

REVIEW

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An overview of recent progress in modern synthetic approach—combinatorial synthesis

Chandravadelu Gopi^{1*}, Gudapati Krupamai¹, Chitikina Satya Sri¹ and Magharla Dasaratha Dhanaraju²

Abstract

Background: In recent times, a powerful tool of combinatorial synthesis has been used for the preparation of large chemical entities through a small set up of reactions between different building blocks using solid-phase and solution-phase techniques. This method reduced the time and cost of the drug discovery process substantially.

Main text: Thousands of compounds are synthesised in a few reactions through combinatorial synthesis instead of getting a few compounds in the traditional method. This method also helps to identify chemical lead of the compounds and optimise them through the biological screening using a high-throughput method. There is no review concerning the recent research finding of combinatorial synthesis. Hence, an attempt had been made on the latest research findings (2002–2020) of newly synthesised compounds using combinatorial synthesis and their biological activities.

Conclusion: To the best of our knowledge, the current review has completely analysed the importance of combinatorial synthesis and furnished an overview of solid-phase and solution-phase techniques as well as helped mankind by improving higher productivity at low cost, lead identification and optimization and preventing environmental pollution.

Keywords: Combinatorial synthesis, Solid phase, Solution phase, Higher productivity

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1 Background

The traditional method of drug synthesis is a useful technique but a time-consuming and expensive process [1, 2]. Therefore, pharmaceutical industries around the world are looking at the alternative method of synthesis of new drug molecules. Combinatorial synthesis is one of the novel methods to reduce the time and expenses and gets a large number of compounds in a short period instead of getting a few compounds in the traditional method of synthesis (Fig. 1) [3, 4]. It is a novel technique in which a large number of structurally distinct molecules can be synthesised simultaneously and finding out their pharmacological activities using a high-throughput screening method [5–7]. It has been used by industries in 1990, but the basic concept of solid-phase peptide synthesis had been proclaimed by Merrifield in 1963 [8]. Since, solid-phase synthesis has been developed as an efficient method of techniques for the preparation of numerous peptides, oligonucleotides, organometallic, small proteins, non-oligomeric organic molecules, inorganic molecules and polymer chemistry (Fig. 2) [9–11]. The key to combinatorial chemistry is that a large range of analogues has been synthesised using the same reaction conditions in the same reaction vessels [12]. Here, the number of compounds produced far exceeds the number of chemical steps taken [13]. In this way, the pharmaceutical industries can synthesise

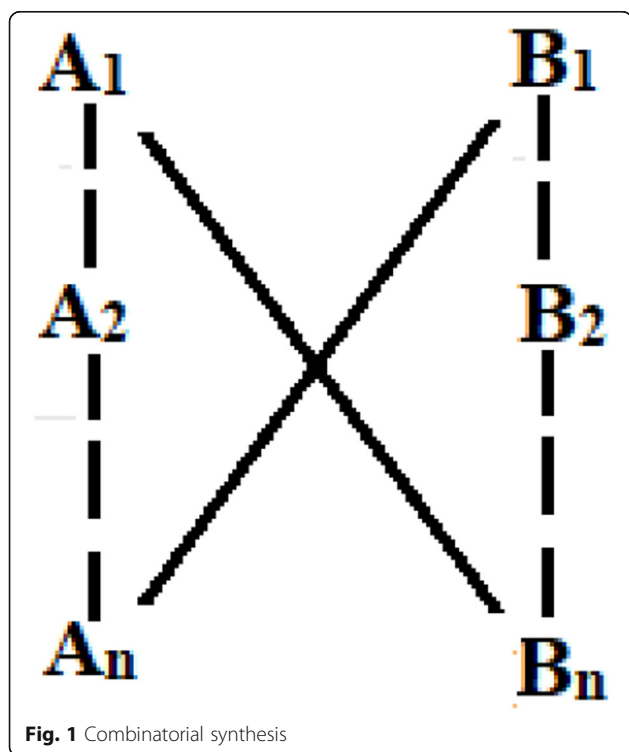


Fig. 1 Combinatorial synthesis

thousands of compounds in a few reactions instead of getting a few compounds by the traditional method [14]. During the literature survey, we have found some of the researchers exclusively used combinatorial synthesis for the preparation of a new drug molecule using solid-phase and solution-phase techniques. These compounds were achieved in a short period. But, there is no review concerning recent research discoveries of novel drug molecules using combinatorial synthesis. Hence, this review provides complete knowledge about the recently synthesised drug molecules using combinatorial synthesis and their biological activities using a high-throughput screening method.

2 Main text

Combinatorial synthesis has two phases such as preparing a combinatorial library or an array and screening of biological activities of the library [15]. These can be achieved by using solid-phase and solution-phase synthesis techniques [16, 17]. Solid-phase synthesis is carried out with the aid of resin beads that are treated as a base for building blocks and linker [18, 19]. The selection of the bead depends on the type of reactions carried out on the surface of the bead [20]. It is allowing the reaction of the substrate with the different reagents to achieve products. Chemical and radio frequency tagging has been used often for the synthesis of the specific compounds in a solid-phase synthesis which act as a code for the individual step of the synthesis and separated them at the end of the synthesis from bead and products [21]. The excess reagent and product have been easily removed from the resin bead by washing with suitable solvents [22]. Solution-phase synthesis performs the chemical reaction preferably in a solution using a well-ordered set of reacting vessels to attain combinatorial libraries [23]. This method has been restricted to synthesise the libraries bearing two to three steps.

2.1 Solid-phase synthesis

Solid-phase synthesis has shown several advantages including the easy process of isolation of products which can be obtained by filtering, ensures complete conversion of a product from the substrates, toxic and safe handling of explosive reagent etc. [24–26]. The essential requirements of solid-phase synthesis are cross-linked insoluble polymer support, linker, substrate, reagent and chemical protecting groups [27]. It has been carried out by using either parallel or split and mix procedures using insoluble polymer support [28]. Geysen had reported a recent development of an encoding strategy in which molecular

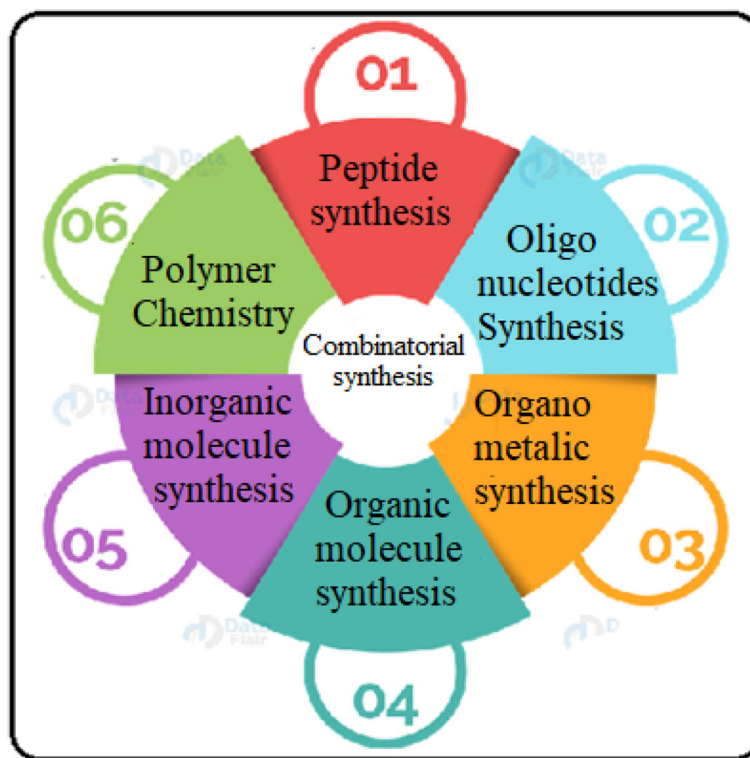


Fig. 2 Application of combinatorial synthesis

tags are attached to beads or linker groups used in solid-phase synthesis at the Coronado conference. It can be used to carry out the appropriate chemical reactions between the building blocks in a proper sequence [29–31] (Fig 3).

2.1.1 Synthesis of heterocyclic compounds

Batra et al. [32] described the synthesis of isoxazole-based libraries such as 3-substituted phenyl-5-isoxazolecarboxaldehydes through solid-phase synthesis. Three highly functionalised isoxazole-based libraries comprising thirty-two, ninety-six and forty-five were synthesised in the parallel method using the Baylis Hilman reaction, Michael addition, reductive amination and alkylation reactions. Out of these synthesised compounds screened for *in vivo* anti-thrombin activity, 2-chlorophenyl substituted compounds showed significant antithrombin activity and their potency has been compared with aspirin (Schemes 1 and 2).

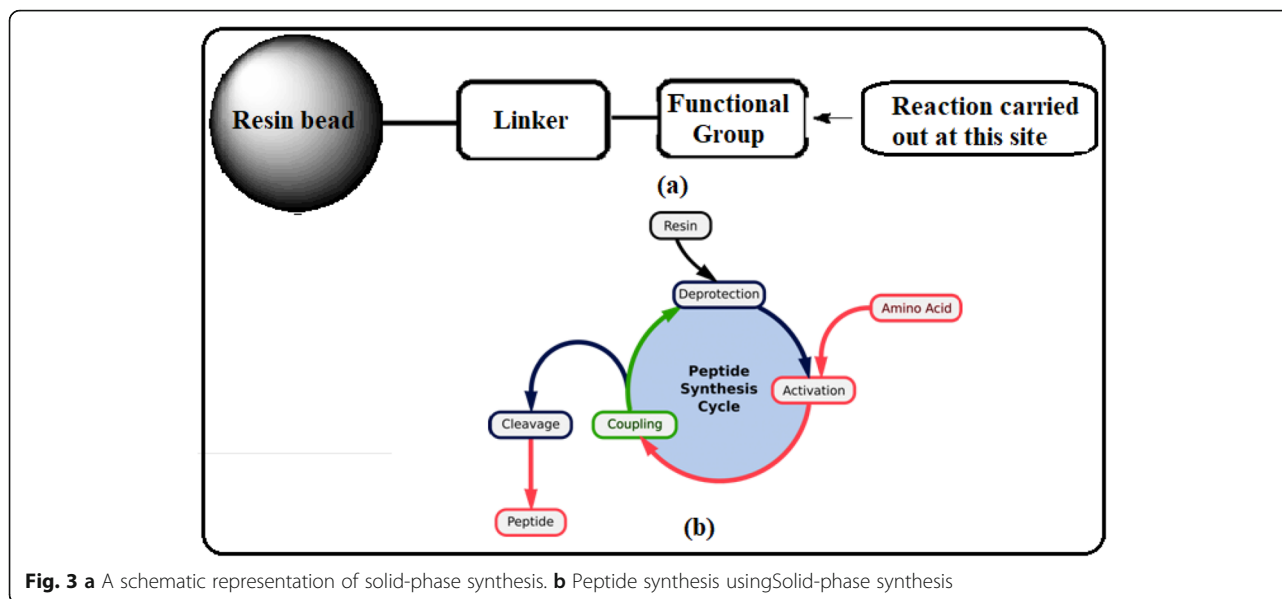
Portilla et al. [17] carried out a novel method of synthesis of 1-pyrazol-3-ylbenzimidazoles from 5(3)-amino-3(5)-substituted-1H-pyrazole and 4-fluoro-3-nitrobenzoate derivatives by using solid-phase and solution-phase syntheses. It is a nucleophilic aromatic substitution reaction that takes place between the activated fluorine and exocyclic amino group of

pyrazole ring which convert the raw materials into title compounds with high yield. The method is very useful to generate the number of libraries of heteroaryl benzimidazoles (Schemes 3 and 4).

Murru et al. [33] synthesised oxazol-thiazole bis heterocyclic compounds with excellent yields and high purity by using solid-phase and solution-phase syntheses. Here, oxazole containing heterocyclic compounds were obtained from serine methyl ester and amino acid through coupling and cyclodehydration in the presence of Fmoc-NCS and α -haloketones, whereas thiazole compounds were obtained from α -haloketones and Fmoc-isothiocyanate (Schemes 5 and 6).

2.1.2 Synthesis of peptide and proteins

On the other hand, a group of researchers led by Drew et al. [34] have been focused and developed a wild-type form of the S^{21} pinholin, $S^{21}68$ and negative-dominant mutant form S^{21} IRS using solid-phase peptide synthesis and studied through biophysics techniques. Later, the duo pinholins have been labelled with nitroxide and successfully incorporated into bicelles and multilamellar vesicles which are membrane mimetic systems. These compounds characterised by NMR spectroscopic data indicated a



strong interaction of pinholes with the membrane headgroups.

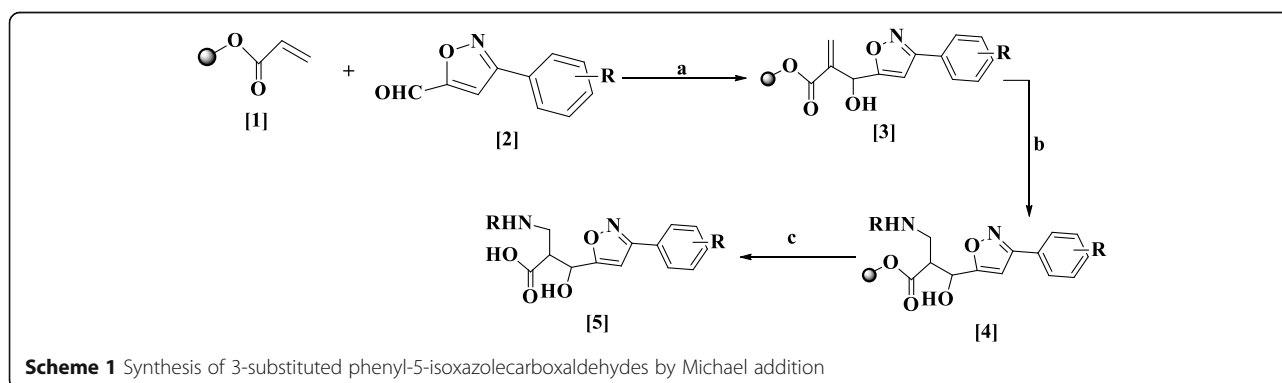
Sun et al. [35] reported a peptide disulphide bond mimics on the incorporation of diaminodiacids through solid-phase synthesis. It is the most effective method for the synthesis of peptide disulphide bond mimics containing a five-atom thioether (C-C-S-C-C). In this work, oxytocin containing a new disulphide bond mimic was achieved. The current diaminodiacid method can do four atom-linked mimics and does not fully meet the activity of the optimization requirement (Schemes 7, 8, 9 and 10).

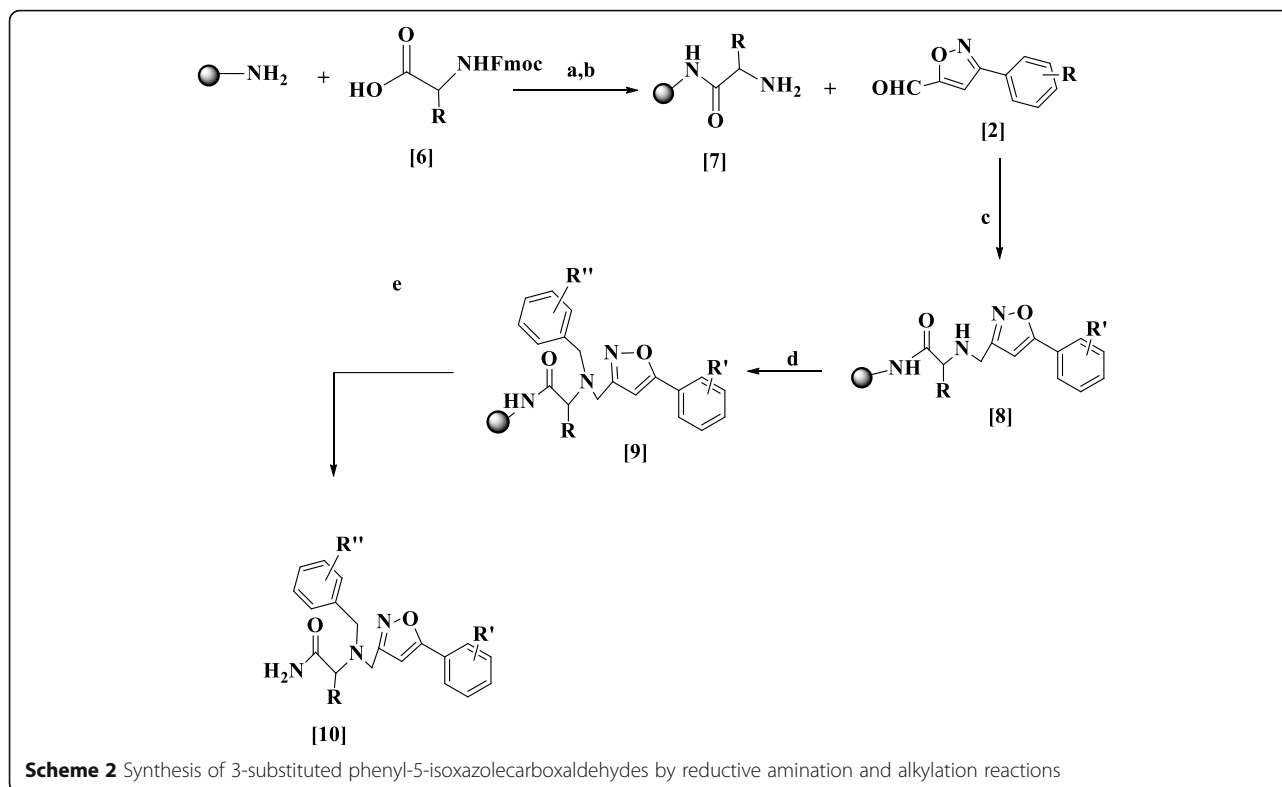
Blanc et al. [36] found that α -amanitin a potent inhibitor of RNA Polymerase II and synthesised two amanitin derivatives using one bead and one compound using solid-phase synthesis. The amatoxin family made up of several rigid bicyclic octapeptides with transannular tryptathionine crosslink had been prepared by Savige-Fontana tryptathionylation of 3a-hydroxyprolo[2,3-b]indoline in neat TFA. Later,

cellular uptake and toxic nature of these derivatives were evaluated (Schemes 11, 12, 13, 14 and 15).

A naked-eye detection of the free amino group has been tested by Rajavenkatesh et al. [37] using solid-phase peptide synthesis. It is a catalytic cyclisation technique of 2-(2-oxo-2H-acenaphthylene-1-ylidene)-malononitrile and oxidative substitution of aryl moiety by free amine group existing in *N*-terminal position of the peptide chain. The above-mentioned reaction is taking place in situ, does not require any heating process and allows *N*-terminal modification of peptides suitable for imaging specific cells (Scheme 16).

Liu et al. [38] prepared a genetically encoded amino acid called selenocysteine (sec) by solid-phase peptide synthesis. It is used to expand the reactivity of enzymes and to modify folding, has high stability and conjugation and facilitates the reactivity. He emphasised a recent advancement of complicated selenoproteins including novel uses of protecting groups and





rapid selenoester-driven chemical ligations and expressed versatile protein ligations (Schemes 17 and 18).

Monaim et al. [39] found a novel method of synthesis of cyclic homodetic peptides by cyclic head to side-chain and cyclative cleavages using Fmoc-MeDbz-resin. It has a cyclic structure formed through amide bonds and is used exclusively in medicinal chemistry. In contrast, for the synthesis of the head to tail counterpart, the cyclative cleavage should be done in the presence of thiophenol (Scheme 19).

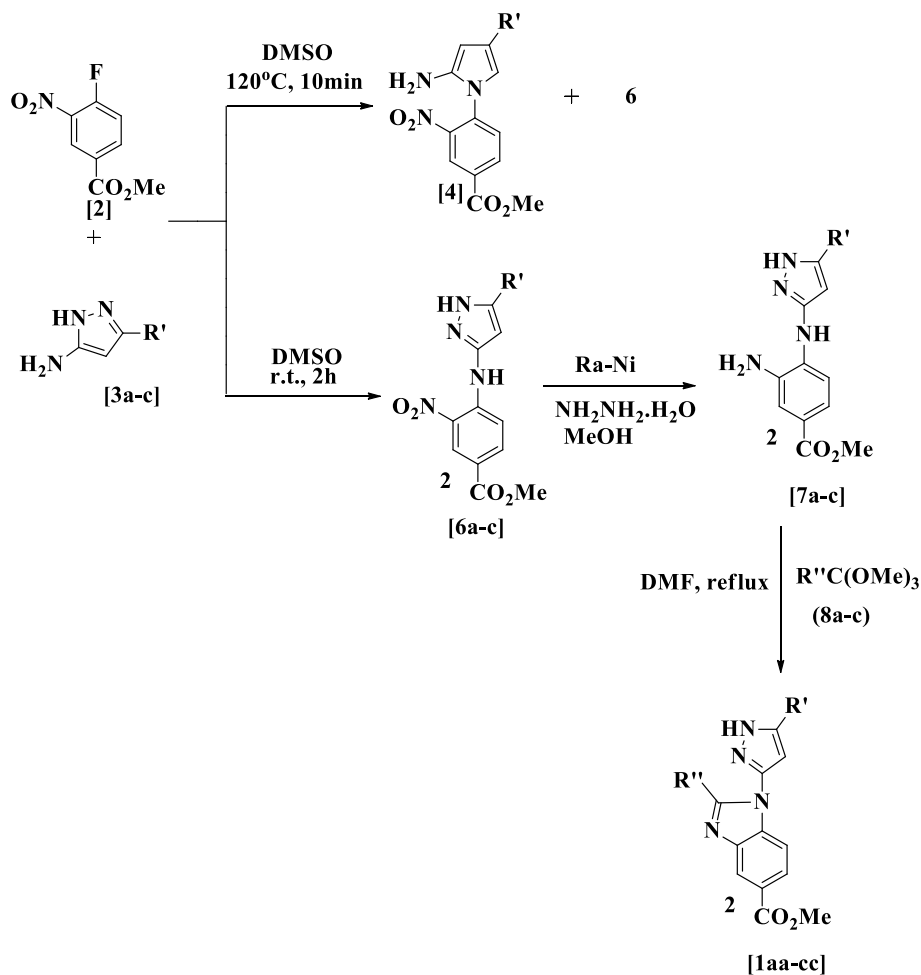
Ng-Choli et al. [40] described a new methodology of synthesis of biaryl bicyclic peptides bearing Phe-Phe, Phe-Tyr or Tyr-Tyr motif through solid-phase synthesis. These compounds were achieved in two steps. The initial step involves the cyclisation of halo and boronoamino acids through microwave-assisted Suzuki-Miyaura cross-coupling. In the second step, biaryl monocyclic peptidyl resin undergoes macrolactamization which leads to the biaryl bicyclic peptide (Schemes 20, 21, 22 and 23).

Shan et al. [41] found the disadvantage of the chemical and enzymatic method of synthesis of dipeptides such as toxic reagents had been used for the synthesis, less yield and least purity of the products. Therefore, he identified a novel method of preparation of dipeptide through solid-phase

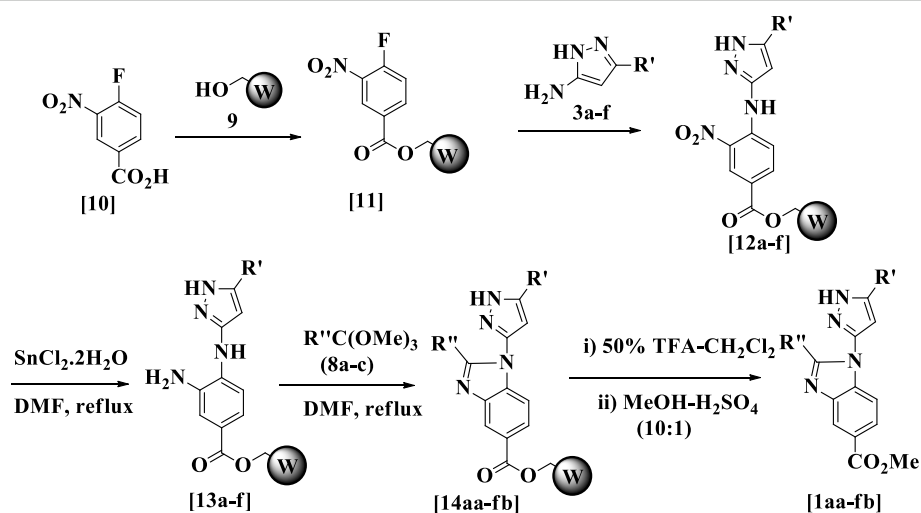
enzymatic synthesis (SPEPS). In this study, a tyrosine-alanine dipeptide (Tyr-Ala) had been synthesised at the end of the third step in the presence of recombinant carboxypeptidase Y (CPY). It includes a N-protected acyl donor covalently linked to the resin followed by the formation of a peptide bond between the acyl donor and nucleophile and removes the dipeptides from solid resin after cleavage. Finally, the synthesised compounds were screened for antioxidant activity by using the ABTS method. The result reveals that the synthesised dipeptide had shown superior antioxidant activity compared with glutathione (Scheme 24).

Ng-Choli et al. [42] synthesised biaryl cyclic peptides bearing His-Phe linkage through a feasible method of solid-phase synthesis strategy. The formation of the above product happened by linking a linear peptidyl resin with 5-bromohistidine and 4-boronophenylalanine and carried out the cyclisation process between the imidazole of histidine and the phenyl group of phenylalanine through microwave-assisted Suzuki-Miyaura cross-coupling reaction. The method could be the useful one for the synthesis of biaryl cyclic peptides bearing histidine and phenylalanine linked at the N- and C-terminus of peptidyl resin (Schemes 25, 26, 27 and 28).

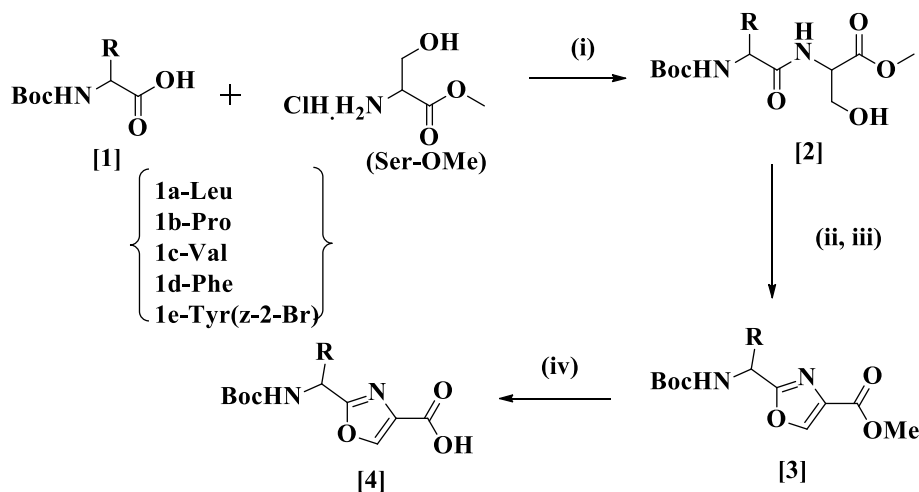
Li et al. [43] reported a novel method of synthesis of naturally occurring cyclic proline-enriched



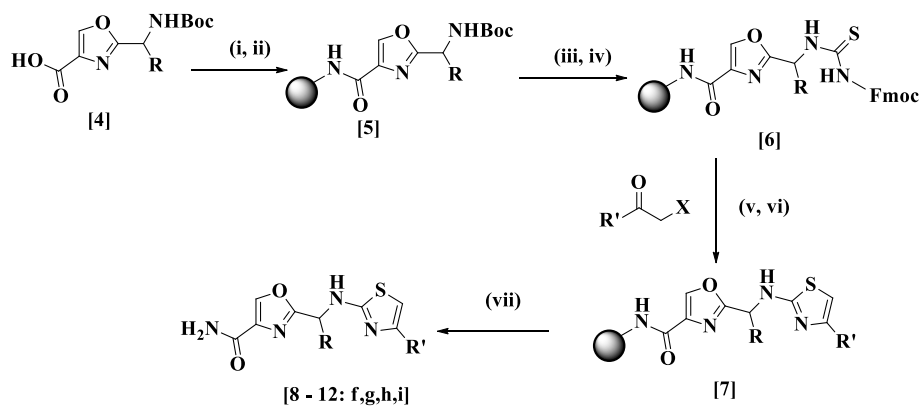
Scheme 3 Solution-phase synthesis of 1-pyrazol-3-ylbenzimidazole derivatives [1aa-cc]



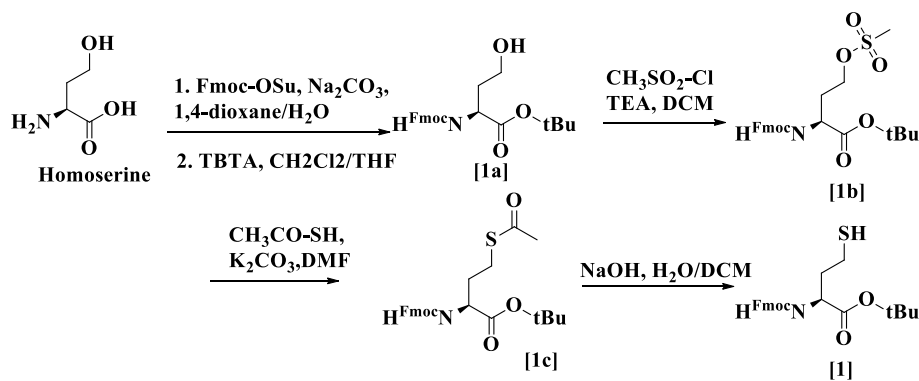
Scheme 4 Solid-phase synthesis of 1-pyrazol-3-ylbenzimidazole derivatives [1aa-cc]



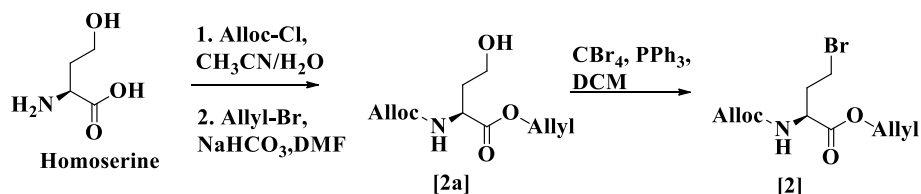
Scheme 5 Biomimetic synthesis of non-natural oxazole amino acid building blocks starting from amino acids and serine methyl ester



Scheme 6 Solid-phase parallel synthesis of oxazol-thiazole bis-heterocycles ($5R \times 4R' = 20 RR'$) via Hantzsch cyclisation starting from resin-bound oxazole amino acids



Scheme 7 The synthetic route of compound [1]



Scheme 8 The synthetic route of compound [2]

octapeptide phakellistatin 15 from marine sponge using solid/solution-phase synthesis. It required two steps of synthetic strategy to get the title compound. The linear octapeptide was assembled by Fmoc chemistry on 2-chlorotrityl chloride resin and cleaved off resin with acetic acid/dichloromethane/trifluoroethanol. Finally, the synthesised compounds were purified and characterised by RP-HPLC system, HR-QTOF-MS, ¹H-NMR and ¹³C-NMR (Scheme 29).

Jad et al. [44] described a novel method of synthesis of peptide through solid-phase synthesis using 2-methyl tetrahydrofuran, ethyl acetate and isopropyl alcohol. These are called green solvents which eliminate the usage of N, N-dimethylformamide, N-methyl-2-pyrrolidone and dichloromethane for deprotecting, washing and coupling process in the organic compound synthesis. The later solvents are creating toxic and hazardous nature to the environment (Scheme 30).

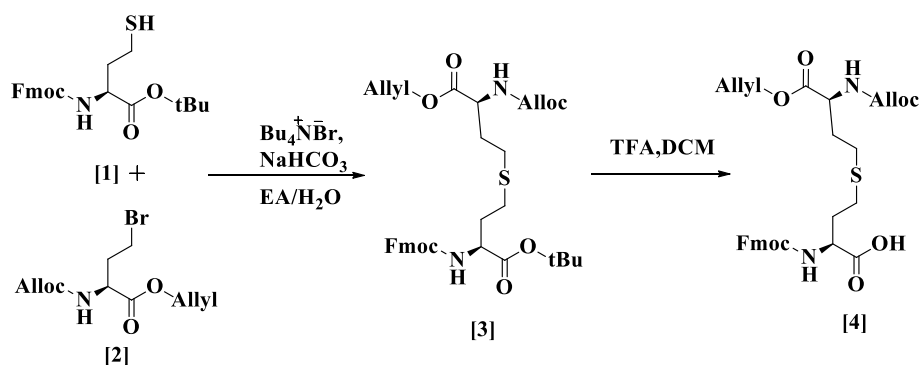
2.1.3 Synthesis of organic compounds

Meschaninova et al. [45] stated a novel synthesis of oligonucleotide conjugates through solid-phase synthesis based on the interaction of free 5-hydroxyl oligonucleotides and amino-containing ligands such as closo-dodecaborate, oestrone, cholesterol and alpha-tocopherol. Initially, functionalization of 5-hydroxyl oligonucleotides catalysed by *N,N*-disuccinimidyl

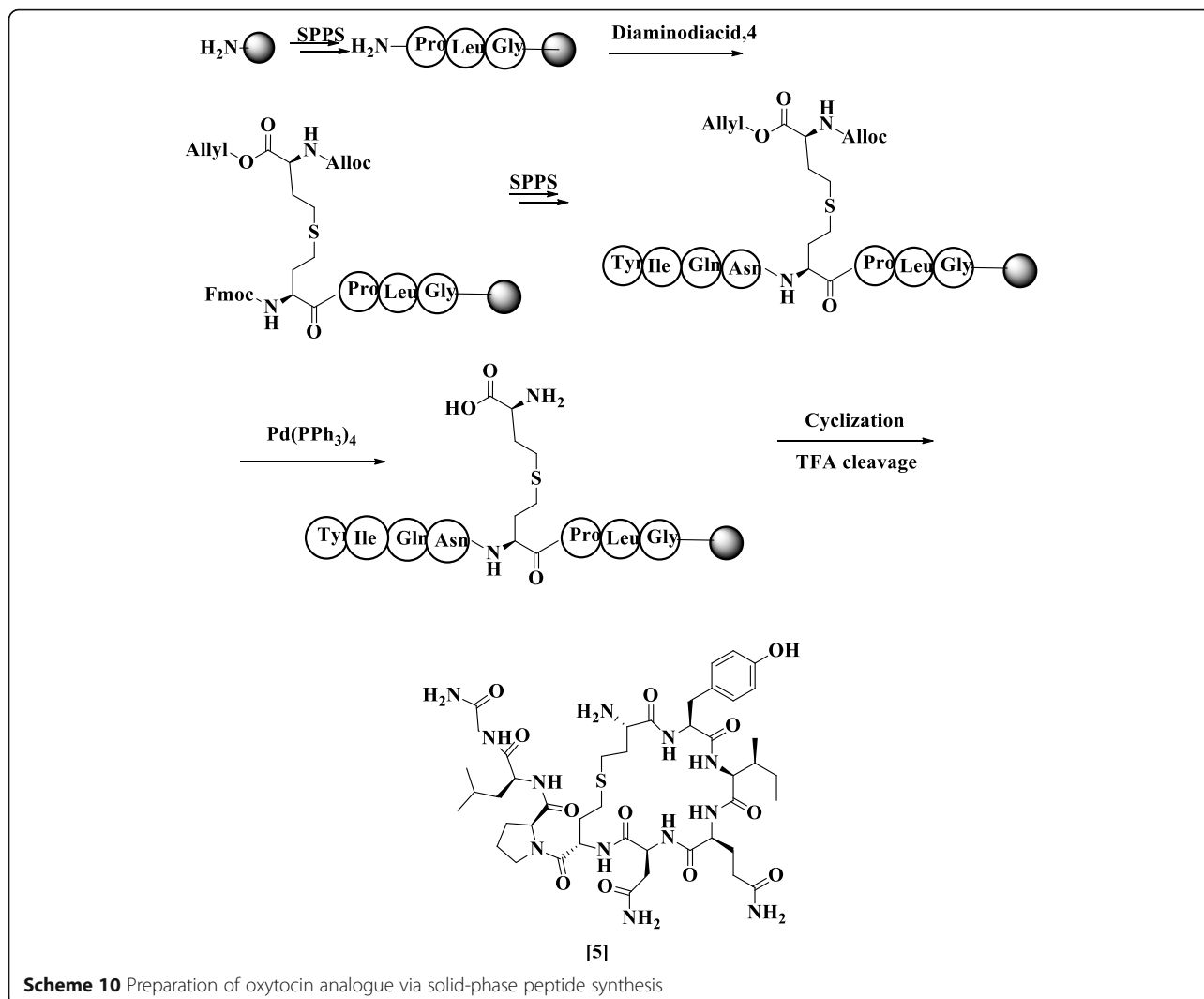
carbonate followed by interaction with an amino group-containing ligand which led to the formation of a wide range of oligonucleotide conjugates such as closo-dodecaborate, lipophilic residues, aliphatic diamines, pyrene, short peptide and propargylamine. These compounds were characterised by ¹H-NMR, mass spectrometry and RP HPLC analyses (Schemes 31, 32 and 33).

Yang et al. [46] established green and rapid microwave-assisted solid-phase synthesis of fluorescent carbon nanoparticles (FCNP). This titled compound has shown excellent chemical stability and biocompatibility and can be fabricated in a short period. It is emitting fluorescence in different solvents including ethanol and water and sensing the pH within the range of 3.47–5.10. Therefore, FCNP is convenient and general fluorescent for bioimaging applications and monitoring pH in living hepatoma cells (Scheme 34).

Hara et al. [47] discussed fluorinated analogues of glycosyl 1-phosphate [β -Gal-(1→4)- α -Man-[1→6)-P-]_n which are glycosyl 1-phosphate repeating structures found in *Leishmania* were synthesised using phosphoramidite method on solid-phase synthesis. It is a stepwise synthesis of glycosyl 1-phosphate has been less extensively studied than *H*-phosphonate chemistry. A compound containing five such repeating units has



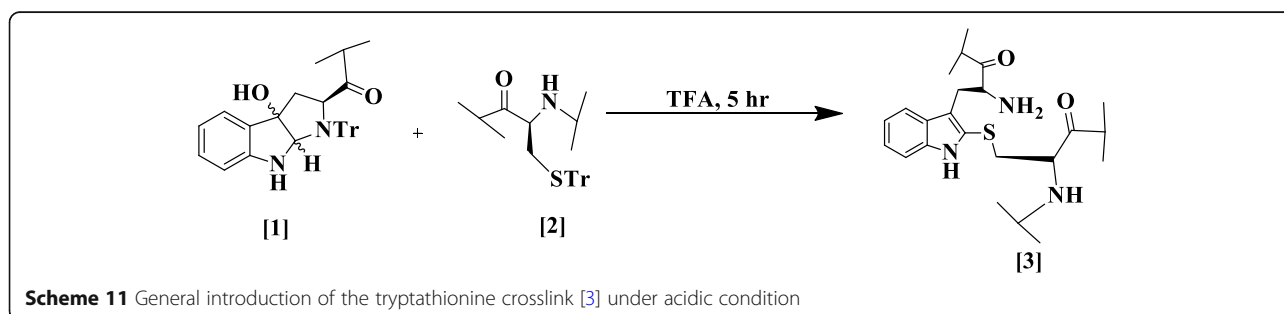
Scheme 9 The synthetic route of five-atom compound [4]

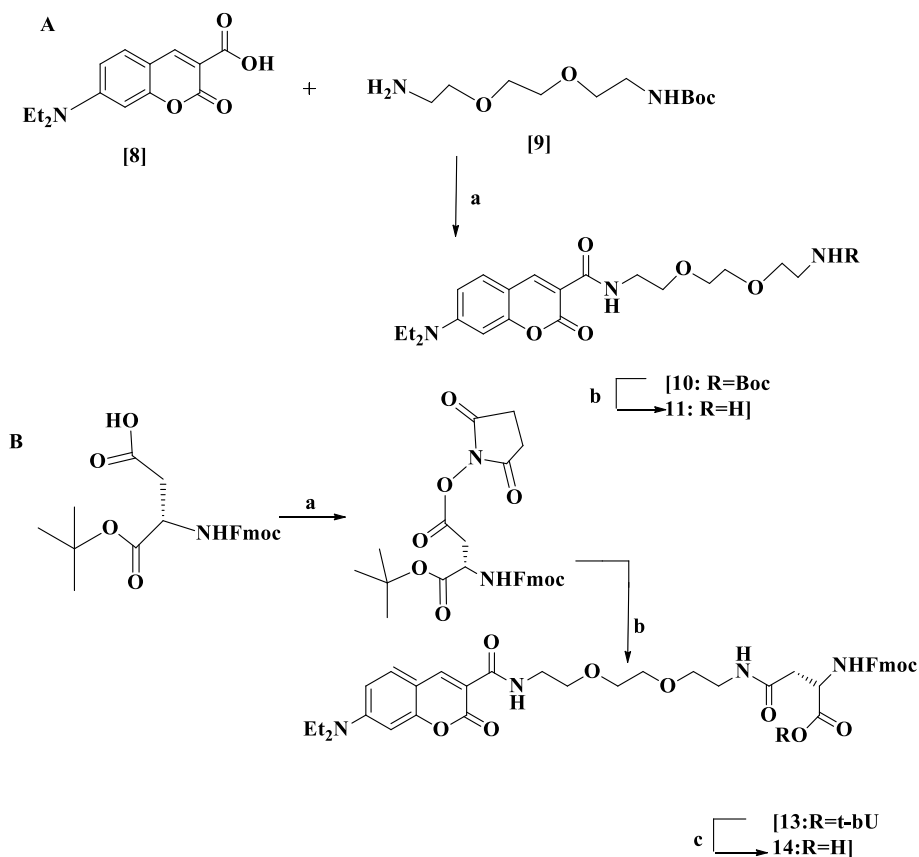
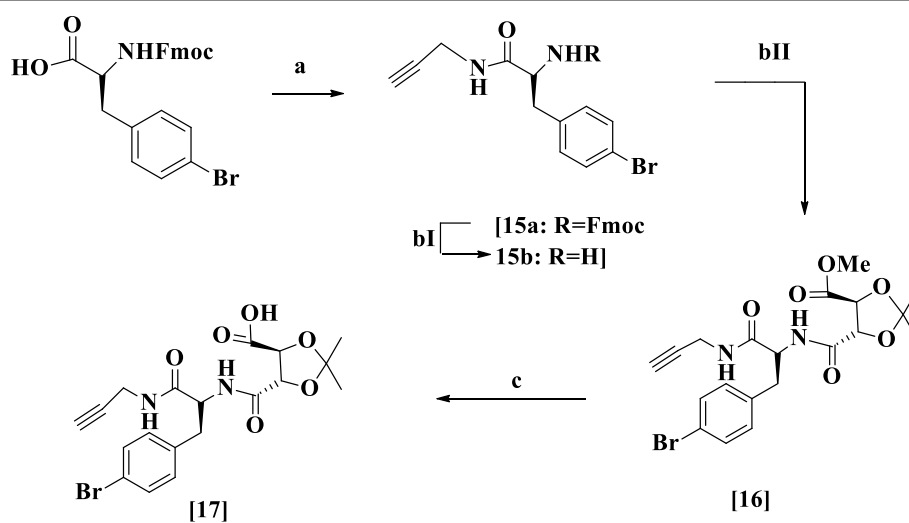


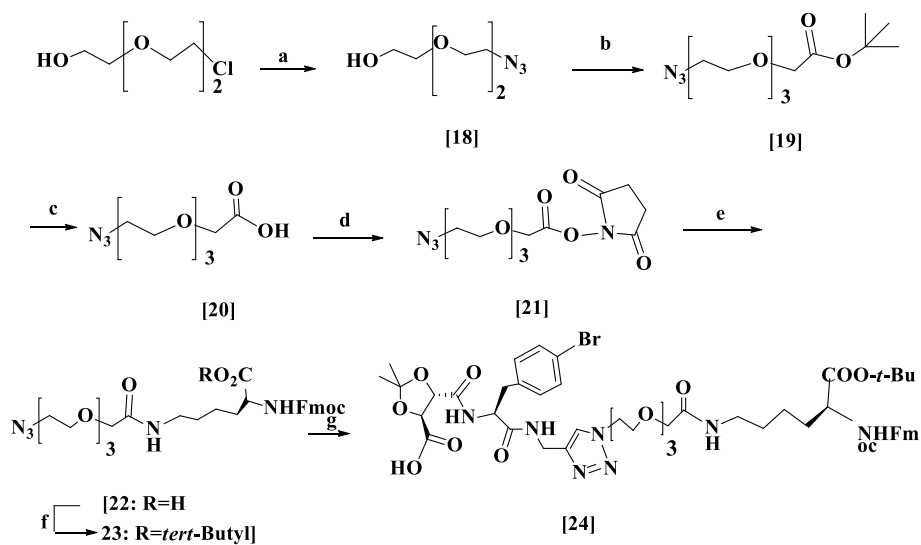
been constructed in a stepwise manner (Schemes 35, 36, 37 and 38).

Kines and co-workers [48] synthesised a novel four series of nucleolipids with either 5-methyluridine, uridine, 6-azauridine and 5-fluorouridine as pyrimidine β -D-ribonucleoside using combinatorial synthesis. These synthesised

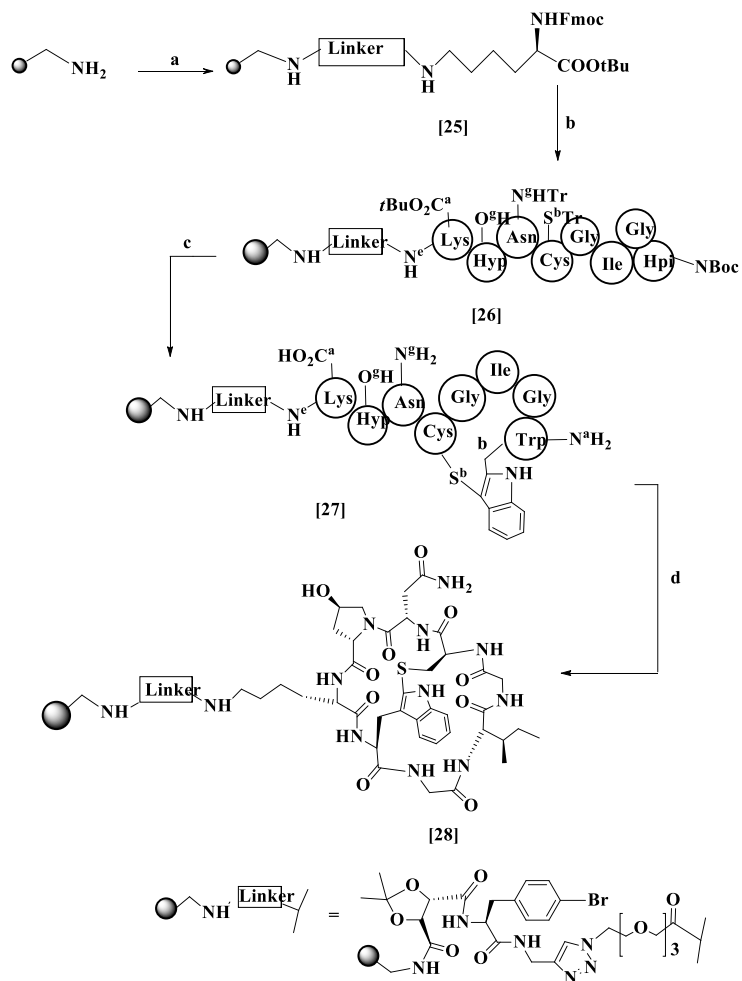
compounds were characterised by ESI mass spectrometry, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, UV spectroscopy and elemental analysis. In addition to that, these compounds were screened for cytotoxic effect against human astrocytoma/oligodendroglioma GOS-3 and rat malignant neuroectodermal BT4Ca cell line. The result reveals that some of the



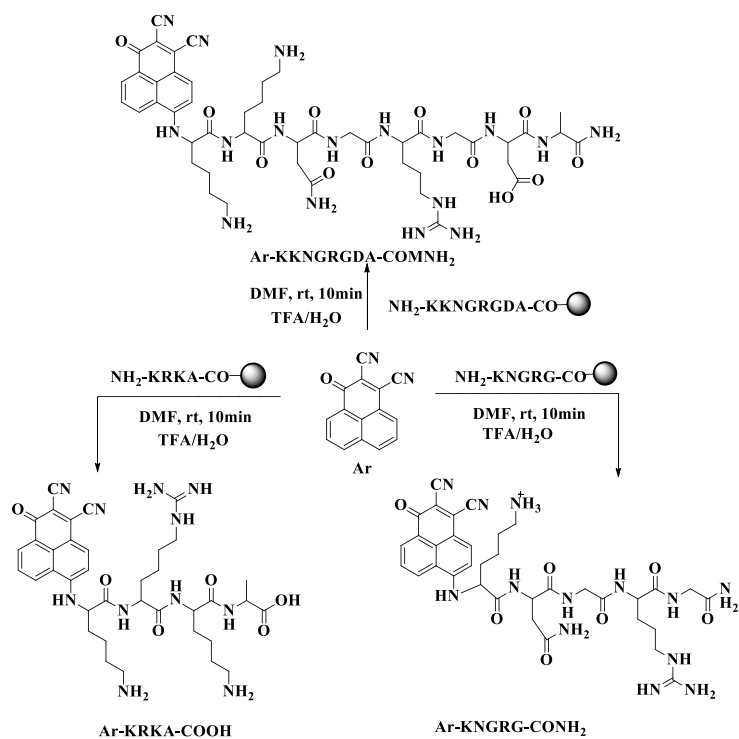
**Scheme 12** Preparation of a fluorescent asparagine derivative [14]**Scheme 13** Synthesis of tartrate-based linker [17]



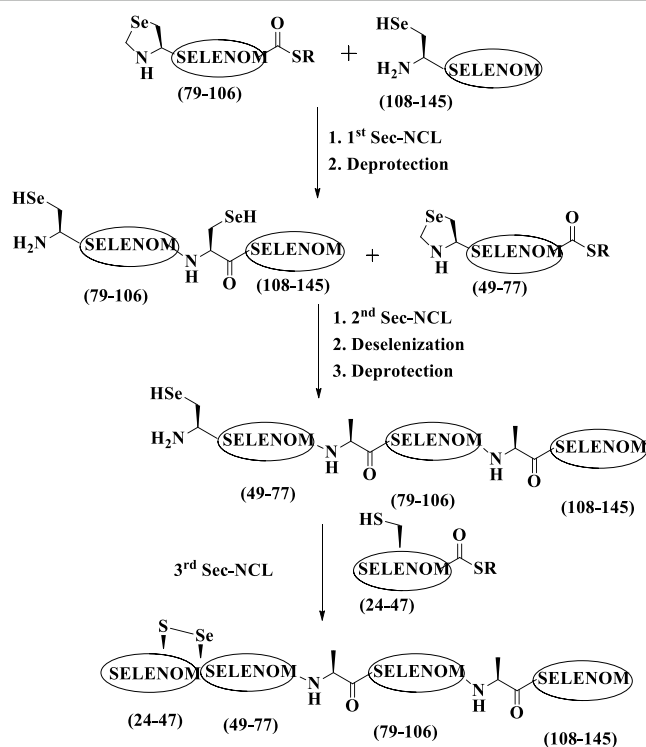
Scheme 14 Lysine condensation with the tartrate-based linker [24]



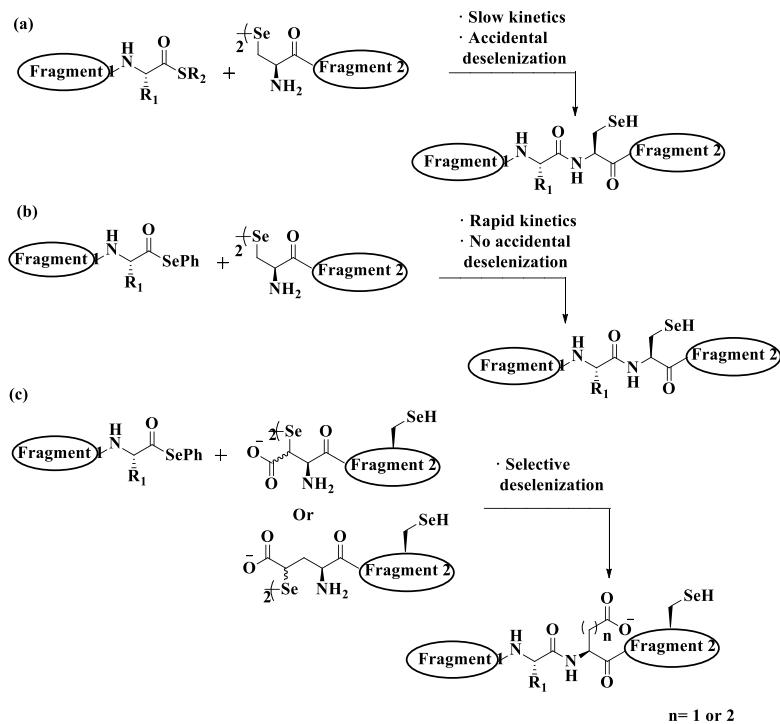
Scheme 15 Synthesis of *S*-deoxo-amaninamide derivative [28]



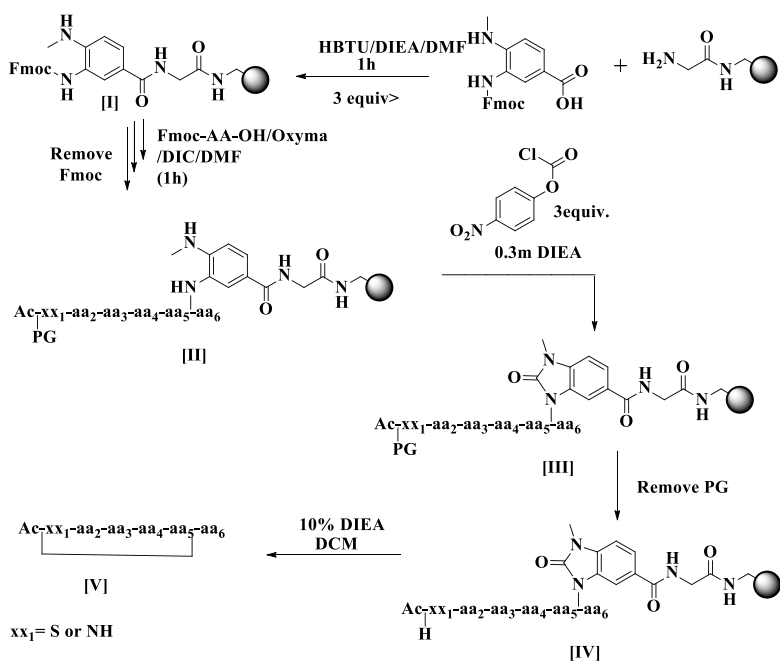
Scheme 16 Synthesis of N-terminal modified peptides



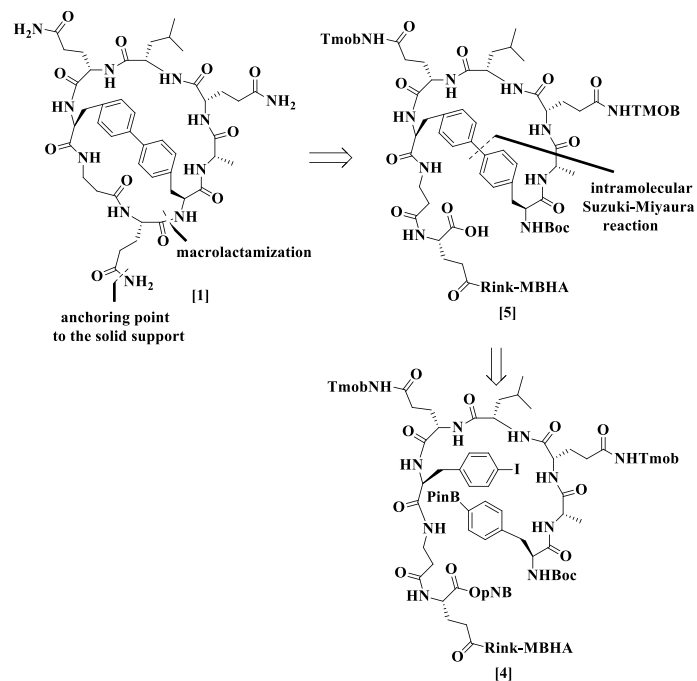
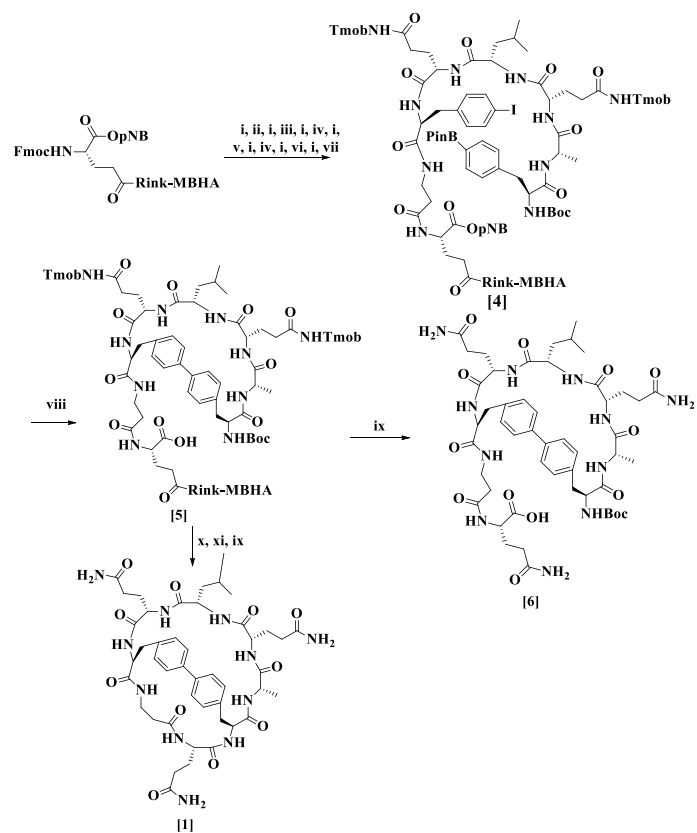
Scheme 17 Three-step synthesis of selenocysteine exemplifies the use of the Sez protecting group for Sec-mediated NCL under reducing conditions

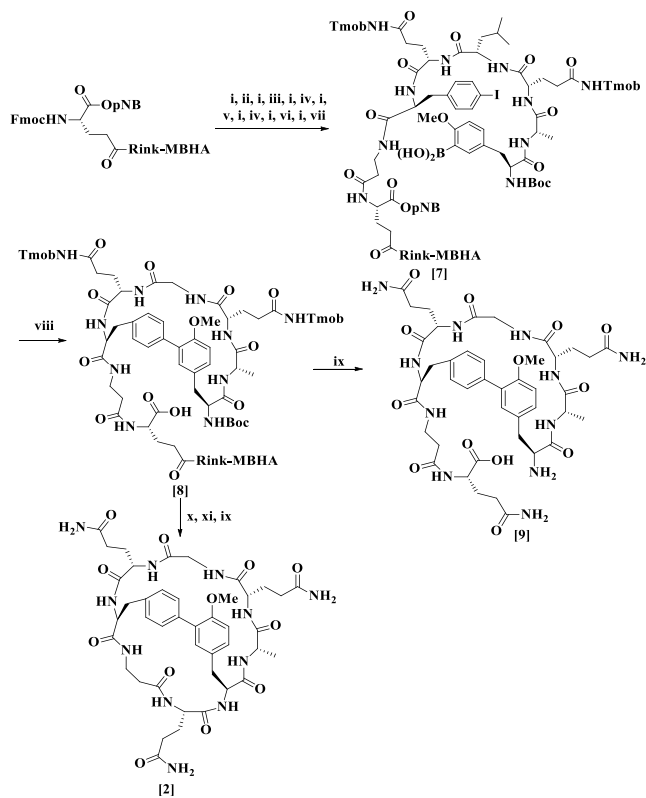


Scheme 18 Principle of Sec-selenoester ligations

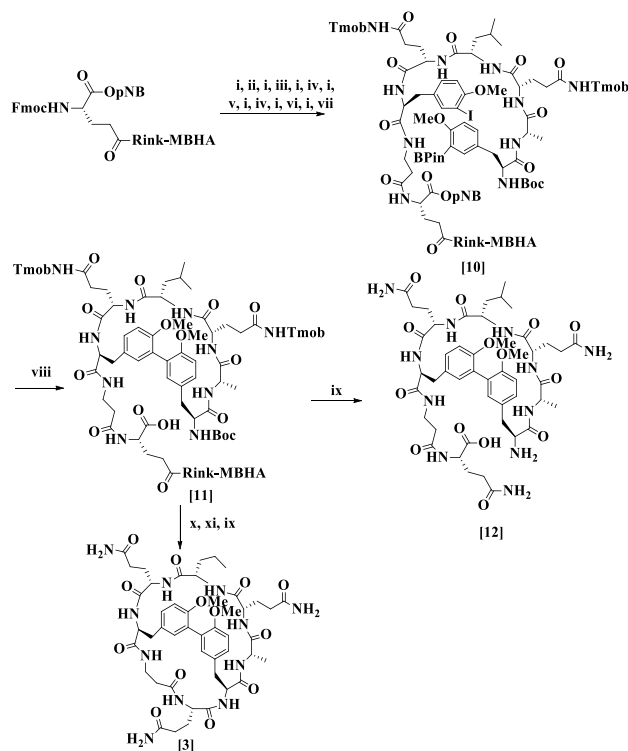


Scheme 19 Cyclisation of peptide models through a nucleophilic intramolecular attack

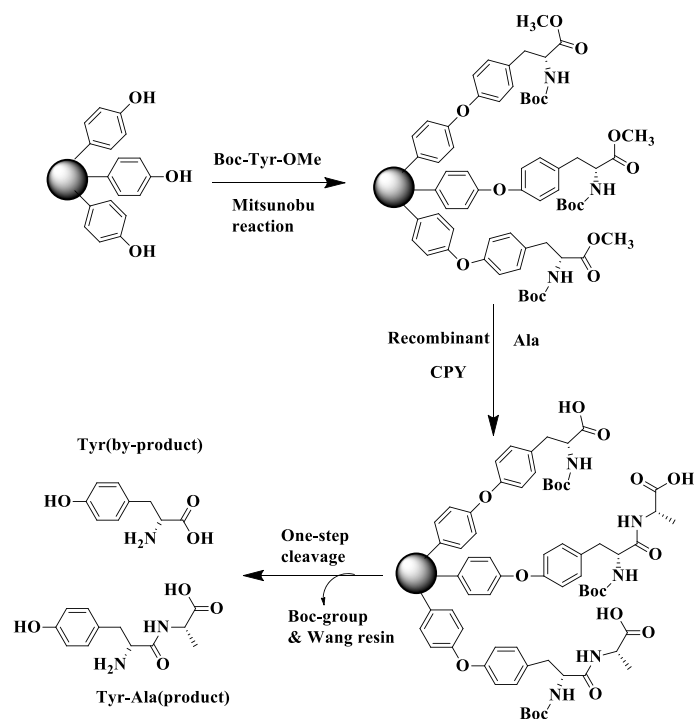
**Scheme 20** Retrosynthetic analysis for the biaryl bicyclic peptide [1]**Scheme 21** Synthesis of the biaryl bicyclic peptide 1 incorporating a Phe-Phe linkage



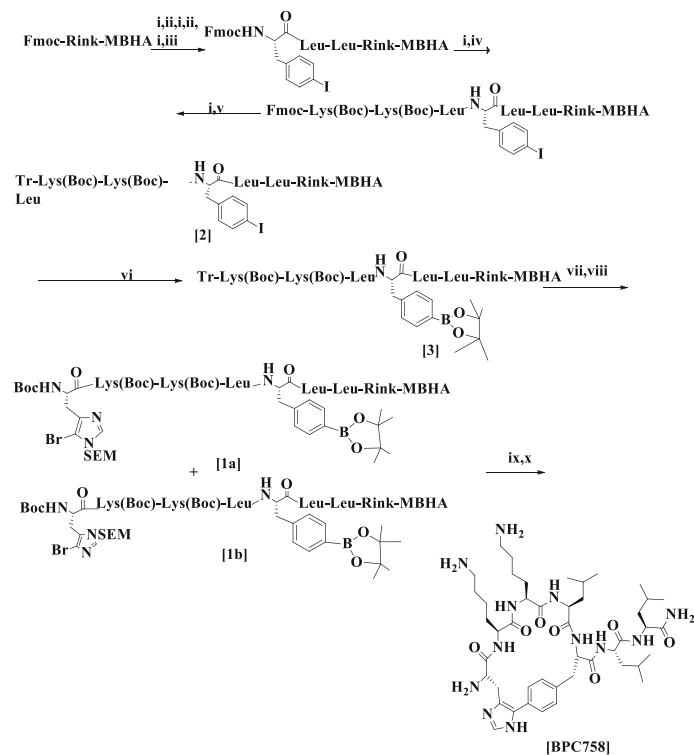
Scheme 22 Synthesis of the biaryl bicyclic peptide 2 incorporating a Phe-Tyr linkage



Scheme 23 Synthesis of the biaryl bicyclic peptide 3 incorporating a Tyr-Tyr linkage



Scheme 24 Solid-phase enzymatic peptide synthesis of Tyr-Ala catalysed by CPY



Scheme 25 Solid-phase synthesis of the biaryl cyclic peptide [BPC758]

Tr-Lys(Boc)-Lys(Boc)-Leu-Phe(4-I)-Rink-MBHA

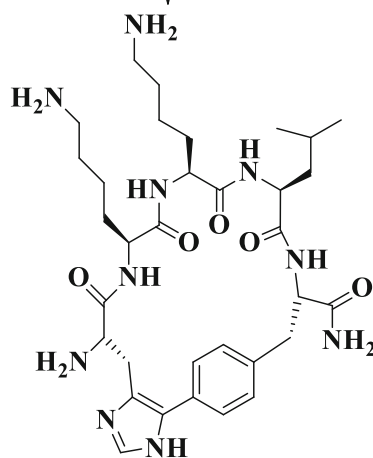
i,ii,iii

Boc-His(5-Br,1-SEM)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA

+

Boc-His(5-Br,3-SEM)-Lys(Boc)-Lys(Boc)-Leu-Phe(4-BPin)-Rink-MBHA

iv,v



[BPC750]

Scheme 26 Synthesis of biaryl cyclic peptides [BPC750]

compounds with N(3) of the pyrimidine has shown the highest probability of killing cancer cells compared with other molecules (Schemes 39 and 40).

Murray et al. [49] identified an easy access to a range of functionalised long-chain alkanethiol oligoethyleneglycols on gold by using solid-phase synthesis. The versatility of synthetic procedure was demonstrated by synthesising LCAT-OEGs with the range of a functional group of the peptide, electroactive redox group for post-assembly conjugation. Finally, the synthesised compound was characterised by XPS, EIS, APM, contact angle measurements and colorimetric method etc. (Schemes 41 and 42).

2.1.4 Synthesis of inorganic compounds

Kerbel et al. [50] prepared cathode material-based lithium iron phosphate powders (LiFePO_4) in the air without the help of inert or reducing medium through continuous solid-phase synthesis. The nanostructured crystal composites of lithium iron phosphate powders are formed by bottom-up self-assembly, resulting in dispersive, crystalline globular

solid and has been used to identify the discharge capacity of synthetic powder. The high concentration of these composites of lithium iron phosphate powders prevented degradation and enhances their absolute values while cycling (Scheme 43).

Li et al. [51] found a simple and convenient way for the synthesis of Cu_2MOS_4 nanoparticles by using the solid-phase method. It is a novel technique introduced for the first time in the synthesis of Cu_2MOS_4 nanoparticles and the Cu_2MOS_4 nanoparticles were evaluated by using X-ray photoelectron spectroscopy, field emission scanning electron microscopy, X-ray diffraction and UV-visible spectrophotometry. It is the best method for a produced photocatalytic agent when compared with other existing methods (Scheme 44).

Kalinkin et al. [52] synthesised a nanocrystalline lanthanum zirconate (LaZr_2O_7) by a solid-phase technique using mechanical activation of a La_2O_3 and ZrO_2 . Hence, the reaction took place between them with the aid of heat and was evaluated by X-ray phase analysis and transmission electron microscopy techniques (Scheme 45).

Tr-Leu-Phe(4-1)-Leu-Leu-Rink-MBHA

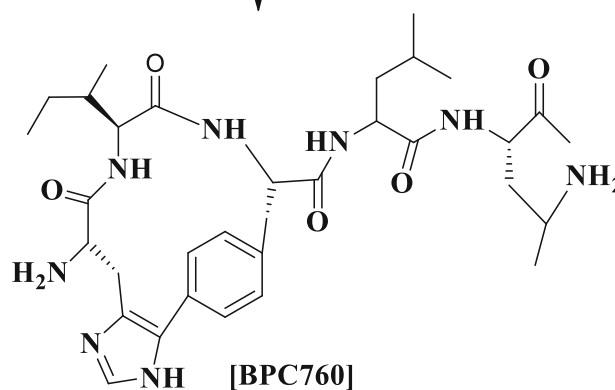
i,ii,iii

Boc-His(5-Br,1-SEM)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA (8a)

+

Boc-His(5-Br,3-SEM)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA (8b)

iv,v



Tr-Leu-Phe(4-1)-Rink-MBHA

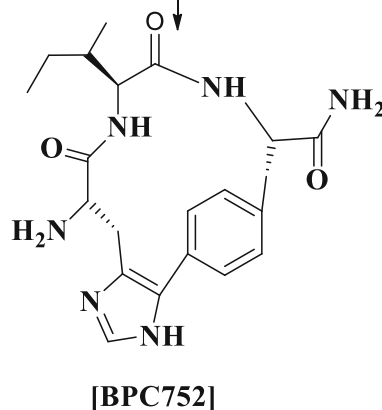
i,ii,iii

Boc-His(5-Br,1-SEM)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA (8a)

+

Boc-His(5-Br,3-SEM)-Leu-Phe(4-BPin)-Leu-Leu-Rink-MBHA (8b)

iv,v

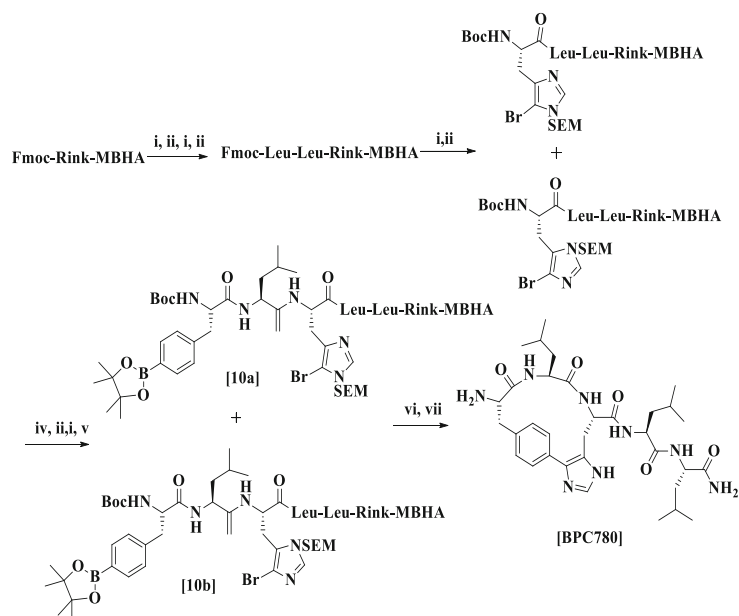


Scheme 27 Synthesis of biaryl cyclic peptides [BPC760 and BPC752]

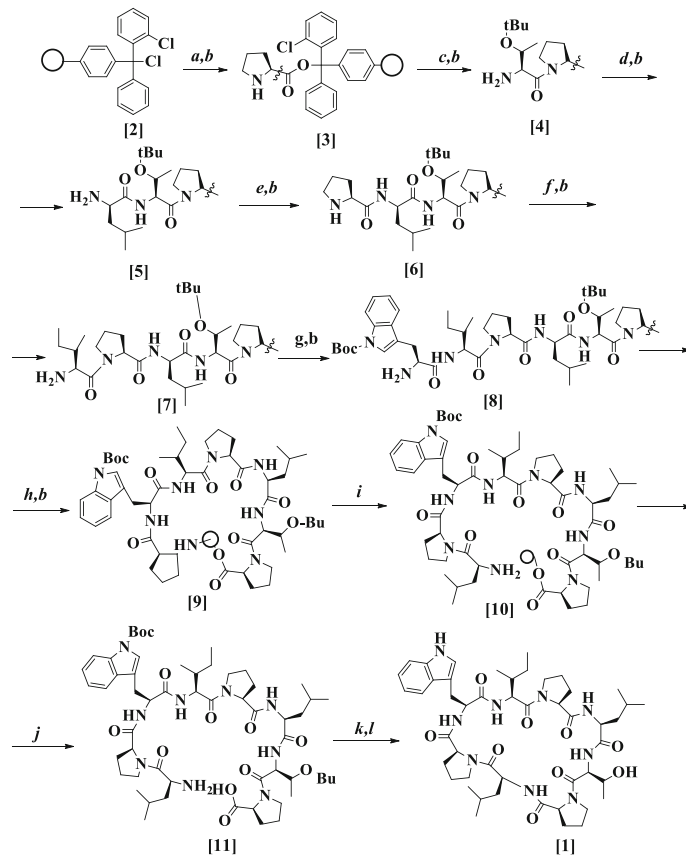
2.2 Solution-phase synthesis

Despite the solid-phase technique, some of the combinatorial libraries were synthesised and screened for their biological activities by solution-phase synthesis

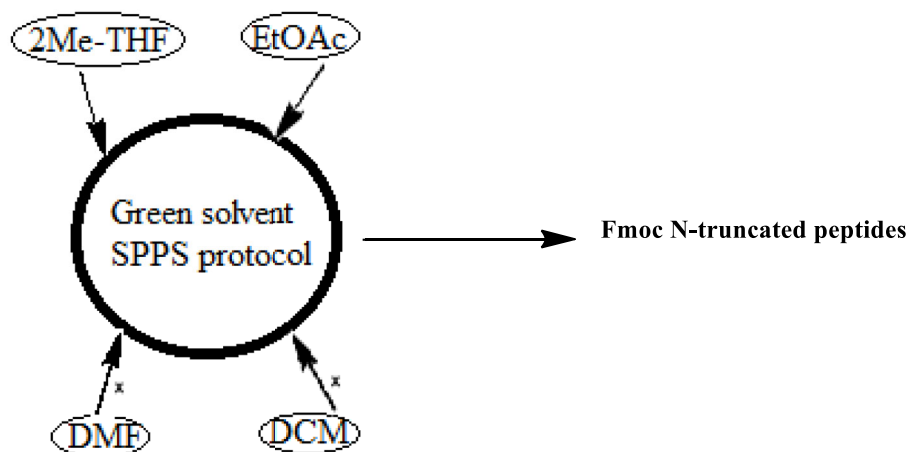
using parallel or split and mix procedure [53–55]. This process is inappropriate for the multistep synthesis because it required tedious purification in each step as compared with solid-phase synthesis



Scheme 28 Synthesis of biaryl cyclic peptide [BPC780]



Scheme 29 Solid-phase synthesis of cyclic octapeptide phakellistatin [15]



Scheme 30 Green solid-phase peptide synthesis

[56]. So that majority of the compounds were synthesised by using solid-phase synthesis (Fig. 4).

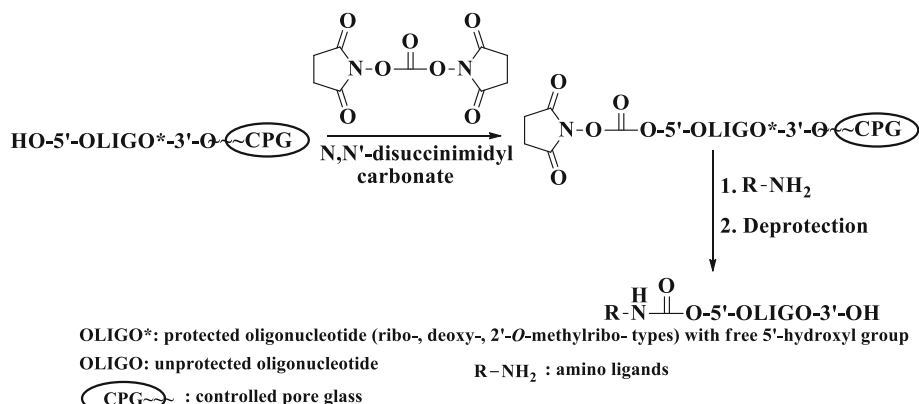
2.2.1 Synthesis of organic and peptide compounds

A group of researchers led by Khan et al. [57] have developed the microwave-assisted synthesis of thirty-eight *N*-aroyl-*N*-aryl thiourea libraries using solution-phase synthesis. In silico docking studies of title compounds were carried out against urease enzyme that acts as a target for lung carcinoma. The studies showed detailed information about the binding mode of title molecules with the targeted site and found an excellent score from compound 17. Later, these analogues were prepared from the raw materials using a similar set of conditions. The authors of the manuscript would like to test the

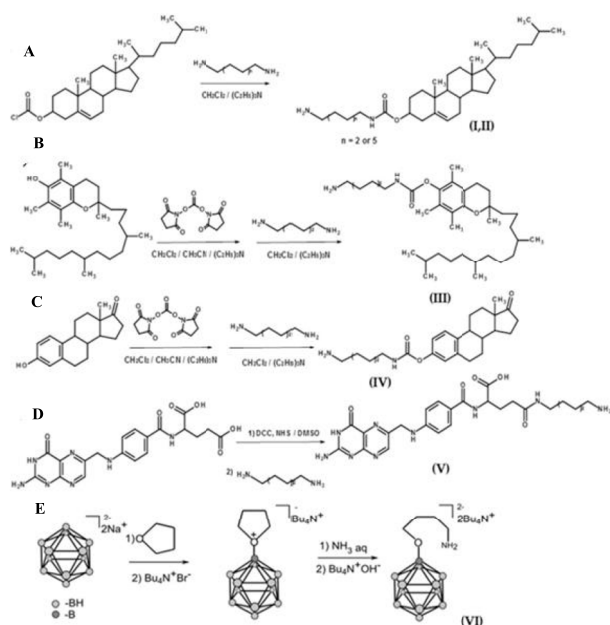
potency of compound 17 with different types of cell lines (Scheme 46).

Kohout et al. [58] prepared a complex sugar molecule using a single coupling protocol or set of reagents. He used a well-known reaction of bench chemistry to achieve the goal of synthesis of a broad range of glycans from sugar fragments. Here, di and trisaccharides of 1 → 2 rhamnan fragments were prepared using a *N*-thioglycoside donor through the solution-phase synthesis in the presence of *N*-iodosuccinamide and trimethylsilyl triflate. Byproducts are compatible with hydrazine-based deprotection conditions, lending broader functionality to this method (Scheme 47, 48 and 49).

Skoblov et al. [59] synthesised a novel *N*-TFA-protected carboxyrhodamine 6G (R6G) phosphoramidite

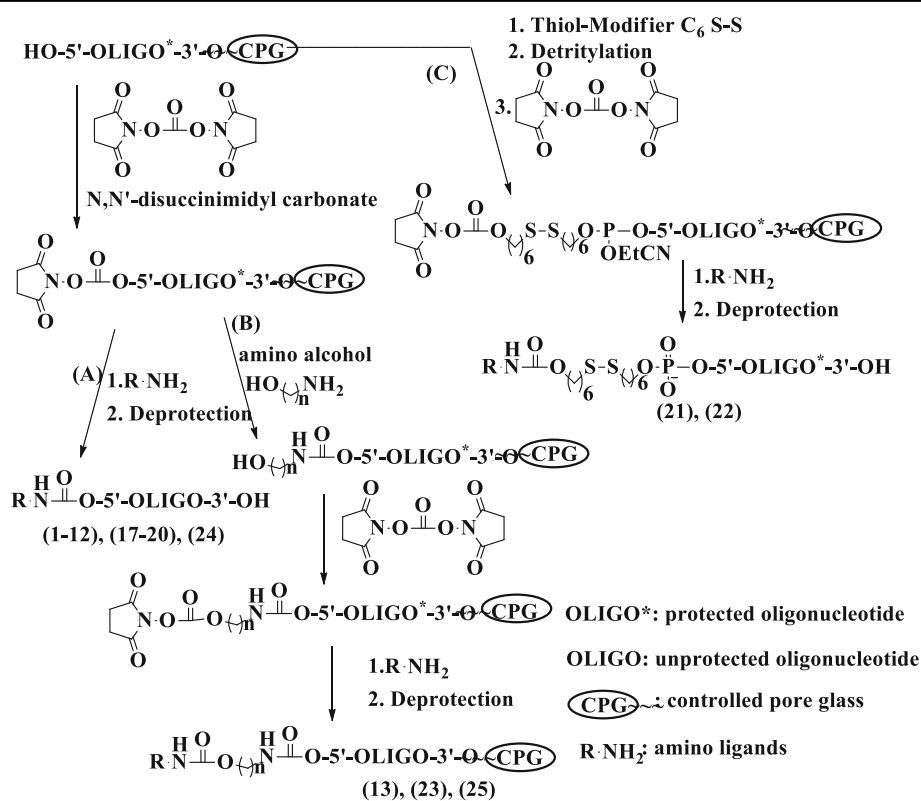


Scheme 31 Synthesis of 5'-functionalisation of oligonucleotides (ribo-, deoxyribo-, 2'-O-methylribo-)

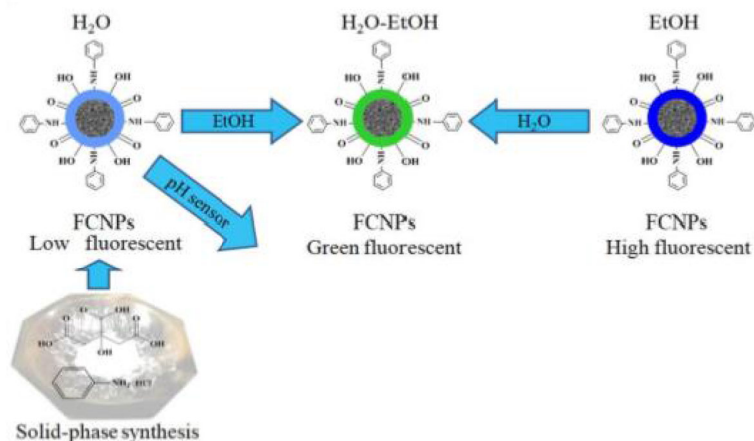


Reagents and conditions: (a) cholesterol (I,II), (b) alpha-tocopherol (III), (c) estrone (IV), (d) gama-amino-modified folate (V), and (e) aminotermethylene oxonium derivative of closo-dodecaborate (VI), N-hydroxysuccinamide; DCC, N,N'-dicyclohexylcarbodiimide.

Scheme 32 Synthesis of amino-modified ligands



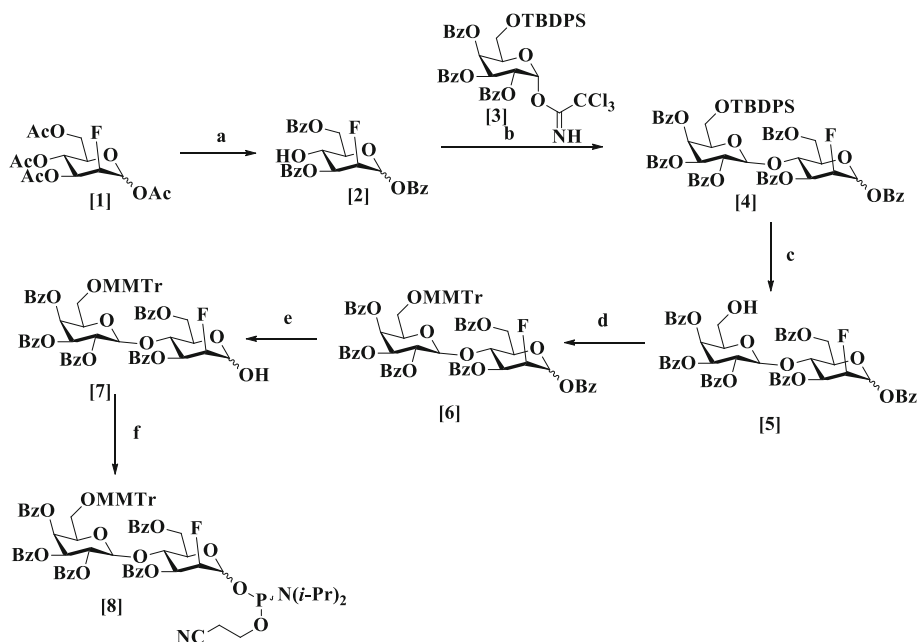
Scheme 33 Synthesis of 5'-conjugates of oligonucleotides based on DSC activation



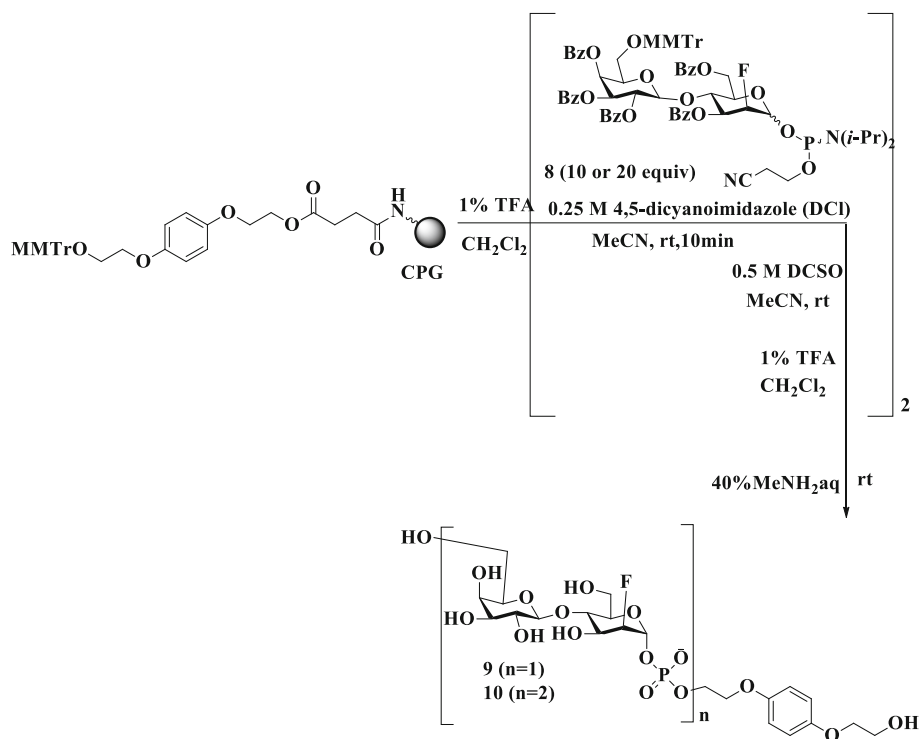
Scheme 34 Synthesis of highly fluorescent carbon nanoparticles

compound through solid and solution phases. An automated DNA method had been used to synthesis the mentioned compound and deprotection & purification condition were optimised 5'-labelled and dual-labelled oligonucleotide probes. The authors also prepared an azide derivative of R6G for CuAAC post-synthetic oligonucleotide labelling as an alternative compound. Both the method has shown the same efficacy in a quantitative PCR assay (Scheme 50, 51, 52 and 53).

Tang et al. [60] discussed the novel method of synthesis of β -1,2-, 1,3-, 1,6-mannan oligomers by applying the β -directing C-5 carboxylate technique using automated solution-phase synthesis. Each synthetic step cycle allowed short β -mannan oligomers with a limited amount of glycosyl donor to purify the product by the fluoros-tag-assisted method. The study encourages the preparation of different challenging glycosides using automated solution-phase synthesis (Schemes 54, 55, 56 and 57).



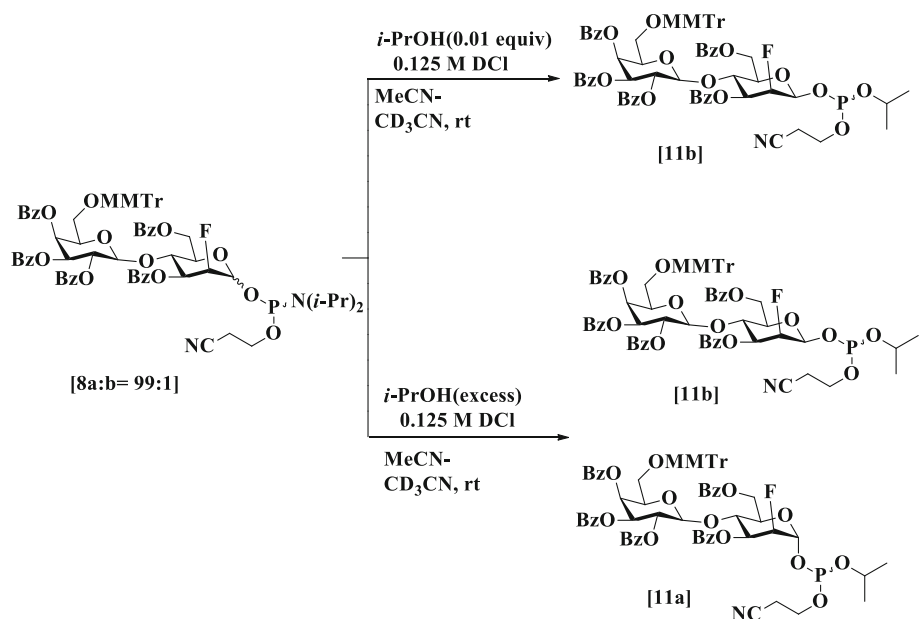
Scheme 35 Synthesis of disaccharide phosphoramidite [8]



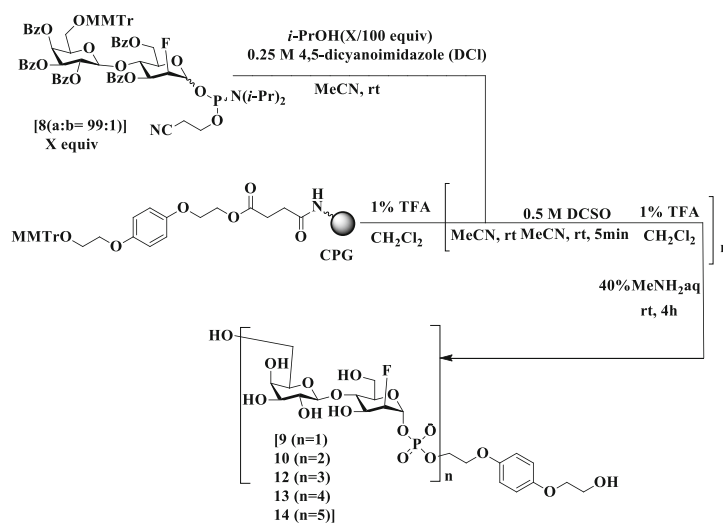
Scheme 36 Solid-phase synthesis of compounds containing glycosyl 1-phosphate repeating units by a phosphoramidite method

Ryakhovsky et al. [61] synthesised Melanotan II by solution-phase synthesis using hexapeptide sequence assembled [(2+2)+1+1] scheme. The titled compound was prepared by the interaction of cyclic intermediate and N-acetylnorleucine. Initially, the ϵ -

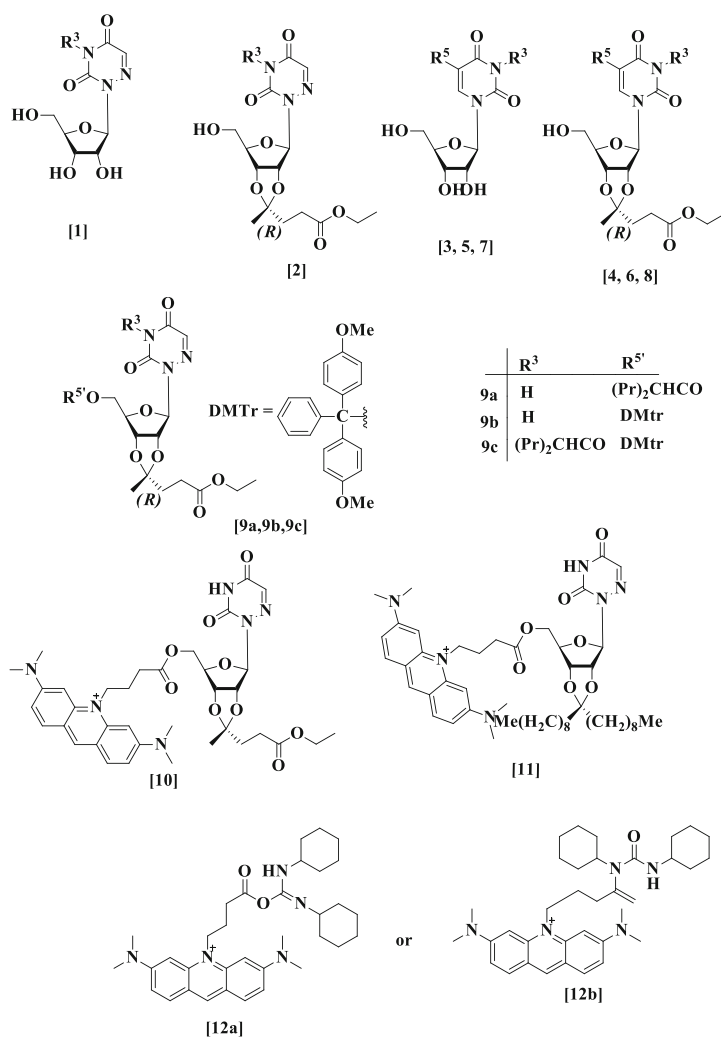
amino acid group, including a γ -carboxy group of aspartic acid, lysine, was involved in the formation of a cyclic intermediate. Later, N-acetylnorleucine converted the intermediate into a Melanotan II molecule. The mentioned method offered a greater



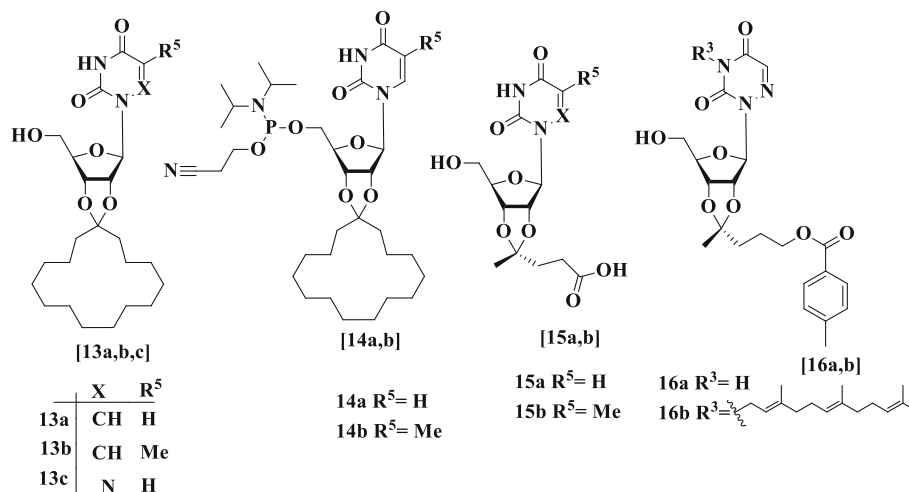
Scheme 37 Condensation reaction of 8 with isopropyl alcohol to form phosphite [11]



Scheme 38 Modified solid-phase synthesis containing a pre-activation step for phosphoramidite [8]



Scheme 39 Synthesis of novel nucleolipids of pyrimidine β -D-ribose nucleosides [1–12].



Scheme 40 Synthesis of novel nucleolipids of pyrimidine β -D-ribose nucleosides [13–16]

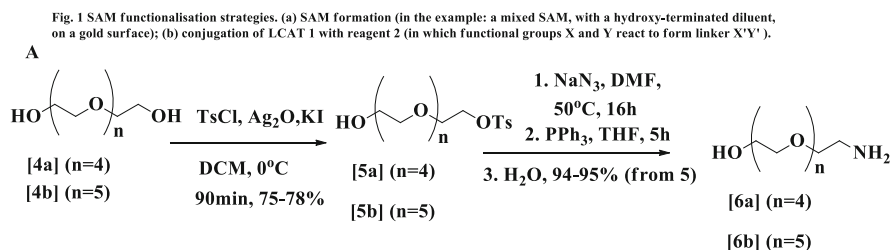
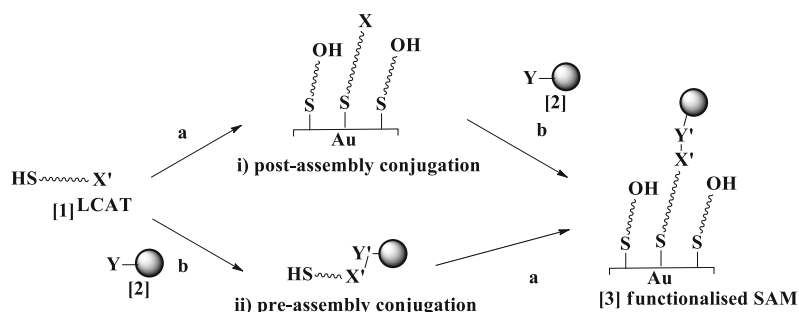
percentage yield of product and obtained purity nearly > 90% (Scheme 58).

2.2.2 Synthesis of inorganic compounds

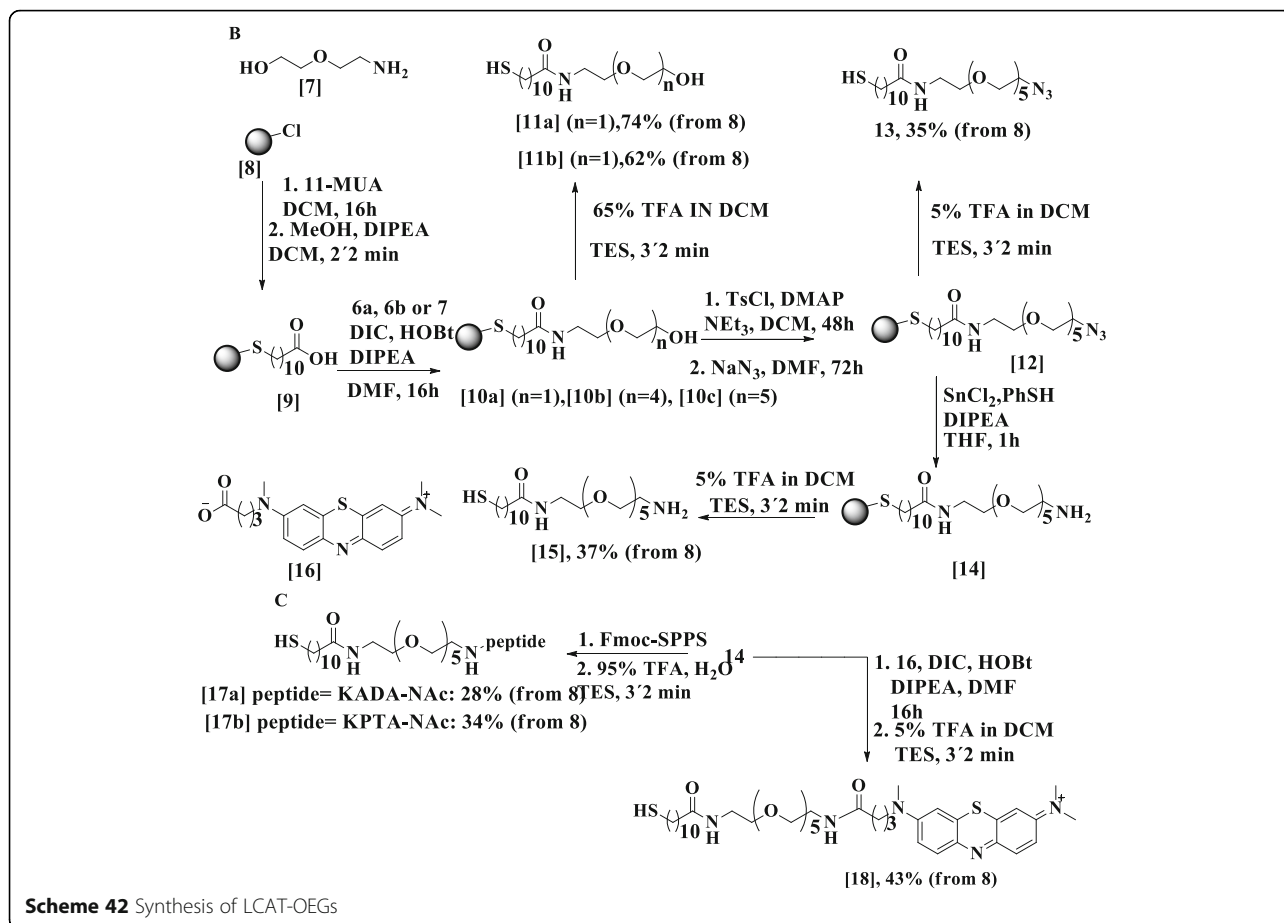
Fenton et al. [62] reported metal tellurides are vital materials used for different applications such as photovoltaic, catalytic and thermoelectric purposes. Hence, he came up with a novel method of synthesising the nanoscale transition metal tellurides by the interaction of pre-formed colloidal metal nanoparticle and bis(trimethylsilyl)telluride using solution-phase synthesis. Nanoparticle Pd, Ni and Pt were used to synthesise corresponding transition metal tellurides.

The formation of metal telluride has been controlled by the reactivity of tellurium reagents (Scheme 59).

Kambe et al. [63] synthesised a superatom Al_{13}^- using a dendrimer template by solution-phase synthesis. It is a well-known superatom developed as clusters with tunable properties and have been identified through mass spectrometry, X-ray photoelectron spectroscopy and scanning transmission of electron microscopy. Later, the superatomic stability of Al_{13}^- is demonstrated by evaluating its tendency towards oxidation. Solution phase synthesis contributed a vital role in cluster science by making different superatoms (Scheme 60).



Scheme 41 SAM functionalisation strategies



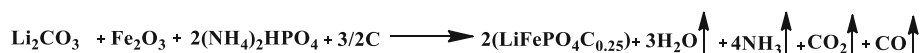
Singh et al. [64] reported the synthesis of doped/undoped cerium (IV) pyrophosphate compounds of different morphologies through the solution-phase synthesis in the presence of cerium (III) nitrate as a metal precursor and hydrogen peroxide as an oxidising agent. The material was studied to ascertain the phase composition and microstructure prior to synthesis. Title compounds were characterised by thermogravimetric analysis/differential thermal analysis, differential scanning calorimetry, X-ray diffraction, sintered specimen, scanning electron microscopy, electrochemical impedance spectroscopy and UV-visible spectroscopy etc. (Scheme 61, 62 and 63).

Yongchun et al. [65] found the new method for nanoparticles through microwave-assisted, heating at

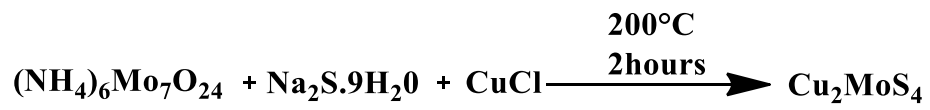
low temperatures, hydrothermal/solvothermal using solution-phase synthesis. The author applied different strategies to control the size, shape and dispersion of nanostructures. Here, some of the semiconductors such as Bi_2S_3 nanorods and Se nanowires are prepared with diethylamine or *n*-butylamine as a solvent using the hydrothermal technique.

3 Conclusion

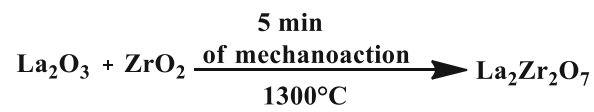
Combinatorial chemistry is an advanced method for the synthesis of several molecules and screening their pharmacological activity rapidly in the drug discovery process using solid- and solution-phase techniques over the past few decades. In a short period, lead identification and optimization have



Scheme 43 Synthesis of nanostructured lithium iron phosphate powders



Scheme 44 Synthesis of Cu_2MoS_4 nanoparticles



Scheme 45 Synthesis of nanocrystalline lanthanum zirconate

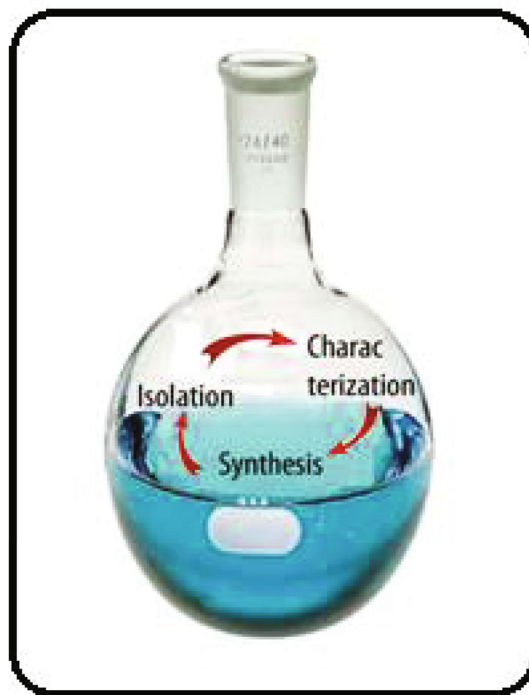
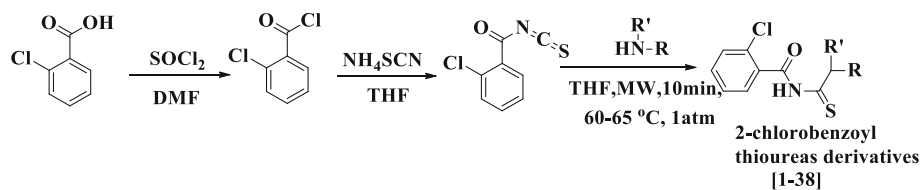
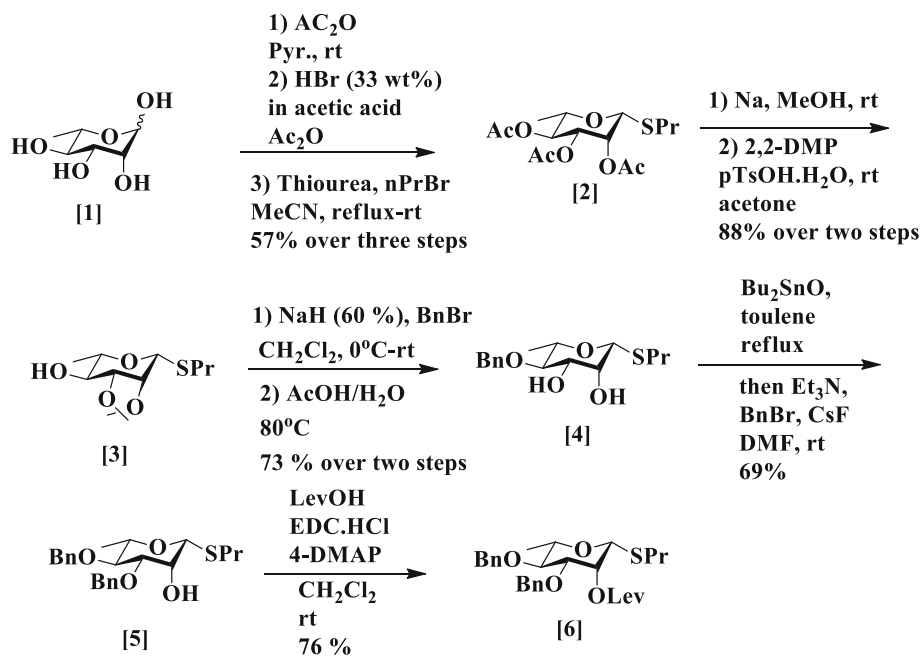


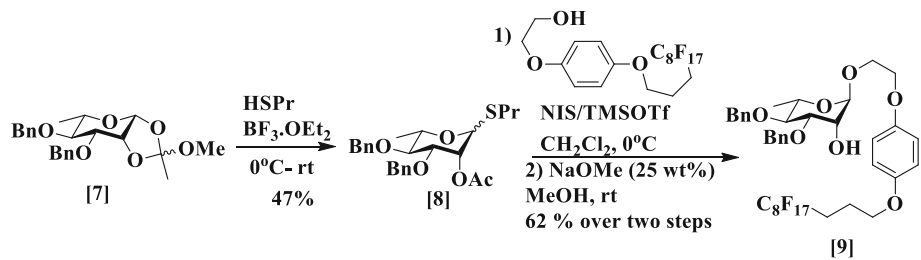
Fig. 4 Solution-phase synthesis



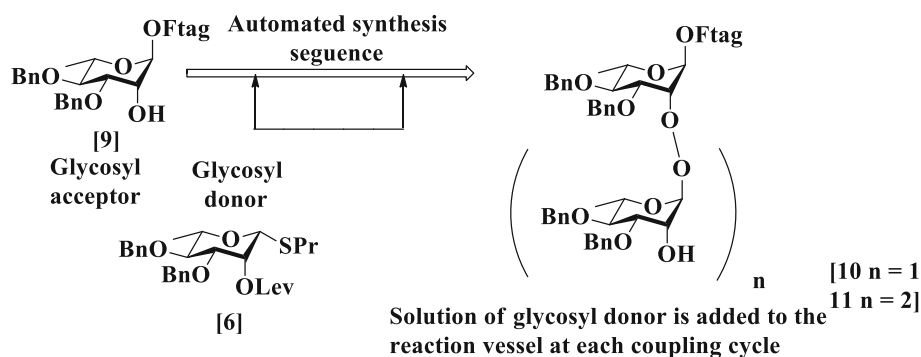
Scheme 46 2-chlorobenzoyl thiourea derivatives [1-37]



Scheme 47 Donor building block synthesis



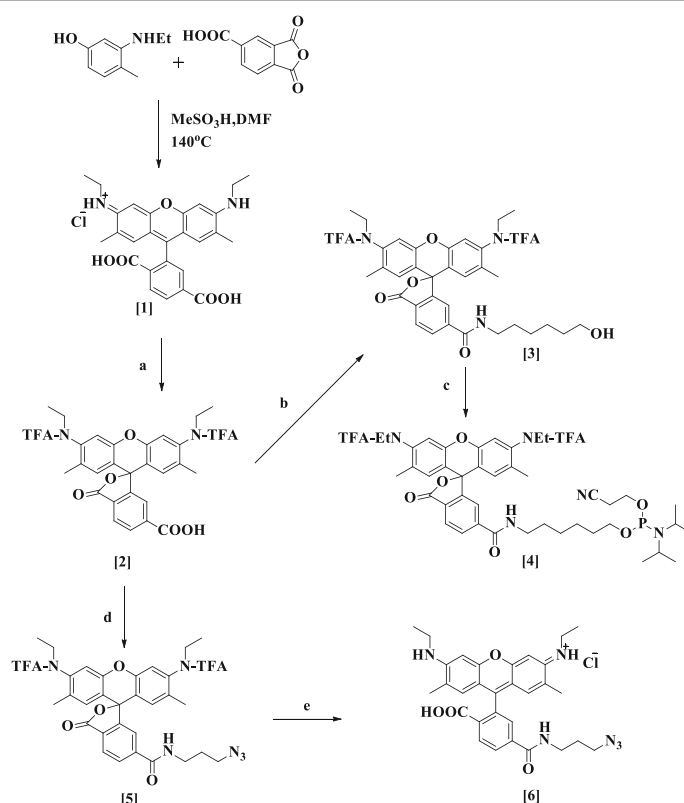
Scheme 48 Acceptor synthesis



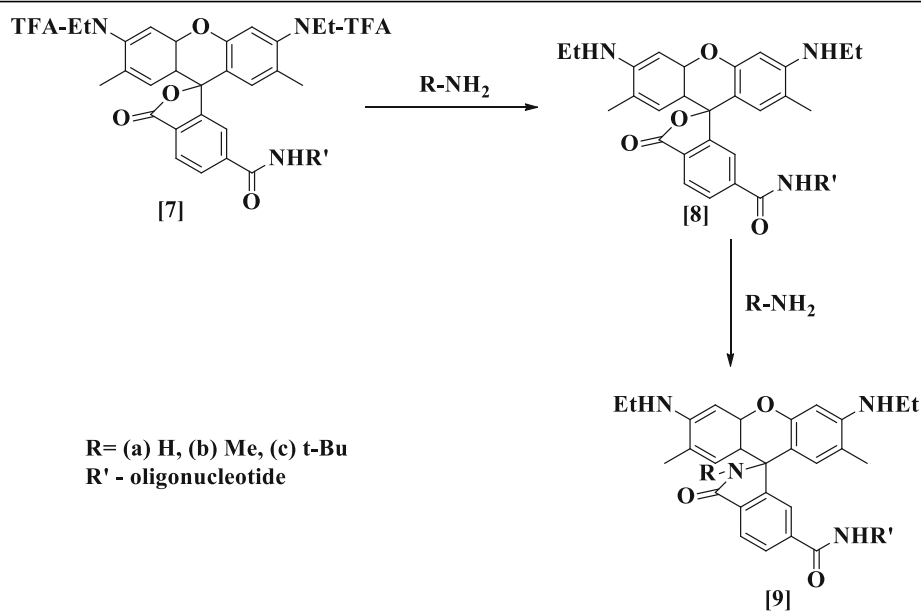
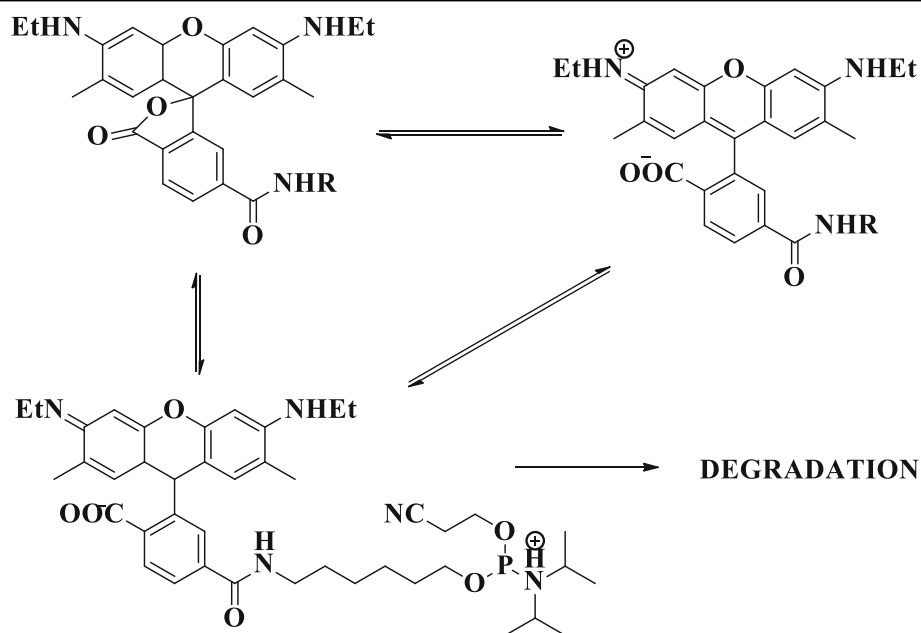
Scheme 49 Solution-phase automation

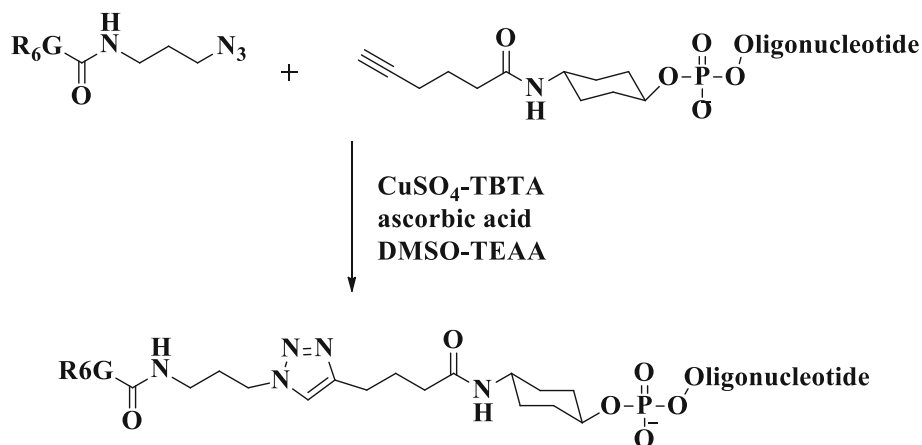
been taking place and accepted widely for the synthesis of peptides, oligonucleotides, organometallic, small proteins, non-oligomeric organic molecules, inorganic molecules and polymer chemistry. Considering all these features, many scientists employ this method for the preparation of medicinal compounds in recent days. The current review summarised a bunch of sixty-six research papers on combinatorial chemistry that witnessed the enormous growth in

the past two decades. However, to the best of our knowledge, these pieces of literature completely analysed the importance of combinatorial synthesis and furnished an overview on solid-phase and solution-phase techniques as well as helped mankind by improving higher productivity at low cost, lead identification and optimization and preventing environmental pollution.

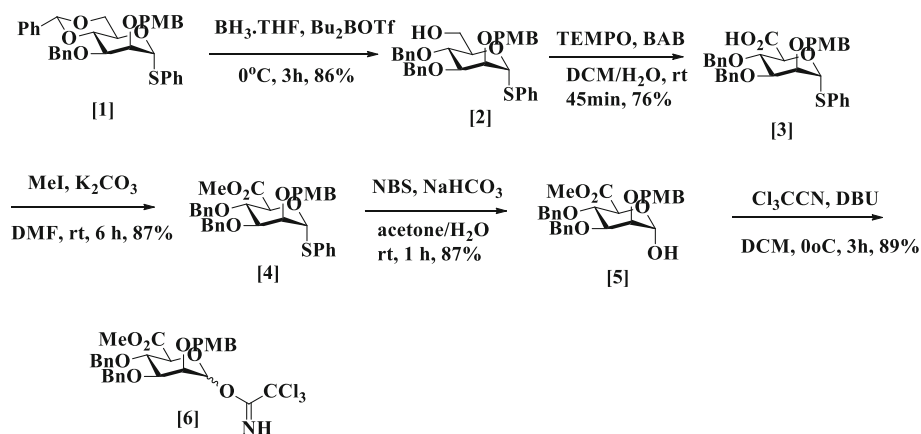


Scheme 50 Synthesis of R6G phosphoramidite 4 and 3-azidopropylamide [6]

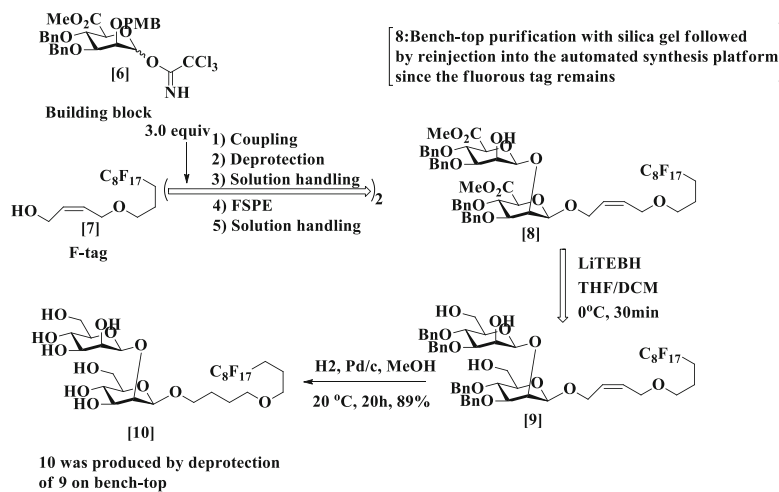




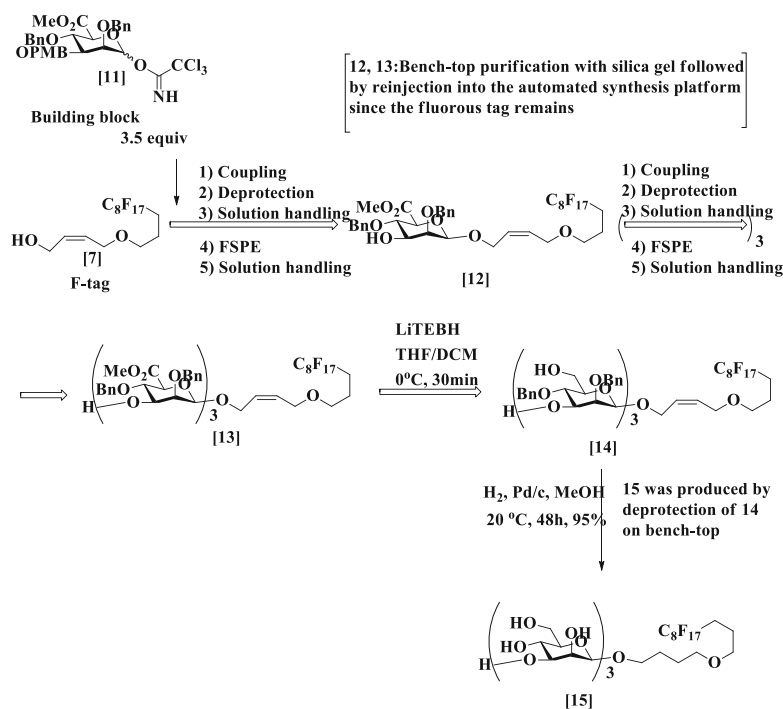
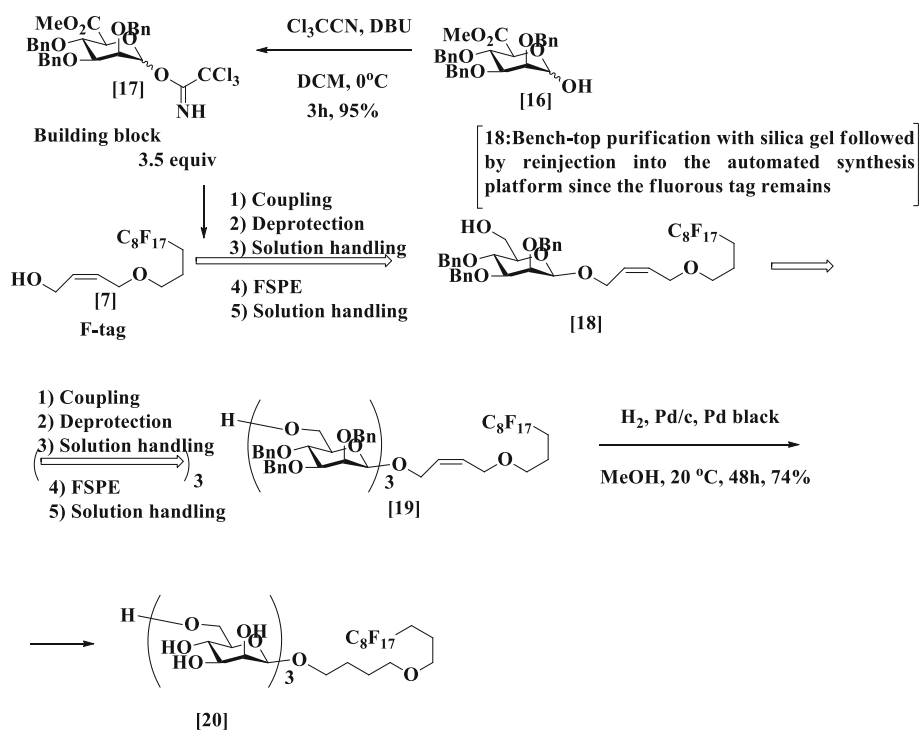
Scheme 53 Synthesis of R6G-labelled oligonucleotides by CuAAC

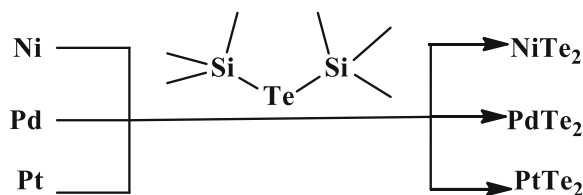
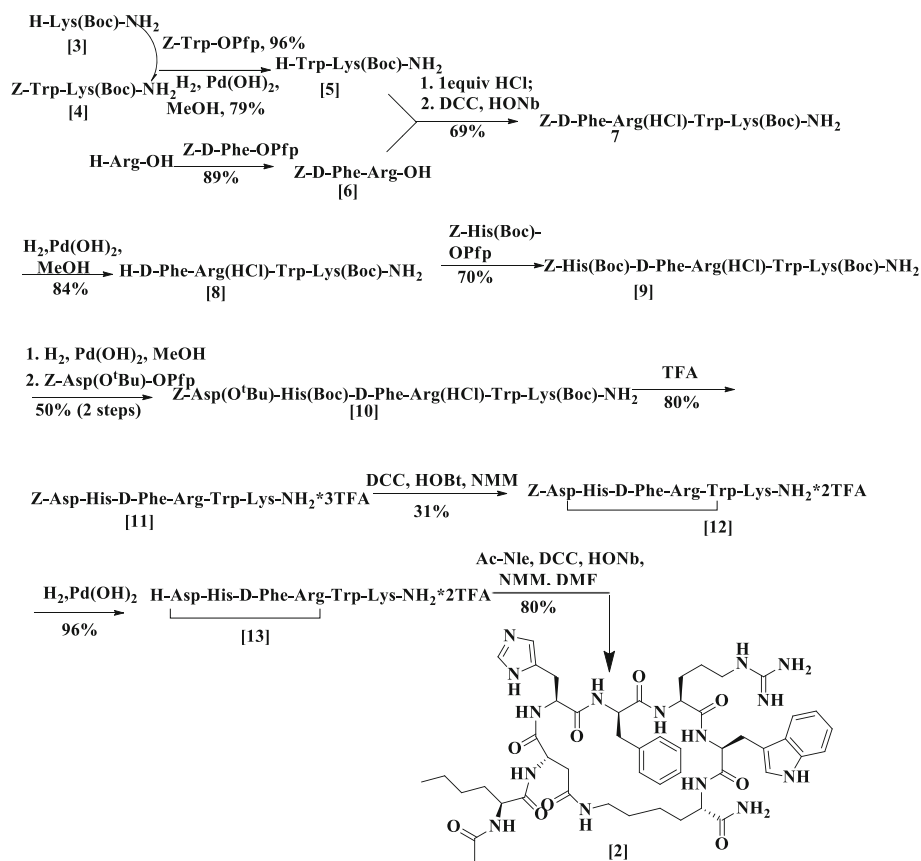


Scheme 54 Synthesis of building block 6 for the automated solution-phase synthesis of β -1,2-mannan



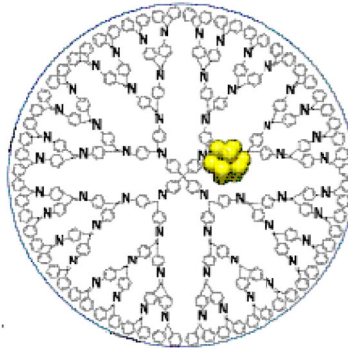
Scheme 55 Automated solution-phase synthesis of β -1,2-mannan 10

Scheme 56 Automated solution-phase synthesis of β -1,3-mannan 15Scheme 57 Synthesis of the trichloroacetimidate building block 17 and automated solution-phase synthesis of β -1,2-mannan 20



py-DPAGA + DPAGA

$\xrightarrow{\text{AlCl}_3}$



Scheme 60 Synthesis of Al_{13}^- superatom using dendrimer

Cerium (III) nitrate hexahydrate (aq.)

\downarrow H_2O_2

Orange-yellow cerium (IV) solution (A)

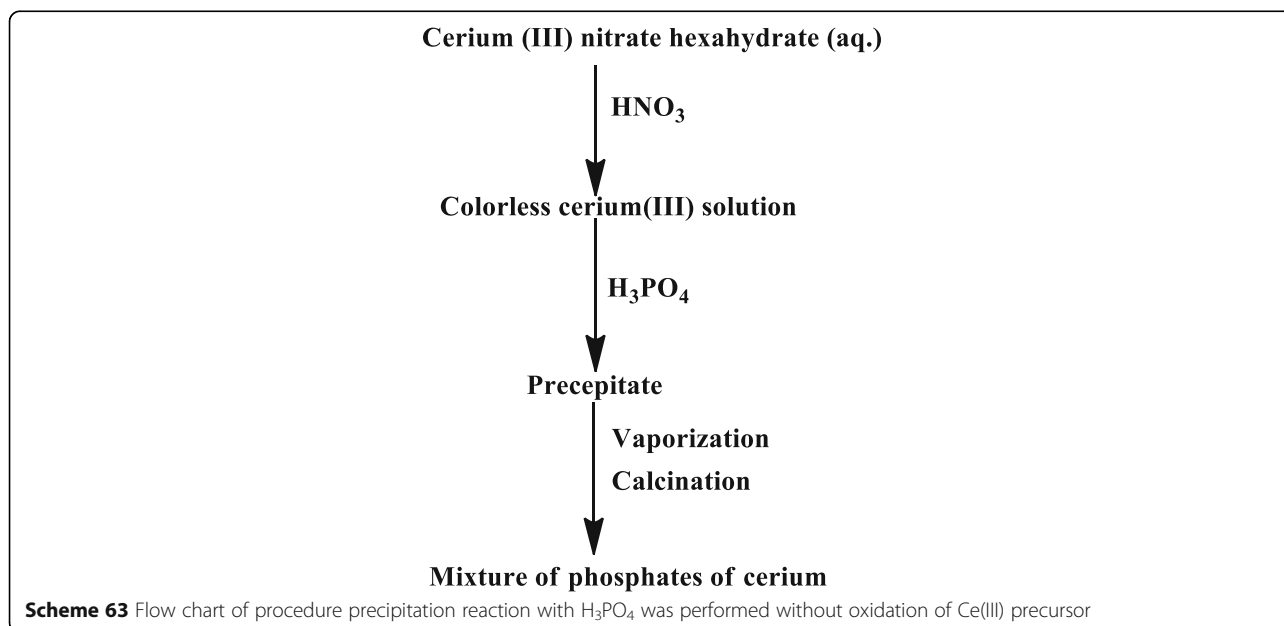
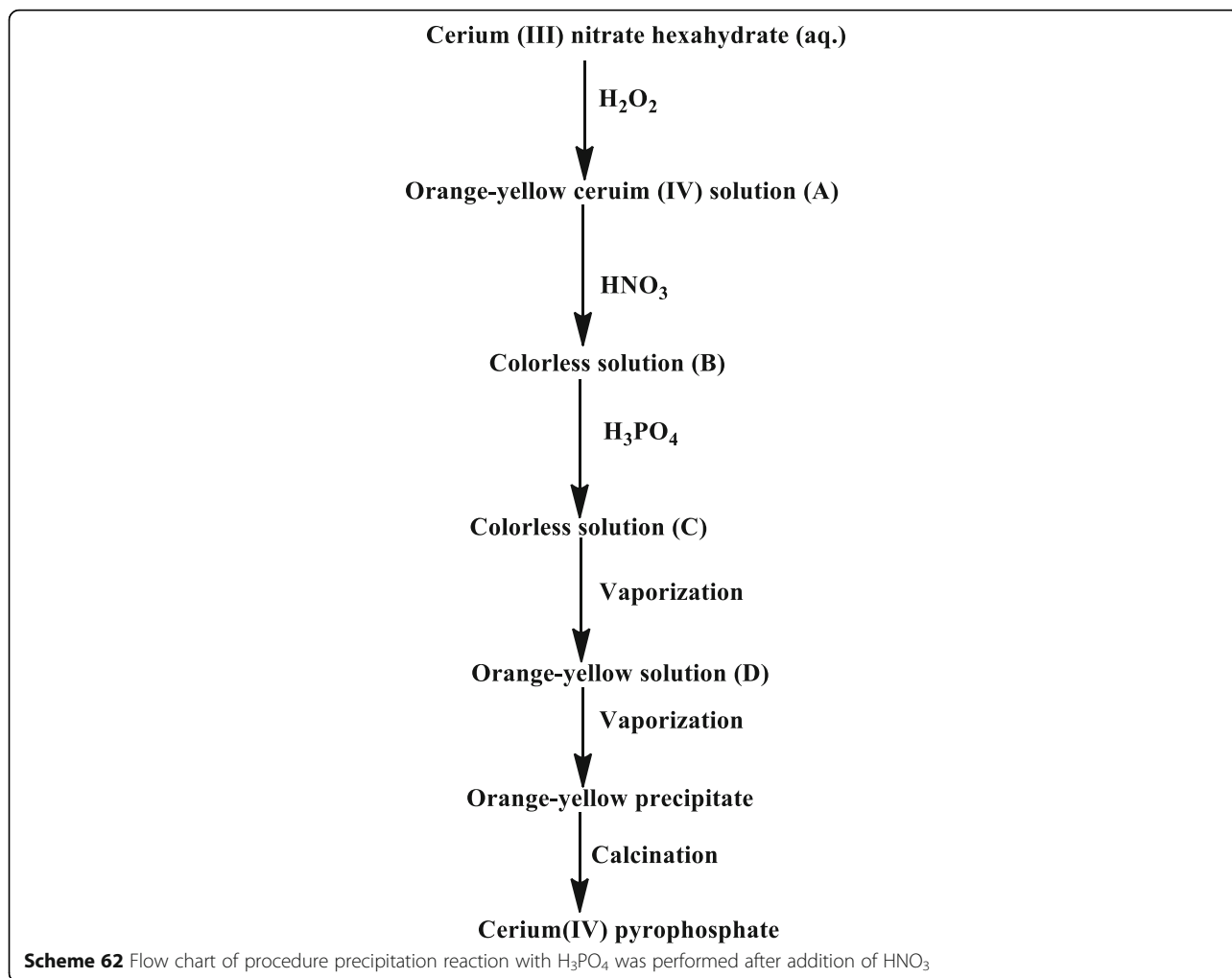
\downarrow H_3PO_4

Preprecipitate

\downarrow **Vaporization
Calcination**

Mixture of phosphates of cerium

Scheme 61 Flow chart of procedure precipitation reaction with H_3PO_4 was performed without the addition of HNO_3



Abbreviations

FT-IR: Fourier transform infrared spectroscopy; ¹H-NMR: Proton nuclear magnetic resonance spectroscopy; RP-HPLC: Reverse-phase high-performance liquid; ¹³C-NMR: Carbon-13 (C13) nuclear magnetic resonance; LiFePO₄: Lithium iron phosphate powders; FCNP: Fluorescent carbon nanoparticles; SPEPS: Solid-phase enzymatic synthesis; CPY: Carboxypeptidase Y; LaZr₂O₇: Nanocrystalline lanthanum zirconate

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Authors' contributions

CG designed the study and write the whole manuscript. GK and CSS contributed the major work in drawing the schem of the mentioned article and assisting to write the manuscript. MDD has analysing the data and structure the manuscript in a journal format. All the author read and approved the final manuscript.

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Availability of data and materials

All the data generated and analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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