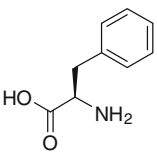
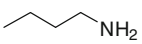
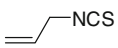
k				403	92%
l				389	84%
m				375	92%
n				389	92%
o				423	90%
p				435	88%
q				387	85%

[a] Confirmed by mass spectra (El)
[b] Yields were determined on weight samples

reduction of *m*-dinitro functionalities and traceless cleavage of 7-amino-3-alkyl-6-(alkyllamino)quinoxalin-2(1H)-one **7** from the support were finally achieved with palladium black in the presence of ammonium formate in methanol (Scheme 2) [37]. The spectroscopic evidences were the disappearance of the signals of polymer support and the upfield shifting of peak of aromatic proton positioned ortho to both nitro-groups to 7.08 from 9.2 ppm. Crude 3,7-dialkyl-6-(alkyllamino)-quinoxalin-2(1H)-one **7** directly released from the support was cyclized with various isothiocyanates in the presence of $HgCl_2$ under the open-vessel microwave heating (200 W) for 10 min. However, it took 16 h for the construction of benzoimidazol-2-amine moiety under conventional refluxing condition. The elucidated mechanism for the benzoimidazol-2-amine formation indicates that the sulfur atom of isothiocyanates chelate to the mercury ion to generate highly electrophilic species in situ. The nucleophilic diamines **7** then attacked on the electrophilic species and extruded H_2S to afford the imidazoquinoxalinones **8**. By the use of thin layer chromatography (TLC), we observe that the less lipophilic diamines **7** were gradually transformed into more lipophilic imidazoquinoxalinones **8**. The ^1H NMR monitoring model also showed the downfield shift of aromatic protons peak and the newly appearance of peaks from isothiocyanate group. Quinoxalin-2(1H)-one (**8**) and quinoxalin-2-ol (**10**) were the possible proposed skeletons for the final target compound. The existence of amide (**8**) over its enol form (**10**) was further confirmed by its IR spec-

trum where the peak at 1690–1640 cm^{-1}specified amide absorption. This multi-step microwave-assisted synthesis and traceless strategy have offered an efficient and convenient approach toward the access the tricyclic imidazoquinoxalinones **8** analogues. Seventeen examples with three different appendages were synthesized in good yields and all the experimental data comprising MS, ^{1}H NMR, and ^{13}C NMR were coincident with these products (Table 1).

Conclusion

In summary, we have demonstrated a high throughput platform for the rapid generation of imidazoquinoxalinone libraries with three points of diversity by the synergistic application of multi-step microwave irradiation and traceless liquid phase synthesis. The libraries of compounds are usually obtained in high purity and yield just by washing each polymer attached intermediates and simple precipitation with minimum column purification. The reaction progress of forwarding synthetic route on the soluble support is successfully monitored by conventional proton NMR spectroscopy without the cleave-and-analyze method. The coupling of microwave technology with a liquid-phase traceless synthetic strategy constitutes a novel and efficient approach for the rapid generation of pharmaceutical interesting small molecules. The tricyclic 2-aminoimidazoquinoxalinone library is ready for in vitro biological screening and the results will be reported in due course.

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References

1. Len GR, Nash HM, Jindal S (2000) Chemical ligands, genomics and drug discovery. Drug Discov Today 5:145–156. doi:10.1016/S1359-6446(00)01468-9
2. Catarzi D, Colotta V, Varano F, Calabri FR, Filacchioni G, Galli A, Costagli C, Carlà V (2004) Synthesis and biological evaluation of analogues of 7-chloro-4,5-dihydro-4-oxo-8-(1,2,4-triazol-4-yl)-1,2,4-triazolo-[1,5-a]quinoxaline-2-carboxylic acid (TQX-173) as novel selective AMPA receptor antagonists. J Med Chem 47:262–272. doi:10.1021/jm030906q
3. Teague SJ, Davis AM, Leeson PD, Oprea T (1999) The design of lead like combinatorial libraries. Angew Chem Int Ed 38: 3743–3748
4. Davis AM, Dixon J, Logan CJ, Payling DW (2002) Accelerating the process of drug discovery. In: Pelkonen O, Baumann A, Reichel A (eds) pharmacokinetic challenages in drug discovery. Springer-Verlag, Berlin, Heidelberg, pp 1–32
5. Zhang L, Yan Y, Liu Z, Abliz Z, Liu G (2009) Identification of peptide substrate and small molecule inhibitors of testis-specific serine/threonine kinase1 (TSSK1) by the developed assays. J Med Chem 52: 4419–4428. doi:10.1021/jm9002846
6. Ma T, Liu L, Xue H, Li L, Han C, Wang L, Chen Z, Liu G (2008) Chemical library and structure-activity relationships of 11-demethyl-12-oxo calanolide a analogues as anti-HIV-1 agents. J Med Chem 51:1432–1446. doi:10.1021/jm701405p
7. Gazit A, Yee K, Uecker A, Böhmer FD, Sjöblom T, Östman A, Waltenberger J, Golomb G, Banai S, Heinrich MC, Levitzki A (2003) Tricyclic quinoxalines as potent kinase inhibitors of PDGFR kinase, Flt3 and Kit. Bioorg Med Chem 11:2007–2018. doi:10.1016/S0968-0896(03)00048-8
8. Catarzi D, Colotta V, Varano F, Cecchi L, Filacchioni G, Galli A, Costagli C, Carlà V (2000) 7-Chloro-4,5-dihydro-8-(1,2,4-triazol-4-yl)-4-oxo-1,2,4-triazolo-[1, 5-a]quinoxaline-2-carboxylates as novel highly selective AMPA receptor antagonists. J Med Chem 43:3824–3826. doi:10.1021/jm0009886
9. Catarzi D, Colotta V, Varano F, Filacchioni G, Galli A, Costagli C, Carlà V (2001) Synthesis, ionotropic glutamate receptor binding affinity, and structure-activity relationships of a new set of 4,5-dihydro-8-heteroaryl-4-oxo-1,2,4-triazolo-[1,5-*a*]quinoxaline-2-carboxylates analogues of TQX-173. J Med Chem 44: 3157–3165. doi:10.1021/jm010862q
10. Lindsley CW, Zhao Z (2007) US Patent 7,273,869 B 20,070,925
11. Cullen E, Becker R, Freter K, Leclerq T, Possanza G, Wong HC (1992) Bis basic substituted diaminobenzobisthiazoles as potential antiarthritic agents. J Med Chem 35:350–361. doi:10.1021/jm00080a022
12. Tang PC, Sun ML (2001) US Patent 6,329,375 B 20,011,211
13. Komarov PG, Komarova EA, Kondratov RV, Christov-Tselkov K, Coon JS, Chernov MV, Gudkov AV (1999) A chemical inhibitor of p53 that proteins mice from the side effects of cancer therapy. Science 285:1733–1737. doi:10.1126/science.285.5434.1733
14. Stieber F, Mazitschek R, Soric N, Giannis A, Waldmann H (2002) Traceless solid-phase synthesis of 2-aminothiazoles: receptor tyrosine kinase inhibitors with dual selectivity for Tie-2 and VEGFR-2. Angew Chem Int Ed 41:4757–4761. doi:10.1002/anie.200290040
15. Dolle RE (1996) Discovery of enzyme inhibitors through combinatorial chemistry. Mol Divers 2:223–236. doi:10.1007/BF01715638
16. Dolle RE, Le Bourdonnec B, Goodman AJ, Morales GA, Salvino JM, Zhang W (2007) Comprehensive survey of chemical libraries for drug discovery and chemical biology. J Comb Chem 9:855–902. doi:10.1021/cc700111e
17. Chanda K, Kuo J, Chen CH, Sun CM (2009) Enantioselective synthesis of benzimidazolyl quinoxalinones on soluble polymer support using focused microwave irradiation. J Comb Chem 11:252–260. doi:10.1021/cc800137p
18. Zhang CX, Tong HB, Yan CG (2007) First soluble multipolymer MPEG-supported liquid-phase convergent synthesis of tripeptide Fmoc-GlyVal-GlyOH. J Comb Chem 9:924–925. doi:10.1021/cc700156r
19. Gravert DJ, Janda KD (1997) Organic synthesis on soluble polymer supports: liquid-phase methodologies. Chem Rev 97:489–510. doi:10.1021/cr9600641
20. Han H, Wolfe MM, Brenner S, Janda KD (1995) Liquid-phase combinatorial synthesis. Proc Natl Acad Sci USA 92:6419–6423
21. Shey JY, Sun CM (2002) Liquid-phase combinatorial reaction monitoring by ^{1}H NMR spectroscopy. Tetrahedron Lett 43:1725–1729. doi:10.1016/S0040-4039(02)00061-8
22. Toy PH, Janda KD (2000) Soluble polymer-supported organic synthesis. Acc Chem Res 33:546–554. doi:10.1021/ar990140h
23. Kappe CO (2008) Microwave dielectric heating in synthetic organic chemsistry. Chem Soc Rev 37:1127–1139. doi:10.1039/b803001b
24. Kappe CO (2004) Controlled microwave heating in modern organic synthesis. Angew Chem Int Ed 43:6250–6284. doi:10.1002/anie.200400655

25. Zhao HY, Liu G (2007) Solution-phase parallel synthesis of diverse 1, 5-benzodiazepin-2-ones. J Comb Chem 9:1164–1176. doi:10.1021/cc7001149
26. Yuan Y, Liu G, Li L, Wang Z, Wang L (2007) Synthesis of diverse benzo[1,4]oxazin-3-one based compounds using 1, 5-difluoro-2,4-dinitrobenzene. J Comb Chem 9:158–170. doi:10.1021/cc060094u
27. Yeh WB, Lin MJ, Lee MJ, Sun CM (2003) Microwave-enhanced liquid-phase synthesis of thiohydantoins and thioxotetrahydropyrimidinones. Mol Divers 7:185–198. doi:10.1023/B:MODI.0000006802.21361.29
28. Wu XH, Liu G, Zhang J, Wang ZG, Xu S, Zhang SD, Zhang L, Wang L (2004) Solution-phase reductive cyclization of 2-quinoxalinol analogs: systematic study of parallel synthesis. Mol Divers 8:165–174. doi:10.1023/B:MODI.0000025639.89179.60
29. Lin MJ, Sun CM (2006) Microwave-assisted and traceless synthesis of imidazoquinoxalinones. J Comb Chem 8:455–458. doi:10.1021/cc060051d
30. Bonora GM, Scremin CL, Colonna FP, Garbesi A (1990) HELP (High Efficiency Liquid Phase) new oligonucleotide synthesis on soluble polymeric support. Nucleic Acids Res 18:3155–3159. doi:10.1093/nar/18.11.3155
31. Bonora GM, Biancotto G, Maffini M, Scremin CL (1993) Large scale, liquid phase synthesis of oligonucleotides by the phosphoramidite approach. Nucleic Acids Res 21:1213–1217. doi:10.1093/nar/21.5.1213
32. Cheng Y, Samia AC, Meyers JD, Panagopoulos I, Fei B, Burda C (2008) Highly efficient drug delivery with gold nanoparticle vectors for in vivo photodynamic therapy of cancer. J Am Chem Soc 130:10643–10647. doi:10.1021/ja801631c
33. Gigante B, Esteves MA, Curto MJM, Ascenso J, Prabhakar S, Lobo AM (1998) New resin acid derivatives: diisocyanate, diurethanes and diureides. Synth Commun 28:639–652. doi:10.1080/00397919808005936
34. Stacy GW, Bresson CR, Harmon RE, Thamm RE (1957) Preparation of some aminotrifluromethyldiphenyl sulfones as possible antibacterial agents. J Org Chem 22:298–302. doi:10.1021/jo01354a019
35. Hart WF, McGreal ME, Thurston PE (1962) 3,3′-sulfonylbis(phenyl isocyanates). J Org Chem 27:338–340. doi:10.1021/jo01048a534
36. Morita S, Kitano K, Matsubara J, Ohtani T, Kawano Y, Otsubo K, Uchida M (1998) Practical application of the palladium-catalyzed amination in phenylpiperazine synthesis: an efficient synthesis of a metabolite of the antipsychotic agent aripiprazole. Tetrahedron 54:4811–4818. doi:10.1016/S0040-4020(98)00175-6
37. Zhao HY, Liu G (2007) Solution-phase parallel synthesis of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones. J Comb Chem 9:756–772. doi:10.1021/cc070036o