Recent Advances in the Solid-Phase Combinatorial Synthetic Strategies for the Quinoxaline, Quinazoline and Benzimidazole Based Privileged Structures

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Abstract: Quinoxaline, quinazoline and benzimidazole based templates have been synthesized on solid-support employing different methodologies. This review enlightens academic and industrial examples of combinatorial synthesis for this type of heterocycles that appeared in the literature in the last decade. Hence, some of the important synthetic strategies for the generation of quinoxaline, quinazoline and benzimidazole based privileged structures, and the important biological activities for these heterocycles have been highlighted. Further, benzothiadiazinone, thioxoquinazolinone, cinnoline and indazole are also examined in this review.

INTRODUCTION

In recent years, the area of combinatorial chemistry has received much attention for the rapid generation of new drug-like heterocyclic scaffolds. Combinatorial libraries can be categorized into different classes based on their utilization, ranging from broad and diverse to focused and targeted libraries [1, 2]. The advances recently made in solid-phase organic synthesis (SPOS) have led to the success of combinatorial chemistry [3]. This has given an opportunity of preparing compounds by new routes [4], which is usually not that easy by employing conventional solution-phase procedures and eventually saving time for purification [5]. Therefore, generation of small molecule libraries derived from heterocyclic structures can be executed effectively by employing combinatorial or simultaneous parallel synthesis on solid-support [6-10]. The exploration of privileged structure in drug discovery process in medicinal chemistry has recently received much attention. These structures usually represent a class of molecules that are capable of binding to multiple receptors with high affinity [11, 12]. Therefore, the investigation of these molecules will allow the medicinal chemistry to rapidly discover biologically active compounds across a broad range of therapeutic areas on a reasonable time frame. Quinoxaline, quinazoline and benzimidazole based heterocyclic compounds comprise of some important privileged structures [13]. These frameworks are ligands for a variety of receptors and exhibiting diverse biological properties.

There are a large number of pharmacologically interesting molecules, where in a six membered ring containing two nitrogen atoms is fused to a phenyl ring. A large number of these compounds comprise of either quinoxaline (**I**), quinoxalinone (**II**), quinazoline (**III**), quinazolinone (**IV**), quinazolindione (**V**), benzothiadiazinone (**VI**), thioxoquinazolinone (**VII**) and cinnoline (**VIII**) ring system (Fig. (**1**)) and usually contain carbonyl functionality in which plays an important role for the biological activity.

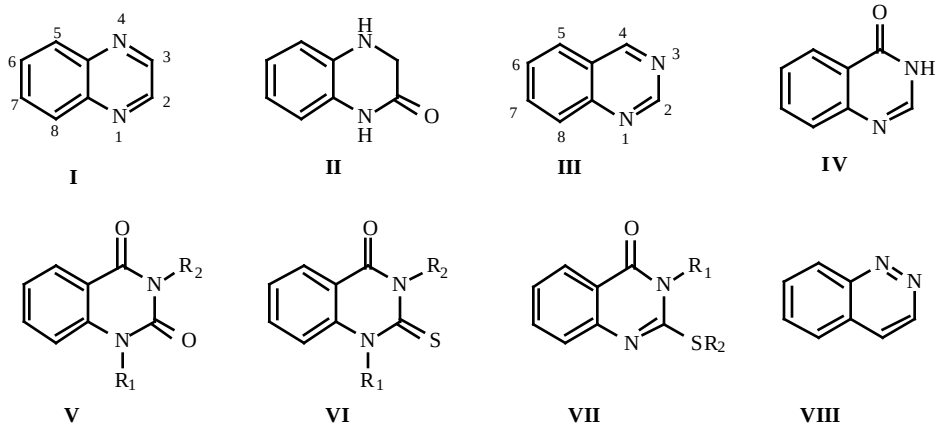

Fig. (1). Privileged substructures based on the quinoxaline (**I**) and quinazoline (**III**) framework.

QUINOXALINES

Quinoxaline (**I**) ring constitute an important part of different antibiotics namely, echomycine, levomycine and actinoleutin. These are known to inhibit the growth of gram-positive bacteria and are active against various transplantable tumors [14-16]. Interestingly, quinoxaline based compounds possess a broad range of biological activities such as

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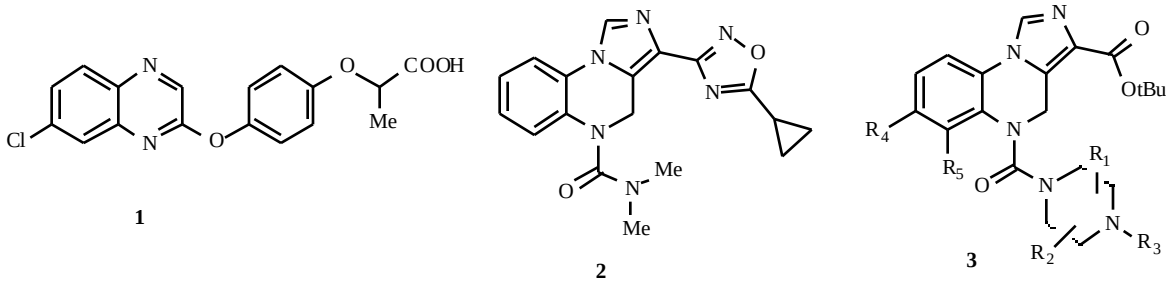


Fig. (2). Structure of biologically active quinoxalines.

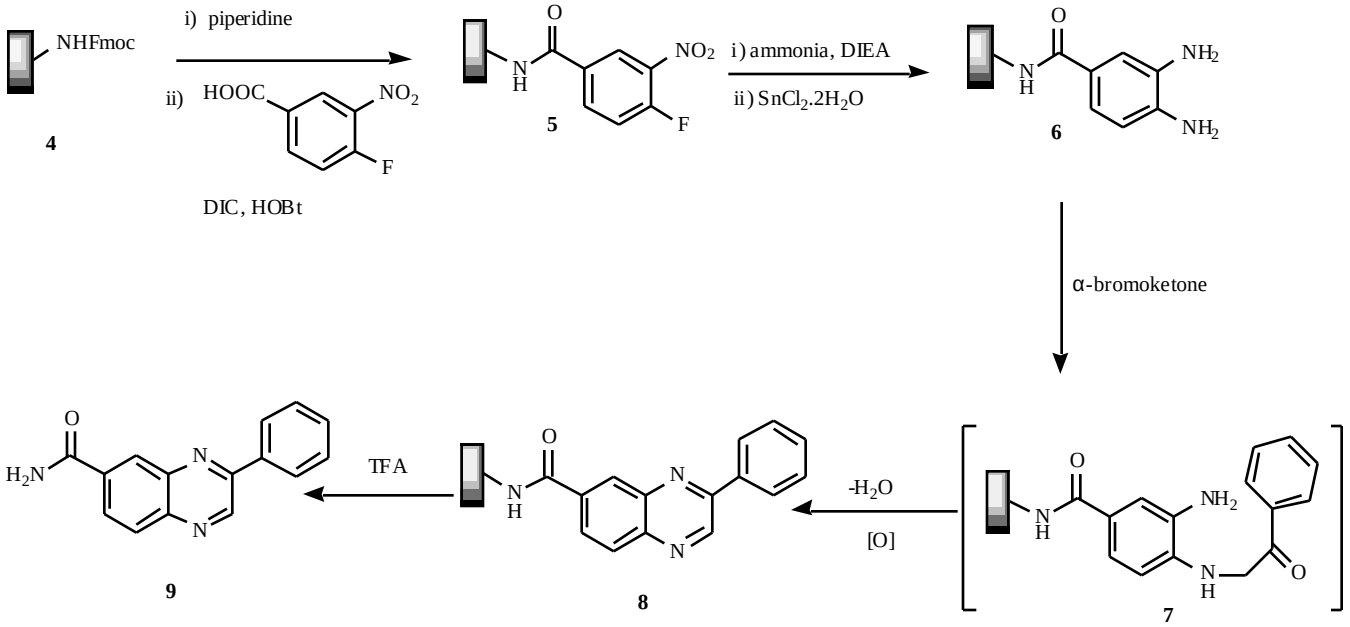
antimicrobial, antifungal, anticancer and antihelmentic [17-19] (Fig. (**2**)).

Wu and Ede [20] described a solid-phase synthesis of quinoxaline by employing polymer-bound *o*-phenylenediamine (**6**) and its reaction with α-bromoketones to produce quinoxaline (**9**) as shown in Scheme **1**. The use of polymer-bound 3-diazenylbut-2-enes as building blocks for the facile solid-phase preparation of quinoxaline derivatives has been reported by Santeusanio and co-workers and same group reported an improved synthesis for quinoxaline derivatives from N=N-polymer-bound 1,2-diaza-1,3-butadienes [21, 22].

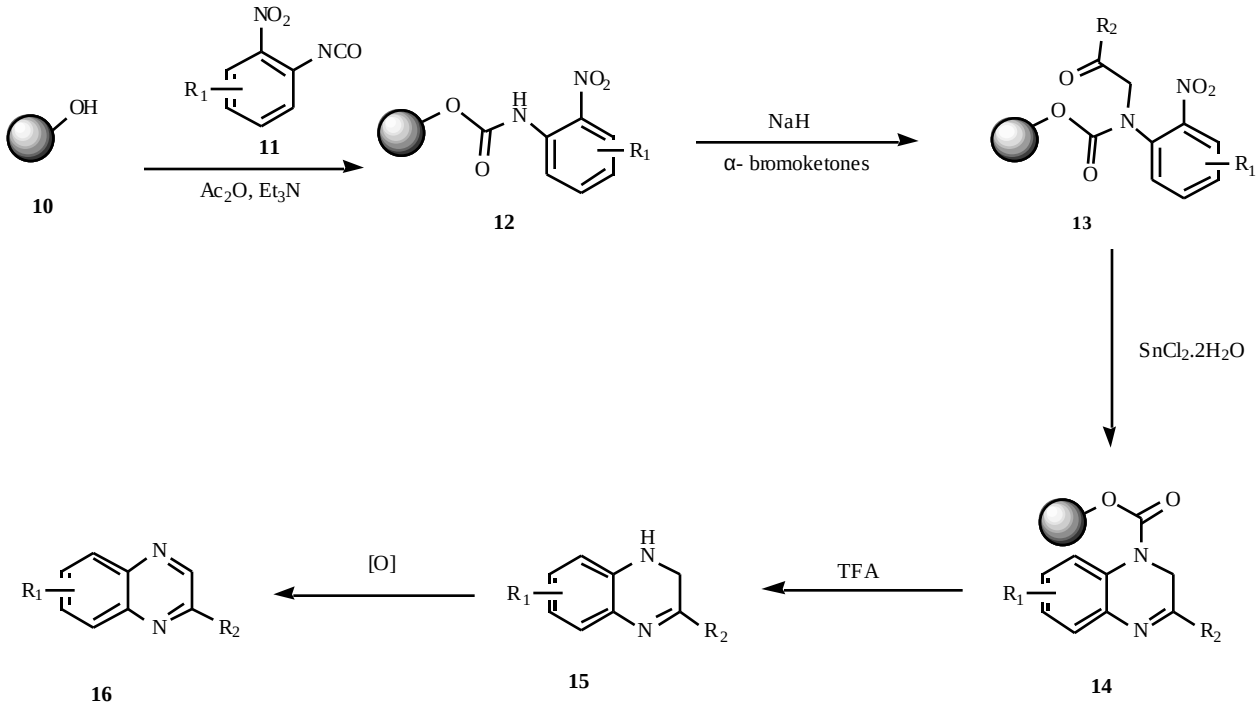
A recent report by Kundu and co-workers [23] on the solid-phase synthesis of quinoxaline (**16**) appears to be a versatile method. In this protocol, polymer-linked 2-nitrophenyl carbamate (**12**) is treated with α-bromoketones followed by reduction of the nitro group. After this reduction, spontaneous intramolecular cyclization takes place to give the polymer bound quinoxaline (**14**) through aerial oxidation. Further, this method is useful for the generation of libraries of quinoxaline ring system (Scheme **2**). An alternative strategy for Pictet-Spengler reaction between N1-substituted imidazole and aldehyde was used by the same group to synthesize a library of imidazoquinoxalines on solid support [24].

QUINOXALINONES

3,4-Dihydroquinoxaline-2-ones or benzopiperizinones are useful for the construction of small heterocyclic libraries particularly for the drug discovery programmes. These molecules posses broad spectrum of biological properties like inhibition of aldose reductase, partial agonists and antagonists of the γ-amino butyric acid (GABA)/benzodiazepine receptor complex. These compounds are also reported as multiple drug resistance antagonists, wherein they target drug transport proteins such as P-glycoprotein (Pgp) [25]. In view of the interesting biological activity of these compounds many groups have developed new solid-phase synthetic approaches for the quinoxalinone ring system. The construction of this ring system involves the use of *o*-fluoronitrobenzene as a common feature for some of the major solid-phase synthetic strategies. Lee and co-workers [26] developed the first solid-phase synthetic pathway involving Rink-amide resin and replacement of fluoro group of 4-fluoro-3-nitrobenzoic acid with different α-amino esters. These intermediates upon reduction of the nitro group facilitate cyclization to the quinoxalinone ring. Selective alkylation and subsequent cleavage of the resin produces the library. A similar protocol has also been reported by Corbett and co-workers [27]. Another similar methodology has been reported by aromatic nucleophilic substitution of the polymer linked *o*-nitro



Scheme 1. Solid-phase synthesis of quinoxalines on SynPhase Lanterns [20].

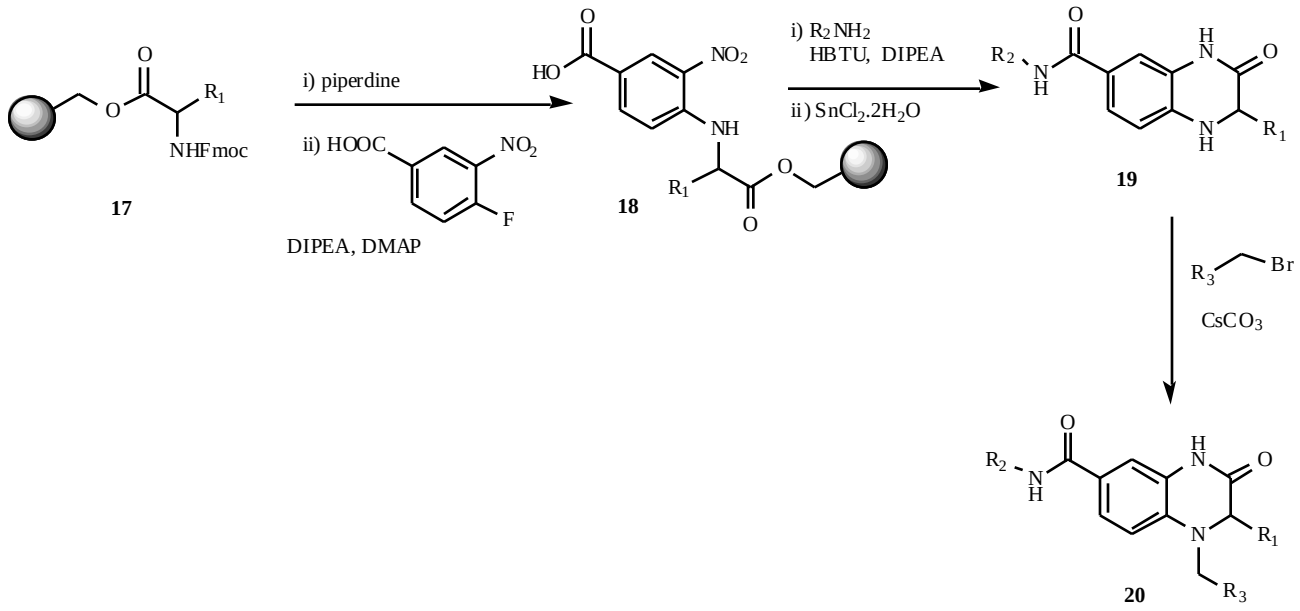


Scheme 2. Solid-phase synthesis of Quinoxalines [23].

benzene followed by reduction and subsequent double acylation to produce chloroacylated intermediate. This upon reaction with different nucleophiles lead to quinoxalinones [28]. Some more combinatorial approaches for the solid-phase synthesis of quinoxalinone have been reported employing principally the same strategy [29-33].

Laborde and co-workers [34] have synthesized 3,4,7-trisubstituted 3,4-dihydroquinoxalin-2-ones (**20**) on solid-phase by employing commercially available *N*-α-Fmoc-amino acids preloaded Wang resin (**17**) with 4-fluoro-3-nitrobenzoic acid and simultaneously treating with the different amines to produce desired nitro compound (**18**). After reduction of nitro group to afford the self-cleaved product (**19**). This upon treatment with different alkylating agents to afford the N4-alkylated product (**20**) (Scheme **3**).

Solid-phase synthesis of branched thiohydantoin tetrahydroquinoxalinediones (**21**) (Fig. (**3**)) has been described by combination of two methods. Namely, generation of thiohydantoins from resin bound dipeptides and heterocycles part from fluoronitrobenzoic acids [35]. Recently, Sun and co-workers described liquid phase synthesis of chiral quinoxalinones by microwave irradiation [36].



Scheme 3. Traceless, self-cleaving parallel solid-phase synthesis [34].

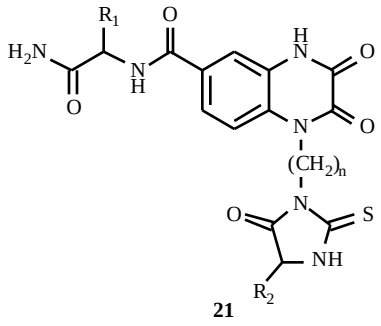


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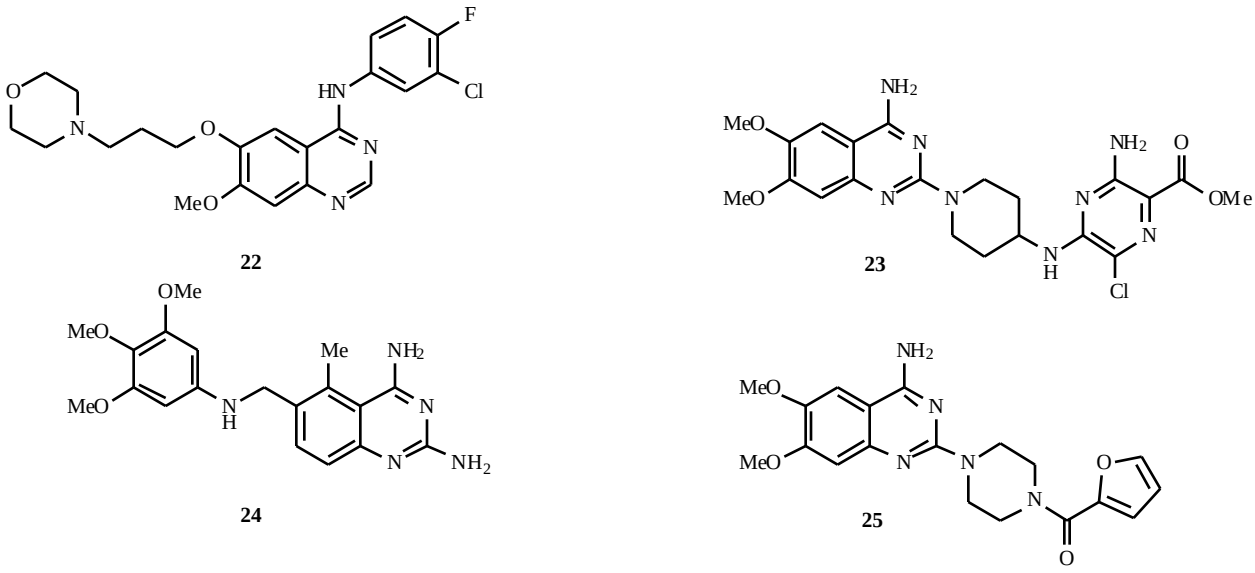
Fig. (3). Branched thiohydantoin tetrahydroquinoxalinediones [35].

QUINAZOLINE

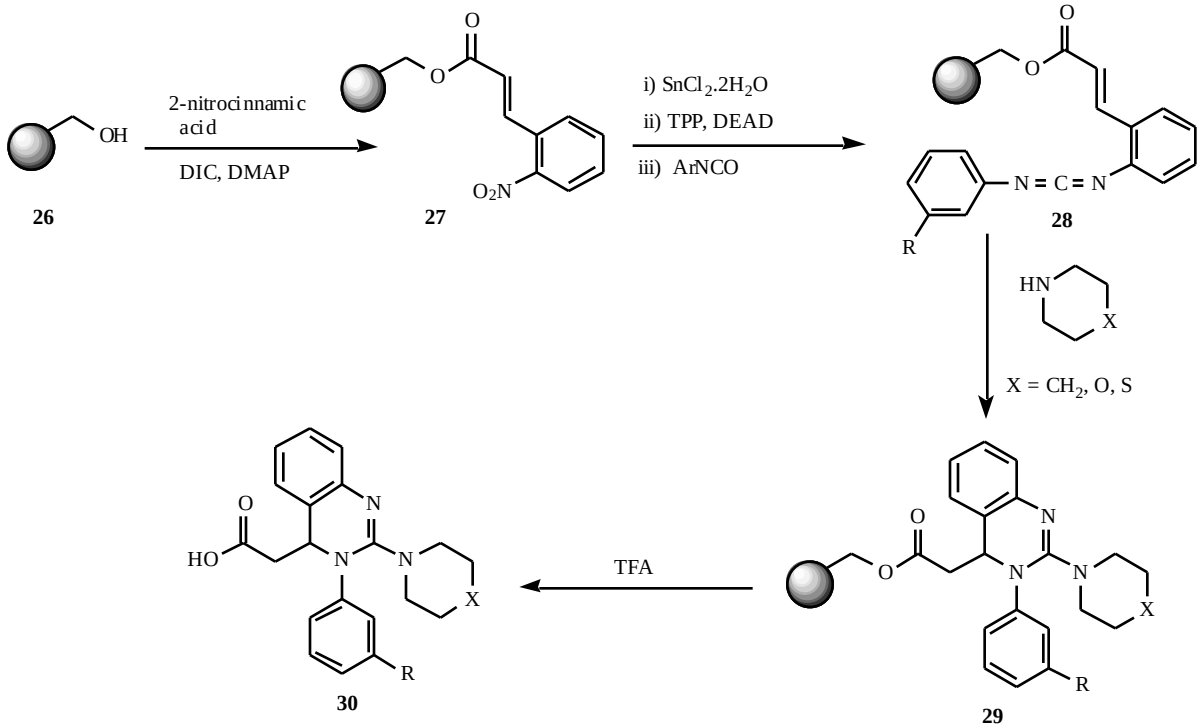
Quinazoline derivatives are attractive targets as they form an important component of pharmacologically active compounds, possessing a broad range of biological activity like antibacterial, antitumoral, treatment of pneumonia thrombocythaemia anticonvulsant and protienkinase inhibitors [37-39] (Fig. (**4**)).

Wang and Hauske [40] described the first solid-phase synthesis of 3,4-dihydroxy quinazolines employing an aryl iminophosphorane as the key intermediate. 2-Nitro cinnamic acid is loaded on the resin **26** and upon reduction provides an aniline that was converted to iminophosphorane under



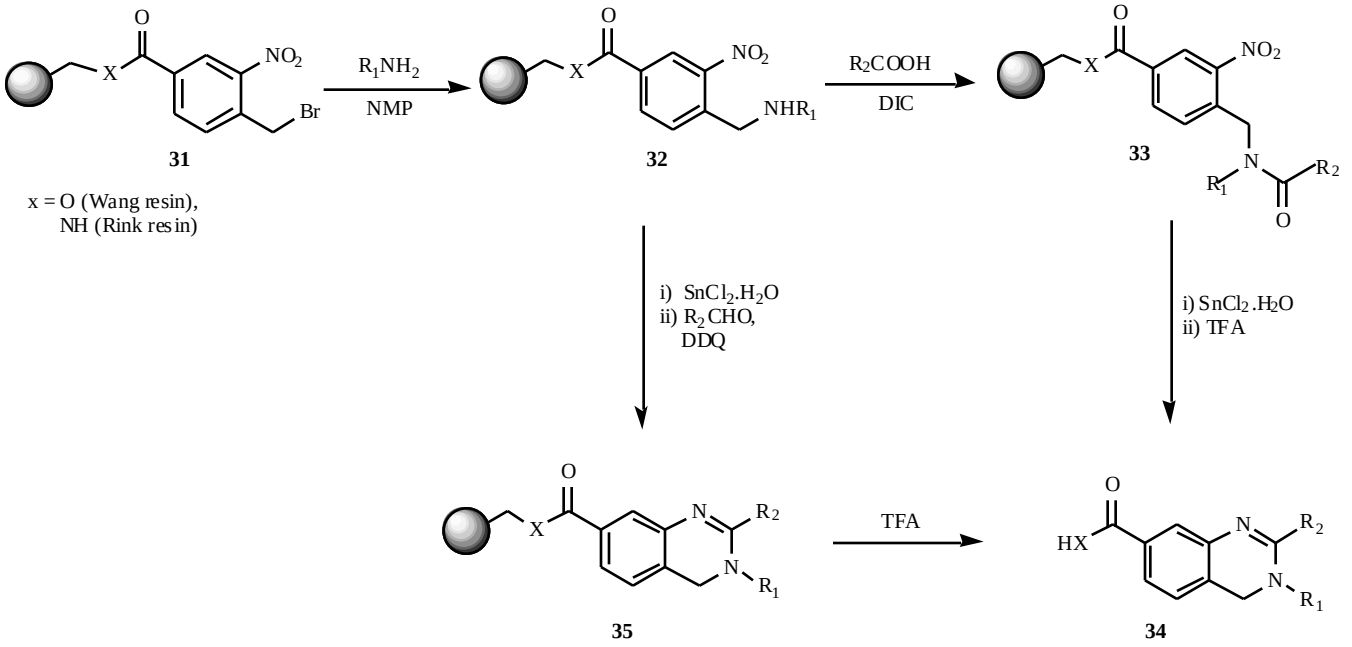
22 **23** **24** **25**

Fig. (4). Relevant molecules with quinazoline moiety.



26 **27** **28** **29** **30**

Scheme 4. Solid-phase synthesis of 3,4-dihydroquinazoline (**30**) [40].



Scheme 5. A novel method for solid-phase synthesis of 3,4-dihydroquinazoline [42].

Mitsunobu conditions. The resulting solid-supported cinnamyl iminophosphoranes has been treated with N-aryl isocyanate to generate corresponding solid-supported carbodiimide (**28**). This upon exposure to a secondary amine undergoes 1,2-addition followed by an intramolecular Michael addition to afford the desired 3,4-dihydroquinazoline (**30**) as shown in Scheme **4**.

Another approach [41] for the solid-phase synthesis of quinazoline has been carried out by attaching the resin bead to the heterocyclic nucleus. This strategy is useful for quinazolines that are unsubstituted at C2–position as the resin is cleaved from the C2–position. Recently Lou and co-workers [42] have developed a solid-phase method for the synthesis of dihydroqunazoline derivatives (**34**, **35**). Polymer-bound 4-bromomethyl-3-nitrobenzoate and the corresponding amide (**31**) are utilized as versatile process that undergo nucleophilic displacement with amines followed by reduction and cyclocondensation reactions provides the structurally diverse dihydroquinazolines (**34**, **35**) (Scheme **5**).

Solid-phase synthesis of 2,4-diaminoquinazolines (**36**) has been first reported by Wilson [43], that involves the sequential condensation of 2-aminobenzonitriles (**39**) and amines (**38**) starting from acyl isothiocyanate resin (**37**) via a traceless cleavage and cyclization (Fig. (**5**)).

Dener and co-workers [44] have also been reported a solid-phase synthesis of 2,4-diaminoquinazoline (**43**) starting from polymer bound amines (**40**). The key steps included, reaction of the polymer-bound amine (**40**) with 6,7-dimethoxy-2,4-dichloroquinazoline followed by the displacement of the second chlorine with an amine and subsequent cleavage to afford the product (**43**) as shown in Scheme **6**.

A general approach [45] for the solid-phase synthesis of various heterocycles has been investigated that includes quinazolines. In this strategy, a resin-bound nucleophilic amino group and primary amines is coupled to a (4-formyl-3,5-dimethoxy)methyl polystyrene resin (PAL-resin) by reductive amination. Recently, Kundu and co-workers developed a solid-phase synthesis for 3-substituted-2-amino quinazolines [46] by treating amino group of polymer linked amino acids (**45**) with 2-nitrobenzaldehyde (**46**) followed by reduction and cyclization to afford the desired quinazolines (**49, 50**). This protocol employed three type of resins namely RAM, non-proteogenic amino acids and α-amino acids (Scheme **7**). In a similar way, the same group described the

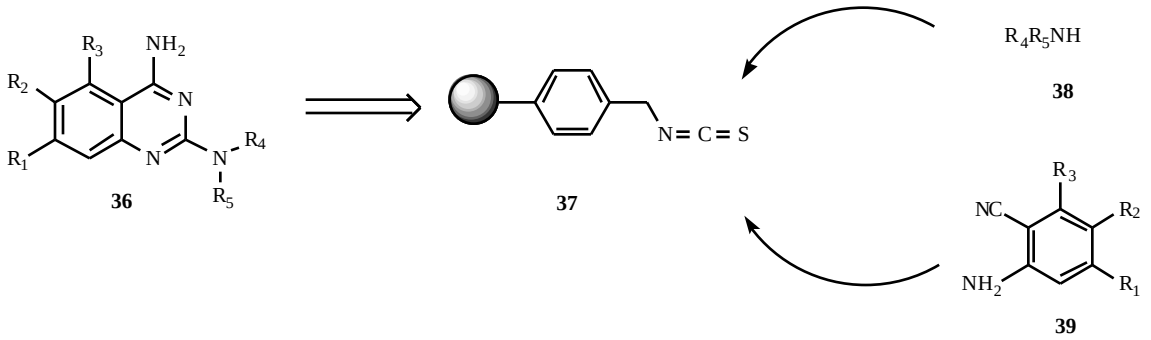
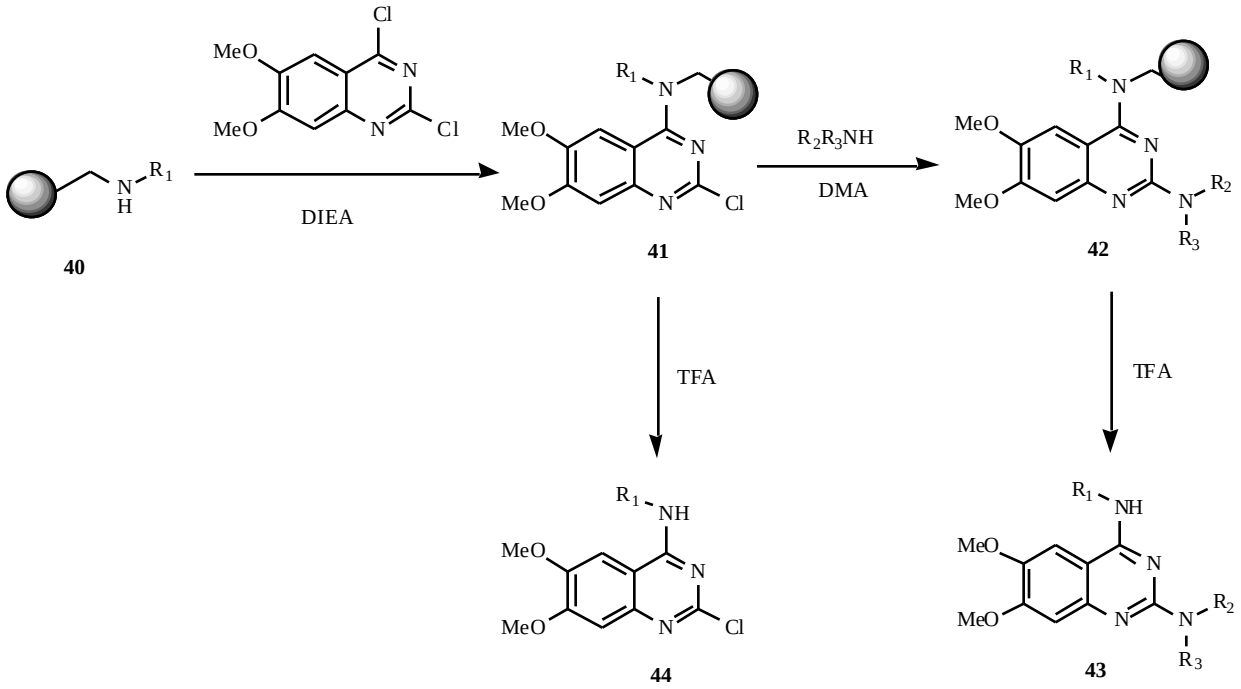


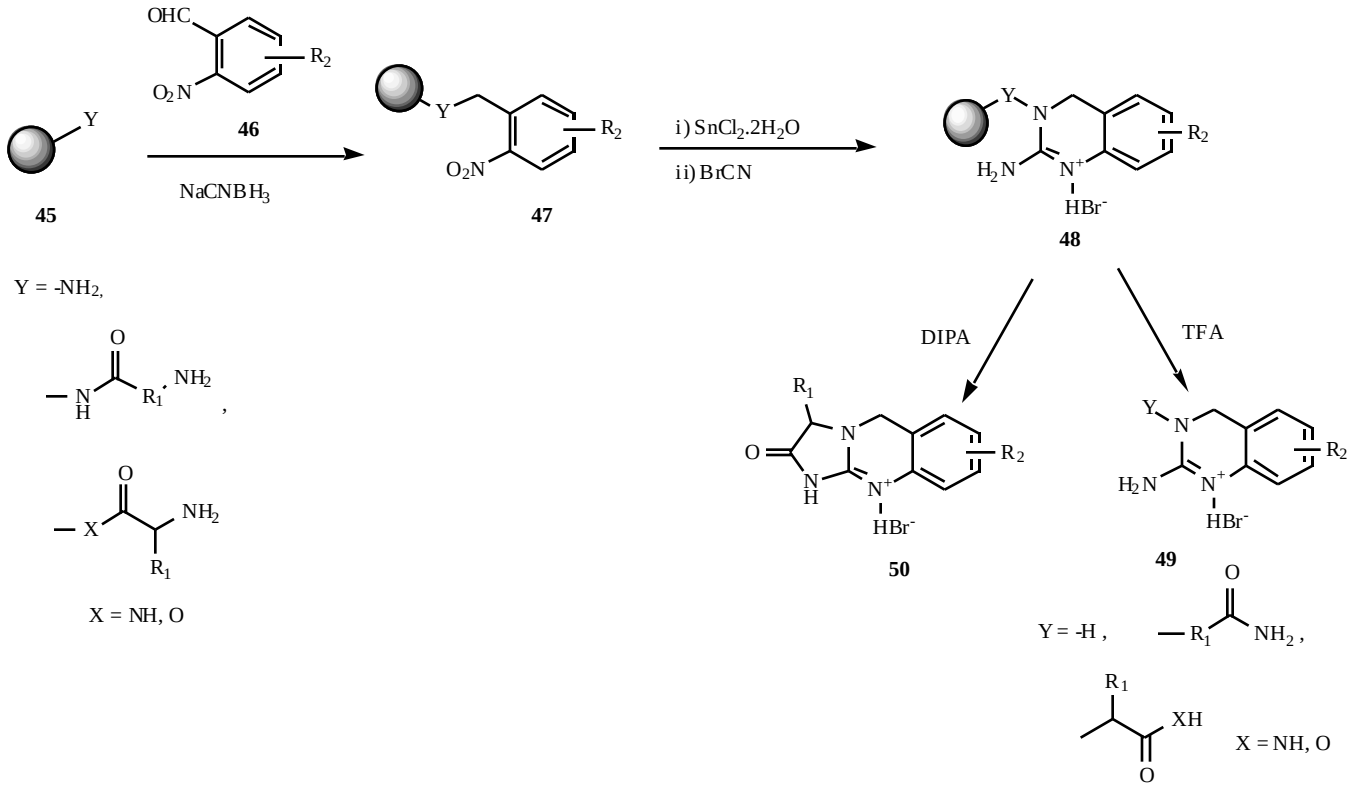
Fig. (5). Retrosynthesis of 2,4-diaminoquinazoline by Willson [43].



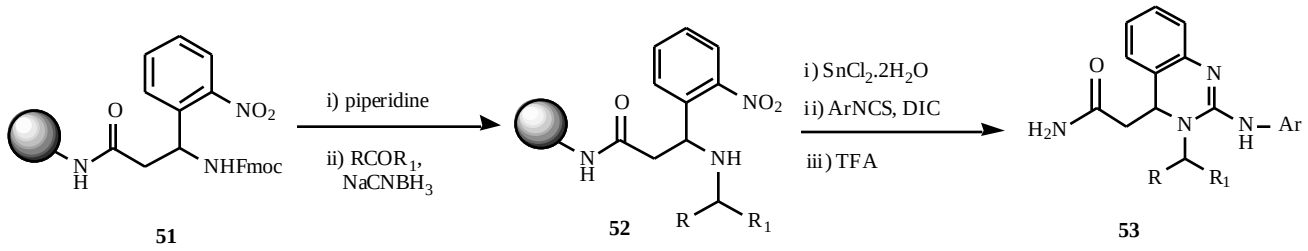
Scheme 6. Combinatorial library of 2,4-dihydroquinazoline from polymer-bound anilines [44].

solid-phase synthesis for imidazoquinazolinone derivatives with three point diversity [47].

3-Alkyl-2-arylamino-3,4-dihydroquinazolines have been prepared [48] on solid-phase using polymer-bound N-Fmoc-β-amino-2-nitro benzene propionic acid scaffold (**51**). This has reductively alkylated with aldehyde and ketones after Fmoc deprotection, followed by reduction of the nitro group. These upon cyclization with aryl isothiocyanates produce the quinazoline (**53**) after cleavage (Scheme **8**). Solid-phase synthesis of dihydroquinazolines using a tetra functional scaffold anchored to Rink resin via its carboxylic group has been reported by Lam and co-workers [49].



Scheme 7. Solid-phase synthesis of 2-aminoquinazolines from different amino group of polymer-linked amino acids by Kundu and co-workers [46].

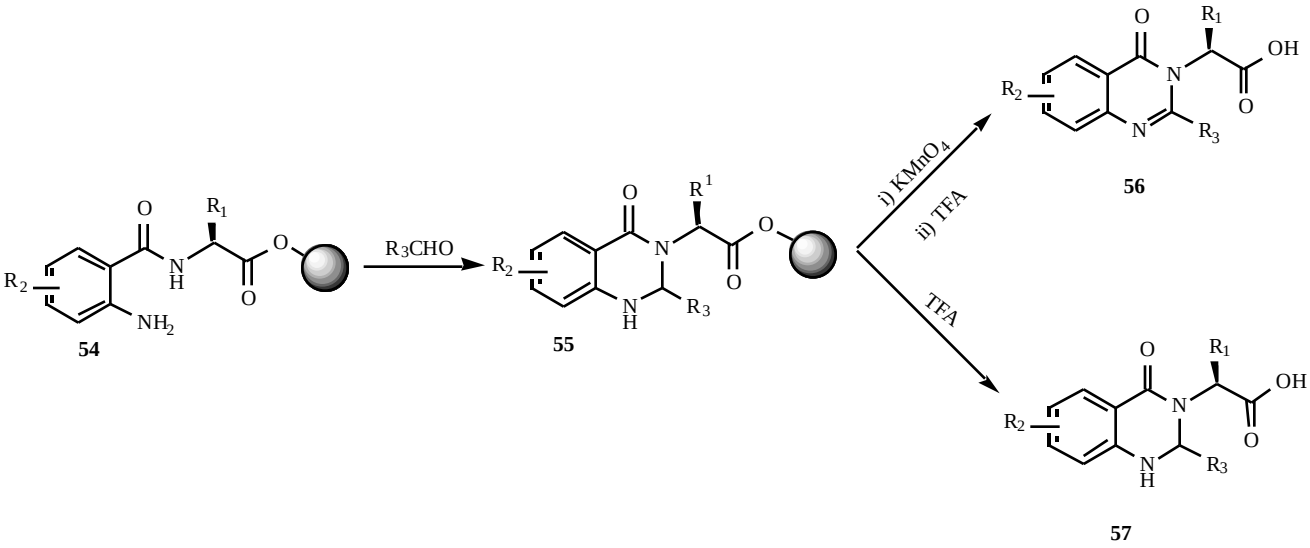


Scheme 8. A new solid-phase method for the parallel synthesis of 3-alkyl-2-arylamino-3,4-dihydroquinazolines (**53**) by Lam and co-workers [48].

QUINAZOLINONES

Quinazolinones (**IV**) like quinazoline (**III**) ring system has numerous applications in medicinal chemistry [50-52]. 2-Substituted quinazolinones have been utilized as peptidomimetic scaffold with specificity for cholecystokinin angiotensin and certain cell adhesion receptor [53-55]. Mayer and co-workers [56] reported the solid-phase synthesis of quinazolinones employing polymer-supported anthranilamide precursors (**55**) and aldehyde inputs. Dehydrogenation using potassium permanganate followed by cleavage afforded the quinazolinones (**56, 57**) (Scheme **9**).

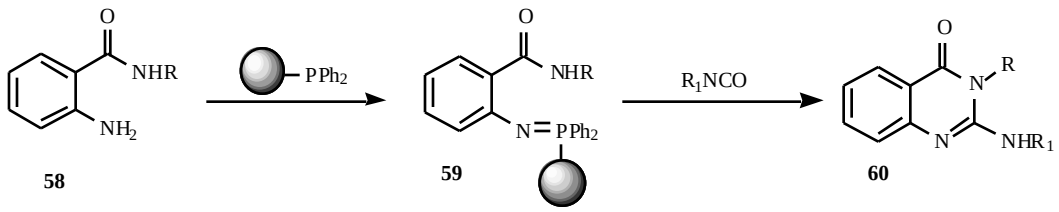
bound amino acids through alkylation, acylation and condensation reaction. Gopalsamy and Yang [60] described a solid-phase synthesis of 2-amino quinazolinones from a resin-bound amine component. In this protocol, the amine is readily converted to the corresponding polymer-bound *S*-methylthiopseudourea followed by condensation with different substituted isatoic anhydride. Solid-phase synthesis of 2-amino-4(3*H*)-quinazolinones has been described by the



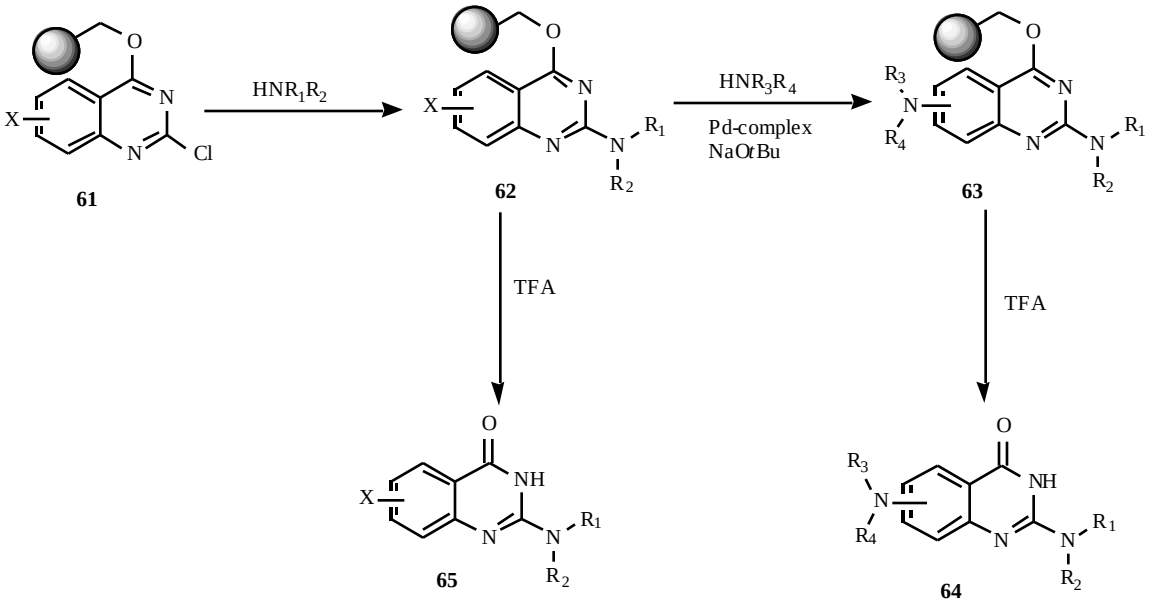
Scheme 9. A straightforward solid-phase synthesis of quinazolinones [56].

Another approach [57] based on an aza-Wittig mediated annulation has also been developed. Makino and co-workers [58] have synthesized a variety of quinazolinones by cyclocondensation of anthranilamides with a variety of orthoformates on solid-support. Solid-phase synthesis of quinazolinones has been described [59] by employing resin-reaction of polymer-bound isothiourea with isatoic anhydride [61]. A polymer-bound iminophosphoranes approach [62] has also been described for the synthesis of 2-amino-4(3*H*)-quinazolinone derivatives. This strategy employs an aza-Wittig reaction followed by the reaction of the iminophosphoranes (**59**) with alkylisocyanates (Scheme **10**). However, the usefulness of this process is depending on the availability of the substituted isocyanates.

Similar methodology has also been described in the literature for solid-phase synthesis of 2-amino



Scheme 10. Solid-phase synthesis of 2-amino-4(*H*)-quinazoline-4-ones [62].



Scheme 11. 2,6- and 2,7-diamino-4(3*H*)-quinazolinones (**64**) combinatorial library [67].

quinazolinones [63, 64]. Kundu and co-workers developed a versatile approach for the synthesis of quinazolin-4(3*H*)-ones from polymer-bound arylguanidines with three point diversity and it can be used for the generation of libraries of quinazolin-4(3*H*)-ones [65]. Makino and co-workers have developed a solid-phase synthesis of 2-amino quinazoline-4-one from various resin bound anilines incorporating the nitrogen atom of anilines in the quinazolinone ring [66].

Solid-phase synthesis of 2,6- and 2,7-diamino-4(3*H*)-quinazolinone via palladium catalyzed amination (Scheme **11**) based on the coupling of dichloroquinazoline derivatives (Scheme **6**) is also described [67].

Hattori and co-workers [68] have prepared quinazolinone analogues by employing the substituted anthranilic acids with Rink-amide resin.

QUINAZOLINDIONES

Quinazoline-2,4-diones (**V**) are one of the most attractive pharmacophores and represent for a wide range of pharmacological activity like quinazolinone. These exhibit anticonvulsant, sedative, hypotensive and antiinflammatory activity [69-71]. They are known to interact with many G-protein coupled receptors, including adrenergic, serotonergic, dopaminergic, and endothelin (ET_A) receptors [72, 73]. Further, this scaffold is extremely important as it inhibits a number of enzymes, including cyclooxygenase, collagenase, aldose reductase and carbonic anhydrase [74]. These molecules also show potential as coagulants, as they are fibrinogen receptor antagonists [75]. The basic strategy that has been employed for the combinatorial synthesis of quinazoline-2,4-diones usually involves the ring closure

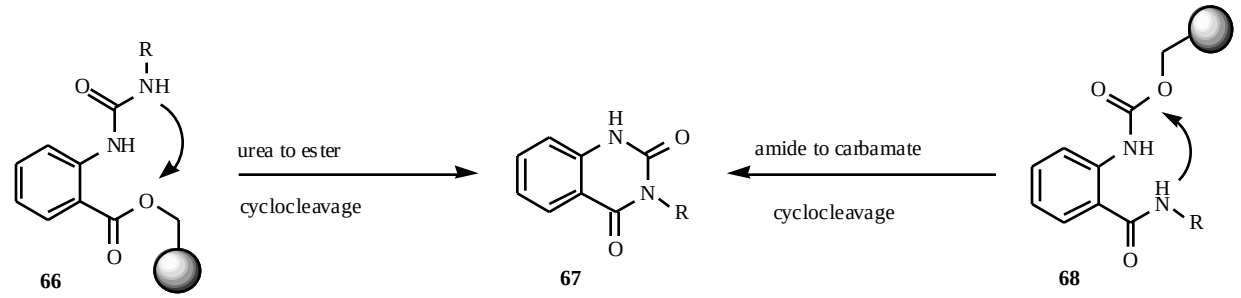
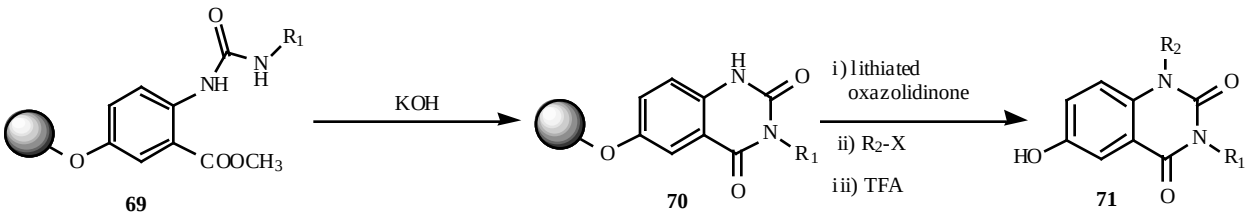
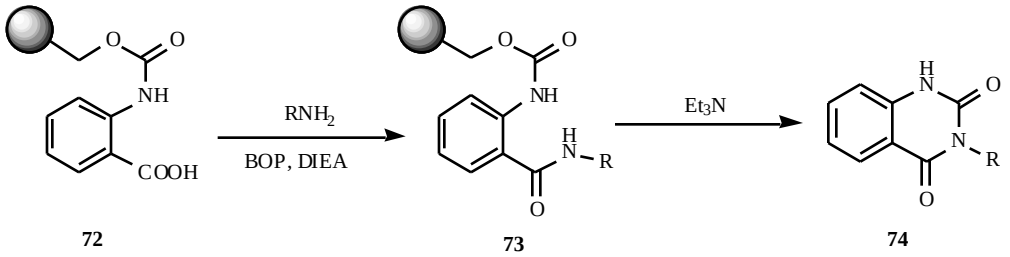


Fig. (6). Cyclocleavage approches for quinazolindiones [72].



Scheme 12. Combinatorial library synthesis of 1,3-dialkyl quinazoline-2,4-diones [76].



Scheme 13. Solid-phase synthesis of quinazoline -2,4-diones [77, 78].

process (Fig. (**6**)) by the attack of an amine to the ester functionality [72].

Buckman and Mohan [76] are the first to develop a solid-phase synthesis of quinazoline-2,4-diones (**V**) that consists of three carbon-nitrogen bond forming reaction on polymer-bound anthranilate (**69**), that is formation of urea, intramolecular cyclization induced by a base and N-alkylation (Scheme **12**).

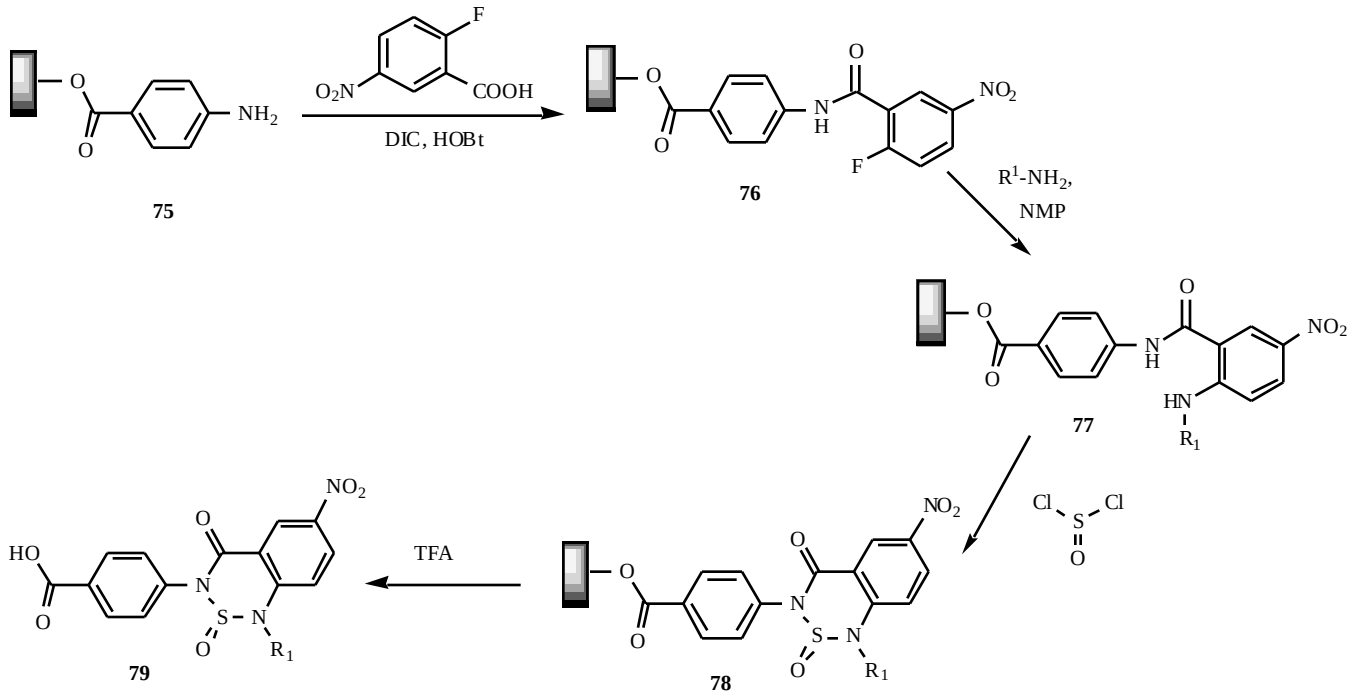
A modified method for the solid-phase synthesis of chiral 3-substituted quinazoline-2,4-diones *via* N-terminal amino group linkage to the solid support (**73**) followed by base catalyzed cyclization and cleavage strategy (Scheme **13**) has been developed [77, 78].

Smith and co-workers developed a solid-phase synthesis for 1,3-disubstituted quinazolinediones [73]. Choo and co-workers adapted the same strategy in the preparation of 3-aryl-2,4-quinazolindiones with various substitutions on aromatic rings [79]. Makino and co-workers have reported 1,3 N-disubstituted quinazoline-2,4-diones [80] by reaction between primary amines and 2-fluoro-5-nitrobenzylamines (S_NAr reaction). They have also described solid-phase synthesis of quinazoline-2,4-diones with various substituents on the aromatic ring [81].

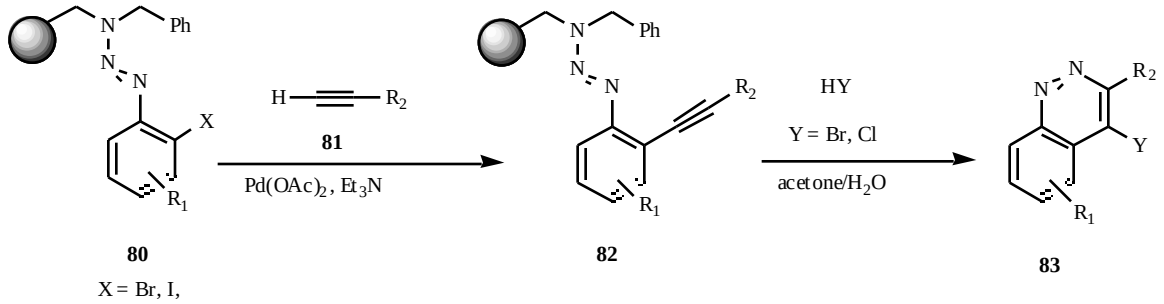
BENZOTHIADIAZINONE AND THIOXOQUINAZOLINONE

The substituted benzothiadiazinone and thioxoquinazolinone moieties showed interesting bioactivities, such as bone regeneration [82], prolylendopeptidase inhibition [83]. The structural similarity of 1,2,4-benzothidiazin-3-one 1,1-dioxide to other important pharmacophores such as quinazoline-2,4-diones [77, 78], 4-quinazolinones [56, 58] and 2-thioxoquinazoline-4-ones [84, 85]) is fascinating from the viewpoint of new drug discovery.

Makino and co-workers reported the first solid-phase synthesis of 2-substituted-3-(substituted sulfanyl)-1,2,4-benzothiadiazine 1,2-dioxides [86] and the same group reported synthesis of 1,2,4-benzothiadiazin-3-one 1,1-dioxides on solid-support [87]. Similarly, they have also reported synthesis of 2,1,3-benzothiadiazin-4-one 2-oxides using SynPhase Lanterns [88]. SynPhase Lantern bearing 4-aminobenzoic acid ester (**75**) was reacted with 2-fluoro-5-nitrobenzoic acid to obtain the linked amide (**76**). S_NAr type reaction was performed by treating (**76**) with various primary amines to give **77** and cyclization of **77** using thionyl chloride affords the Lantern bearing final product **78** followed by cleavage to provides **79** (Scheme **14**).



Scheme 14. Synthetic scheme for 2,1,3-benzothiadiazin-4-oxides [88].



Scheme 15. Solid-phase synthesis of cinnolines (**83**) [90].

Makino and co-workers have developed a strategy for the solid-phase synthesis of quinazoline-2-thioxo-4-ones by treating amines with 2-methoxycarbonylphenyl isothiocyanate [84]. Furthermore, the same group described [85] a synthetic strategy on solid-phase for the synthesis of 1,3-disubstituted 2-thioxoquinazoline-4-ones that could not be synthesized with the previous reported method [84]. In this process, the key reaction step is the reaction between 2-fluoro-5-nitrobenzoic acid and the Lantern bearing amine.

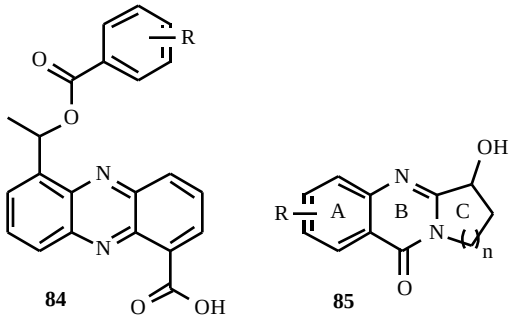


Fig. (7). Saphenamycin and pyrrolo[2,1-*b*]quinozoline structures.

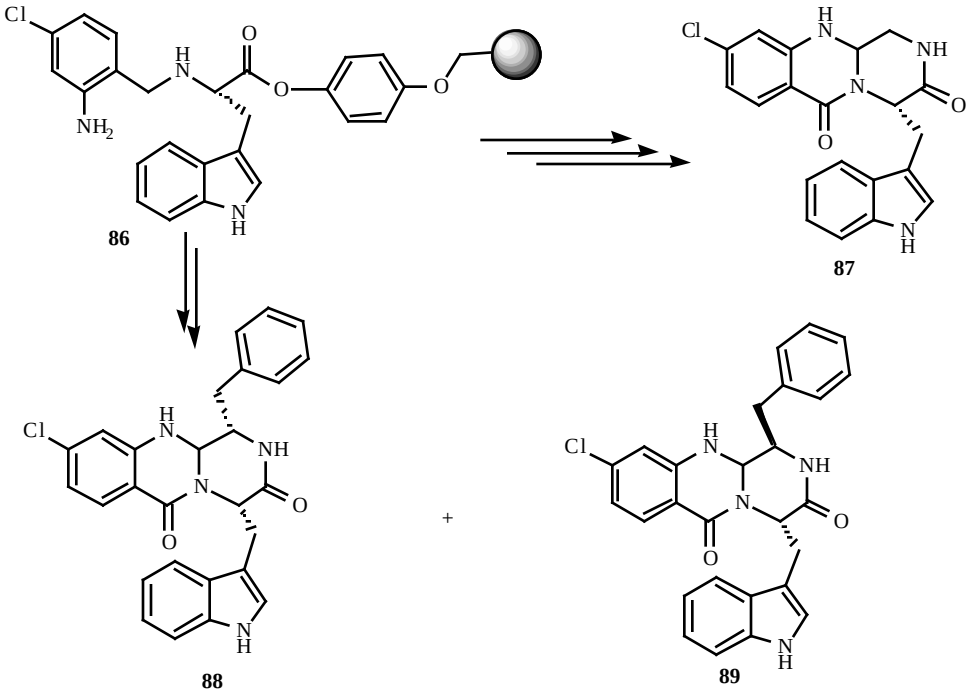
CINNOLINES AND PHTHALAZINES

Polycyclic nitrogen heterocycles like cinnolines (**VIII**), indolocinnolines are considered as good pharmacophores for the antineoplastic activity due to that ability to bind the DNA [89]. Brase and co-workers [90] have described a solid-phase synthesis by employing triazine bound orthohalo arenes (**80**) on a solid-support followed by cross coupling reaction with the alkynes (**81**) catalyzed by palladium. Finally, Richter type cleavage reaction produces the cinnoline ring system (**83**) as shown in Scheme **15**. Gong and co-workers described a synthetic strategy for the solid-phase synthesis of phthalazine derivatives [91].

FUSED QUINOXALINES AND QUINAZOLINES

Benzofused quinoxalines like saphenamycin (**84**) derivatives has been prepared on solid-phase. The key step is a chemoselective anchoring of saphenic acid through the carboxyl group to a 2-chlorotrityl functionalized polystyrene resin [92].

Solid-phase synthesis of pyrazine[2,1-*b*]quinazoline-3,6-diones fumiquinazoline scaffold (**87, 88, 89**) has been



Scheme 16. Fumiquinazoline alkaloids synthesized on solid-support [93].

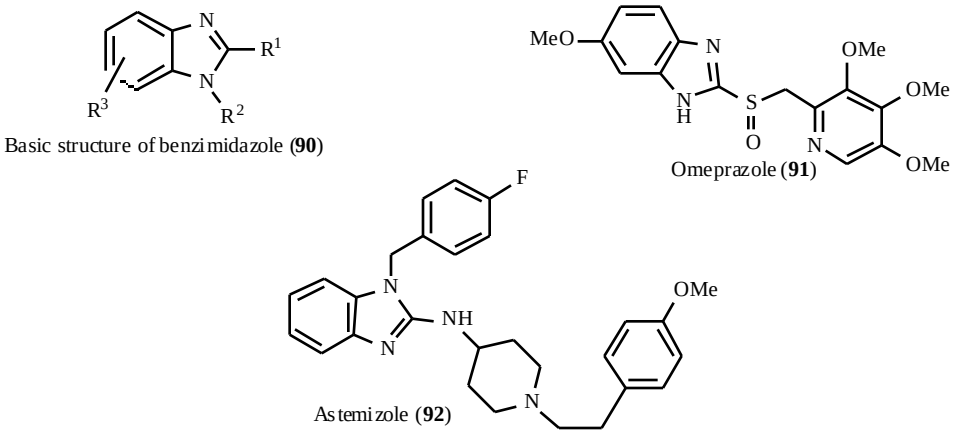


Fig. (8). Biologically important compounds with a benzimidazole scaffold.

described in four steps by Ganesan and Wang (Scheme **16**) [93]. Synthesis of pyrrolo[2,1-*b*]quinazoline alkaloids by azido reductive cyclization strategy employing polymer-supported reagents have been developed [94] and the generation of large libraries with diversity in A and C rings is under investigation (Fig. (**7**)).

BENZIMIDAZOLES

Benzimidazole ring represents an important heterocyclic pharmacophore in medicinal chemistry. These compounds have shown diverse biological activity including anticancer, antiviral and antiulcer properties [95-98]. Omeprazole (**91**), a proton pump inhibitor and astemizole (**92**), an antihistamine drug represent some notable examples that are in clinical usage (Fig. (**8**)).

Compounds based on this heterocyclic system have also exhibited diverse biological activity including α-receptor stimulation, vasodepressor activity, α-adrenergic inhibition, cholenomimetic activity and antihyperglycemic activities [99].

In the solid-phase synthesis of benzimidazoles (**96**), three type of strategies have been employed for the construction of the five membered ring. In the first type, the polymer-supported resin is attached to the carboxylic acid group of 4-fluoro-3-nitro benzoic acid (**93**). In the second type of strategy, the resin is attached to the amino group of 2-nitro anilines (**94**), while in the third strategy the resin is linked to the C2-carbon fragment (**95**) as shown in Fig. (**9**).

STRATEGY I

Phillips and Wei reported [100] one of the first solid-phase syntheses of benzimidazole from polymer-bound *o*-fluoronitroaromatic compound (**97**) is treated with an amine

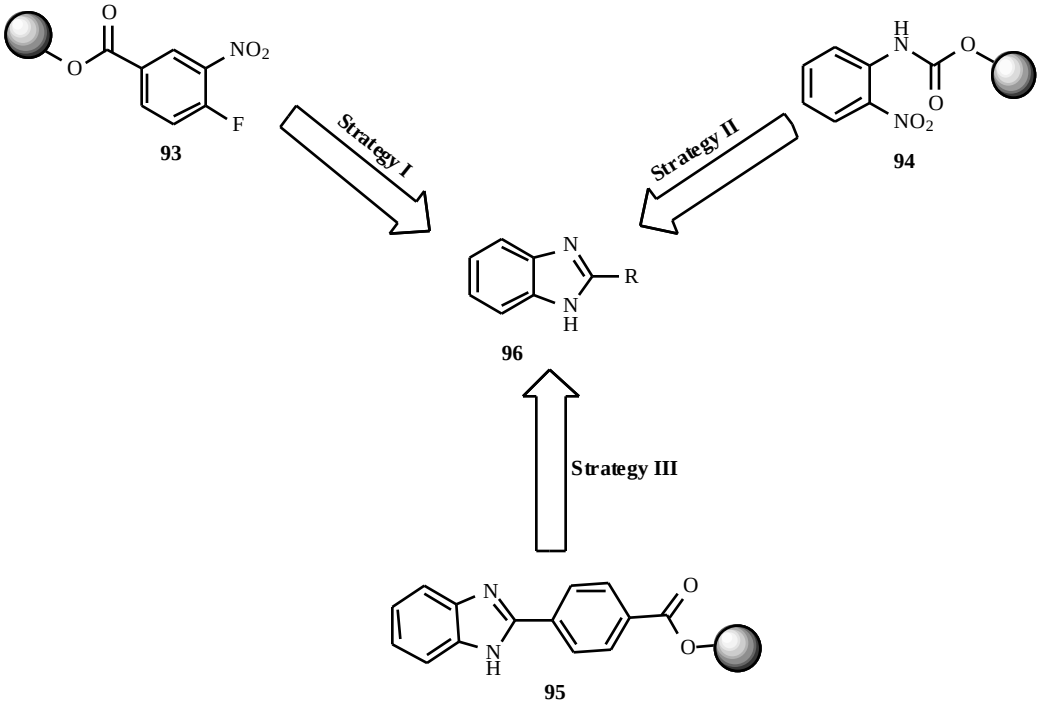
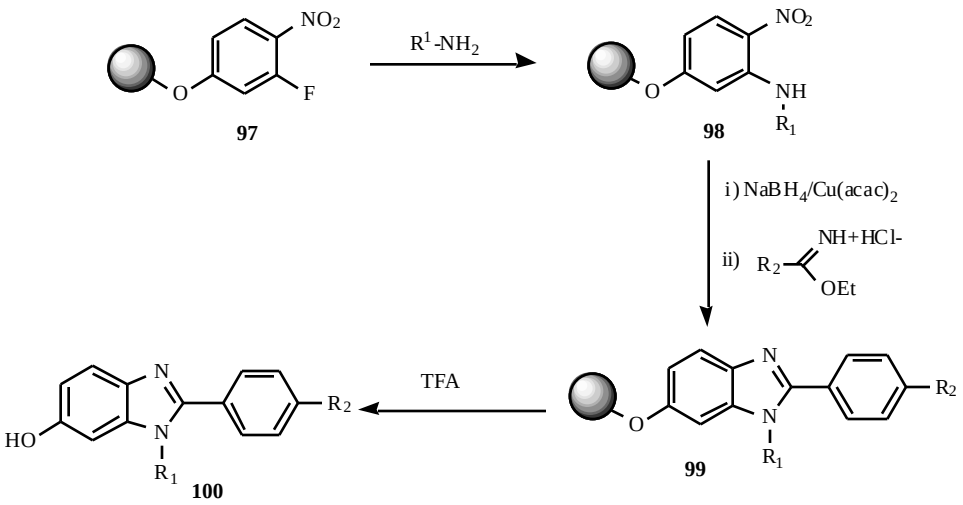


Fig. (9). Common synthetic pathways for benzimidazoles.

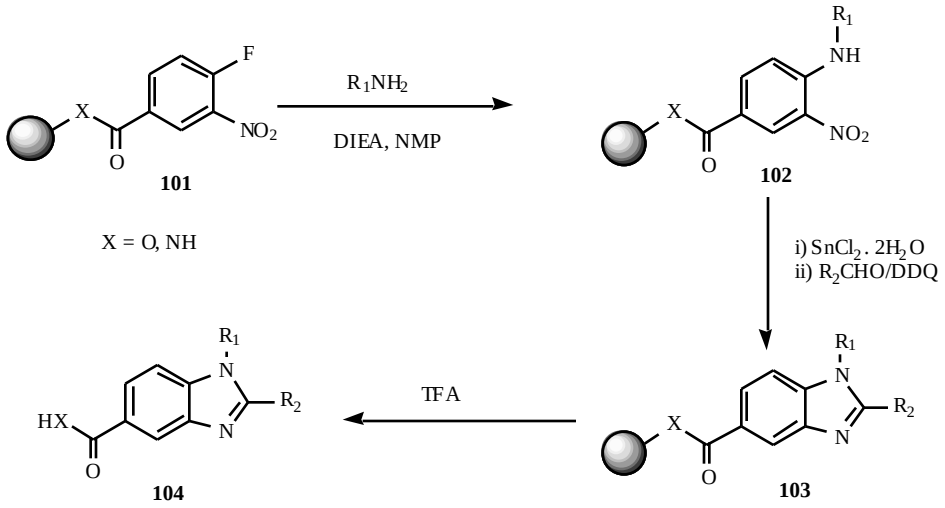


Scheme 17. An efficient preparation of benzimidazoles on solid-support [100].

to provide *o*-nitroaniline derivative (**98**). Reduction of **98** with $NaBH_4$-$Cu(acac)_2$ followed by cyclization with aryl imidate and cleavage with TFA affords **100** (Scheme **17**).

Later, Mayer and co-workers [101] and many other researchers have linked the resin to 4-fluoro-3-nitrobenzoic acid to provide 4-nitroaryl intermediate (**102**), then following previous strategies provides the benzimidazole ring system (**104**). In this case, after the cleavage of resin, an amide group or a carboxylic group is retained on the benzene ring (**104**). This strategy ideally suits for automated application since the entire reaction sequence can be carried out in DMF at room temperature (Scheme **18**).

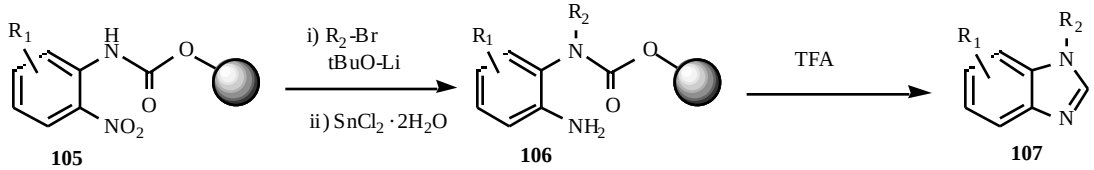
A novel tracking protocol introduced by Krchnak and co-workers with necklace coding has been utilized for the solid-phase synthesis of 2-arylaminobenzimidazoles on SynPhase crowns [102]. Similar synthetic strategies have been established for the construction of benzimidazole libraries on solid-support by employing insoluble [99, 103-106] and soluble [107-112] resins.



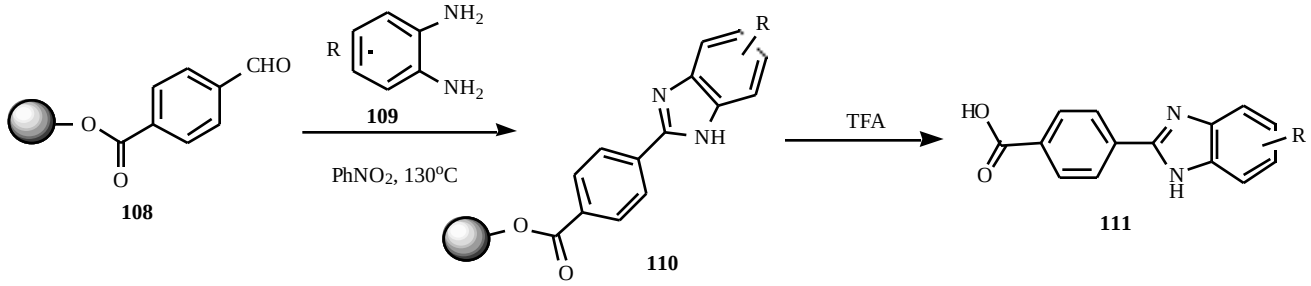
Scheme 18. Solid-phase synthetic approach to diverse benzimidazoles [101].

STRATEGY II

Huang and Scarborough developed the first "traceless" solid-phase synthetic strategy for benzimidazoles by solid-support attachment through the N1 nitrogen of the precursor to the imidazole ring (**107**), which allows diversity on the benzene ring (Scheme **19**) [113]. A number of researchers employing modified resin types have reported similar "traceless" solid-phase synthesis of benzimidazoles [114-



Scheme 19. The "traceless" solid-phase synthesis of benzimidazoles [113].

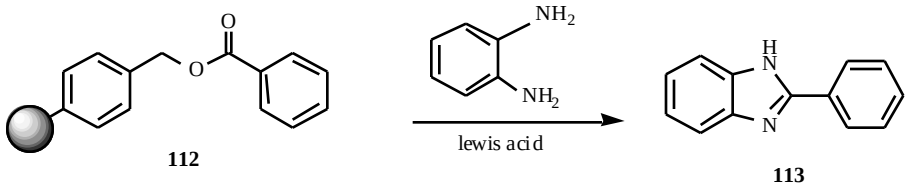


Scheme 20. Solid-phase synthesis of benzimidazoles [122].

117]. Similarly, synthetic strategies have been appeared for substituted benzimidazole libraries on polymer-support [118-121].

STRATEGY III

Yan and Sun reported [122] a solid-phase synthesis of benzimidazoles by coupling of phenylenediamines (**109**) to antagonists acting as good NMDA (N-methyl-D-aspartate) antagonists [125], and also form versatile intermediates. Phillips and Wei reported [126] a solid-phase synthesis for benzimidazolones (**117**) (Scheme **22**) which is very much analogous to the solid-phase synthesis of benzimidazoles previously discussed (Scheme **17**) [99] and the cyclization occurs by employing disuccinimidocarbonate (DSC) where



Scheme 21. Preparation of benzimidazoles from polymer-bound esters [124].

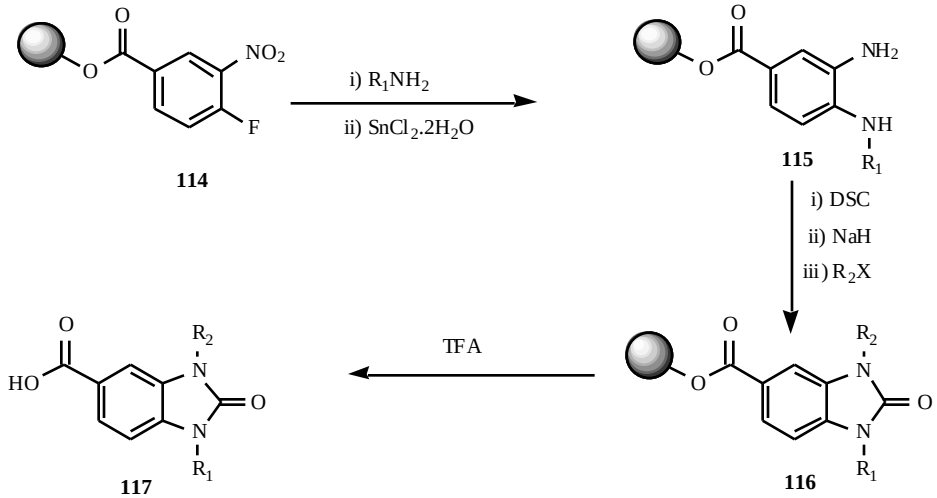
the resin-bound 4-carboxybenzaldehyde (**108**) (Scheme **20**). Similarly, parallel synthesis of 2,5-biaryl benzimidazoles has been generated on soluble PEG support [123].

Recently, Janda and co-workers [124] have prepared benzimidazoles from polymer-bound esters (**112**) by treating with 1,2-phenylenediamine in the presence of Lewis acid to afford benzimidazole cleavage products (Scheme **21**).

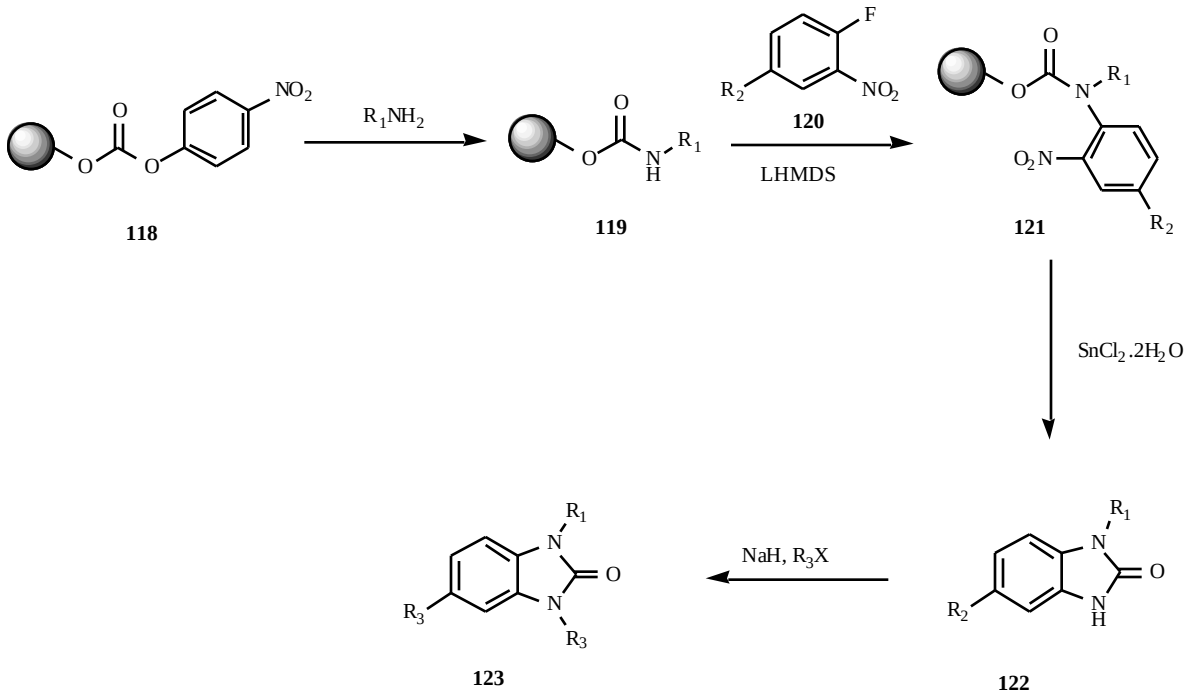
BENZIMIDAZOLONES

Benzimidazolones are also a unique class of building blocks exhibiting potent biological activity. They have been reported as first potent opioid receptor-like (ORL-1) as aryl imidate has been employed for cyclization of benzimidazoles. Synthesis of a benzimidazolone library using soluble polymer-support has been described by Sun and Pan [127]. Houghten and co-workers reported the solid-phase synthesis of substituted dihydroimidazoles [125]. Involving a cyclative cleavage of a carbamate linkage as the key reaction process Ermann and co-workers presented a versatile route for the solid-phase synthesis of imidazo[4,5-*b*]pyridin-2-ones and related urea derivatives [128].

Recently, Li and Wang described the parallel synthesis of benzimidazolones with a 3-fold functional diversity (**123**) using a combination of solid and solution-phase strategy. In this traceless technique, the key step of the sequence



Scheme 22. The efficient preparation of benzimidazolones on solid-support [126].



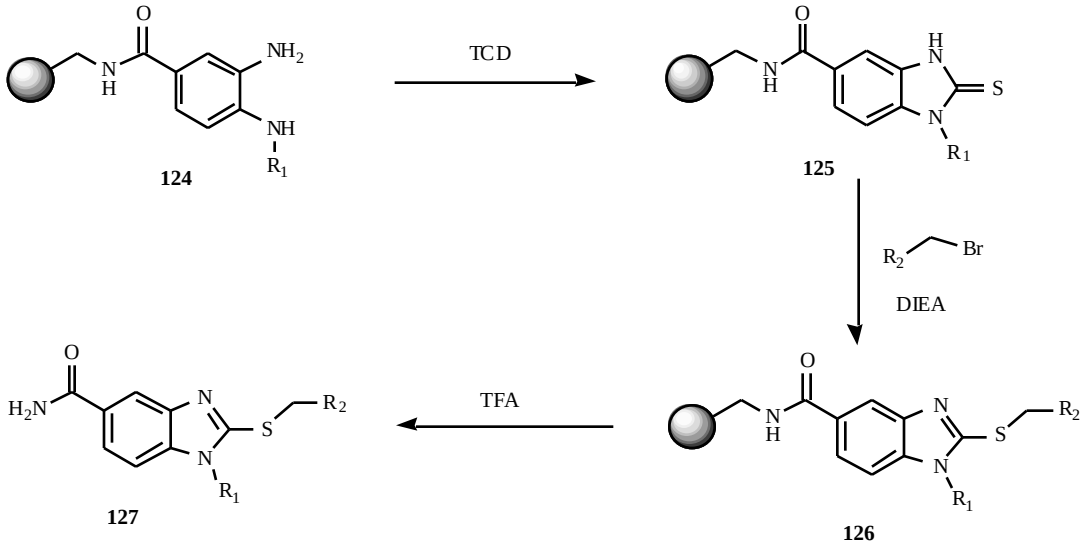
Scheme 23. Solid-phase synthesis of substituted benzimidazolones [129].

involves the introduction of one of the nitrogens by nucleophilic addition of a carbomate to an *o*-fluoronitrobenzene. Spontaneous cyclization and detachment of the benzimidazolones (**122**) from the resin (**121**) occurs under reductive conditions on solid-support. To incorporate a third element of diversity, benzimidazolones (**122**) were treated with NaH and various alkyl halides in DMF to afford fully functionalized benzimidazolones (**123**) (Scheme **23**) [129].

THIOBENZIMIDAZOLES

Lee and co-workers described [130] solid-phase synthesis for 1-alkyl-2-alkylthio-5-carbamoylbenzimidazole library. The synthetic strategy includes the cyclization of a resin-bound *o*-phenylenediamine (**124**) with thiocarbonyldiimidazole (TCD) in THF provides benzimidazole-2-thione (**125**). Treatment of **125** with benzylic halides in the presence of DIEA resulted in the resin-bound 1-alkyl-2-alkylthio-5-carbamoylbenzimadazoles (**126**), and the final products (**127**) were cleaved from the resin with TFA (Scheme **24**). Recently, Ladlow and co-workers presented a high automated, polymer-assisted strategy for the preparation of alkylthiobenzimidazoles and dialkylbenzimidazoline-2-ones [131].

Substituted-2-alkylthiobenzimidazoles represent an important heterocyclic structure in medicinal chemistry. The 2-alkylthiobenzimidazoles and their corresponding sulfoxides have been shown to be proton pump inhibitors



Scheme 24. Parallel synthesis of benzimidazoles [130].

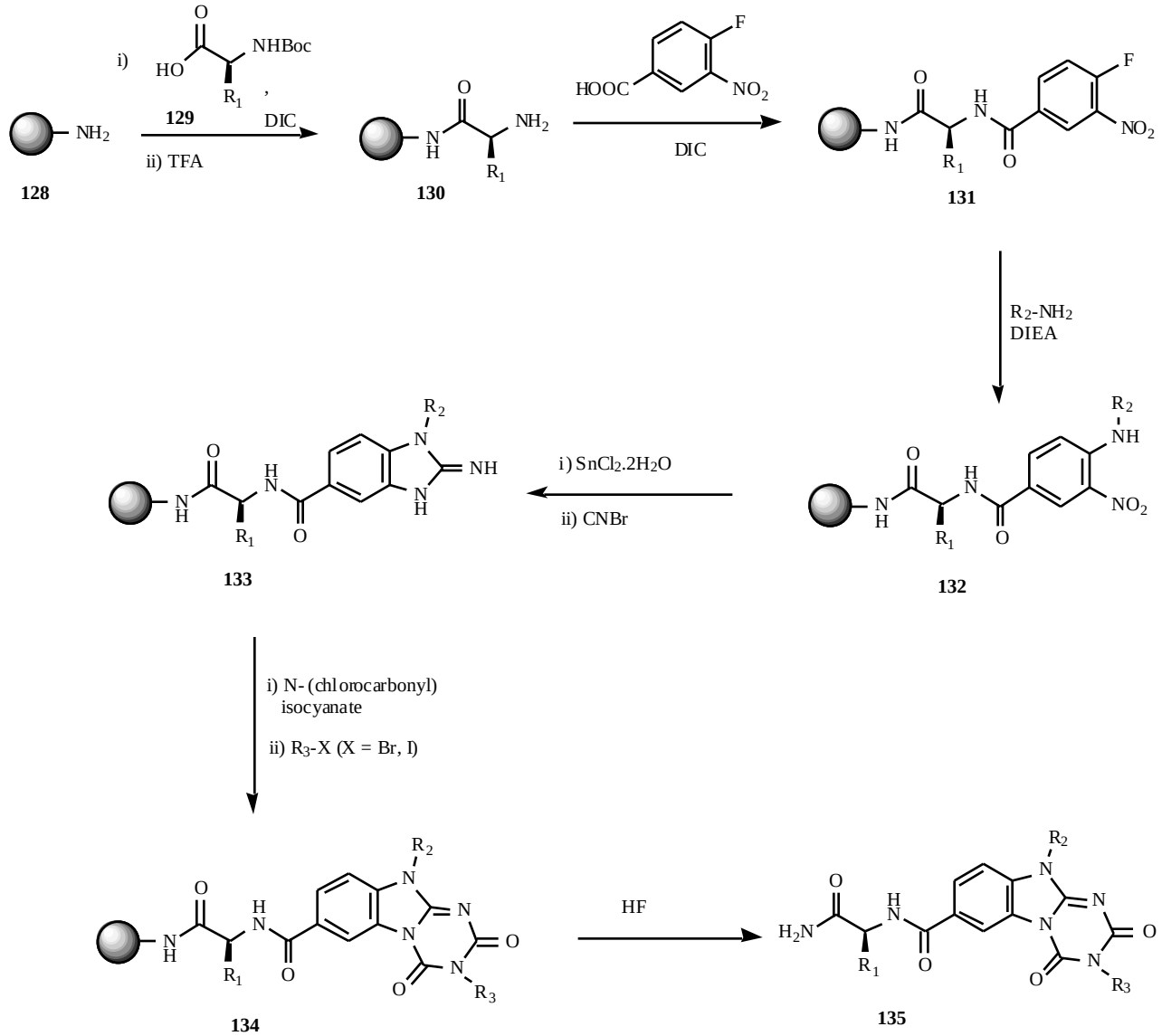
[132], antiulcer compounds [133], and antivirals [134]. Few reports have been appeared for the thiobenzimidazole libraries generation with varied diversity on solid-support representing the above synthetic strategy [135-137].

TRIAZINOBENZIMIDAZOLEDIONES AND TRIAZABENZOAZULENONE

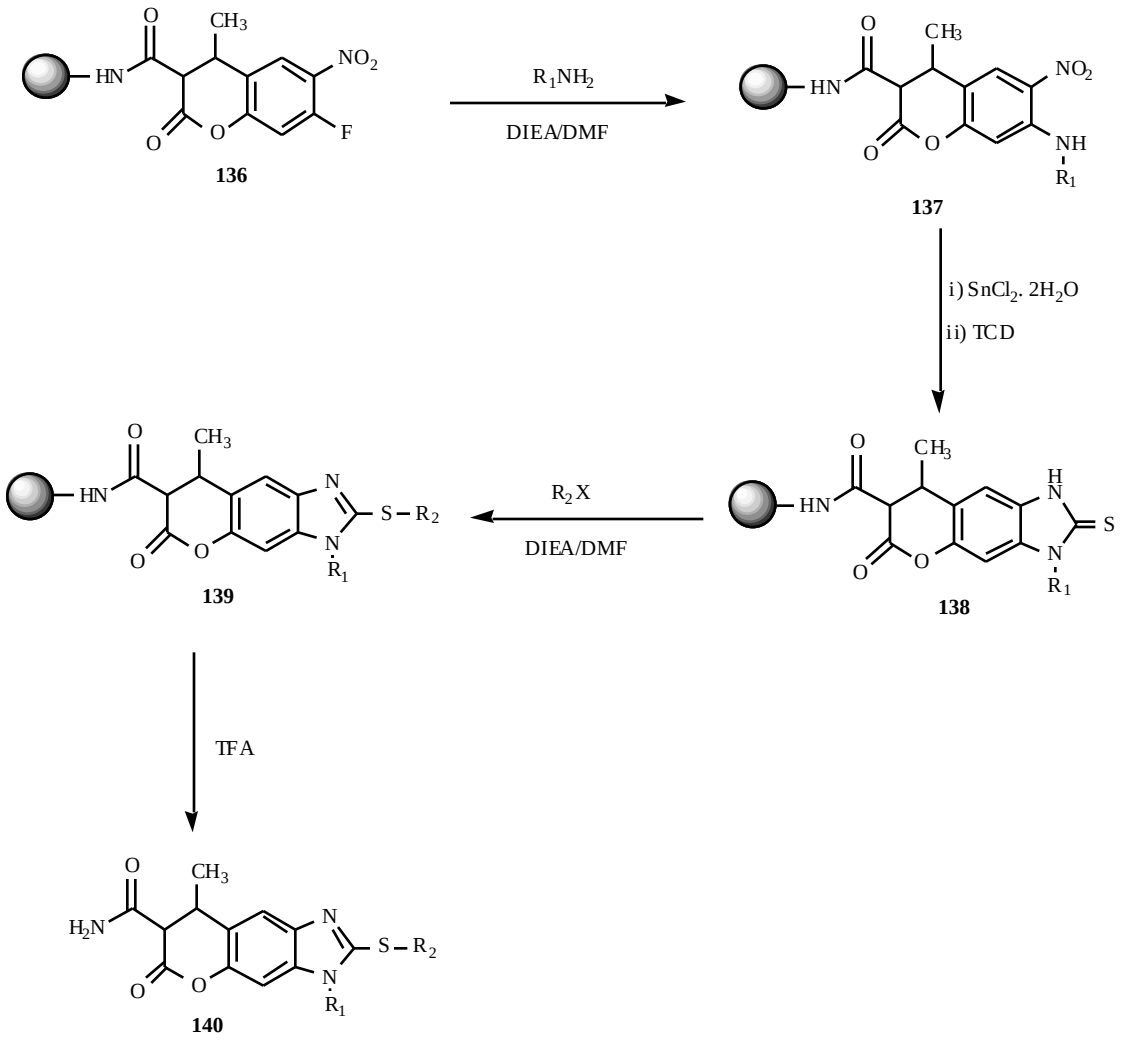
The related triazinobenzimidazolediones are reported to act as selective A_1 adenosine receptor antagonist [138] and as benzodiazepine receptor inverse agonists [139]. Houghten and co-workers recently reported [140] a solid-phase synthesis of substituted [1,3,5]triazino[1,2-*a*]benzimadazole-2,4(3*H*,10*H*)-diones. The synthetic strategy starts from resin-bound amines. *N*-acylation of the primary amine of a resin-bound amino acid with 4-fluoro-3-nitrobenzoic acid, followed by displacement of the fluoro group and reduction of the nitro group, generated a resin-bound *o*-dianilino derivative (**132**). The dianilino compound (**132**) was treated with cyanogen bromide to generate the corresponding iminobenzimidazole (**133**), which, following treatment with *N*-(chlorocarbonyl)isocyanate, afforded the resin-bound triazinodione derivative (**134**). Alkylation, following cleavage of the solid-support, results in the formation of trisubstituted triazinobenzimidazolediones (**135**) (Scheme **25**). Similarly, a couple of synthetic strategies have been established for the synthesis of substituted benzimidazoles with varied diversity employing aza-Wittig mediated conditions by the same group [141, 142]. Recently, for the first time Kundu and co-workers generated a library of 48 compound triazadibenzoazulenones from structurally diverse amino acids, *o*-fluoronitrobenzenes and *o*-nitrobenzaldehydes [143].

PYRANOBENZIMIDAZOLES

Lam and co-workers [144] have developed solid-phase synthesis of 2-alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones (**140**). 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid was coupled to Rink-amide resin via its carboxyl group. The resin-bound scaffold (**136**) then underwent aromatic nucleophilic substitution with



Scheme 25. Parallel solid-phase synthesis of triazinobenzimidazolediones [140].



Scheme 26. Solid-phase synthesis of 2-alkylthio-6*H*-pyrano-[2,3-*f*]benzimidazole-6-ones [144].

primary amines, followed by reduction of the nitro group with tin(II) chloride. Subsequent cyclization of the *o*-dianilino intermediate with thiocarbonyldiimidazol (TCD) afforded the resin-bound 1,3-dihydro-2-thioxo-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones (**138**), which then S-alkylated with alkyl halides in the presence of DIEA and cleaved the products from resin (**139**) with TFA (Scheme **26**). Same group developed a parallel solid-phase method for the preparation of 2-arylaminoimidazocoumarins [145].

INDAZOLES

Yan and Gstach described [146] an indazole (**141)** synthesis on solid-support, involving a multi-step synthesis of a heterocyclic compound and direct on-bead analysis of each synthetic step using single bead IR which is a powerful tool for a quick and convenient analysis of a wide range of solid-phase organic chemistry.

Molina and co-workers reported [147] an efficient solid-phase synthetic method towards bis(guanidines) (**144**) *via* aza-Wittig coupling of a solid-supported bis(iminophosphorane) (**142**) with an aromatic isothiocyanate to generate the corresponding solid-supported iminophosphorane (**143**), which upon exposure to a second aromatic isothiocyante underwent aza-Wittig/intramolecular cyclization and simultaneous cleavage to give the desired bis(guanidines) (**144**) (Scheme **27**).

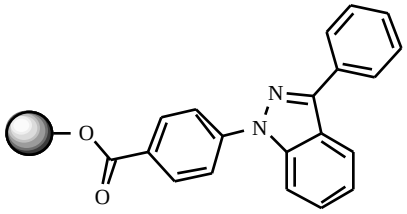
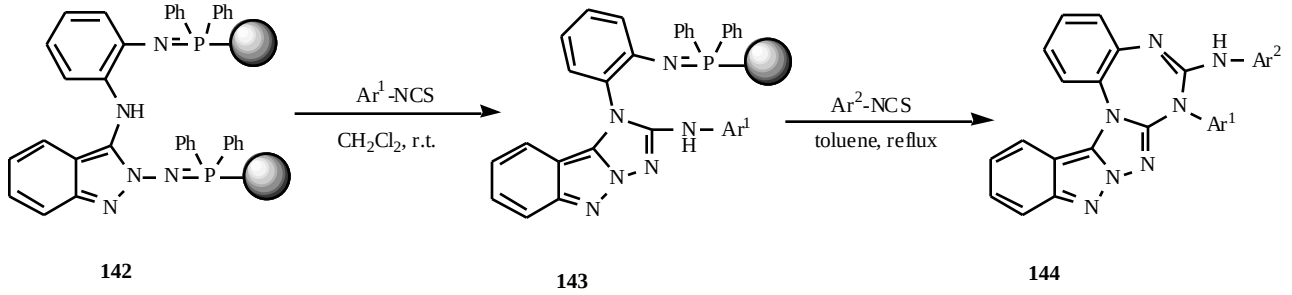


Fig. (10). Polymer-bound indazole.

CONCLUSION

It is hard to imagine lead discovery or optimization without a combinatorial component. It is observed in this review that a large number of privileged structures could be prepared by various synthetic strategies on solid-support. The solid-phase synthesis of these privileged structures/substructures based on quinoxaline, quinazoline and benzimidazole heterocycles reported in the literature could provide a way for generating numerous lead



142 **143** **144**

Scheme 27. Solid-phase synthesis of bis(guanidines) based on an aza-Wittig/carbodiimide mediated annulation process [147].

compounds for a variety of receptors. Thus, the potential importance of privileged structures in the field of medicinal chemistry in combination with combinatorial chemistry is illustrated. Integration of innovative chemistry technologies and state-of-the-art automation is equally important to achieve these goals.

ACKNOWLEDGMENT

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