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Review Article

A review on the synthesis of scaffolds directed benzimidazole based biheterocyclic molecules

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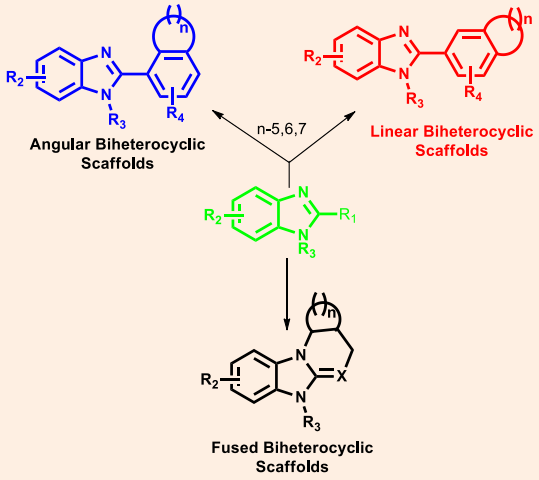
Abstract

Heterocyclic compounds are one of the common structural motifs for 80% of the marketed drugs reported in 2014. Benzimidazole and its derivatives are regarded as important heterocyclic motifs exhibiting a wide range of pharmaceutical applications. It is always necessary to focus on the synthesis of heterocyclic molecules contains benzimidazole as one of the moiety. This review focuses on the synthesis of different classes of benzimidazole based biheterocyclic molecules on solid support. In this review paper detailed synthetic steps were represented by schemes involved for the synthesis of benzimidazole based biheterocyclic molecules. The synthesis covers the scaffold directed linear, angular, and fused benzimidazole based biheterocyclic molecules by combinatorial approach and open a new avenue for the utilization of these privileged molecules for pharmaceutical applications.



Keywords: Benzimidazoles, Biheterocyclic scaffolds, polyethylene glycol, Ionic liquid

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Introduction

As reported by US retail sales in 2014, heterocyclic compounds play one of the major roles as these are the common structural motif for 80% of the marketed drugs in drug discovery research [1]. Therefore significant effort has been given for its construction by combinatorial approach both on the solid phase as well as on solution phase [2]. In general, the heterocyclic compounds developed by combinatorial approach having only one or two diversity points such as CH_3, Et, Pr groups have limited bioactivity. However, the problem can be overcome by the introduction of another heterocyclic rings which will pave the way for the synthesis of biheterocyclic scaffolds as depicted in **Figure 1**.

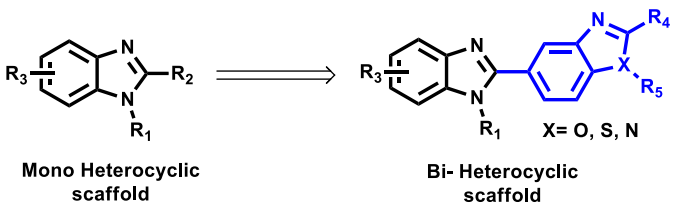


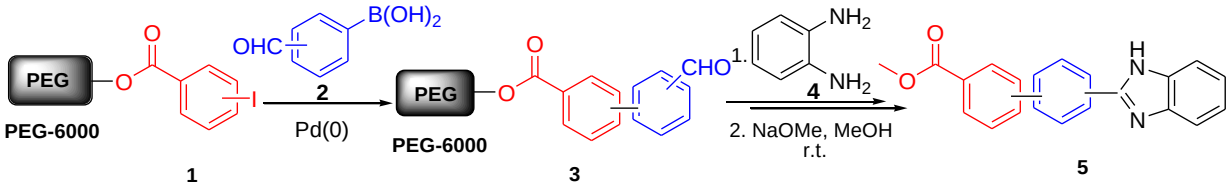
Figure 1

Moreover, in view of the increased structural complexity observed in current drugs, biheterocyclic compounds provide greater chemical space and better binding opportunities [3]. For this purpose, considerable efforts have been made for the biheterocyclic compounds nevertheless it lacks the effort to investigate structurally and functionally

modified biheterocyclic compounds linked directly rather than through a spacer or linker. In the past ten years, large volume of scientific publications have appeared in the literature on the synthesis of biheterocycles but there is no single review which describes the synthesis and the biological evaluation of various biheterocycles were developed and published in the literature. The present article deals with the main advances regarding the synthesis of benzimidazole based five, six and seven membered biheterocyclic scaffolds through solid phase as well as solution phase approach with substantial potential to become a possible drug candidate.

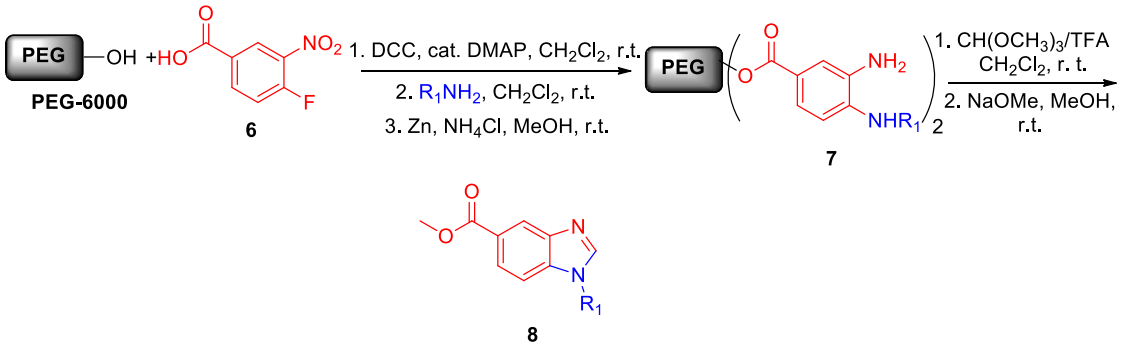
Linear benzimidazole linked biheterocyclic molecules

Benzimidazole consists of a benzene ring fused with imidazole ring and is also called as 1,3-diazaindene with diverse pharmaceutical properties such as antiviral, antifungal, antimicrobial, antiprotozoal, anti-inflammatory, anticancer, antioxidant, anticoagulant, antidiabetic and antihypertensive activities [4]. In nature, N-ribosyl-dimethyl benzimidazole serves as an axial ligand for cobalt in vitamin B_{12} [5]. The synthetic strategy for the synthesis of benzimidazole derivaties commences with condensation of acid chlorides/carboxylic acids or aldehydes with o-phenylendiamnine derivatives with or without the presence of catalyst [6]. Our objective is to discuss the efficient methodologies involved for the solid-phase synthesis of benzimidazole linked biheterocyclic molecules. In 1999, Schotten *et al*. synthesized the biaryl benzimidazole derivatives **5** from polyethylene glycol (PEG) immobilized biaryl aldehydes **3** by the condensation with *o*-phenylene diamine derivatives **4** followed by the cleavage of polymer support with NaOMe in MeOH. The benzimidazole derivatives **5** were obtained with excellent yields as shown in **Scheme 1** [7].



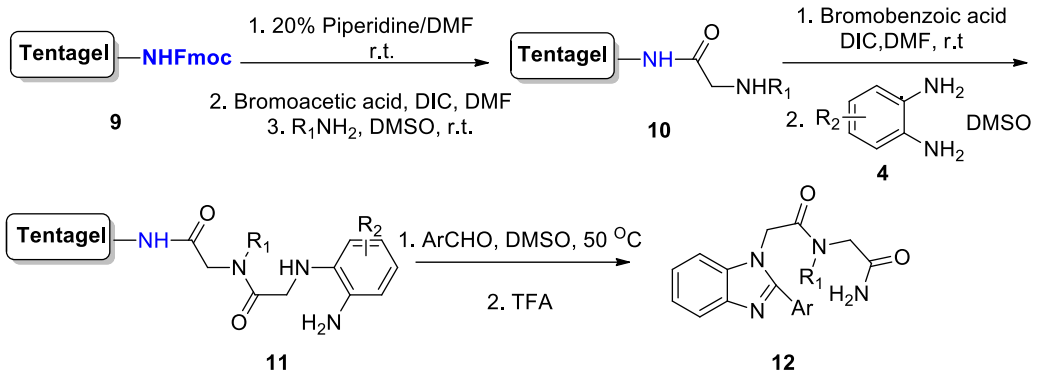
Scheme 1 PEG supported synthesis of biaryl benzimidazole derivatives.

In 2000, Sun *et al*. described the rapid parallel synthesis of benzimidazole derivative on soluble polymer support as outlined in **Scheme 2** [8]. PEG immobilized *o*-fluoronitrobenzene conjugates obtained from readily available 4-fluoro-3-nitro benzoic acid **6** underwent SnAr reactions with diverse primary amines followed by Zn/NH_4Cl mediated nitro group reduction to obtain the polymer conjugated *o*-phenylenediamine derivatives **7**. Cyclisation of polymer conjugates **7** to benzimidazole derivatives **8** was achieved by trimethyl orthoformate/TFA (0.5 eq) in CH_2Cl_2 solution at room temperature followed by the cleavage with NaOMe in MeOH with one point of structural diversity.

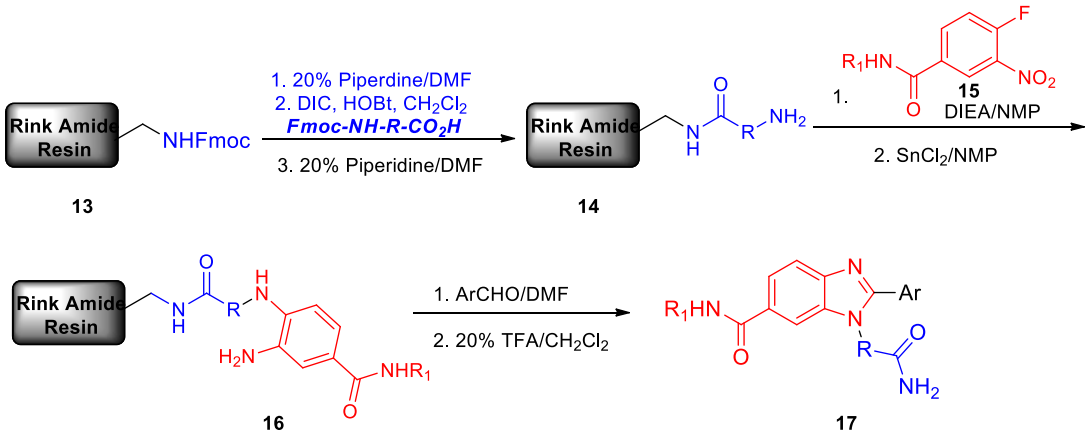


Scheme 2 PEG synthesis of benzimidazole derivatives with single diversity.

Followed by the synthesis of benzimidazole derivatives with one structural diversity, the Sun group also reported the synthesis of 2-alkylthio, 2-arylamino benzimidazole derivatives with two points of structural diversity [9]. In 2002, Fukase *et al*. have developed the solid phase synthesis of benzimidazole derivatives which is depicted in **Scheme 3** [10]. In 2003, Vourlumis *et al*. synthesized the trisubstituted benzimidazole derivatives **17** utilizing the Rink Amide Resin **14** as solid support. for targeting RNA as depicted in **Scheme 4** [11].

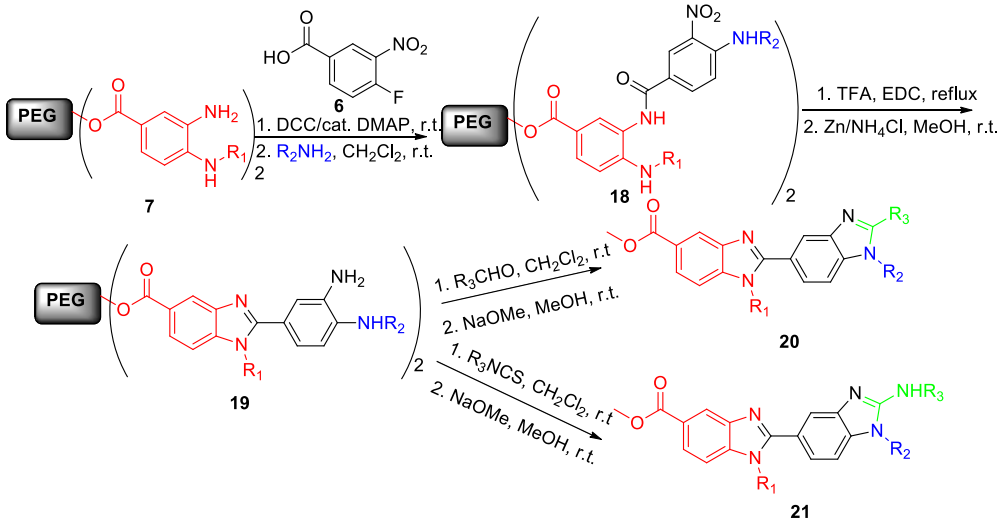


Scheme 3 Tentagel S RAM supported synthesis of benzimdiazole derivatives.



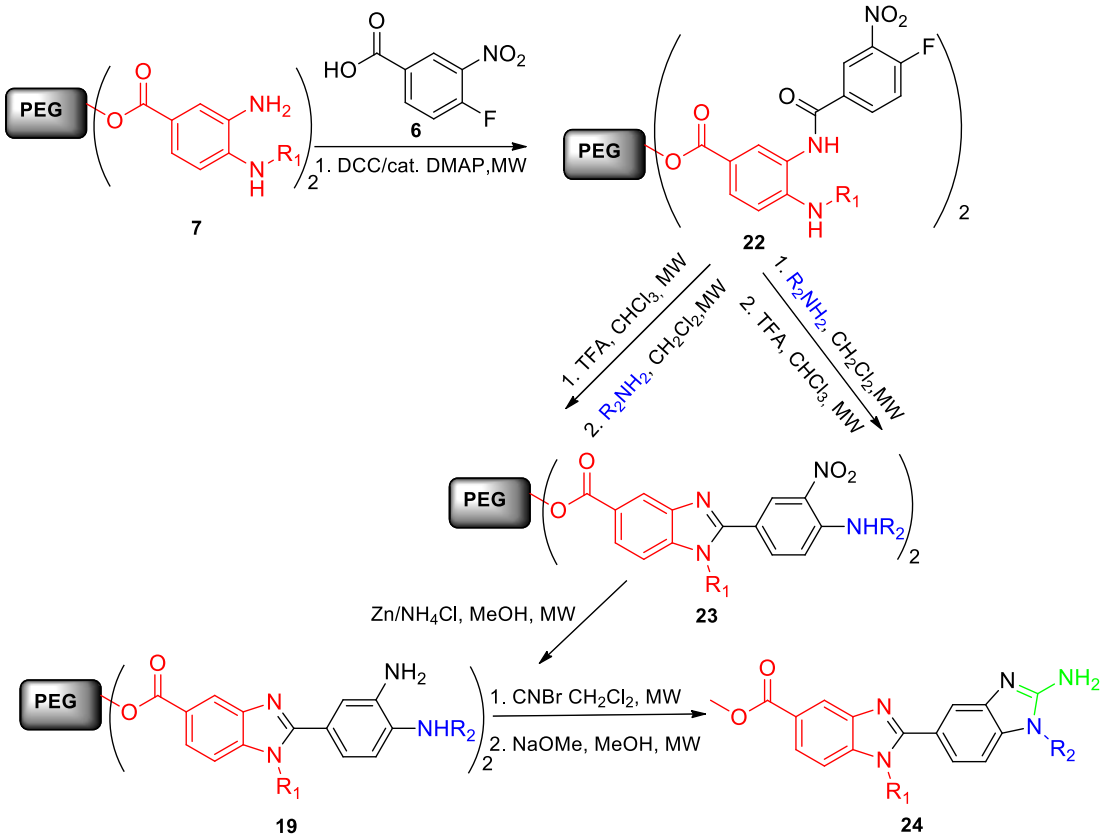
Scheme 4 Rink Amide Resin supported synthesis of benzimidazole derivatives for RNA targets.

In 2004, Sun *et al*. utilized the soluble polymer support such as PEG for the synthesis of bis-benzimidazole derivatives [12]. As shown in **Scheme 5**, continuous N-acylation of polymer immobilized diamines **7** with 4-fluoro-3-nitro benzoic acid **6** at the primary amine functionality followed by the SnAr reaction with primary amines to obtain the intermediate **18.** The intermediate **18** were cyclized in acidic solution to obtain the benzimidazole derivatives **19** which further underwent reduction and subsequent heteroccyclization with various aldehydes and isothiocyanates to obtain the bis-benzimidazole derivatives **20**, and **21** respectively with three points of structural diversity in good yields.



Scheme 5 PEG supported synthesis of bis-benzimidazole derivatives with three points of structural diversity.

In 2006, Sun *et al*. achieved the synthesis of amino bis-benzimidazoles via microwave irradiation in two pathways as shown in **Scheme 6** [13]. In the first case, SnAr reaction with various amines followed by the intramolecular cyclization using acidic solution under MW irradiation leading to the polymer bound 2-arylbenzimidazole derivatives **23**. The second pathway was arrived by the reverse sequence of reactions to obtain the polymer bound 2-arylbenzimidazole derivatives **23**. Reduction of the nitro group under MW conditions to obtain the polymer conjugates **19**. The polymer bound 2-amino bis-benzimidazole derivatives were generated by the [4+1] approach with CNBr under microwave irradiation followed by the cleavage of polymer support obtained the amino bis-benzimidazoles **24** derivatives in good yields.

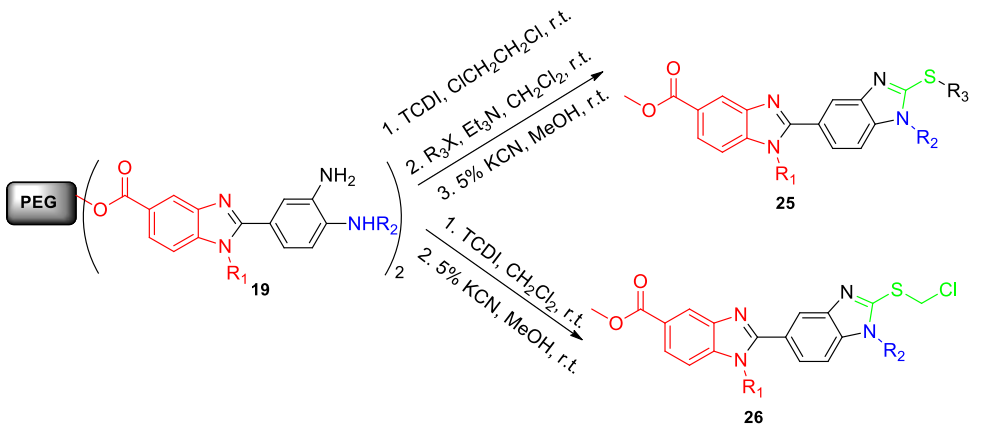


Scheme 6 PEG supported synthesis of amino bis-benzimidazole derivatives.

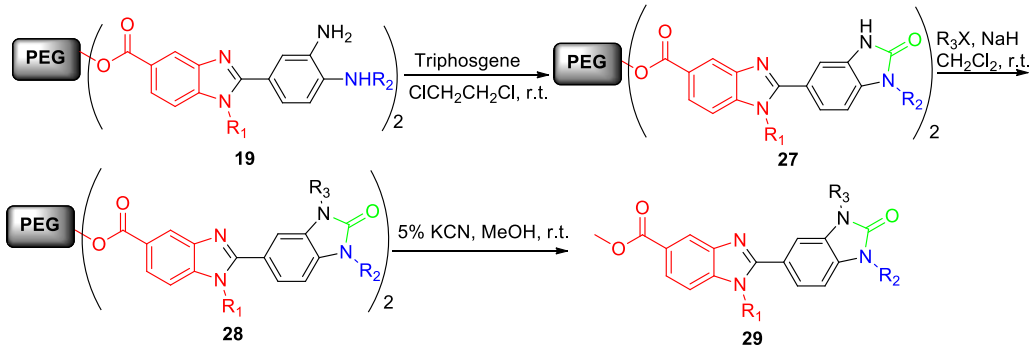
Further in 2008, Sun *et al*. have developed the multistep synthetic protocol to generate the 2-alkylthio bis-benzimdiazole derivatives in **Scheme 7** [14]. The synthetic strategy commences by the reaction with thiocarbonyl imidazole in 1,2-dichloroethane to generate the bis-benzimidazole-2-thione derivatives at room temperature for 15 hrs followed by N-alkylation with different alkyl halide to generate the 2-alkylthio bis-benzimidazole derivatives **25** with three points of structural diversity. However the same set of reaction under refluxing dichloromethane gave rise to an unexpected product, which was confirmed after cleavage from the polymer support as bisbenzimidazole-2-chloromethyl sulfide derivatives **26**.

In the same year, Sun *et al*. reported the synthesis of diverse benzimidazolyl benzimidazolones on PEG support by reaction with triphosgene in 1,2-dichloroethane to generate the bis-benzimidazole-2-one derivatives **27** at room temperature for 12 hrs as shown in **Scheme 8** [15]. Finally the cleavage of polymer support obtained the benzimidazolyl benzimidazolones **29** with three diversity points.

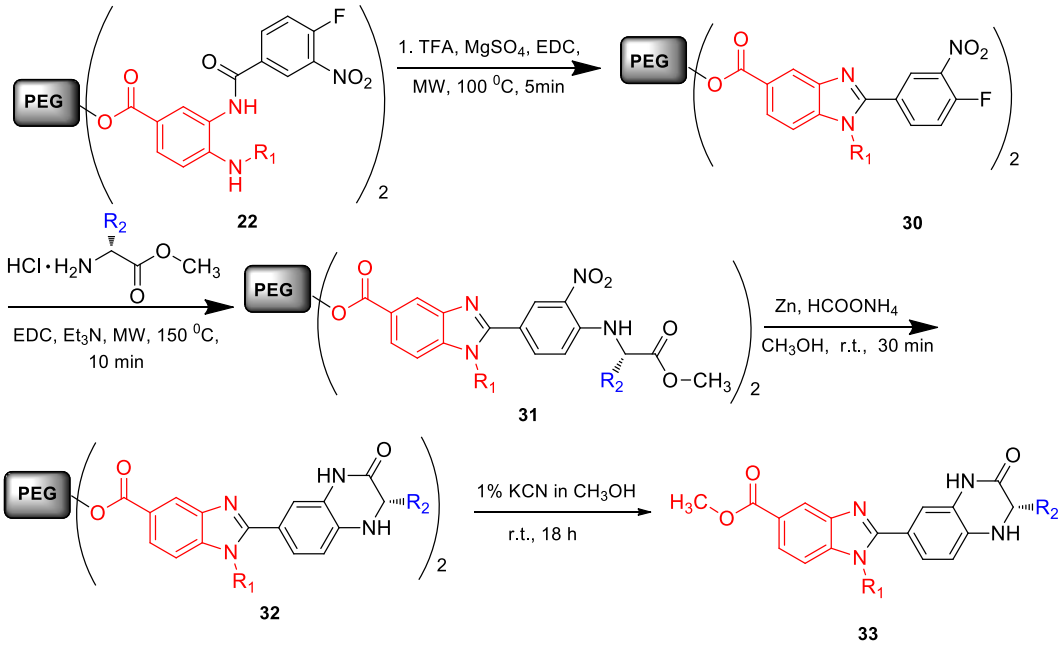
In 2009, Sun *et al*. have developed the enantioselective synthesis of benzimidazolylquinoxalinones on PEG support via focused microwave irradiation in **Scheme 9** [16]. The key step in this multistep sequence involves the *ipso*-fluoro displacement with various chiral amino esters on the polymer conjugates **30** in microwave irradiation followed by NO_2 group reduction under neutral condition to generate the polymer immobilized conjugates **32** via intramolecular cyclisation. The chiral libraries of benzimidazolylquinoxalinones **33** with high enantiomeric excess (80-98%) were obtained from the polymer cleavage by 1% KCN in MeOH in good yields.



Scheme 7 PEG supported synthesis of 2-alkylthio bis-benzimidazole derivatives.



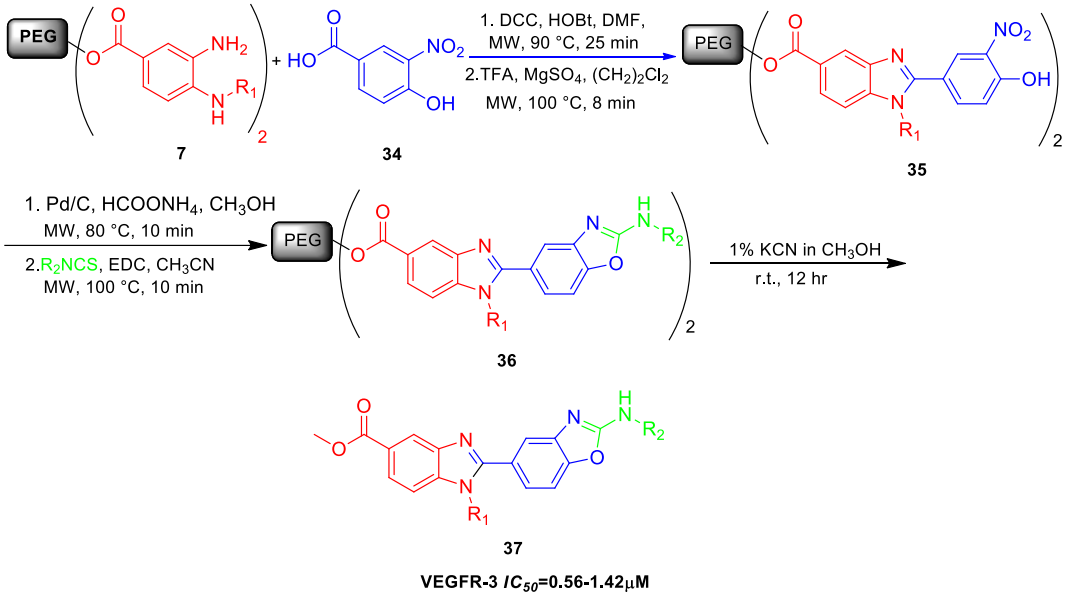
Scheme 8 PEG supported synthesis of benzimidazolyl benzimidazolones derivatives.



Scheme 9 PEG supported synthesis of chiral librarires of benzimidazolylquinoxalinone derivatives.

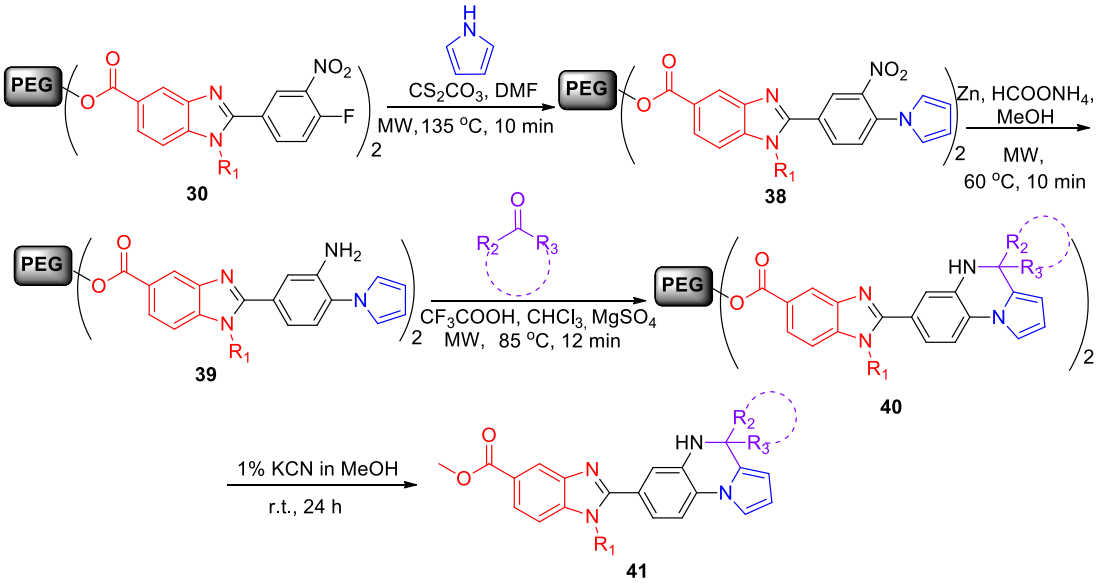
In 2011, Sun, *et al.* had introduced the combinatorial synthesis of substituted benzimidazolylbenzoxazoles using 4-hydroxy-3-nitrobenzoic acid **34** on soluble polymer support [17]. The reduction of NO_2 group in polymer conjugates **35** was done by 10% Pd/C in $HCOONH_4$ followed by the heterocyclisation with various alkyl, aryl and heteroaryl isothiocyanates to generate the polymer bound benzimidazolylbenzoxazoles **36** as shown in **Scheme 10**.

The biheterocyclic combinatorial library with two sites of structural diversity **37** was finally cleaved from polymer support using 1% KCN in MeOH for 12 hrs. Further the designed compounds were studied against receptor tyrosine kinase VEGFR-3 involved in lymphogenesis showed high inhibition percentage with IC_{50} value ranges from 0.56 to 1.42 µm.



Scheme 10 PEG supported synthesis of benzimidazolylbenzoxazol derivatives.

In the same year, Sun, *et al*. have synthesized the benzimidazole-pyrrolo[1,2-*a*]quinoxaline core of medicinal interest by the Pictet-Spengler reaction in **Scheme 11** [18]. For the first time secondary amine such as electron rich pyrrole moiety was utilized for aromatic nucleophillic substitution reaction (SnAr) with the polymer immobilized substrate **30**. By the use of judicious choice of base such Cs_2CO_3 in DMF solvent the polymer conjugates **38** were obtained in 95 % yield under focused microwave irradiation for 10 min at 135 °C.

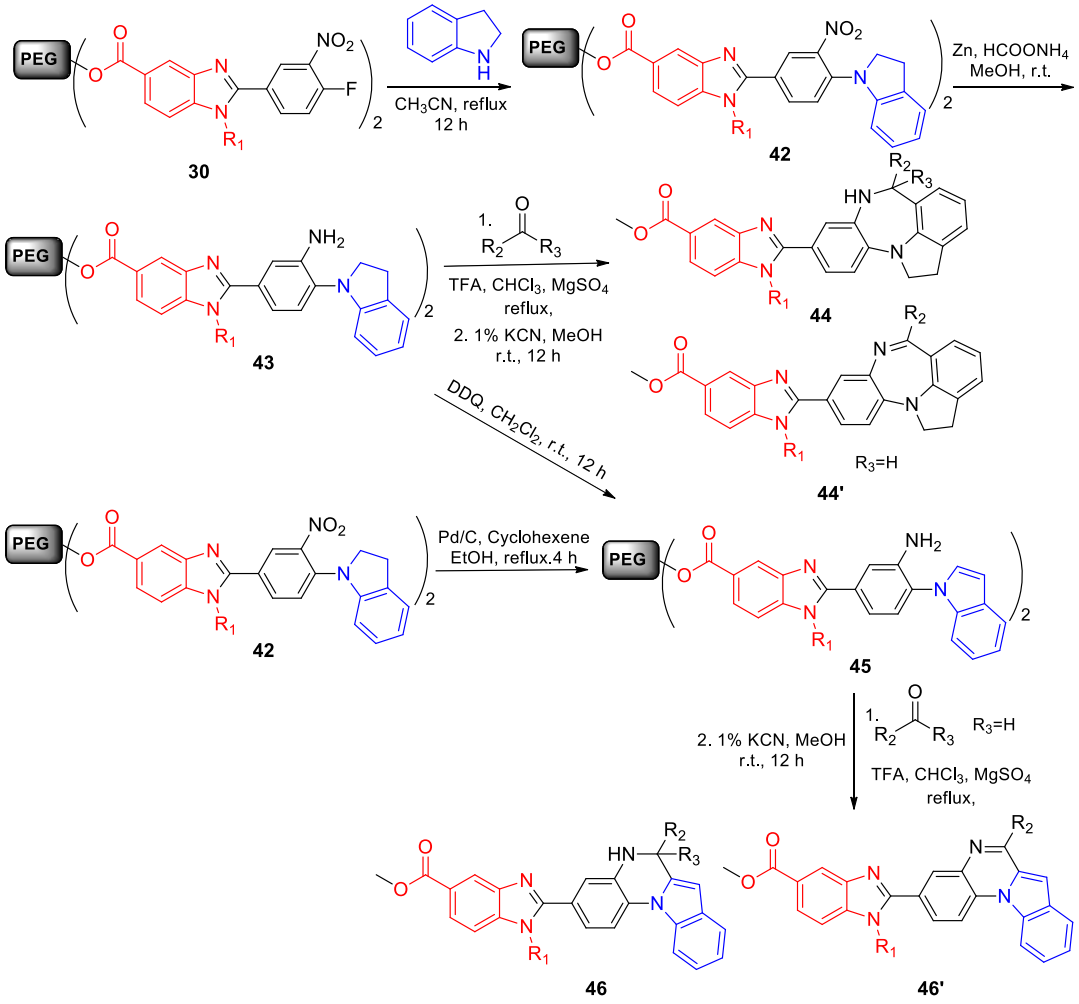


Scheme 11 PEG supported synthesis of benzimidazole-pyrrolo [1,2-*a*] quinoxalines

The next effort was to reduce the nitro group ortho to the pyrrole moiety of polymer ester conjugates **38** using zinc dust in methanol buffered with ammonium formate under microwave irradiation for 10 min to obtain the intermediate **39**. Accordingly the ring closure of intermediate **39** was achieved using Pictet-Spengler reaction with

various ketones. The intermediates **39** were treated with various symmetrical and unsymmetrical ketones using TFA as catalyst in presence of chloroform solvent under focused microwave irradiation at 85 °C within 12 min to obtain the polymer bound conjugates **40**. The desired biheterocyclic benzimidazole-pyrrolo[1,2-*a*]quinoxaline library with two sites of structural diversity **41** was finally obtained from cleavage of polymer support using 1% KCN in MeOH.

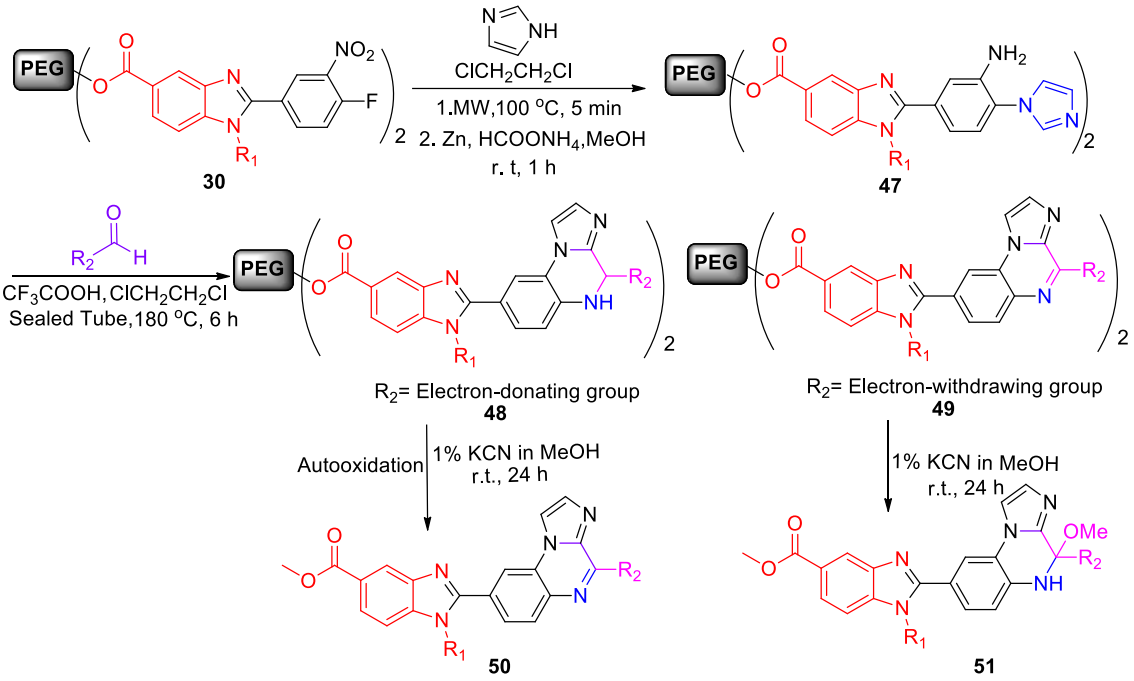
In the same year, Sun, *et al*. have discovered the benzimidazole linked four annulated rings in one scaffold by the application of Pictet-Spengler reaction using indoline as depicted in **Scheme 12** [19]. Polymer bound intermediate **30** underwent SnAr reaction with indoline moiety under refluxing CH_3CN solution to obtain **42** followed by NO_2 reduction to obtain the intermediate **43**. The intermediate **43** was reacted with various aldehydes and ketones under Pictet-Spengler cyclisation strategy followed by cleavage using 1% KCN in MeOH at room temperature for 12 hrs to obtain the benzimidazole linked tetrahydro indolodiazepine library **44** along with oxidized benzimidazole linked dihydro indolodiazepine analogous **44´**. However the reduction of NO_2 group in intermediate **42** using Pd/C and cyclohexene in refluxing ethanol yielded indole-substituted polymer conjugates **45** which could also be obtained from intermediate **43** by dehydrogenating the indoline to indole using DDQ oxidation. Treatment of polymer conjugates **45** with various aldehyde or ketones in refluxing $CHCl_3$ solution using TFA as acid catalyst and $MgSO_4$ as dehydrating agent followed by polymer cleavage obtained the benzimidazole-linked indoloquinoxalinones **46** along with the more stable aromatic skeleton **46´**.



Scheme 12 PEG supported synthesis of benzimidazole linked four annulated rings in one scaffold.

After successfully incorporating the pyrrole and indole fused biheterocyclic system, Sun *et al*. introduced the imidazole into aromatic moiety as depicted in **Scheme 13** [20]. As shown in **Scheme 14**, polymer bound intermediate

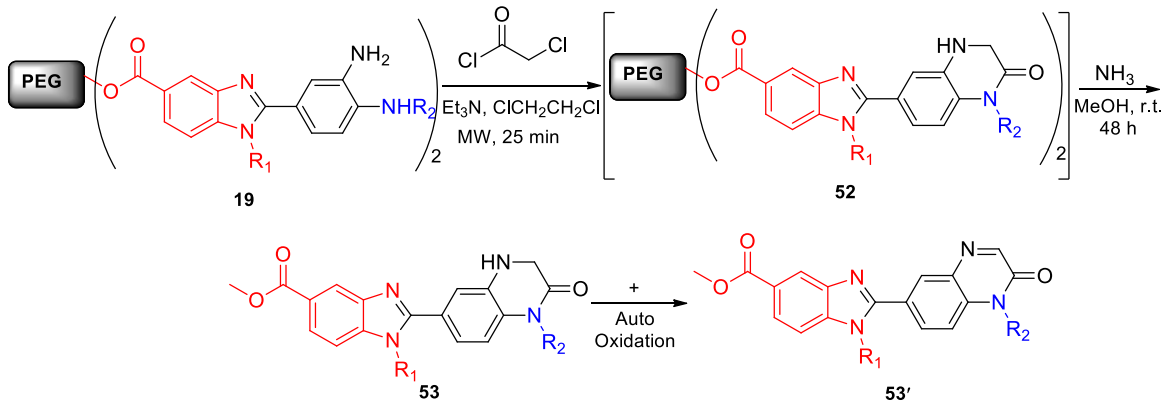
30 underwent SnAr reaction with imidazole moiety under microwave irradiation followed by nitro group reduction to obtain the intermediate **47**. The intermediate **47** underwent unconventional regioselective Pictet-Spengler cyclization with C-2 position on imidazole ring system under seal tube condition for 6 h to obtain the intermediate **48** and **49**.



Scheme 13 PEG supported synthesis of novel benzimidazole-linked imidazo[1,2-*a*]quinoxalines.

However it has observed that the aldehydes bearing electron –donating groups generated the 4,5-dihydroimidazoquinoxalines **48** after polymer cleavage which then auto-aromatize into benzimidazole-linked imidazo[1,2-*a*]quinoxazlines **50**. But during the Pictet-Spengler cyclisation with electron withdrawing aldehydes directly provide the aromatized benzimidazole-linked imidazo[1,2-*a*]quinoxazlines **49** which after polymer cleavage with 1% KCN in MeOH at room temperature obtained the novel methoxylated benzimidazole-linked imidazo[1,2-*a*]quinoxalines **51.**

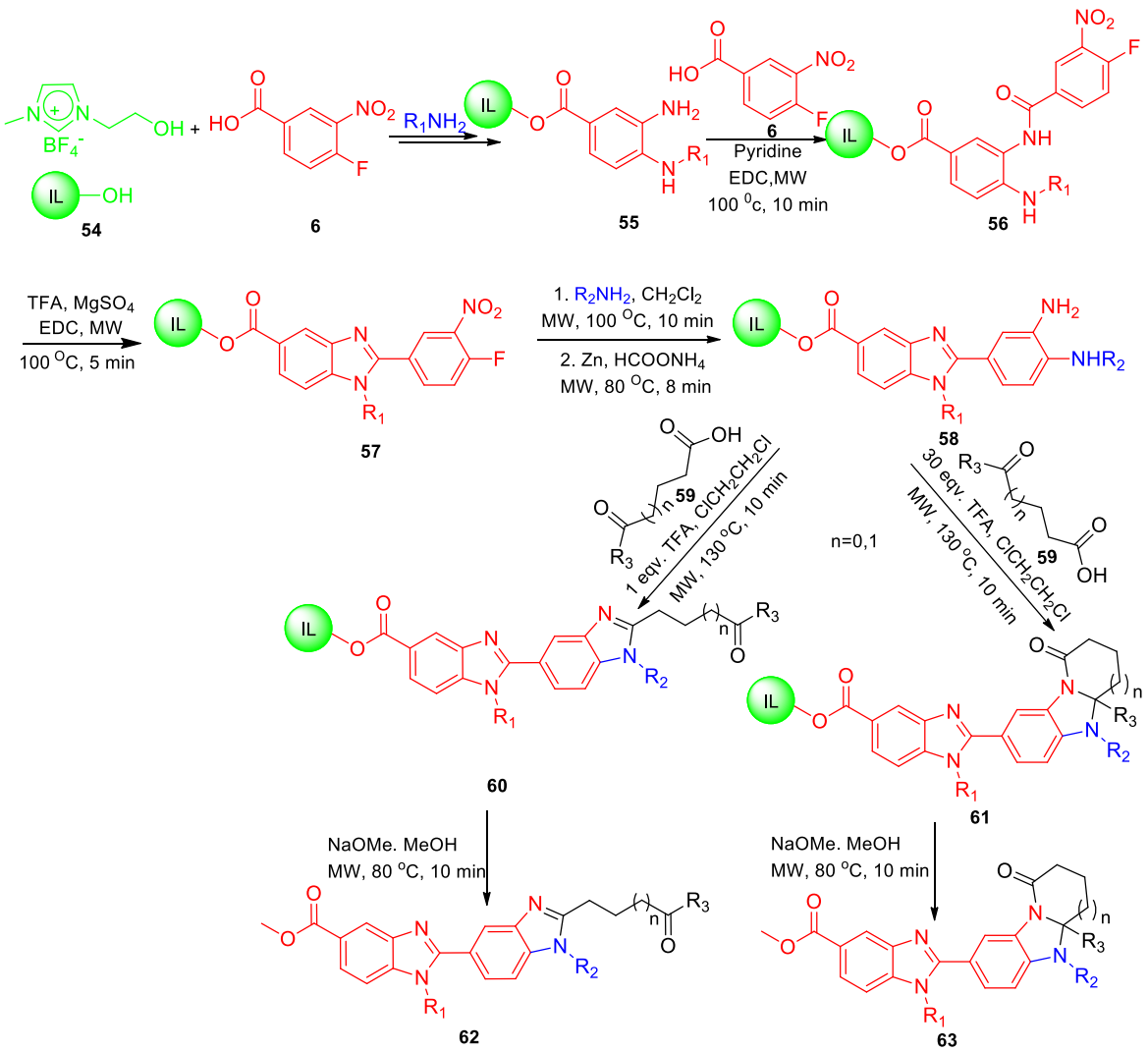
Subsequently, Sun, *et al*. have reported the microwave assisted approach to benzimidazole linked quinoxalinone on PEG support with two diversity position as shown in **Scheme 14** [21].



Scheme 14 PEG supported synthesis of novel benzimdiazole-linked quinoxalinones.

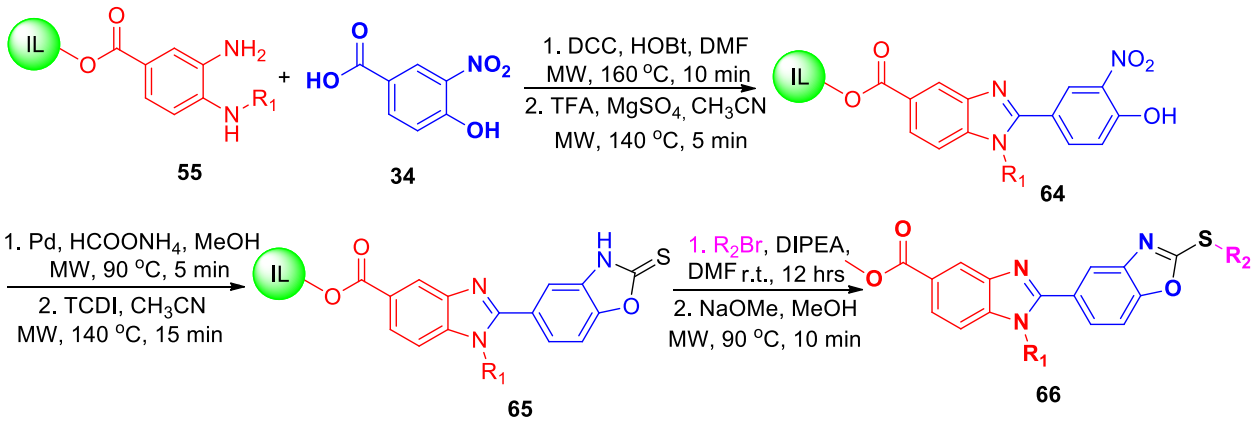
Because of heterogeneous nature of solid phase and low loading capacity of soluble polymer support such as PEG, researchers have recently demonstrated the ionic liquid supported synthesis of small molecule which have the advantages over solution phase chemistry [22]. Generally 3-hydroxyethyl-(1-methylimidazolium)-tetrafluoroborate

[HEMIm]BF_4 **54** is choosen as a suitable ionic liquid (IL) support for multistep synthesis in **Scheme 15**. In 2011, Sun *et al.* successfully coupled the 4-fluoro-3-nitrobenzoic acid **6** with [HEMIm]BF_4 **54** via esterification followed by the ipso-fluoro substitution of primary amines and subsequent reduction of nitro-group obtained the IL immobilized *o*-phenylenediamine **55** by microwave irradiation as shown in **Scheme16** [23]. Compound **55** underwent continuous N-acylation with 4-fluoro-3-nitrobenzoic acid **6** in presence of pyridine using microwave heating for 10 min to obtain the IL immobilized amide **56** followed by cyclisation to benzimidazole derivative **57** under microwave irradiation for 5 min at 100 ^{0}C. Further to introduce the second diversity, IL-supported fluoronitrobenzoate **57** was treated with various primary amines in microwave conditions for 5 min followed by nitro group reduction under neutral condition to furnish IL immobilized diamine **58**. Accordingly, IL conjugate **58** was treated with 3 or 4-keto acids **59** in presence of TFA under microwave irradiation. The use catalytic quantity of TFA to obtain the 2-alkyl substituted bis benzimidazoles **60** where as the use of 30 equiv of TFA under focused microwave irradiation for 10 min obtain the desired tricyclic framework **61** respectively. The ionic liquid support was cleaved using NaOMe in methanol solution under microwave irradiation for 10 min to obtain benzimidazole linked pyrrolo/pyrido-benzimidazolone derivatives **62** and **63**.



Scheme 15 Ionic liquid supported synthesis of benzimidazole linked tricyclic framework.

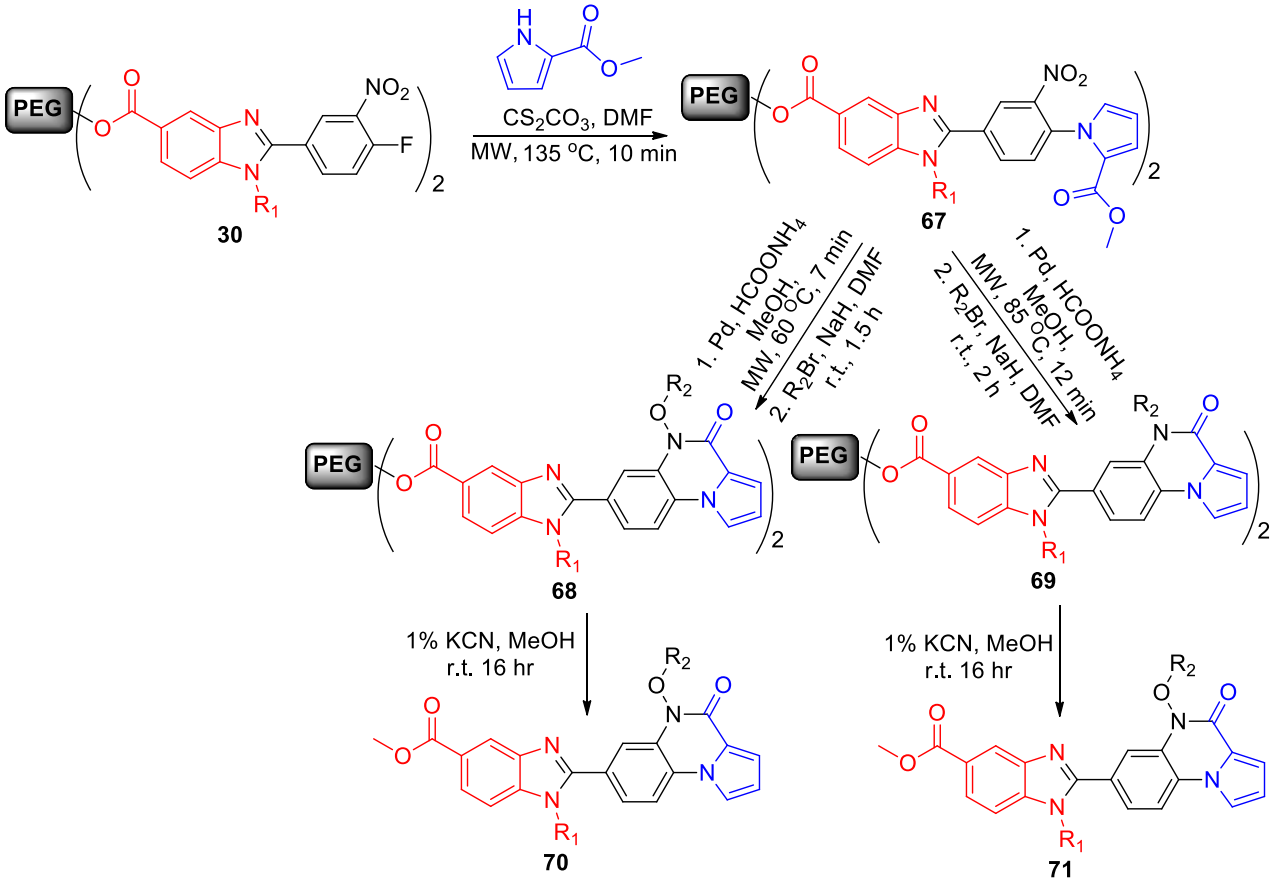
In 2012, Sun, *et al.* reported the diversity-oriented synthetic approach to benzo[*d*]oxazol-5-yl-1*H*-benzo[*d*]imidazole on ionic liquid support via microwave irradiation [24]. As drawn in **Scheme 16**, coupling of 4-hydroxy-3-nitrobenzoic acid **34** on to the ionic liquid immobilized *o*-phenylenediamine **55** followed by acid mediated ring closure reaction generates the benzimidazole derivatives **64**.



Scheme 16 Ionic liquid supported synthesis of thioanalogs of benzimidazole linked benzoxazols.

After hydrogenating the nitro group to amines, the resulted ionic liquid conjugates underwent efficient heterocyclization with 1,1-thiocarbonyldiimidazols to provide the biheterocycles **65** on the ionic liquid support. The second diversity of the present scaffold **66** was achieved by S-alkylation with substituted bromides followed by the cleavage from the support with sodium methoxide in methanol under microwave irradiation.

Recently, Sun *et al*. have explored the cascade synthesis of novel benzimidazole linked alkyloxypyrrolo[1,2-*a*]quinoxalinones on soluble polymer support under microwave irradiation [25]. As depicted in **Scheme 17**, the desired benzimidazole linked methyl 1-(2-nitrophenyl)-1H-pyrrole-2-carboxylate **67** was obtained in 10 min under microwave irradiation. Polymer immobilized N-hydroxy pyrroloquinoxalinones **68** were obtained by partial reductive cyclization for 7 min at 60 °C, and the synthesis of polymer conjugate pyrroloquinoxalinones **69** was accomplished by full reductive cyclization at 85 °C for 12 min under microwave irradiation followed by N-or O-alkylation with alkyl bromide.



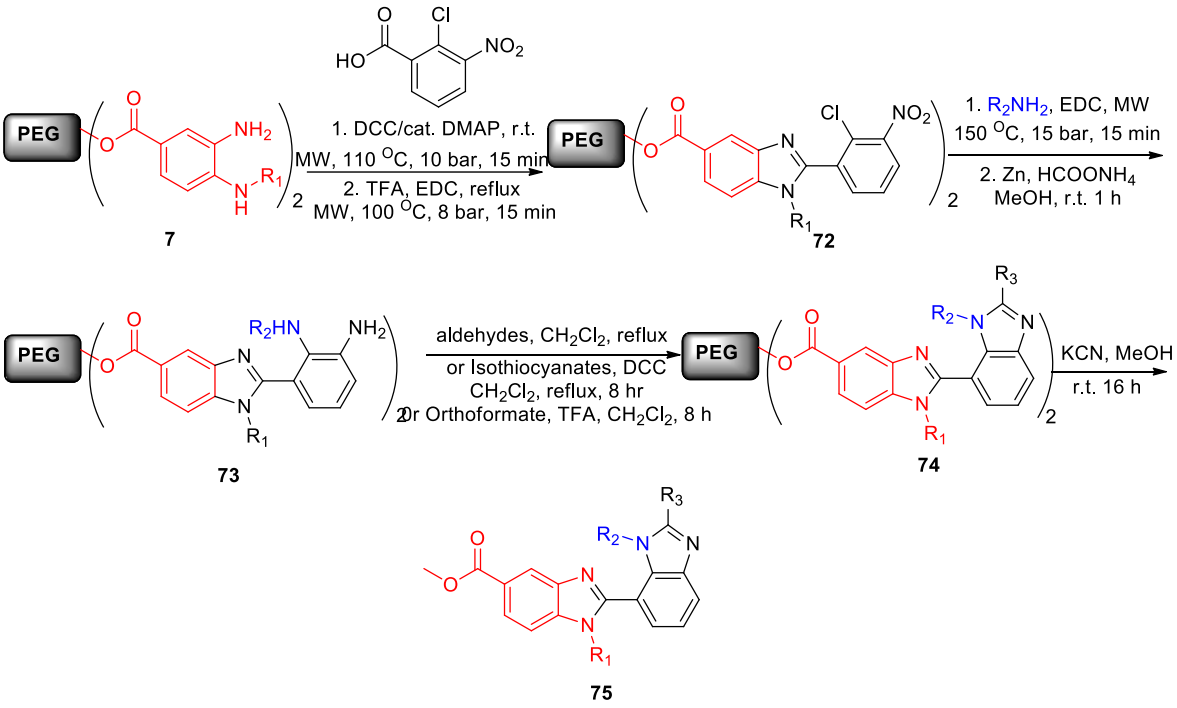
Scheme 17 PEG supported synthesis of novel benzimidazole-linked alkyloxypyrrolo[1,2-*a*]quinoxalinones.

The title compounds **70**, and 7**1** were obtained after cleavage from polymer support using 1% KCN in MeOH solution for 16 hr with high purity and good yield.

Angular benzimidazole linked biheterocyclic molecules

The 2nd part of this review describes the design and synthesis of angularly oriented biheterocycles in which the substituents are positioned strategically on which the construction of a second angularly tilted heterocycle can be carried out.

In 2009, Sun *et al*. have synthesized the angular bisbenzimidazoles with three appendages on soluble polymer support using microwave irradiation [26]. As depicted in **Scheme 18**, polymer bound *o*-phenylenediamine conjugate **7** was reacted with 2-chloro-3-nitro benzoic acid for the installation of angular moiety followed by cyclization to obtain the intermediate **72**.



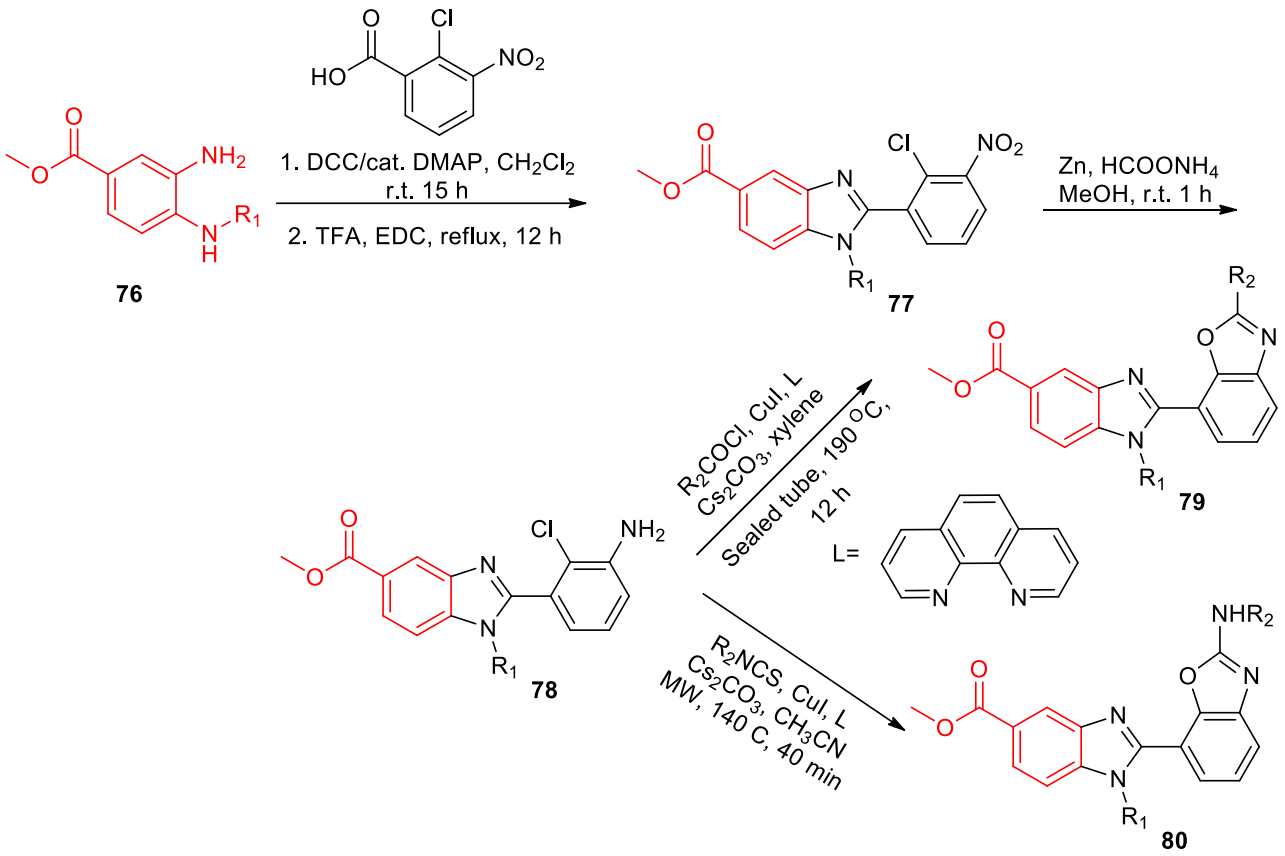
Scheme 18 PEG supported synthesis of trisubstituted angular bisbenzimidazole derivatives.

The second diversity was installed through *ipso*chloro displacement with various primary amine followed by the reduction of nitro group to generate the intermediate **73**. The intermediate **73** underwent heterocyclisation with aldehydes or isothiocyanates or orthoformates followed by cleavageto provide angular bis benzimidazole derivatives **74**. Finally, PEG support was cleaved in KCN solution to deliver trisubstitiuted angular bis-benzimidazoles **75** in good yield.

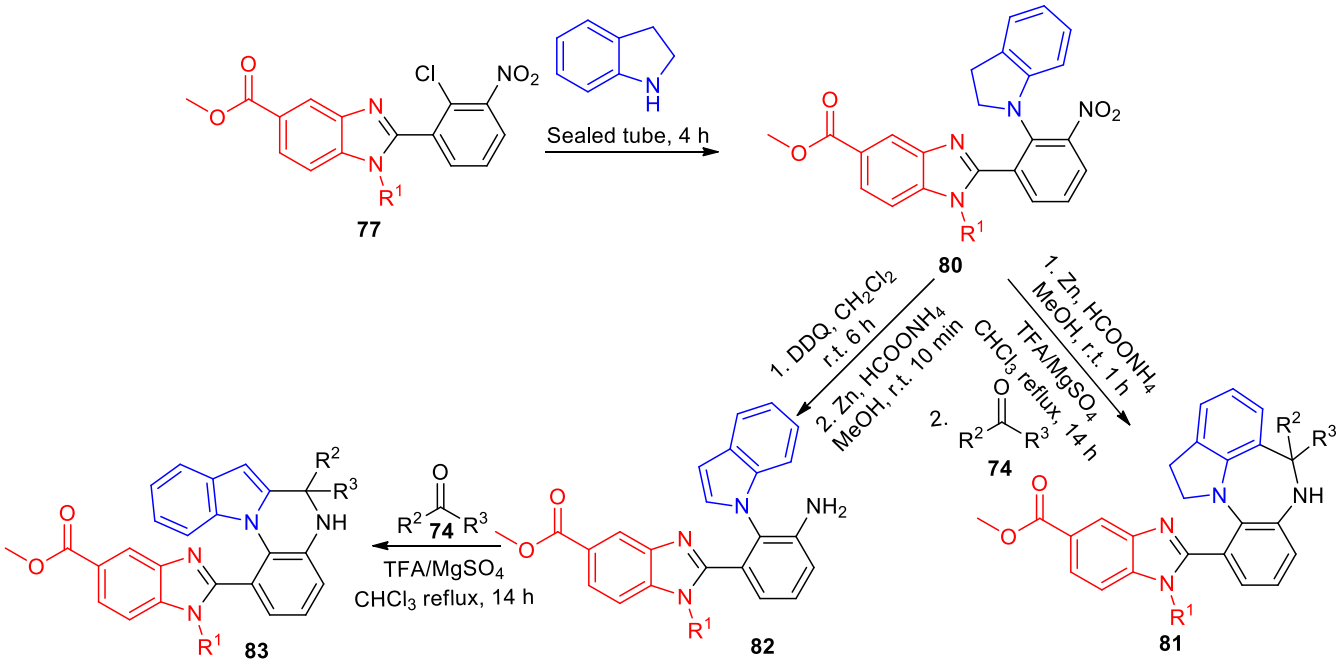
In 2013, the same group reported the solution phase synthesis of angular benzimdiazole linked benzoxazoles/benzothiazoles via Cu catalyzed domino annulations in **Scheme 19**. [27]

In 2012, Sun, *et al*. have synthesized the biprivileged molecular scaffolds with three diversity points. Pictet-Spengler cyclization was used as a key step to construct angularly oriented benzimidazole linked tetracyclic scaffolds such as indolo-benzodiazepines **81** and indolo-quinoxalines **83** as shown in **Scheme 20**. [28]

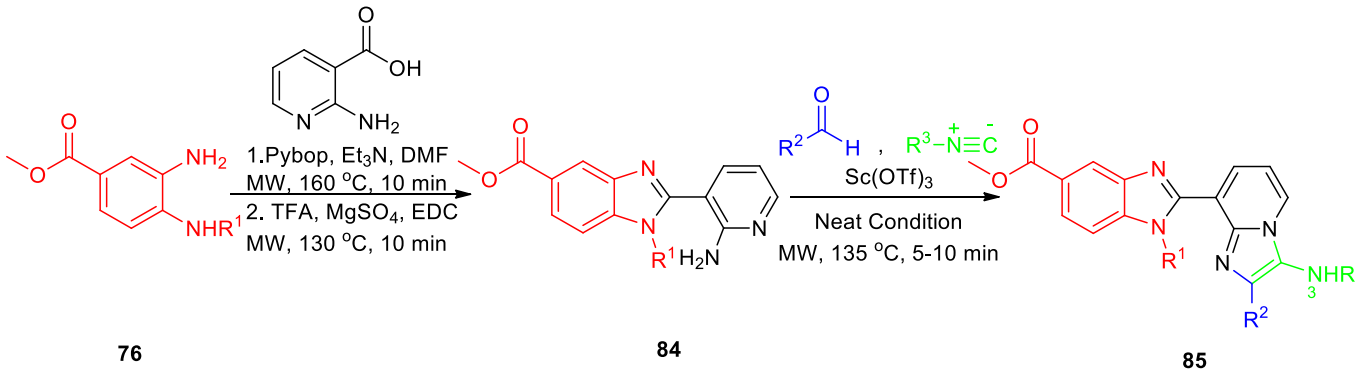
In 2013, the Sun group has reported the synthesis of benzimidazolyl Imidazo[1,2-a]-pyridine under solvent free condition with three points of structural diversity as shown is **Scheme 21** [29]. The methyl ester of *o*-phenylenediamine derivative **76** was reacted with 2-amino nicotinic acid via an amide linkage followed by the cyclisation using TFA to obtain the benzimidazole linked amino pyridine **84**. The key step in the present scaffold is to accomplish the three component Groebke−Blackburn−Bienaymé reaction involving benzimidazole linked aminopyridine **84**, aldehyde and isonitrile using $Sc(OTf)_3$ as acid catalyst under neat microwave condition to afford the angularly oriented biheterocyclic scaffolds **85** in good yield.



Scheme 19 Solution phase approach to benzimidazole linked benzoxazols/benzothiazoles via Cu(I) catalysed domino reaction.



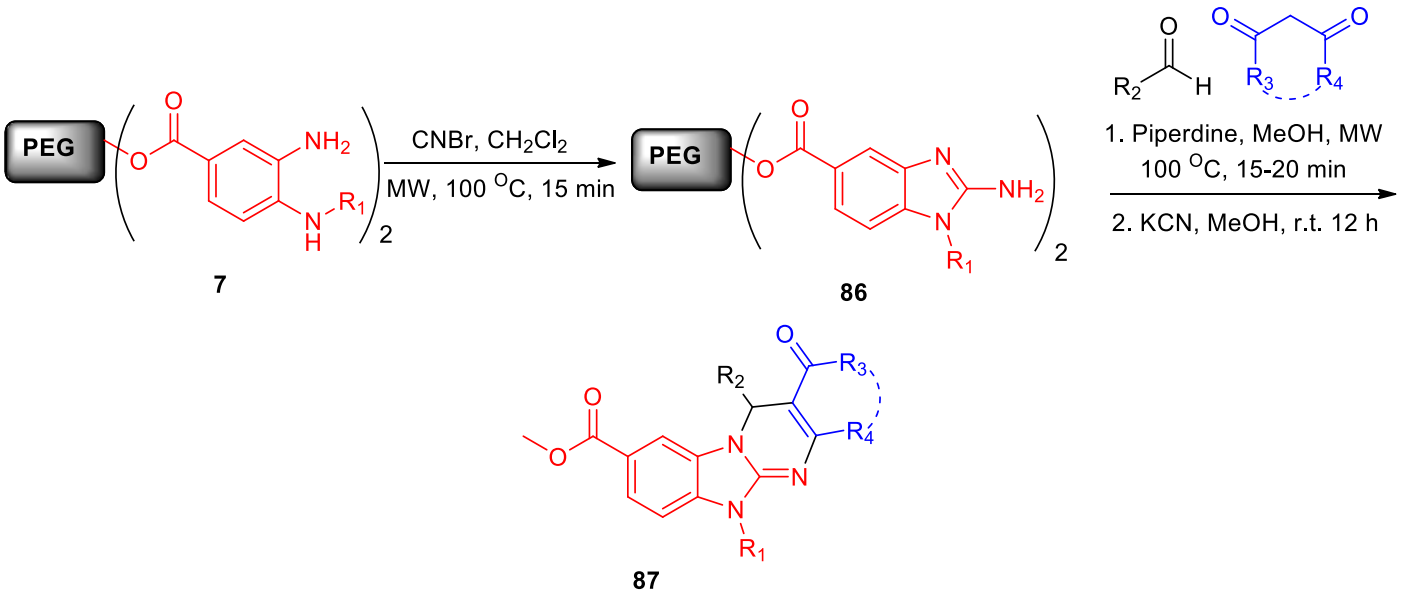
Scheme 20 Solution phase approach to angularly oriented benzimidazole linked indolo-benzodiazepines and indolo-quinoxalines.



Scheme 21 Solution phase approach to angularly oriented benzimidazolyl imidazo[1,2-*a*]-pyridine.

Fused benzimidazole linked biheterocyclic molecules

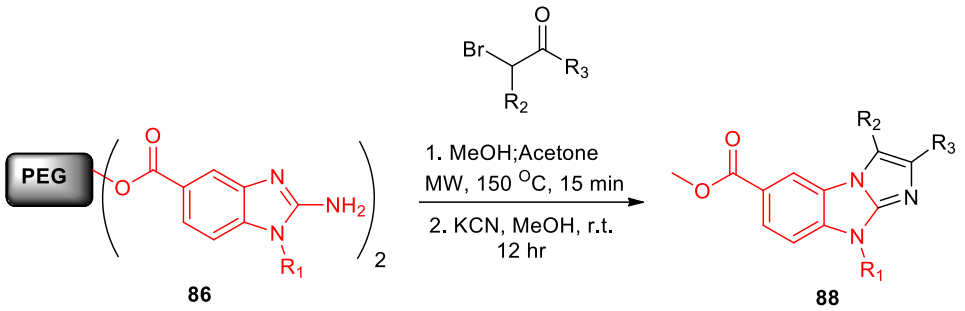
In view of important bioactivities shown by fluorene and aza fluorenes, Sun *et al*. have developed the multidisciplinary synergetic approach to triaza fluorene library on soluble polymer support using microwave irradiation [30]. As depicted in **Scheme 22**, heterocyclisation of polymer immobilized *o*-phenylenediamine derivatives **7** with CNBr to obtain the PEG immobilized benzimidazole derivatives **86**. To furnish the triaza fluorine derivatives **87**, the benzimidazole derivatives **86** underwent multicomponent reaction with substituted aldehydes, and 1,3-diones or 3-oxoesters using 10 mol% of piperidine in MeOH solution under microwave heating condition which took just 30 mintutes for completion followed by polymer cleavage.



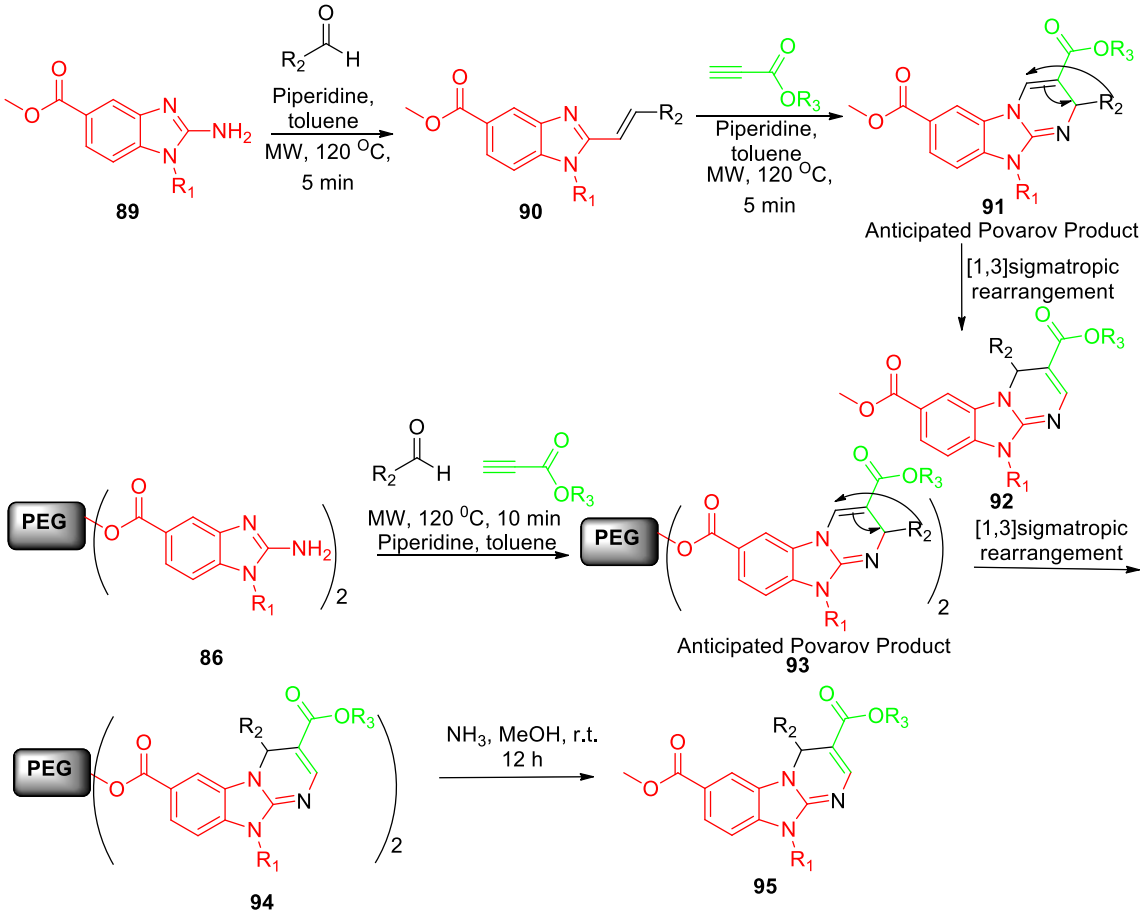
Scheme 22 Soluble polymer supported synthesis of triaza fluorene library

In 2011, Sun *et al*. have established a polymer supported approach to novel imidazo[1,2-*a*]benzimidazoles using microwave irradiation regioselectively [31]. Polymer immobilized benzimidazole derivatives **87** underwent nucleophillic bromo substitution with α-bromo ketones followed by intramolecular cyclisation and subsequent aromatization to obtain the polymer immobilized imidazo[1,2-*a*]benzimidazole derivatives in **Scheme 23**. Finally the polymer was cleaved using 1% KCN in MeOH solution to obtain the imidazo[1,2-*a*]benzimidazoles **88** regioseletively.

In the same year, Sun *et al*. have demonstrated the synthesis of dihydropyrimidobenzimidazoles on soluble polymer support by unusual 1,3-sigmatropic rearrangement [32].



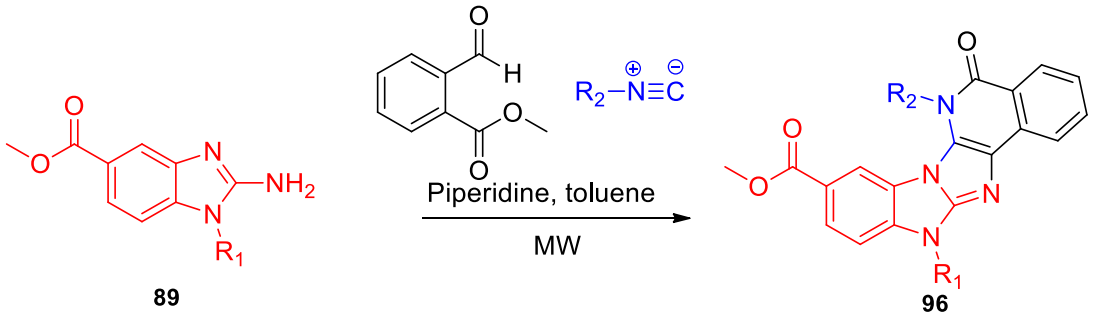
Scheme 23 PEG supported regioselective synthesis of imidazo[1,2-*a*]benzimidazoles **172**.



Scheme 24 Base catalysed Povarov reaction on soluble support.

As depicted in **Scheme** 24, 2-aminobenzimidazole derivatives **89** underwent imination reaction with substituted aldehyde using piperidine as base under microwave irradiation. The resultant benzimidazole-2-imine **90** was further reacted with methyl propiolate as electron deficient dienophile in presence of piperidine as base to obtain the anticipated Povarov reaction product **91**. However an unprecedented [1,3] sigmatropic rearrangement transpired to the Povarov reaction product **91** to obtain the dihydropyrimido[1,2-*a*]benzimidazoles **92** regioselectively. Moreover, applying the same methodology to polymer immobilized benzimidazole derivatives **86** with substituted aldehyde, and electron deficient dienophile in presence of piperidine as base under microwave irradiation to obtain the polymer cleaved dihydropyrimido[1,2-*a*]benzimidazoles **95** through a multicomponent Povarov reaction and in-situ [1,3]sigmatropic rearrangement.

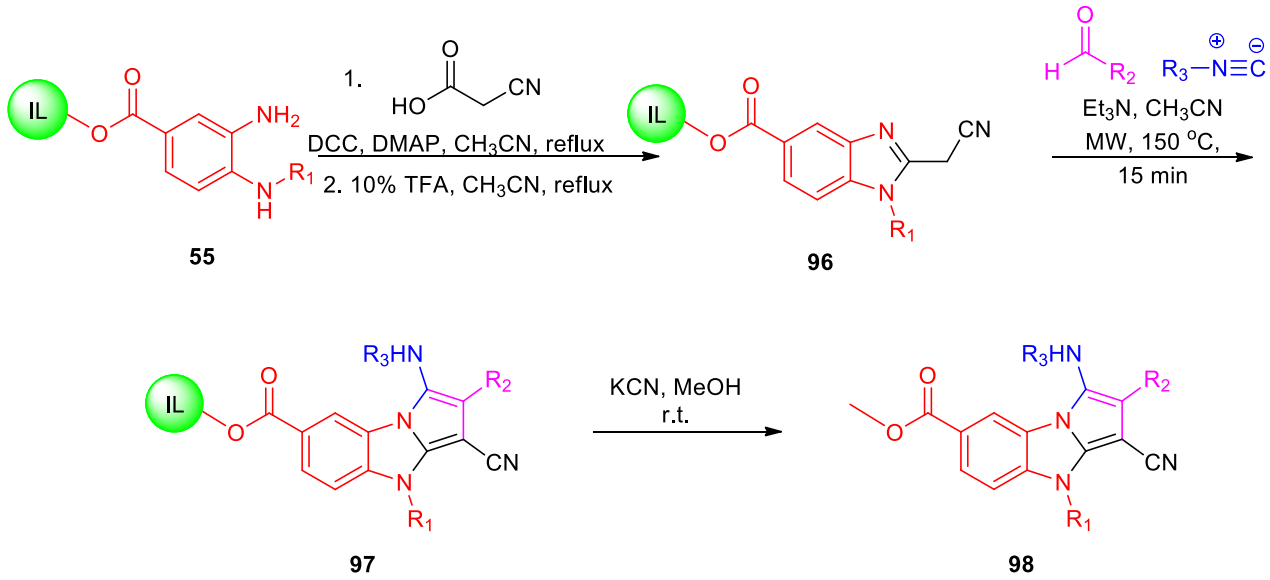
In 2013, Sun *et al*. have achieved the synthesis of complex pentacyclic heterocycles through piperidine mediated Groebke- Bienayme-Blackburn multicomponent reaction as shown in **Scheme 25 [**33]



89 96

Scheme 25 Piperidine mediated solution phase multicomponent approach to isoquinolinone embedded imidazo[1,2-*a*]benzimidazoles.

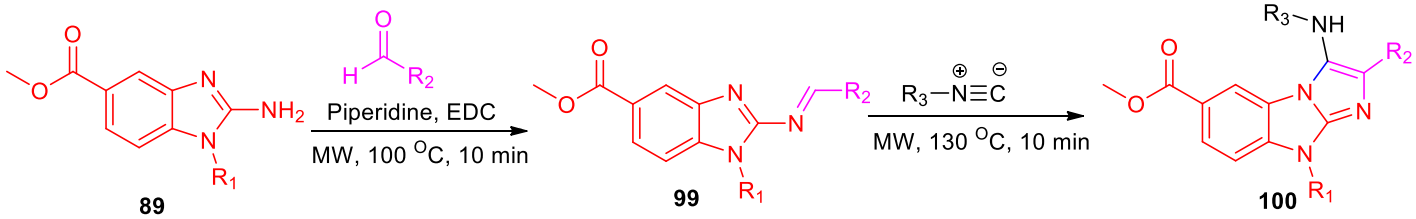
Further inspired by the above results, Sun *et al*. have developed the multicomponent approach to pyrrolo[1,2-*a*]benzimidazoles on ionic liquid support via Knoevenagel condensation and a [4+1]-cycloaddition reaction as depicted in **Scheme 26** [34].



55 96 97 98

Scheme 26 Ionic liquid supported synthesis of pyrrolo[1,2-*a*]benzimidazole derivatives.

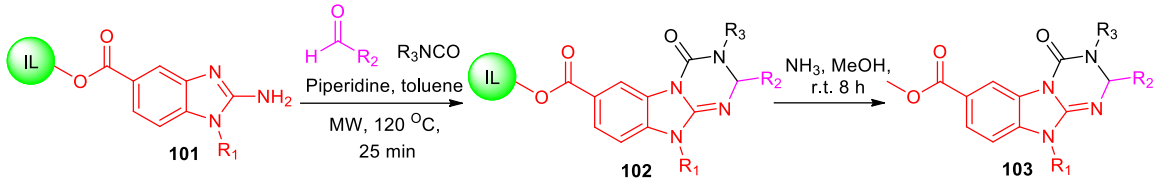
In 2013, Sun *et al*. have again accomplished the synthesis of imidazo[1,2-*a*]benzimidazoles via one-pot two-step multicomponent (4+1) cycloaddtion reaction under solution phase strategy as drawn in **Scheme 27** [35]. 2-aminobenzimidazole derivatives **89** underwent initial condensation with substituted aldehyde to form imine **99** under microwave irradiation for 10 min which was oriented in s-cis conformation for favorable (4+1) cycloaddition. The intermediate **99** was reacted with substituted isocyanides to obtain the imidazo[1,2-*a*]benzimidazoles **100** with three structural diversity in good yields.



89 99 100

Scheme 27 Microwave assisted telescoped synthesis of imidazo[1,2-*a*]benzimidazoles.

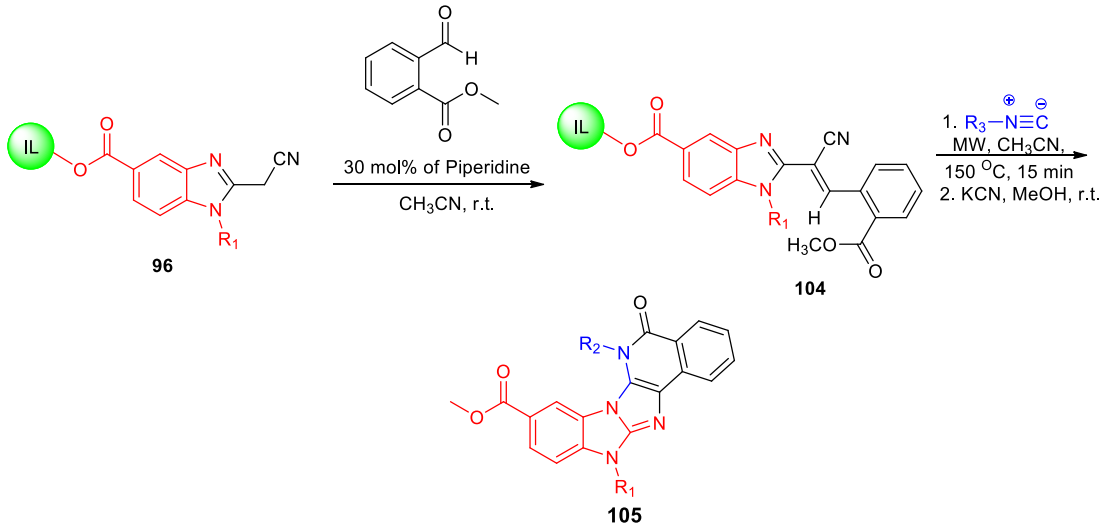
In 2014, the Sun group reported the synthesis of fused tricyclic triazenes via tandem imination–isocyanate-mediated annulations reaction on ionic liquid support [36] As reported in **Scheme 28**, synthetic modifications on the IL-immobilized 2-aminobenzimidazoles **101** were carried out using piperidine mediated imination reaction of 2-aminobenzimidazoles **101** with aldehydes followed by substituted isocyanate backed annulation reaction to obtain the triazenes derivatives **102**.



Scheme 28 Ionic liquid supported synthesis of fused tricyclic traizenes.

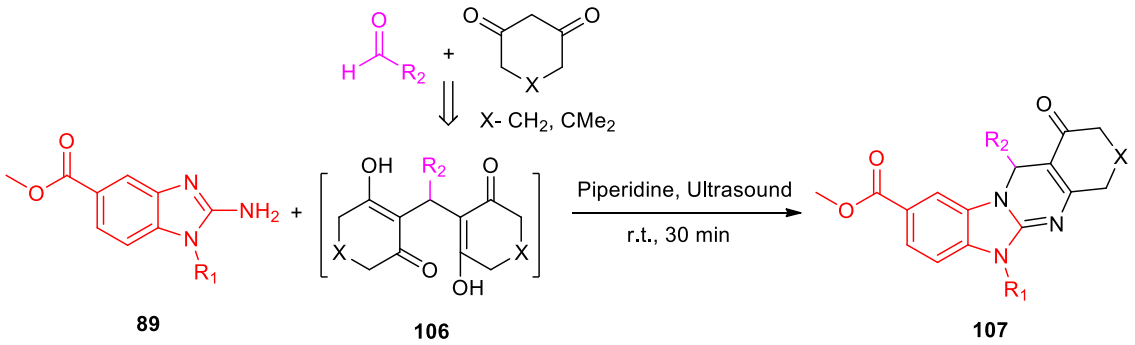
Finally the ionic liquid was cleaved using a solution of ammonia in methanol at room temperature for 8 h to obtain the trisubstituted triazenes **103** in excellent yields.

Sun *et al*. further reported the synthesis of benzimidazo[1′,2′:1,5]-pyrrolo[2,3-*c*]isoquinolines by a three-component coupling reaction on ionic liquid support under microwave irradiation as shown in **Scheme 29 [**37].



Scheme 29 Ionic liquid supported rapid two-step synthesis of fused pentacyclic scaffolds.

In 2016, Sun, *et al*. have developed the ultra sound promoted three component coupling reaction towords the synthesis of benzimidazo[2,1-a]quinazolin-1(1*H*)-ones **107** shown in **Scheme 30** [38]. In this methodology, substituted 2-aminobenzimidazoles **89**, aldehydes, and 1,3-diones experienced 3-component coupling reaction using piperidine as catalyst under green synthetic condition.



Scheme 30 Ultrasound promoted multicpomponent approach to benzimidazo[2,1-a]quinazolin-1(1*H*)-ones.

The key step in this methodology involved the nucleophillic attack by the 2-aminobenzimidazole on the *in-situ* generated Michael adduct **106** of 1,3-diones and substituted aldehydes followed by the electrocyclic ring closure to generate the target compound. As predicted initially, reaction of 2-aminobenzimidazole **89** with piperidine catalyzed Knovenagel product did not yield the desired scaffold **107**.

Conclusion and Outlook

Since the benzimidazole based linear, angular, and fused biheterocyclic molecules are regarded as an important scaffold with wide range of pharmaceutical applications, a large number of synthetic methods have been developed both on the solid phase as well as on solution phase from time to time. In this review, efforts have been taken to highlight on the latest informations available on the syntheses and applications of benzimidazole based biheterocyclic derivatives from 1999 to 2016. Moreover, these biheterocyclic molecules could be subjected to a range of different modifications with interesting structures for the design of novel libraries for future use of drug discovery and research. The synthetic methodologies incorporated in this review article will help to improve the status of these biheterocyclic scaffolds in its future synthesis and medicinal applications.

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References

[1] Top Prescription Drugs by U.S. Sales 2014|Statistic. Available online: http://www.statista.com/statistics/258010/top-branded-drugs-based-on-retail-sales-in-the-us/ (accessed on 28 May 2015).
[2] (a) Dolle, R. E.; Bourdonnec, B. L.; Goodman, A. J.; Morales, G. A.; Thomas, C. J.; Zhang. W. J. Comb. Chem., 2008, 10, 753-802.
(b) Nandy, J. P.; Prakesch, M.; Khadem, S.; Reddy, P. T.; Sharma, U.; Arya. P. Chem. Rev., 2009, 109, 1999–2060.
[3] (a) Dolle, R. E. J. Comb. Chem., 2005, 7, 739-798.
(b) Kodihalli, C. R.; Hosadu, M. V.; Vaidya, V. P. Arkivoc 2008, xi, 1-10.
[4] (a) Achar, K. C.; Hosamani, K. M.; Seetharamareddy, H. R. Eur. J. Med. Chem. 2010, 45, 2048-2054.
(b). Bauer, J.; Kinast, S.; Burger-Kentischer, A.; Finkelmeier, D.; Kleymann, G.; Rayyan, W. A.; Schroppel, K.; Singh, A.; Jung, G.; Wiesmuller, K. H.; Rupp, S.; Eickhoff, H. J. Med. Chem. 2011, 54, 6993-6997.
(c) El-Nassan, H. B. Eur. J. Med. Chem. 2012, 53, 22-27.
(d) Garudachari, B.; Satyanarayana, M. N.; Thippeswamy, B.; Shivakumar, C. K.; Shivananda, K. N.; Hegde, G.; Isloor, A. M. Eur. J. Med. Chem. 2012, 54, 900-906.
(e) Mavrova, A.; Vuchev, D.; Anichina, K.; Vassilev, N. Eur. J. Med. Chem. 2010, 45, 5856-5861.
(f) Mizuno, C. S.; Chittiboyina, A. G.; Shah, F. H.; Patny, A.; Kurtz, T. W.; Pershadsingh, H. A.; Speth, R. C.; Karamyan, V. T.; Carvalho, P. B.; Avery, M. A. J. Med. Chem. 2010, 53, 1076-1085.
(g) Neochoritis, C. G.; Zarganes-Tzitzikas, T.; Tsoleridis, C. A.; Stephanatou, J.; Kontogiorgis, C. A.; Hadjipavlou-Litina, D. J.; CholiPapadopoulou, T. Eur. J. Med. Chem. 2011, 46, 297-306.
(h) Patel, R. V.; Patel, P. K.; Kumari, P.; Rajani, D. P.; Chikhalia, K. H. Eur. J. Med. Chem. 2012, 53, 41-51.
[5] Bansal, Y.; Silakari, O. Bioorg. Med. Chem. 2012, 20, 6208-6236.
[6] Panda, S.S.; Malik, R.; Jain, S.C. Cur. Org. Chem., 2012, 16, 1905-1919.
[7] Blettner,, C. G.; König, W. A.; Rühter, G.; Stenzel, W.; Schotten, T. Synlett 1999, 307-310.
[8] Chi, Y. C.; Sun, C. M. Synlett 2000, 591-94.
[9] (a) Yeh, C. M.; Sun, C. M. Tetrahedron Lett. 1999, 40, 7247-7250.
(b) Yeh, C. M.; Sun, C. M. Synlett 1999, 6, 810-812.
(c) Yeh, C. M.; Tung, C. L.; Sun, C. M. J. Comb. Chem., 2000, 2, 341–348.
(d) Bendale, P. M.; Sun, C. M. J. Comb. Chem., 2002, 4, 359–361.
(e) Wu, C. Y.; Sun, C. M., Tetrahedron Lett. 2002, 43, 1529-1533.
(f) Huang, K. T.; Sun, C. M. Bioorg. Med. Chem. Lett. 2002, 12, 1001-1003.
[10] Akamatsu, H.; Fukase, K.; Kusumoto, S. J. Comb. Chem., 2002, 4, 475-483.

[11] Vourloumis, D.; Takahashi, M.; Klaus B. Simonsen, K. B.; Ayida, B. K.; Barluenga, S.; Winters, G. C.; Hermann, T. Tetrahedron Lett. 2003, 44, 2807–2811.
[12] (a) Lin, M. J.; Sun, C. M. Synlett 2004, 663-666.
(b) Yeh, W. B.; Lin, M. J.; Sun, C. M. Comb.Chem. High Throughput Screen., 2004, 7, 251-255.
[13] Wu, C. H.; Sun, C. M. Tetrahedron Lett. 2006, 47, 2601-2604.
[14] Chang, C. M.; Kulkarni, M. V.; Chen, C. H.; Wang, C. H.; Sun, C. M. J. Comb. Chem., 2008, 10, 466–474.
[15] Chen, H. Y.; Kulkarni, M. V.; Chen, C. H.; Sun, C. M. Tetrahedron, 2008, 64, 6387-6394.
[16] Chanda, K.; Kuo, J.; Chen, C. H.; Sun, C. M. J. Comb. Chem. 2009, 11, 252–260.
[17] Chanda, K.; Maiti, B.; Yello, G. S.; Chien, M. H.; Kuo, M. L.; Sun, C. M. Org. Biomol. Chem. 2011, 9, 1917-1926.
[18] Maiti, B.; Sun, C. M. New. J. Chem. 2011, 35, 1385-1396.
[19] Chen, L.H.; Mao, C. C.; Salunke, D. B.; Sun, C. M. ACS. Comb. Sci. 2011, 13, 391-398.
[20] Chen, C. H.; Kuo, J.; Yellol, G. S.; Sun, C. M. Chem. Asian. J. 2011, 6, 1557-1565.
[21] Chou, C. T.; Yellol, Y. S.; Jin, C. W.; Sun, M. L.; Sun, C. M. Tetrahedron, 2011, 67, 2110-2117.
[22] (a) Miao, W.; Chan, T. H. Org. Lett. 2003, 5, 5003–5005.
(b) Miao, W. S.; Chan, T. H. Acc. Chem. Res. 2006, 39, 897–908.
(c) Ni, B.; Headley, A. D. Chem. Eur. J. 2010, 16, 4426–4436.
[23] Thummanagoti, S.; Yello, G. S.; Sun, C. M. Tetrahedron Lett. 2011, 52, 2818-2822.
[24] Chanda, K.; Maiti, B.; Tseng, C. C.; Sun, C. M. ACS Comb. Sci. 2012, 14, 115-123.
[25] Dhole, S. Selvaraju, M.; Maiti, B.; Chanda, K.; Sun, C. M. ACS Comb. Sci. 2015, 17, 310-316.
[26] Chen, C. H.; Chien, M. H.; Kuo, M. L.; Chou, C. T.; Lai, J. J.; Lin, S. F.; Thummanagoti, S.; Sun, C. M. J. Comb. Chem. 2009, 11, 1038-1046.
[27] Liao, J. Y.; Selvaraju, M.; Chen, C. H.; Sun, C. M. Org. Biomol. Chem. 2013, 11, 2473-2481.
[28] Barve, I.; Chen, C. Y.; Salunke, D. B.; Chung, W. S.; Sun, C. M. Chem. Asian. J. 2012, 7, 1684-1690.
[29] Maiti, B.; Chanda, K.; Selvaraju, M.; Tseng, C. C.; Sun, C. M. ACS Comb. Sci. 2013, 15, 291-297.
[30] Hsiao, Y. S.; Yellol, G. S.; Chen, L. H.; Sun, C. M. J. Comb. Chem. 2010, 12, 723-732.
[31] Chen, L. H.; Hsiao, Y. S.; Yellol, G. S.; Sun, C. M. ACS Comb. Sci. 2011, 13, 112-119.
[32] Chen, C. H.; Yellol, G. S.; Lin, P. T.; Sun, C. M. Org. Lett. 2011, 13, 5120-5123.
[33] Lee, C. H.; Hsu, W. S.; Chen, C. H.; Sun, C. M. Eur. J. Org. Chem., 2013, 2201–2208.
[34] Hsu, W. S.; Paike, V.; Sun, C. M. Mol Divers. 2013, 17, 285–294.
[35] Hsiao, Y. S.; Narhe, B. D.; Chang, Y. S.; Sun, C. M. ACS Comb. Sci. 2013, 15, 551-555.
[36] Barve, I. J.; Chen, C. H.; Kao, C. H.; Sun, C. M. ACS Comb. Sci. 2014, 16, 244-249.
[37] Narhe, B. D.; Tsai, M. H.; Sun, C. M. ACS Comb. Sci. 2014, 16, 421-427.
[38] Chen, L. H.; Chung, T. W.; Narhe, B. D.; Sun, C. M. ACS. Comb. Sci., 2016, 18, 162-169.

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