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COMPREHENSIVE REVIEW

Groebke–Blackburn–Bienaymé multicomponent reaction: emerging chemistry for drug discovery

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Abstract The Groebke–Blackburn–Bienaymé reaction (GBBR) is used for the one-pot synthesis of therapeutically relevant fused imidazoles bridgehead nitrogen heterocyclic compounds from readily available aldehyde, isocyanide and amidine building blocks. The reaction is driven by a wide range of catalysts and can be performed either under solvent or solvent-free conditions, or under microwave irradiation as heat source. The GBBR products can be used for the synthesis of a variety of more complex scaffolds *via* postmodification reactions. These include cyclization and nucleophilic substitution as well as further MCRs. The GBBR reaction has seen diverse applications in combinatorial and medicinal chemistry and its products are of great use in drug discovery. In this review, we summarize the efforts of the chemistry community in the progress and applications of GBBR since 1998. This review also includes some biological profiles and synthetic scopes of GBBR products. The component variations, postmodifications and secondary transformations will also be discussed throughout this review.

Keywords Diversity-oriented synthesis · DOS · Isocyanide multicomponent reactions · MCRs · Kinase inhibitors · Microwave · Passerini reaction · Ugi reaction

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Background

Diversity-oriented synthesis (DOS) is an emerging synthetic strategy developed to access small libraries with multiple molecular scaffolds for biological screening purposes. Compounds obtained through DOS are often structurally more complex, possess greater stereochemical variations and have diverse core skeletons [1,2]. These compounds have shown significant success in modulating the activities of numerous targets that thought to be intractable and 'undruggable'. In this context, DOS plays a crucial role at the interface of organic synthesis and chemical biology *via* the continuous discovery of novel drugs with enhanced features compared to traditional drugs [3,4].

Multicomponent reactions (MCRs) are typically suited for DOS since diversity can be achieved in a single step by varying each component participating in the reaction [5]. These types of reactions are often the method of choice of organic and medicinal chemists for lead discovery and they have a role in optimization and targeted drug design as well. This approach involves the use of three or more reactants in one-pot to afford a product containing most, if not all, atoms of the starting materials [6].

Recently, many MCRs have been applied for the construction of different heterocycles. This is where isocyanide-based multicomponent reactions (IMCRs) come into play. IMCRs form the backbone of today's MCR arsenal, among which their applications lie mainly in pharmaceutical chemistry and drug discovery projects [7]. Furthermore, IMCRs possess different advantageous features over classical organic synthetic approaches; among them are their simplicity and superior atom economy [8].

The first IMCR was developed by the Italian Mario Passerini in 1921. This involves the reaction of an isocyanide with a carboxylic acid and an aldehyde or ketone to give α-

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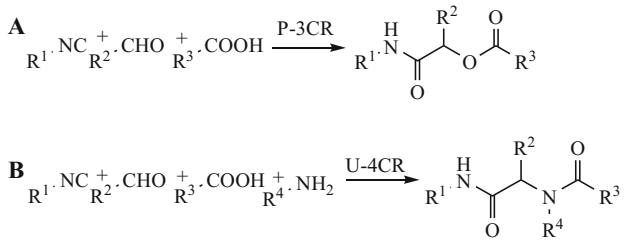


Fig. 1 Isocyanide-based multicomponent reactions. **a** Passerini three-component reaction. **b** Ugi four-component reaction

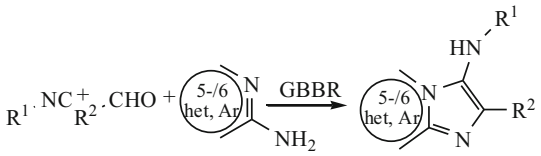


Fig. 2 Groebke–Blackburn–Bienaymé multicomponent reaction

acyloxy amides (Fig. 1a; [9,10]). This reaction was further expanded by Ugi and Steinbrückner in 1961 by using amines to give a dipeptide-like backbone (Fig. 1b; [10–13]).

In 1998, a new variant of the Ugi MCR was described by three independent research groups (Blackburn [14], Bienaymé [15] and Groebke [16]) and they are overall frequently referred to as the GBBR. This reaction usually involves the reaction of heterocyclic amidines with aldehydes and isocyanides to render *N*-bridgehead heterobicyclic compounds in a one-pot approach (Fig. 2).

In recent years, GBBR became highly widespread and numerous reports have arisen covering a wide scope and applications of this reaction. Very recently, Devi et al. [17] published a review on the same topic reporting the reaction since its first discovery. The Devi et al. review was mainly oriented towards the historical development of the reaction and exploration of different catalysts (e.g., Lewis, Brønsted and solid acids) used. Furthermore, there are many aspects that Devi et al. did not cover in his review (i.e., the biological importance and applications of GBB products in drug discovery). Furthermore, the advancement of the reaction was only depicted on the basis of various catalysts explored, neglecting its synthetic applications, scopes and secondary transformations. With this in mind and our interest in MCRs and drug discovery [18–23], we herein summarize the efforts of the chemical community in the progress and applications of GBBR since 1998. This review will cover the biological profiles, synthetic scopes and respective proposed mode(s) of action of GBBR products. The component variations, post-modifications and secondary transformations will also be discussed. For general information about MCRs, IMCRs and their applications in the synthesis of biologically relevant heterocycles, the reader is directed towards more comprehensive reviews and monographs [13,18,19,22–37].

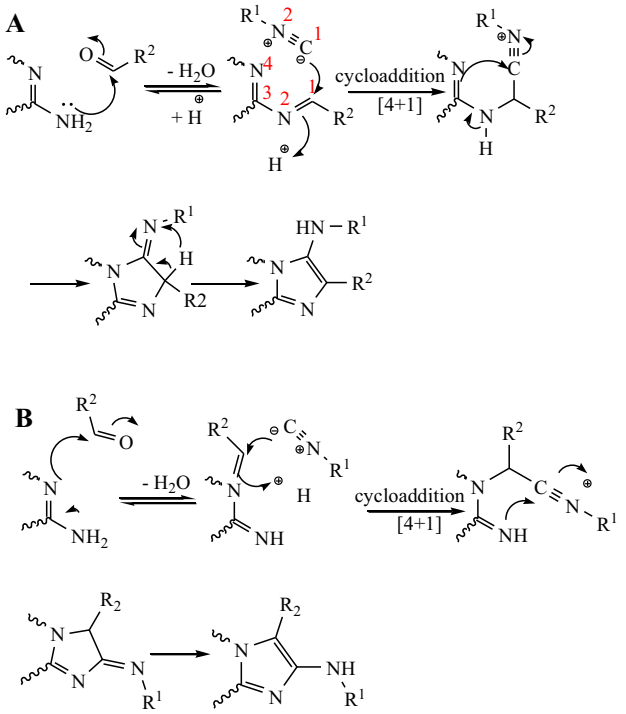


Fig. 3 Intra-molecular non-concerted GBBR mechanism

Scope and variations of GBBR

GBBR is considered to proceed *via* an intra-molecular non-concerted mechanism similar to that of the Ugi reaction; however, the cyclization takes place *via* the formation of a new ring system rather than the flexible peptidic-like Ugi product. The mechanism includes the in situ formation of an iminium species followed by a non-concerted [4+1] cycloaddition with the isocyanide to give the corresponding fused imidazoles (Fig. 3; [37,38]). It is worth noting that the reaction of aldehydes, isocyanides and 2-aminoazines is not always straightforward and regioisomers could be found (anti-Groebke products) in the reaction mixture (Fig. 3b). In this case, the reaction starts from the endocyclic nitrogen and the ratio of the two regioisomers depends on the nature of the substrate and type of the catalyst used (for more details see Scheme 27).

Bridgehead nitrogen heterocycles are abundant in nature and exhibit a diverse range of biological activities, such as anticancer, anti-microbial and antiviral activities [37,39,40]. The biological activities of bridged head nitrogen heterocycles are attributed to their ability to inhibit different signalling pathways (e.g., p. 38 MAP kinase, cyclin-dependent kinases and HIV-1 reverse transcriptase). In this context, *N*-fused bicyclic imidazo-azines represent a special class of scaffold that are found in several bioactive compounds and many marketed drugs (e.g., zolimidine, zolpidem, alpidem, olprinone and divaplon) [37,38,41]. Furthermore, a wide range of ther-

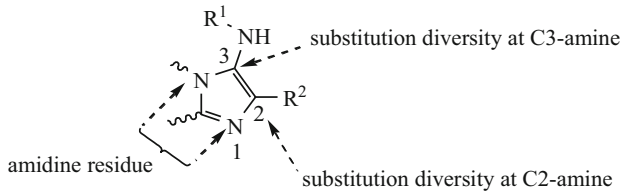


Fig. 4 Substitution diversity on GBBR products

apeutic activities are exhibited by this class of heterocycles (e.g., analgesic, anti-inflammatory, anti-proliferative, GABA receptor allosteric modulatory of, antiviral, antibacterial and anti-microbial) [37,39,41].

The synthesis of these compounds usually takes place in multiple steps, with long reaction times and low yields under harsh reaction conditions. GBBR was therefore developed as a more efficient method for the synthesis of the biologically relevant substituted fused imidazole heterobicyclic systems (e.g., imidazo-azines, imidazopyridines, imidazopyrimidines, imidazopyrazines and imidazo-diazines). Notably, this approach is superior to traditional strategies as it is one-pot, performed under mild conditions and usually includes excellent yields.

Variations of reaction components

After the publication of GBBR first report by Blackburn [14], Bienaymé [15] and Groebke [16], the reaction became vastly common and numerous reports have emerged covering wide scopes of the reaction.

Highly substituted *N*-fused imidazo heterocycles are accessible through the reaction of an isocyanide with an aldehyde and an amidine in the presence of a suitable catalyst. The reaction relies on a plethora of readily available starting materials and displays a broad reactivity domain with prominent structural variety (Fig. 4).

Variations of the isocyanide component

The isocyanide component is responsible for the generation of substitution diversity at C_3-amine (Fig. 4). Aliphatic and aromatic isocyanides were successfully used in GBBR. The aliphatic isocyanides can be of primary, secondary or tertiary nature (Fig. 5).

Variations of the aldehyde component

The prominent structural variety of GBBR is mainly due to the diversity of the aldehyde components which in turn used to access compounds with functionalization diversity at

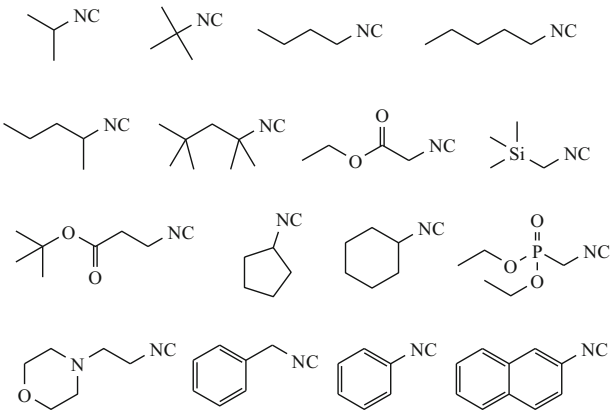
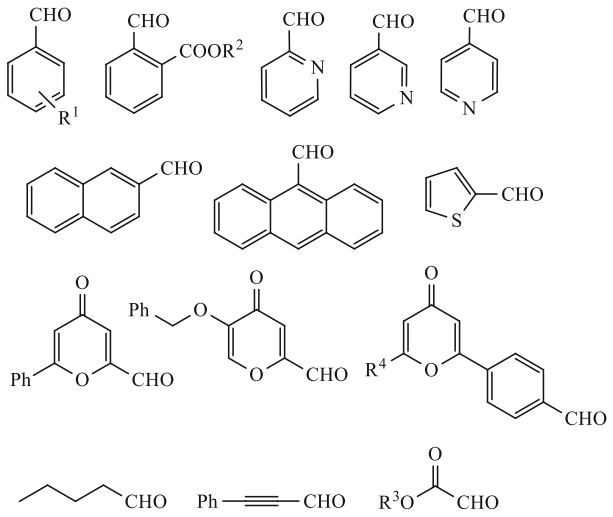


Fig. 5 Examples of aliphatic and aromatic isocyanides used in GBBR

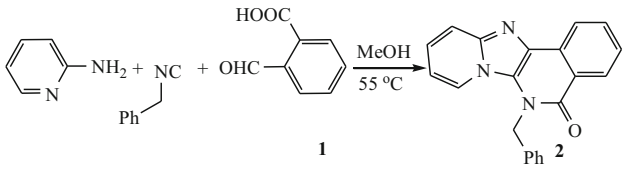


R^1= H, 4-Cl,4-Br, 4-CH_3, 2,3-$(OCH_3)_2$, 3,4,5-$(OCH_3)_3$, 3-OH, 4-NO_2
R^2= H, CH_3, C_2H_5; R^3= H, MP-CO_3; R^4= CH_3, C_6H_5

Fig. 6 Aldehyde components used in GBBR

C_2 which could be used for further postmodifications (e.g., cyclization) [42,70]. GBBR reaction is compatible with a wide range of aldehydes including aromatic (e.g., *ortho*-, *meta*- or *para*-substituted benzaldehyde, naphthaldehyde, anthracene-9-carbaldehyde, salicylaldehyde and phthalaldehydic esters), aliphatic (e.g., valeraldehyde, pivalaldehyde and 3-phenylpropiolaldehyde) and heteroaromatic (e.g., thiophenaldehyde, pyridoxal, nicotinaldehyde, picolinaldehyde and isonicotinaldehyde) aldehydes (Fig. 6).

It is worthwhile to mention that aliphatic aldehydes are less reactive than aromatic aldehydes in this reaction due to the formation of relatively unstable imines. On the other hand, aldehydes having electron-withdrawing groups are basically more reactive in GBBR than those having electron-releasing groups.



Scheme 1 Synthesis of substituted pyrido[2′, 1′ : 2, 3]imidazo[4,5-c]isoquinolinones

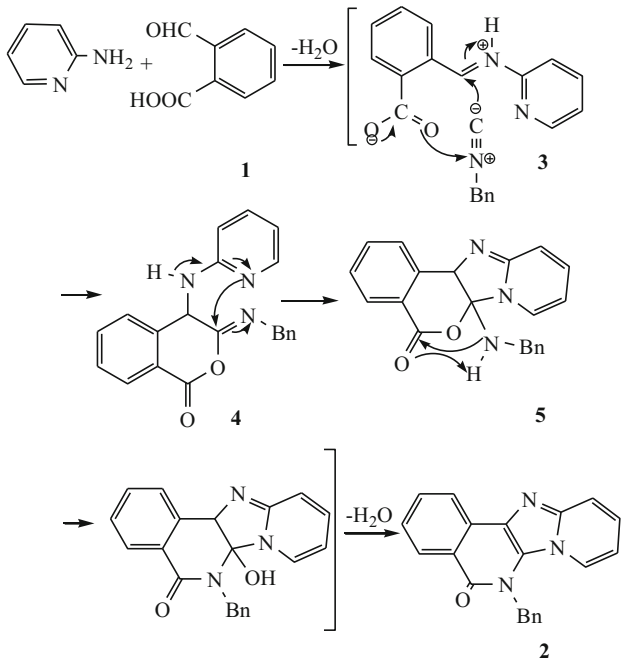


Fig. 7 Lactam formation mechanism

Meng et al. [42] reported the solution-phase combinatorial synthesis of substituted pyrido[2′, 1′ : 2, 3]imidazo[4,5-*c*]isoquinolinones **2** in good yields (up to 82 %) employing 2-formylbenzoic (**1**) acid as the aldehyde component (Scheme 1).

The in situ-formed iminium species **3** is attacked by the benzyl isocyanide to give **4** which in turn underwent 5-exo cyclization followed by addition of the carboxylic acid oxygen to the imino carbon affording the internal ester **5**. In addition, the latter underwent acyl transfer rearrangement to give lactam **2** (Fig. 7; [42]).

Furthermore, novel scaffolds could also be achieved by varying the aldehyde component. For example, 3-aminoimidazo[1,2-*a*]pyridines possessing 4-pyrone **7** were synthesized using the 4-pyrone carbaldehydes **6** as the aldehyde component (Scheme 2; [43]).

Surprisingly, formaldehyde—which has been intensively used in the Ugi reaction—has a limited success in GBBR. In this case, 2-unsubstituted-3-aminoimidazo heterocycles can be obtained; however, the reaction is not always successful and low yielding.

Lyon et al. [44] reported the synthesis of 2-unsubstituted-3-aminoimidazo heterocycles **9** by using a convenient formaldehyde equivalent, glyoxylic acid immobilized on MP-carbonate (MP−CO_3) **8**. The latter was used as the formaldehyde source and the product is easily liberated through decarboxylation/self-release from the resin (Scheme 3).

In 2011, Sharma et al. [45] examined different formaldehyde equivalents (e.g., paraformaldehyde, trimethyl orthoformate and glyoxylic acid) for the synthesis of 2-unsubstituted-3-aminoimidazoazines **9**. It was found that glyoxylic acid (**10**) is the only one which provides enhancement in the yield (up to 88 %) (Scheme 4). This method is superior to previous methods in terms of regioselectivity, use of inexpensive formaldehyde source, yield, simplicity and broad applicability.

Variations of amidine component

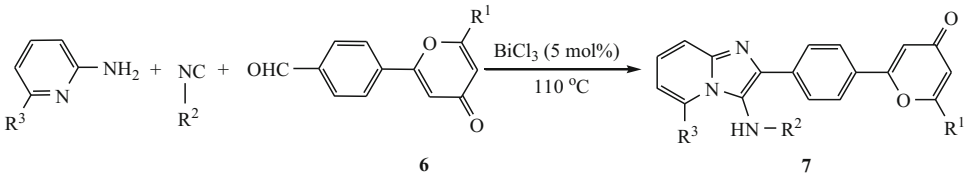
The structural diversity in the GBBR products is not only attained *via* variation of the aldehydes and isocyanides building blocks, but also by the multitude of the amidine components. Different heterocyclic moieties comprising the 2-amidine functionality were explored in GBBR and led to both structural and functional diversity. Of note, commercially available 2-aminothiazoles, 2-aminopyridines, 2-amino-pyrimidines, 2-aminopyrazines and 2-aminoquinolines were commonly used as the amidine components (Fig. 8). Aliphatic amidines were not evaluated due to their scarce commercial availability and lack of synthetic accessibility.

Sun et al. [46] described the sythesis of benzo[d]imidazo[2,1-*b*]thiazoles **12** in 73 % yield employing 2-aminobenzothiazole (**11**), for the first time, as the amidine component (Scheme 5).

In 2011, Lamberth et al. [47] reported the GBBR one-pot synthesis of imidazo[1,2-*b*]pyridazines **14** in good yields (66–93 %) by using 3-aminopyridazines **13** as the amidine component (Scheme 6). Commercially available 3-amino-6-chloropyridazine could also be used for further derivatisation. In this case, nucleophilic substitution reactions can give access to imidazo[1,2-*b*]pyridazines (**13**) with several substituents patterns in position 6 (Scheme 6, see also secondary transformations).

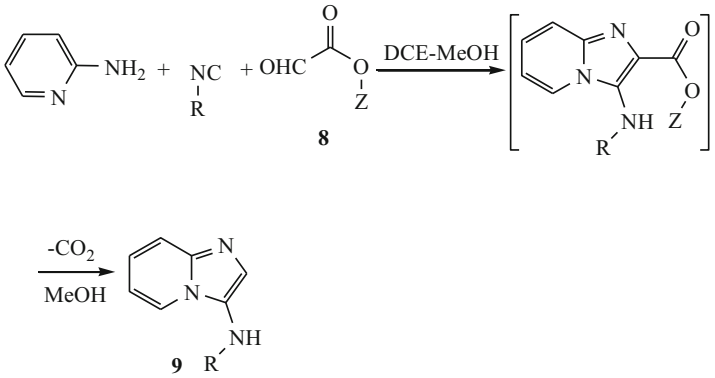
Guchhait et al. [48] reported the implication of 2-amidine functionality of nucleobases (adenine, guanine and cytosine) in GBBR for the synthesis of aminoimidazole-condensed nucleobases **15**–**17**. The reaction proceeded smoothly in DMSO using $ZrCl_4$ (10 mol %) as the catalyst at 70 °C and the products were obatined in good yields (up to 72 %) (Scheme 7).

Scheme 2 Synthesis of aminoimidazo[1,2-*a*]pyridines possessing 4-pyrone scaffolds

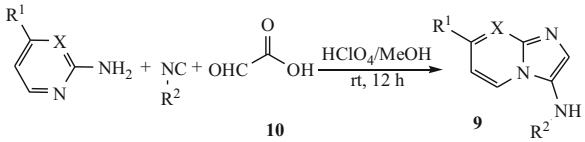


R^1= CH_3, C_6H_5; R^2= cyclohexyl, tert-butyl; R^3= H, CH_3

Scheme 3 Glyoxylic acid immobilized on MP-carbonate (MP–CO_3) as convenient formaldehyde equivalent in GBBR



R= Bn, -$CH_2CO_2CH_3$, 4-OCH_3-C_6H_4-, -Cl-C_6H_4-; Z= H, MP-CO_3



R^1= H, Cl, Br; R^2= Bn, $CH_2CO_2CH_3$, 4-OCH_3-C_6H_4, 4-Cl-C_6H_4; X= -CH, -N

Scheme 4 Synthesis of 2-unsubstituted-3-aminoimidazoazines using glyoxylic acid

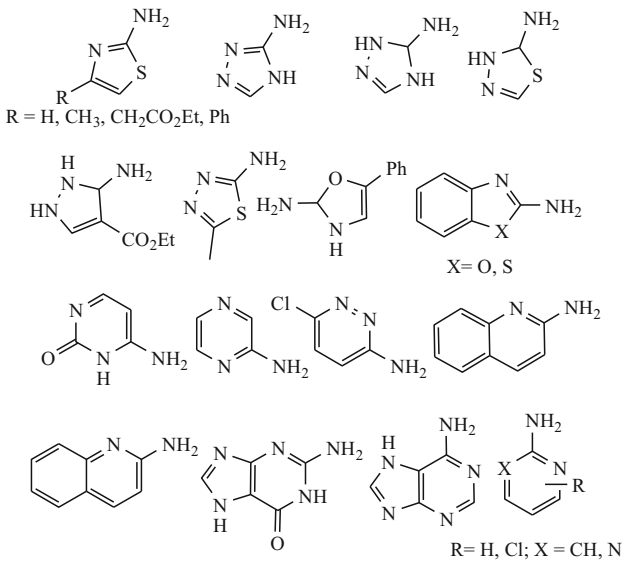


Fig. 8 Examples of the amidine components used as a part of the GBBR

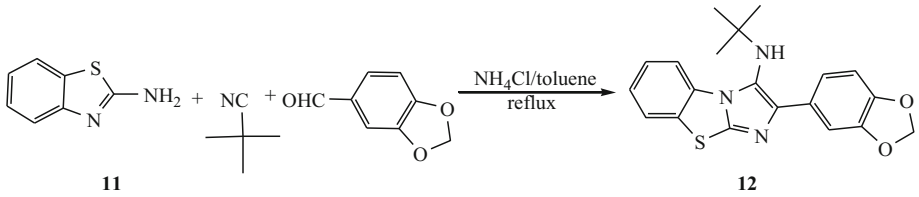
Variations of the catalyst and solvent

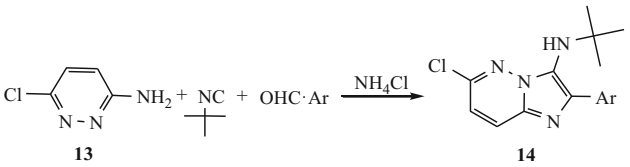
Since the GBBR was first published, numerous methods have been developed to improve reaction yields, time and conditions. The mild reaction conditions and the availability of the starting building blocks offer by far high levels of diversity and brevity. The reaction can be performed either under solvent-free (neat) conditions or by using different solvents such as methanol [49], toluene [50], acetonitrile [51], dimethyl sulfoxide [48], polyethylene glycol [52], ionic liquids [71] and water [53].

Furthermore, diverse catalysts were reported to accelerate the reaction. This included Brønsted acids, such as acetic acid [16], perchloric acid [14–16], tosylic acid [54], silica-sulfuric acid [55], NH_4Cl [50,56], clay (montmorillonite K-10) [57] and PTSA/*N*-hydroxysuccinimide [58]. Additionally, several Lewis acids were used, such as $Sc(OTf)_3$[14–16], $MgCl_2$[59], $InCl_3$[60], $ZnCl_2$[61], $RuCl_3$ [62], tin(II) chloride dehydrate [63], trimethylsilyl chloride (TMSCl) [64], $ZrCl_4$[65] and $Yb(OTf)_3$[66]. A super paramagnetic nanoparticle of modified sulphuric acid (c-Fe_2O_3 · SiO_2 − OSO_3H) was also used as both straightforward and green catalyst [67]. Moreover, the reaction has also been reported to be conducted under solid-phase [68], catalyst-free [53] and fluorous liquid-phase conditions [69].

Contrary to conventional GBBR, Lee et al. [70] reported for the first time that GBBR reaction can be also car-

Scheme 5 Synthesis of benzo[d]imidazo[2,1-*b*]thiazoles





Ar= C_6H_5,3-CF_3-C_6H_4, 4-OCF_3-C_6H_4, 3-F-4-CH_3-C_6H_3

Scheme 6 One-pot synthesis of imidazo[1,2-*b*]pyridazines using 3-amino-6-chloropyridazine

ried out using a Brønsted-base, such as piperidine. In this case, postmodification at C_3-amine of the GBBR adduct was performed without the redundant dealkylation step. GBBR of 2-aminobenzimidazoles, methyl 2-formylbenzoate using piperidine as a catalyst proceeded smoothly in dichloromethane to give the desired benzimidazo[2′, 1′:2, 3]imidazo[4,5-*c*]isoquinoline-9-carboxylate **18** with high regioselectivity, atom economy and in moderate to good yields (34–95 %) (Scheme 8).

Postmodification of the resulting GBBR adducts afforded the corresponding isoquinolinone-embedded imidazo[1,2-*a*] benzimidazoles *via* functionalization of the secondary amine derived from the used isocyanide as depicted in Fig. 9. This strategy has been achieved without the laborious dealkylation step(s).

It is worth noting that ionic liquids (e.g., guanidinium or imidazolium salts) were used instead of conventional solvents. In this case, the guanidinium salt act as a solvent and in the same time as a catalyst and the yield was up to 68 % (Scheme 9; [71]).

Microwave-assisted GBBR

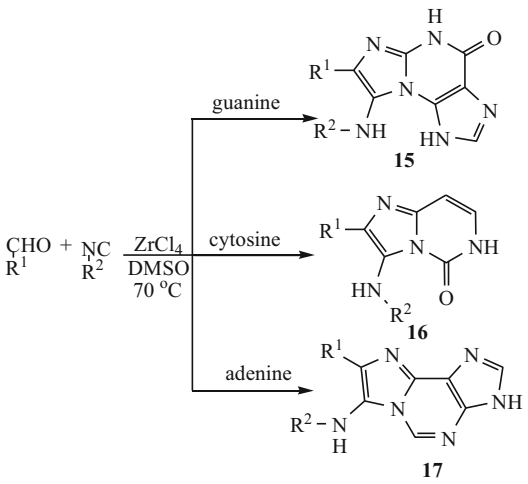
Microwave irradiation not only affords better yields and cleaner reactions than conventional heating, but even leads to chemo-, regio- or stereoselectivities that differ from those obtained by classical heating.

Microwave technology has been applied for the rapid synthesis of chemical libraries (including heterocyclic compounds) using MCRs in combinatorial and medicinal chemistry [72,73]. Many examples were presented whereby microwave irradiation was used as an energy-efficient heat source that directly transferred to the molecules of the reaction mixture *via* dielectric heating. Furthermore, this direct heat transfer allows reactions to proceed much faster, in higher yields, with improved selectivities than classical heating methods [74–76].

In 1999, Varma and Kumar reported the first solvent-free microwave-assisted GBB synthesis of imidazo[1,2-*a*]pyridines **19**, imidazo[1,2-a]pyrazines **20** and imidazo[1,2-*a*]pyrimidines **21** on clay in moderate to good yields (56-88 %) (Scheme 10) [57].

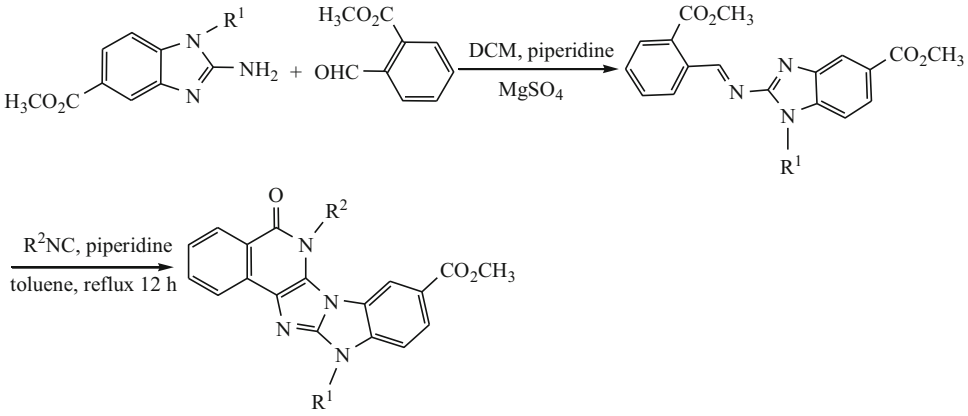
Based on Varma and Kumar's report, Ireland et al. [77] investigated further the potential of microwaves to accelerate Lewis acid-catalyzed GBBR in solution. They

Scheme 7 Synthesis of aminoimidazole-condensed nucleobases



R^1 = 4-Cl-C_6H_4, 4-Br-C_6H_4, -CH=CH-C_6H_5; R^2 = *tert*-butyl, cyclohexyl, 4-OCH_3-C_6H_4

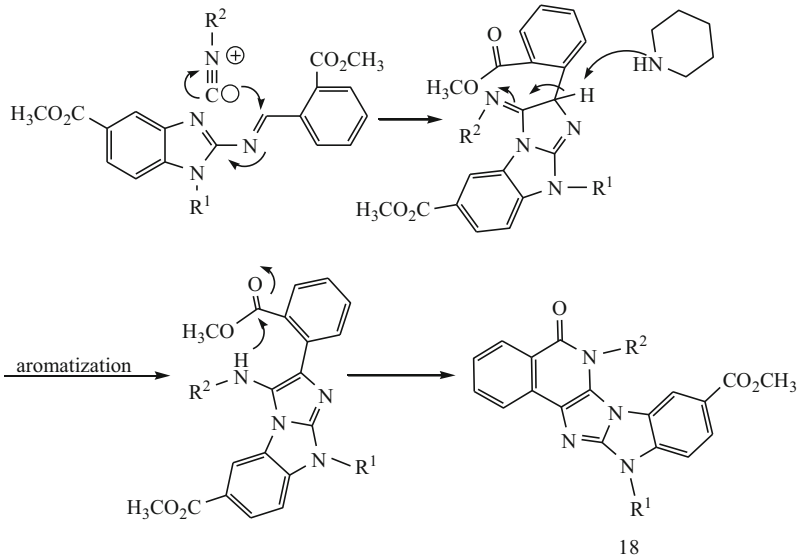
Scheme 8 Synthesis of benzimidazo[2′, 1′ : 2, 3]imidazo[4,5-*c*]isoquinoline-9-carboxylate using piperidine as catalyst



18

R^1= $(CH_2)_5NH_2$, $CH_2O(CH_2)_3NH_3$, $CH_2CH(CH_3)(CH_2)_2NH_2$; R^2= Bn, n-pentyl, isopropyl, cycloheyl

Fig. 9 Synthesis of isoquinolinone-embedded imidazo[1,2-*a*] benzimidazoles *via* postmodification of the resulting GBBR adduct



18

R^1 = $(CH_2)_5NH_2$, $CH_2O(CH_2)_3NH_3$, $CH_2CH(CH_3)(CH_2)_2NH_2$; R^2 = cycloheyl, Bn, $CH_3(CH_2)_4$, $CH(CH_3)_2$

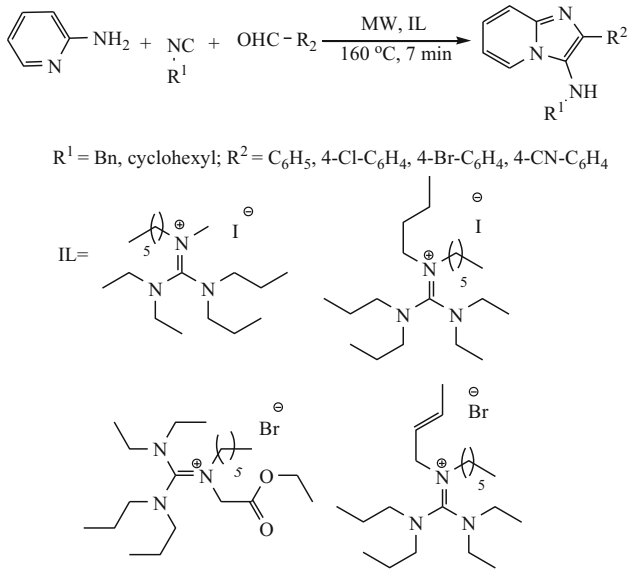
reported the microwave-assisted GBB synthesis of fused 3-aminoimidazoles **22** employing different amidines (e.g., 2-aminopyridine, 5-methyl-2-aminopyridine, 5-bromo-2-aminopyridine, 2-amino-pyrazine, 2-amino-quinoline and 2-amino-thiazole) using $Sc(OTf)_3$ as a catalyst in methanol. The reaction proceeded in a short time (10 min) using a simple one-stage procedure and in moderate to good yields (33–93%) (Scheme 11).

In 2007, Rousseau et al. [61] developed the one-pot preparation of imidazo[1,2-a]pyridines **23** using cheaper and recyclable catalysts ($ZnCl_2$ and Montmorillonite clay K10) rather than the expensive $Sc(OTf)_3$. The reaction proceeded under microwave irradiation or conventional heating in moderate yields (up to 75 %) (Scheme 12).

In 2012, Mert-Balci et al. [71] reported the quick (7 min) and efficient synthesis of 3-amino-substituted-imidazo[1,2-*a*]pyridines **24** *via* microwave-assisted GBBR between 2-aminopyridines, aldehydes and isocyanides in toluene using montmorillonite in moderate to good yields (16–98 %) (Scheme 13).

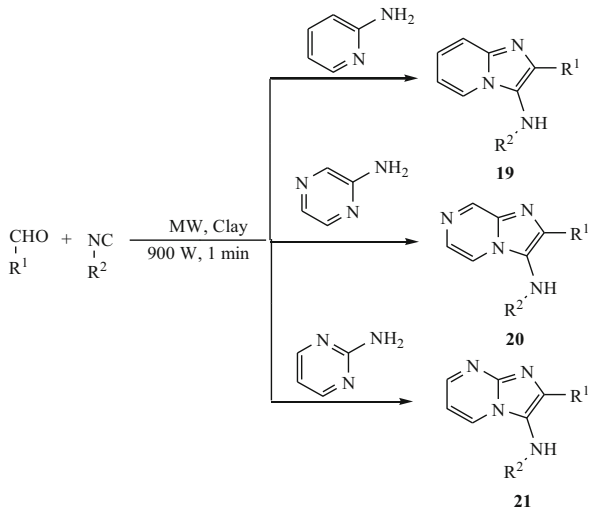
Secondary transformations of GBBR products (diversification of imidazo scaffolds)

Interestingly, the GBBR products may undergo further secondary transformations/postmodification reactions (e.g., cyclization, nucleophilic substitution and additional MCRs) to give access to a variety of heterocyclic scaffolds in exquisite fashion. In this case, the GBBR adducts are considered as a convenient substrate for the synthesis of natural product mimics, therapeutic agents and combinatorial libraries.



R^1 = Bn, cyclohexyl; R^2 = C_6H_5, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CN-C_6H_4

Scheme 9 Synthesis of imidazopyridines using ionic liquids

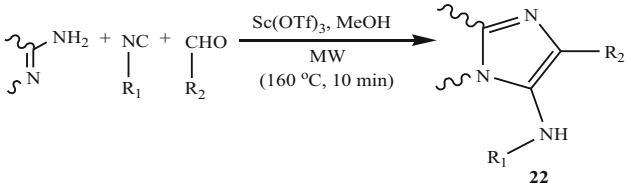


R^1 = C_6H_5, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 3,4-C_6H_3; R^2 = cyclohexyl, *tert*-butyl, Bn

Scheme 10 Solvent-free microwave-assisted GBB synthesis of imidazo-azines on clay

One of the most elaborated postmodifications is the use of cleavable/convertible isocyanides and subsequent derivatisation at the formed primary amine site (Scheme 15; [64]). Furthermore, the GBBR adducts may be also designed from the beginning in order to possess a tethered internal good leaving group (i.e., halogens) suitable for postnucleophilic substitution and offering higher levels of molecular complexity in few chemical manipulations (Fig. 10; [47,65]).

In 2008, Krasavin et al. [64] reported for the first time the two-step solution-phase de-*tert*-butylation of various GBBR adducts **25** obtained by employing *tert*-butyl isocyanide as a convertible reagent. Preliminary experiments using different mineral and Brønsted acids (e.g., conc. HCl, dil. HCl in MeOH or dioxane, conc. H_2SO_4 and glacial acetic acid) failed or were inefficient to remove the *tert*-butyl group from GBBR products. On the other hand, neat refuxing trifluoroacetic acid was able to convert the *tert*-butyl group in **25** into the corresponding trifuoroacetamides **26** (the key step) in 3 h cleanly and effectively (Scheme 14). Subsequent alkaline hydrolysis afforded the corresponding primary amines **27**. It is worth noting that this two-step procedure could be achieved on a gram scale without the need for tedious workup and chromatographic purification with good overall yields (up to 78 %) [64].



R_1 = Bn, $CH_2CO_2C_2H_5$; R_2 = 2-naphtyl, 2-pyridinyl

Scheme 11 Lewis acid-catalyzed synthesis of 3-aminoimidazoles **22** under microwave irradiation conditions

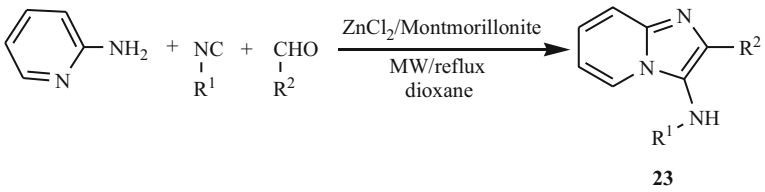
Two years later, a tandem one-step de-*tert*-butylation procedure was reported by Guchhait et al. [65] using one equivalent of HBF_4 in 1-butanol under microwave irradiation conditions in excellent yields (90 %) (Scheme 15).

As far as the one-pot tandem GBBR–de-*tert*-butylation method was concerned, its scope of application was further explored by Guchhait et al. [65] for the construction of molecular diversity at the amino group [65]. This included an in situ cyclization of primary amine with a tethered internal functional group to give access to isoquinolinoneimidazole-heterocycles. The phthalaldehydic esters **29** were chosen as representative aldehydes for the in situ cyclization purpose. The one-pot reaction of **29** with heterocyclic-2-amidines and *tert*-butyl isocyanide followed by tandem dealkylation-cyclization afforded *N*-fused isoquinolinoneimidazole-heterocycles **30** in good yields (72–89 %) (Scheme 16).

In 2011, Lambert also exploited the advantage of the de-*tert*-butylation strategy for further functionalization at the amine group [47]. Compound **32** was easily acylated and sulfonylated to give the corresponding sulfonamide **33** and the amide **34** in good yields (75 and 72 %, respectively) (Scheme 17; [47]).

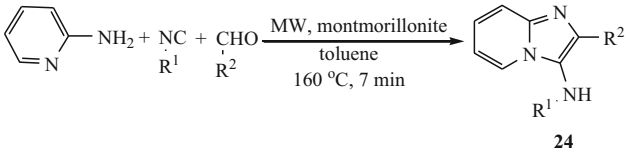
Another simple and straightforward postmodification strategy is the incorporation of a good leaving group to one of the GBBR starting building blocks. The resulting GBBR adducts can therefore undergo postnucleophilic substitution offering higher levels of diversity. For example, 6-chloro-2-phenylimidazo[1,2-*b*]pyridazine (**35**) is a GBBR adduct (synthesized employing 3-amino-6-chloropyridazine as the

Scheme 12 One-pot preparation of imidazo[1,2-a]pyridines using $ZnCl_2$ or Montmorillonite clay K10 as catalysts



23

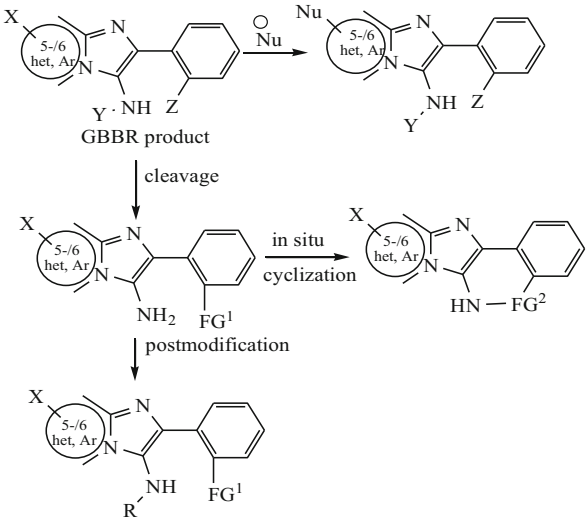
R^1 = cyclohexyl, *tert*-butyl, 2,6-dimethyl-C_6H_3
R^2 = C_6H_5, 4-OCH_3-C_6H_4, 3,4-C_6H_3



24

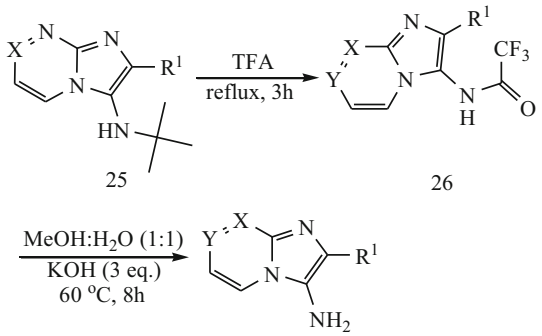
R^1 = Bn, cyclohexyl; R^2 = C_6H_5, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CN-C_6H_4

Scheme 13 Microwave-assisted synthesis of 3-amino-substituted-imidazo[1,2-*a*]pyridines



X= good leaving group, Y= convertible group, Nu= nucleophile
FG^1= H, CHO, FG^2= CH=, R= CH_3CO, PhCO

Fig. 10 Postmodifications and secondary transformation of GBBR adducts



R^1= C_6H_5, 4-C_6H_4, $CH(CH_3)_2$; X= CH, NH,

Scheme 14 Two-step de-*tert*-butylation of various GBBR adducts using TFA

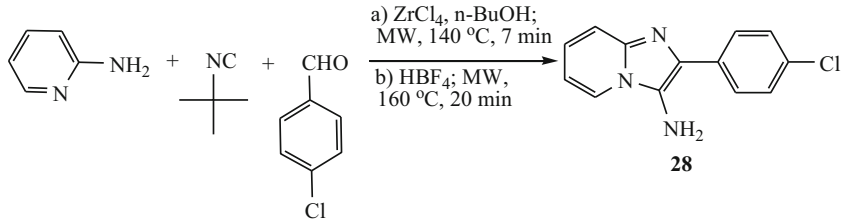
amidine component) which possesses a chloro function with good leaving-group properties in position 6. This allows an easy entry into imidazo[1,2-b]pyridazines with several different substituents patterns at position 6. In this context, Lamberth exploited the structural versatility feature of 6-chloro-2-phenylimidazo[1,2-*b*]pyridazine **35** and used it for further derivatisation [47]. The chlorine atom was replaced (aromatic nucleophilic substitution) either via reaction with a secondary amine, primary alcohol or with pyrimidine-2-thiol in the presence of a suitable base. The corresponding amines **36**, alkoxides **37** and thiolates **38** were delivered in 63, 84 and 64 % yields, respectively (Scheme 18; [47]).

Guasconi et al. [78] reported a two-step synthesis of 3,8-diaminoimidazo[1,2-a]pyrazines **40**. The first step includes the GBBR of 2-amino-3-chloropyrazine with different aldehydes and isocyanides in the presence of TMSCl as a catalyst to afford the corresponding 3-amino-8-chloroimidazo[1,2-*a*]pyrazines **39** in a good yield (up to 77 %). The chlorine atom at position 8 is convenient for further aromatic nucleophilic substitution. Conventional heating (100 °C, overnight) of **39** with ammonia, primary or secondary amines in dioxane led to the formation of 3,8-diaminoimidazo[1,2-*a*]pyrazines **40** in good yields (up to 91 %) (Scheme 19).

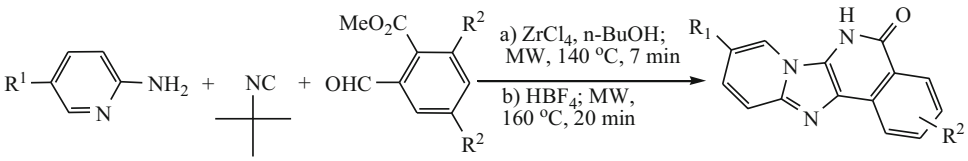
Once more, Salunke et al. [79] described the synthesis of 8-aminoimidazo[1,2-]pyrazines **42** *via* modification of Guasconi et al. [78] method. The microwave-mediated reaction of 2-amino-3-chloropyrazine with different isocyanides and aromatic aldehydes in dioxane using catalytic amounts of HCl afforded the desired 8-chloro-*N*-cyclohexyl-2-phenylimidazo[1,2-a]pyrazin-3-amine **41**. The latter underwent ipso-chloro displacement *via* conventional heating with ammonium hydroxide in a sealed tube (110 °C, 16 h) to give the corresponding 8-aminoimidazo[1,2-*a*]pyrazines **42** in fair yields (up to 30 %) (Scheme 20; [79]).

Interestingly, the use of pyridoxal (**43**) as the aldehyde afforded the hitherto unknown furo[2,3-*c*]pyridines **45** rather than the expected imidazo[1,2-*a*]pyridines **44** adduct. This was confirmed *via* spectroscopic characterization using

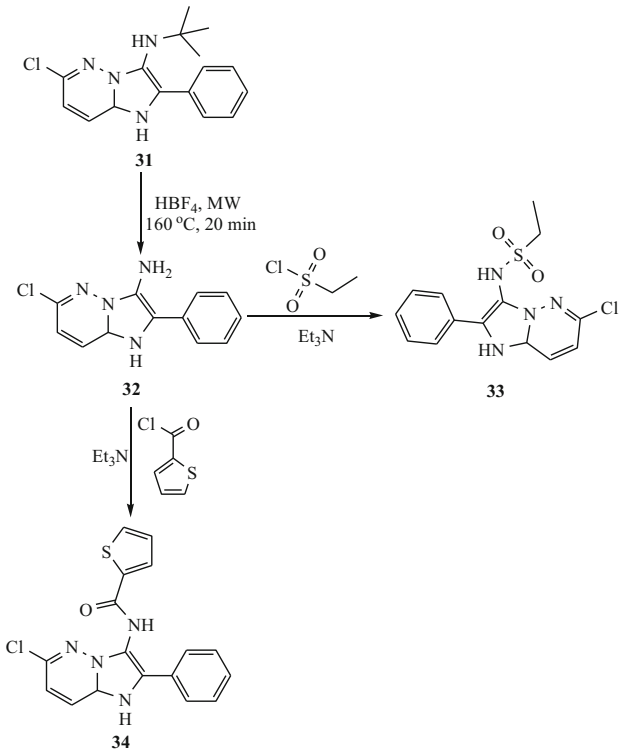
Scheme 15 Microwave one-step de-*tert*-butylation of GBBR adducts using HBF_4 in 1-butanol



Scheme 16 Isoquinolin-oneimidazoles synthesis *via* postmodifications of GBBR adducts



R^1=H, Br; R^2= H, OCH_3



Scheme 17 Diversification of GBBR adducts

NMR spectroscopy (^1H and ^{13}C) and X-ray crystallography (Scheme 21; [79]).

The mechanism includes the in situ formation of an iminium species **46** followed by cycloaddition with the isocyanide to give the corresponding nitrilium ion **47**. The latter is further attacked by the phenolic hydroxyl group of pyridoxal to give the corresponding furo[2,3-c]pyridines **45** as shown in Fig. 11.

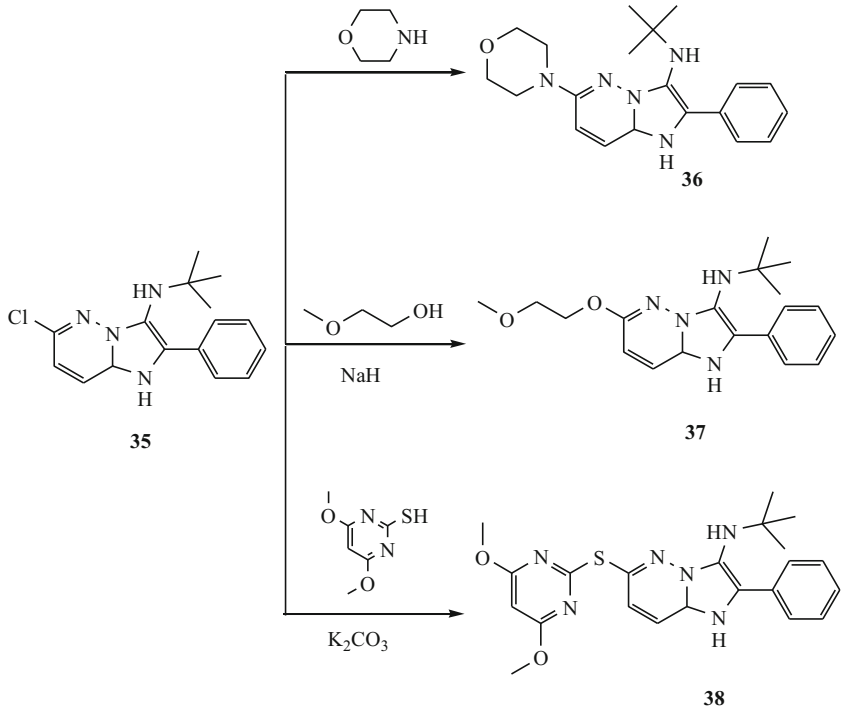
Lu et al. [69] reported a novel two-step fluorous-based synthesis of 3-aminoimidazo[1,2-*a*]pyrazines **50**. These scaffolds are easily accessible *via* employing GBBR followed by Suzuki coupling post-condensations. The reaction of fluorous benzaldehyde **48** with 2-aminopyridine and cyclohexylisocyanide was conducted under microwave irradiation conditions (150 °C for 10 min). The corresponding imidazo[1,2-*a*]pyrazines **49** were further detagged with the Suzuki coupling reaction using 4-methoxybenzeneboronic acid, Pd(1,1′-bis(diphenylphosphino)ferrocene)Cl_2 and K_2CO_3 under microwave irradiation conditions (130 °C for 20 min) to afford the desired products **50** in moderate yields (up to 58 %) (Scheme 22).

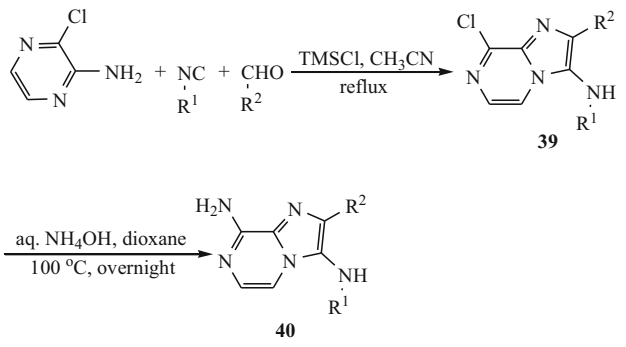
Arnould et al. [80] reported an efficient two-step synthesis of various pyrido[2′, 1′ : 2, 3]imidazo[4,5-b]quinolines **53** using propargyl aldehydes **51** for the first time in GBBR. In this context, imidazo[1,2-*a*]pyridines **52** were firstly synthesized in yields up to 70 % *via* the reaction of 2-amino-5-chloropyridine, propargyl aldehydes **51** and different substituted isocyanobenzenes in methanol using perchloric acid as the catalyst (Scheme 23). Subsequent electrophilic cyclization was next promoted in dioxane under microwave irradiation conditions (220°C for 5 min) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst.

It is worth noting that the cyclization process was insensitive to steric hindrance regardless of the type or position of the substituents and the desired products were obtained in yields up to 96 % (Scheme 30). The alkyne moiety of the propargyl aldehydes were utilized for post-cyclization as shown in the depicted mechanism (Fig. 12; [80]).

GBBR final products could be also modified in order to constitute a convenient functionality suited for further types of MCRs without intermediate isolation. In this context, Semreen et al. [81] reported the six components synthesis of polysubstituted imidazopyridines and imidazopyrazines through the orthogonal union of GBBR and Ugi reactions. Such combination allowed the construction of complex and diverse drug-like compounds in a single, economic and

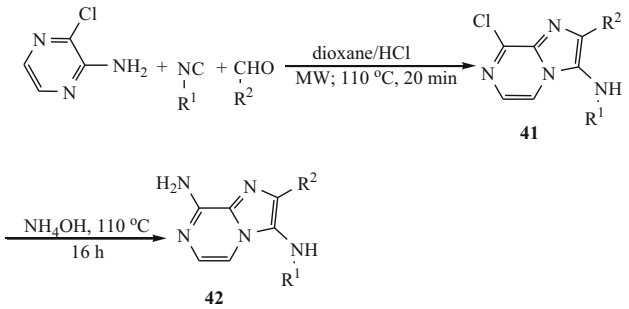
Scheme 18 Secondary aromatic nucleophilic substitution of 6-chloro-2-phenylimidazo[1,2-*b*]pyridazine





R^1 = *tert*-butyl, cyclohexyl; R^2 = C_6H_4, biphenyl, 4-Cl-C_6H_4, 4-NO_2-C_6H_4

Scheme 19 Two-step synthesis of 3,8-diaminoimidazo[1,2-a]pyrazines



R^1 = Bn, cyclohexyl, C_6H_4-OCH_3; R^2 = C_6H_5, Biphenyl

Scheme 20 Synthesis of 8-aminoimidazo[1,2-]pyrazines

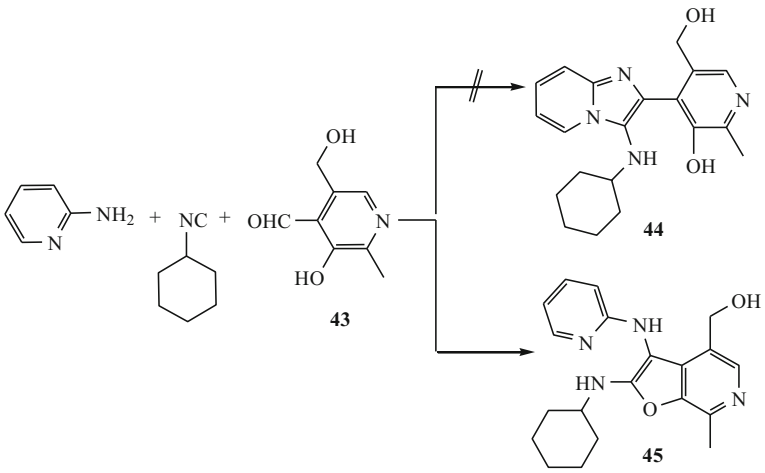
tandem operation. This could be achieved if one of the starting building blocks was designed in order to have suitable functionality that may be selectively exploited for further manipulation.

Semreen et al. [81] selected the aldehyde and the amidine components to possess an unprotected carboxylic suitable for subsequent Ugi reaction. GBBR adducts with a pendant carboxylic group **55** were synthesized in good yields (55–74 %) by using 2-imino-pyridine, suitable isocyanides and 3-carboxybenzaldehyde/4-carboxybenzaldehyde **54** employing methanol and dichloromethane mixed solvents in the presence of 5 mole % of $Sc(OTf)_3$. The reaction mixture is used further without isolation of the intermediate and the pendant carboxylic group provides in this case a linkage for a subsequent Ugi MCR as shown in Scheme 24.

The scope of this strategy was further validated by moving the position of the carboxylic acid group from the aldehyde to the heterocyclic amidine component. In this context, 5-carboxy-2-aminopyridine **57** was condensed with benzaldehyde and the in situ-formed imine was allowed to react with benzyl isocyanide. The subsequent obtained product **58** was further subjected to different Ugi components to produce the polysubstituted imidazopyridines **59** in good yields (65–73 %) (Scheme 25; [81]).

Very recently, Lacerda and colleagues [82] reported the synthesis of novel potent imidazo[1,2-a]pyridine-*N*-glycinylhydrazones **63** which acted as good inhibitors of the tumour necrosis factor alpha (TNF − α) production. These compounds were synthesized in three steps employing the GBBR as the key reaction. Imidazo[1,2-*a*]pyridine esters **61** were firstly synthesized in 65–75 % yields *via* the

Scheme 21 Synthesis of furo[2,3-*c*]pyridines using pyridoxal as the aldehyde component



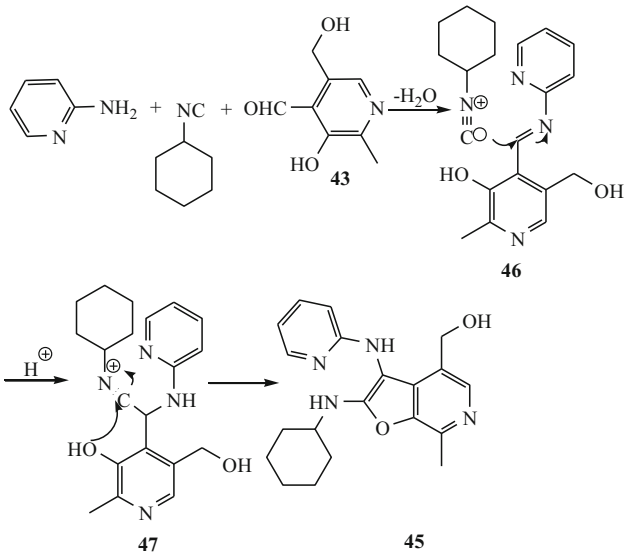
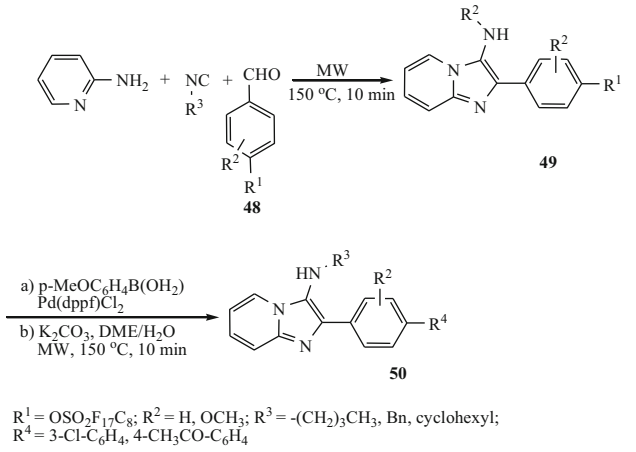


Fig. 11 Proposed mechanism for the synthesis of furo[2,3-*c*]pyridines



Scheme 22 Synthesis of 3-aminoimidazo[1,2-*a*]pyrazines

reaction of 2-aminopyridine, appropriate aldehydes and ethyl isocyanoacetate **60** using ethanol as a solvent. Hydrazinolysis of **61** in refluxing ethanol afforded the corresponding hydrazides **62** in 70–80 % yields. The acid-catalyzed condensation of the hydrazides with different aromatic aldehydes furnished imidazo[1,2-*a*]pyridine-*N*-glycinylhydrazone derivatives **63** in yields up to 90 % (Scheme 26).

The reaction of aldehydes, isocyanides and 2-aminoazines is not always straightforward and regioisomers could be found in the reaction mixture. This was firstly noticed by Bradley et al. reporting that the regioisomeric 2-aminoimidazo[1,2-*a*]pyrimidines **64** and 3-aminoimidazo[1,2-*a*]pyrimidines **65** were both isolated from the GBBR of 2-amino-pyrimidine with different aromatic aldehydes and isocyanides in MeOH (Scheme 27 [83]). It is worth noting that the ratio of the two regioisomers relays on the nature of the substrate and type of the catalyst used.

Applications of GBBR in drug discovery

The aim of this part is not only to list the observed pharmacological activities, but also to further guide medicinal chemistry in developing novel scaffolds that might be of enhanced biological properties for future drug development. Imidazoles are one of the most widespread structural motifs in heterocyclic chemistry that constitutes distinguished structures in medicinal chemistry and can be also found in a large number of therapeutic agents [81,84]. Indeed, the imidazole ring system is considered as one of the key moieties responsible for enhanced biological activities [15,37,85].

Fused imidazo heterobicyclic scaffolds are widely incorporated in the backbone of multiple bioactive molecules and are often considered as important motifs of interesting biological activities. In the field of drug discovery, the pharmacological values of these scaffolds are well appreciated due to their versatile pharmacological and biological profiles. In view of this, several imidazo-annulated heterocycles bearing pyridines, pyrimidines, pyrazines, azines and diazines have emerged as versatile drug templates in

Scheme 23 Two-step synthesis of pyrido[2′, 1′: 2, 3]imidazo[4,5-b]quinolines using different propargyl aldehydes

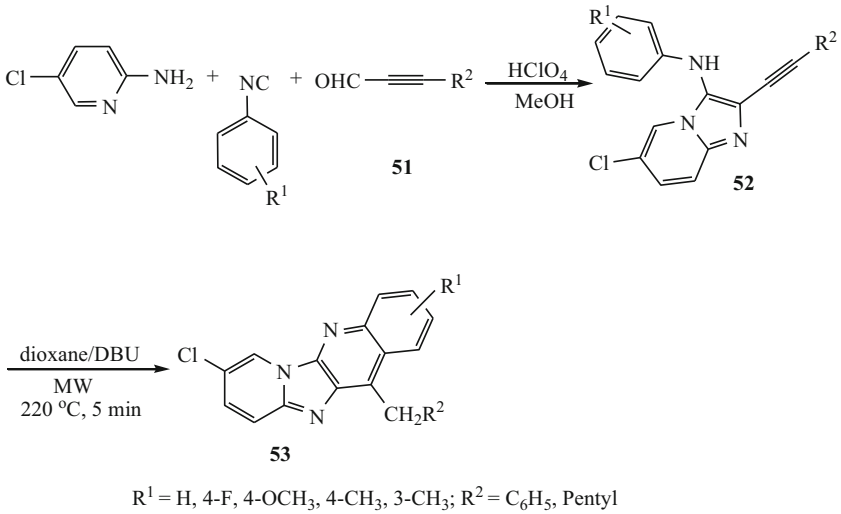
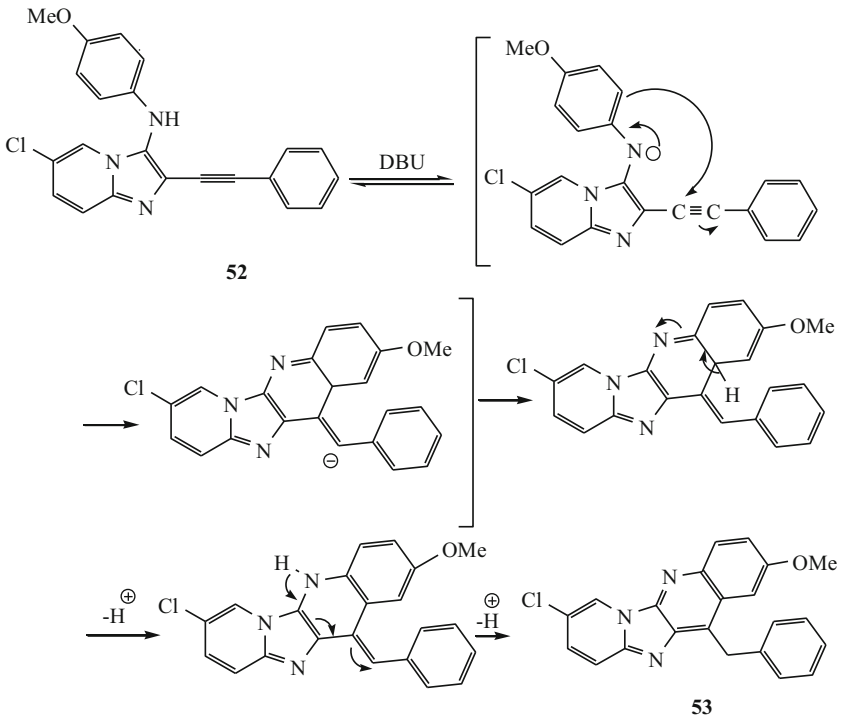


Fig. 12 Proposed mechanism for the synthesis of pyrido[2′, 1′: 2, 3]imidazo[4,5-b]quinolines



broad areas of medicinal chemistry, ranging from antiviral, antibacterial, fungicidal, anti-ulcer and anti-inflammatory applications [37].

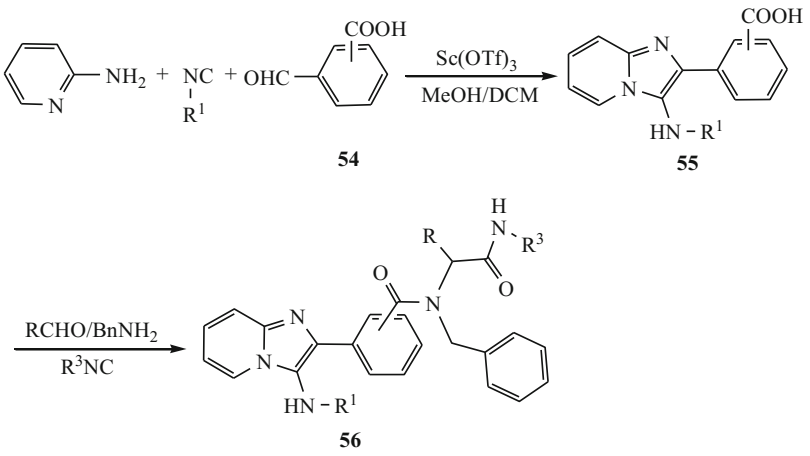
Fluorescent dyes have been widely used in the photovoltaic cells, optical sensors, light-emitting diodes (LEDs), fluorescent colourants and biological labels [86,87]. The latter are most often used to prepare various bioconjugates for immunochemistry and histochemistry *via* modification of antibodies, amino acids, peptides, oligonucleotides, nucleic acids, carbohydrates and other biological molecules [88–90].

Among fluorescent dyes, imidazo[1,2-*a*]pyridine derivatives have been reported as potential candidates for fluorescent probes, which can be used for fluorescence imaging in clinical diagnostics and biomedical research [91]. Furthermore, these compounds have been also used in dye-sensitized solar cells and dye lasers as well as important organic LEDs [92–94].

In 2012, Khan et al. [49] reported the synthesis of imidazo[1,2-*a*]pyridines *via* one-pot GBBR using 5 mol % of bromodimethylsulfonium bromide (BDMS) at room temperature. Compounds **66** and **67** exhibited interesting fluorescence properties with UV–Visible intense absorption maxima at 250 ± 5 and at 335 ± 2 nm (Fig. 13).

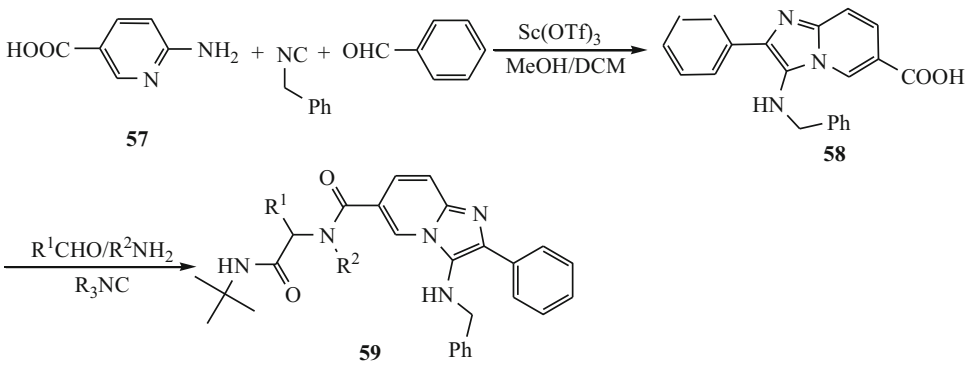
In 2014, imidazo[1,2-*a*]pyridines **68** possessing a 5-benzyloxy-4H-pyran-4-one moiety were found to exhibit the highest fluorescence emissions in dichloromethane com-

Scheme 24 Polysubstituted imidazopyridines synthesized by GBBR followed by an Ugi reaction



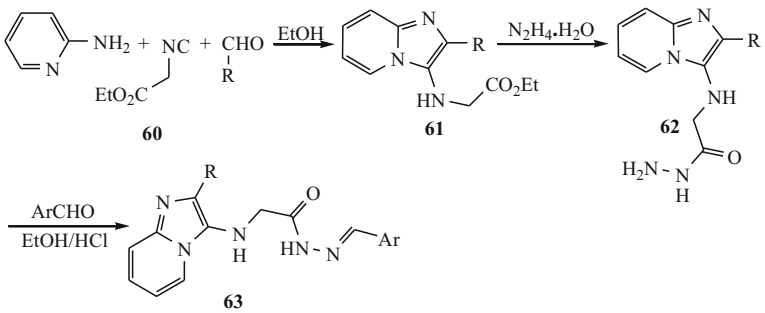
R^1 = *tert*-butyl, Bn; R^2 = $CH_2(CH_3)_2$, 4-F-C_6H_4, 3-OCH_3-C_6H_4, pyridine; R^3 = *tert*-butyl, Bn, $CH_2COOC_2H_5$

Scheme 25 5-Carboxy-2-aminopyridine allows a secondary Ugi reaction for the construction of polysubstituted imidazopyridines



R^1 = C_6H_5, 4-F-C_6H_4, 4-C_6H_3(-OCH_2CH_2O-); R^2 = Bn, $CH_2CH(CH_3)_2$, cyclopropyl;
R^3= *tert*-butyl, $CH(CH_3)_2$, $CH_2COOC_2H_5$

Scheme 26 Synthesis of imidazo[1,2-a]pyridine-*N*-glycinylhydrazones with potent tumour necrosis factor alpha (TNFα) inhibitor activity



R = *tert*-butyl, C_6H_5; Ar = C_6H_5, 4-Cl-C_6H_4, 4-OH-C_6H_4

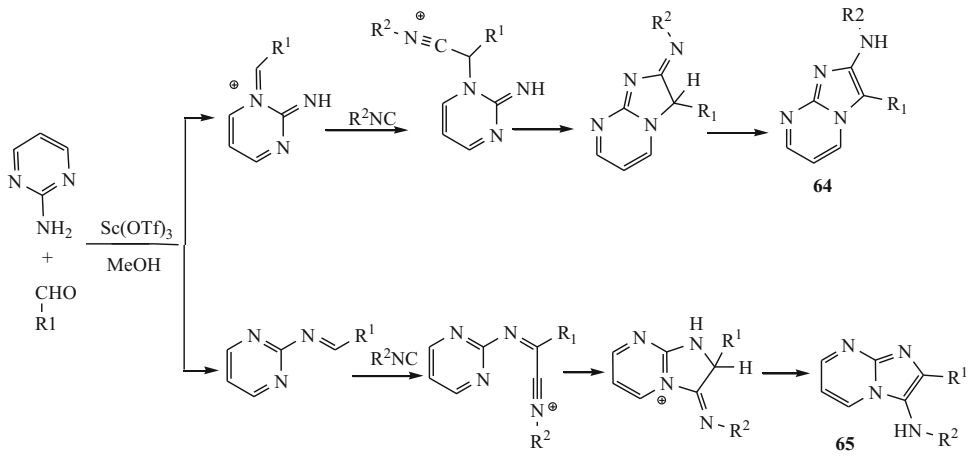
pared to other GBBR products [43]. The photophysical properties of these compounds showed a fluorescence quantum yields (Φ_f = 0.209 and 0.203) and relatively Stokes shifts (≈120 nm) (Fig. 14; [43]).

In 2011, Li et al. [95] descried the synthesis of various ^{18}F-labelled imidazo[1,2-a]pyridines **70** by employing GBBR between 4-[^{18}F]fluorobenzaldehyde aminopyridines **69** and benzyl isocyanide using $Sc(OTf)_3$ as a catalyst and 3-methyl-1-butanol as a solvent in moderate yields (62 and 73 %) (Scheme 28).

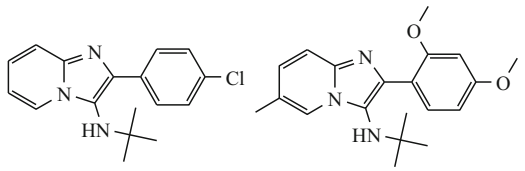
Many drug formulations bearing fused imidazo heterocycle scaffolds have been developed and are currently available on the market, for example, zolimidine **71** (anti-ulcer), olprinone **72** (PDE 3 inhibitor), zolpidem **73** (hypnotic), alpidem **74** (anxiolytic), saripidem **75** (sedative agents), necopidem **76** (sedative agent), GSK812397 **77** (HIV), ponatinib **78** (chronic myeloid leukaemia) and candesartan **79** (hypertension) as depicted in Fig. 15 [82,96].

In 2011, Baviskar et al. [96] reported the synthesis of *N*-fused imidazole scaffolds employing GBBR and evaluated

Scheme 27 GBBR of 2-aminoazines afforded 2-aminoimidazo[1,2-*a*]pyrimidines and 3-aminoimidazo[1,2-*a*]pyrimidines regioisomers

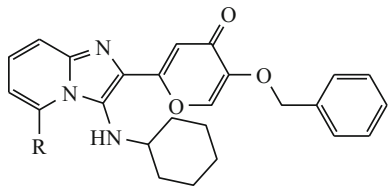


R^1 = C_6H_5, 4-CO_2CH_3-C_6H_4, 4-OCH_3-C_6H_4; R^2 = *tert*-butyl, $C(CH_3)_2CH_2$-*tert*-Butyl



66 **67**

Fig. 13 Fluorescent imidazo[1,2-a]pyridines synthesized *via* GBBR



68

R = H, CH_3

Fig. 14 Fluorescent imidazo[1,2-a]pyridines possessing 5-benzyloxy-4H-pyran-4-one

their anticancer activity against kidney and breast cancer cell lines. It was found that imidazopyridines **80**, imidazopyrazines **81, 82** and imidazopyrazoles **83, 84** showed relatively higher anticancer activities compared to standard drugs, 5-fuorouracil and etoposide. Their selective anticancer activities were further confirmed *via* their lower cytotoxicity to normal cells. These compounds exhibited potent cell migration inhibition and exert apoptotic effect in G1/S phase [96]. Furthermore, these compounds exhibited potent inhibition of hTopoIIα catalytic activity but did not show any DNA intercalation activity. Molecular modelling studies proposed that these compounds exert their inhibitory activity *via* occupying the ATP binding pocket of the ATPase domain of hTopoIIα and thus making favourable interactions with its key residues (Fig. 16).

In 2012, Salunke et al. [79] described the synthesis of furo[2,3-*c*]pyridines **85** as novel candidate vaccine adjuvants with structural similarity to the known TLR7/8 ligands. The synthesized compounds were subsequently screened in NF-κB reporter gene assays specific for human TLR-3, -4, -5, -7, -8 and -9. It was found that these compounds possess a strong adjuvantic activity *via* activation of TLR8-dependent NF-κB signalling. Furthermore, the most potent compounds were examined for their cytokine-inducing properties using the reference TLR8 agonist, 2-propylthiazolo[4,5-*c*]quinolin-4-amine (CL075) **86**. Interestingly, the compounds showed potent dose-response profiles in primary TLR8-agonistic screens (Fig. 17).

Imidazo[1,2-*a*]pyridine-*N*-glycinylhydrazones synthesized by Lacerda et al. [82] were structural analogues of the orally active anti-inflammatory prototype p38 MAPK inhibitors: BIRB-796 **87**, LASSBio-1504 **88** and SB-203580 **89** [82]. For diversification purposes, the *N*-phenyl-pyrazole nucleus of LASSBio-1504 was replaced by the isosteric heterocycles imidazo[1,2-*a*]pyridine. Furthermore, the naphthyl motif attached to the imine side of the *N*-acylhydrazone was also substituted with other aromatic scaffolds (Fig. 18).

Interestingly, the incorporation of imidazo[1,2-*a*]pyridine scaffolds and addition of more lipophilic groups to the imine framework of the *N*-acylhydrazone moiety were associated with increased anti-TNF-α potency. Among the synthesized compounds, LASSBio-1749 **90** was the most potent derivative of this series. Indeed, the latter was found to be equipotent to SB-203580 **89** and even more active than the reference LASSBio-1504 **88** (Fig. 18). Furthermore, evaluation of the corresponding cytotoxicity and selectivity index revealed that LASSBio-1749 **90** was safer than LASSBio-1504 **88** and SB-203580 **89** [82].

Scheme 28 Synthesis of ^{18}F-labelled imidazo[1,2-a]pyridines

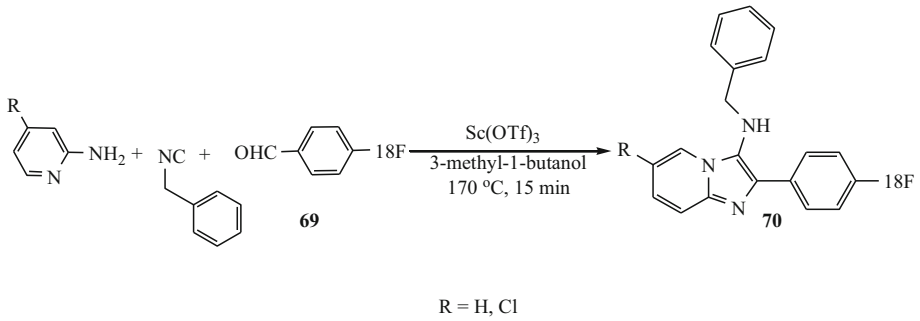


Fig. 15 Fused imidazo heterocycles drugs

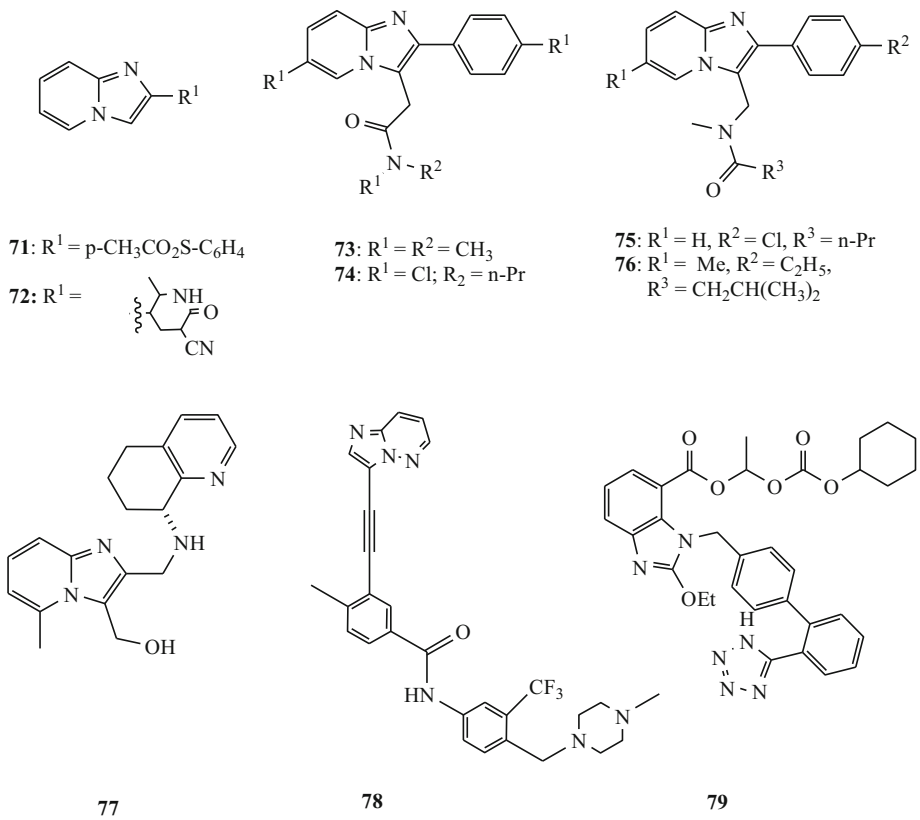
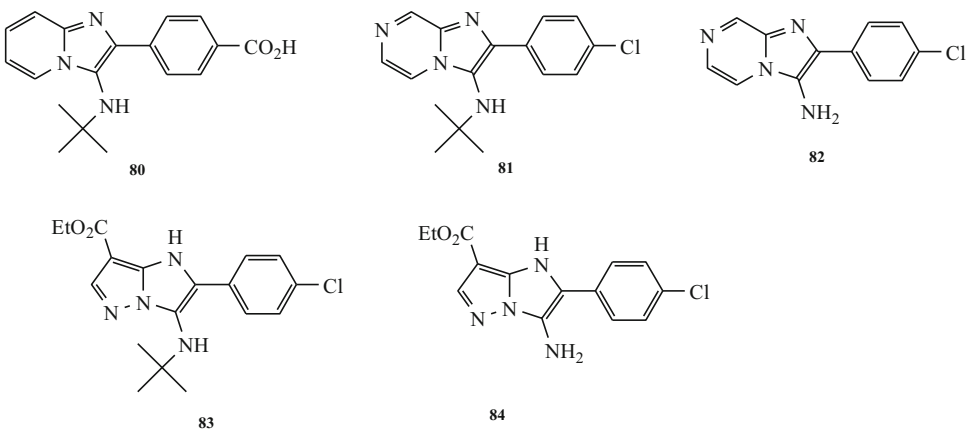
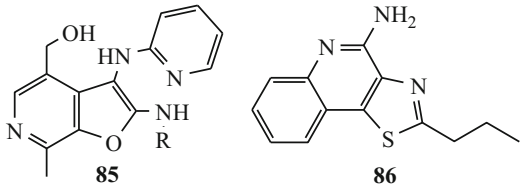


Fig. 16 *N*-fused imidazoles with potent inhibition of hTopoIIα catalytic activity





85 **86**

R= Bn, n-butyl,n-hexyl, CH_2 $Si(CH_3)_3$

Fig. 17 TLR7/8 agonistic scaffolds

In addition, 3,8-diaminoimidazo[1,2-a]pyrazines synthesized by Guasconi et al. [78] were used as potential kinase inhibitors. These compounds were designed in order to mimic the purine nucleus which is present in many kinase inhibitors (e.g., AP23846, a potent c-Src kinase inhibitor, **91**) which could compete with ATP in the catalytic domain. In view of this, synthesized compounds were investigated for their inhibitory activity on PI3Ks and STAT5-dependent transcription (Fig. 19). Surprisingly, none of the synthesized compounds exhibited any sensible inhibitory activity on PI3Ks. On the other hand, only four compounds (**92**–**95**) were able to potently inhibit STAT5-dependent transcription (Fig. 19). This further suggests the compounds' inhibitory activity on kinases *via* inhibition of the fundamental kinase, STAT5-dependent transcription, in this cascade.

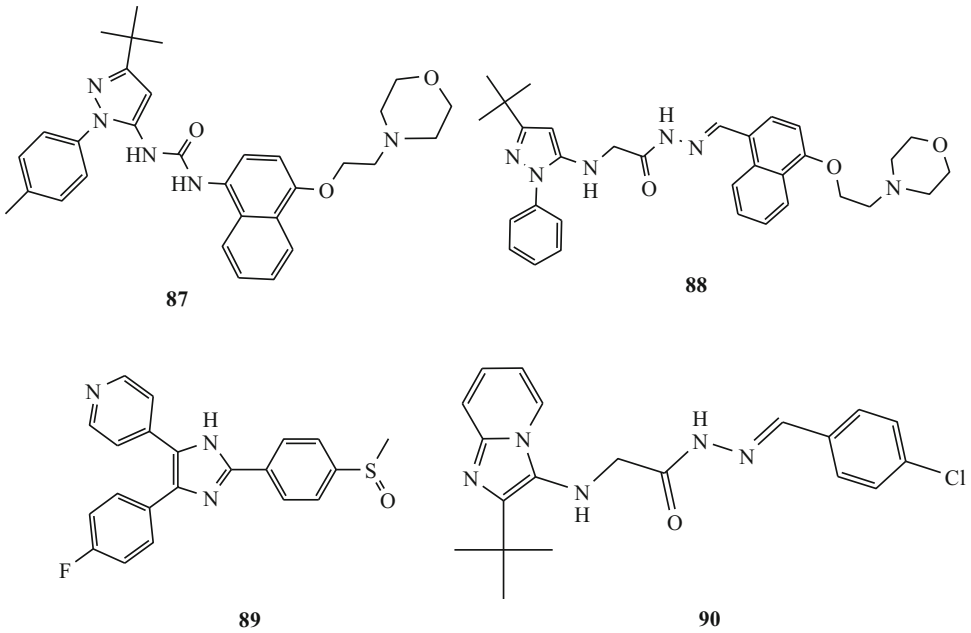
In 2014, Sanghai et al. [97] reported the synthesis of novel synthetic analogues of the tubulin polymerization inhibitor, combretastatin A-4. Compounds **96**-**102** (Fig. 20) showed potent anticancer activities in different cancer cell lines (kidney, breast and cervical) and relatively lower toxicity in normal cells. These compounds inhibited both tubulin polymerization and tubulin-microtubule dynamics disruption. Furthermore, they induced DNA and chromosomal damage, cell cycle arrest in the G2/M phase and activation of caspase-3 in HEK 293T cells leading to cell death *via* apoptotic-mediated pathway. These results were confirmed by several biophysical and immunological assays including DAPI nuclear staining, expression of representative apoptotic protein markers, immunocytochemistry, comet assay and cytokinesis-block micronucleus assay in HEK 293T cells [97].

Molecular docking studies and molecular dynamics (MD) simulations were performed on all the synthesized compounds to figure out the mode of binding, atomistic level interactions and binding affinity of these compounds with the α,β-tubulin heterodimer. Interestingly, the compounds showed docking score and binding free energy values comparable to that of CA-4 which further underlined the mode of tubulin polymerization inhibition, i.e., *via* interacting on colchicine binding site [97].

In 2009, Odell and colleagues [98] reported the synthesis of imidazo[1,2-*a*]pyridines **103** as novel non-amino acid inhibitors of the mycobacterium tuberculosis glutamine synthetase (MtGS). Some of these compounds were more potent than the known inhibitors, *L*-methionine (S,R)-sulfoximine **104** and phosphinothricin **105** (Fig. 21). The inhibitory activities of these compounds were in the low micro-molar and sub-nano molar range.

X-ray technique was used to explore the binding mode of this class of compounds with MtGS. It was found that this class of inhibitors binds in a slightly different manner than the previously crystallized ATP-site MtGS inhibitor of the commercially available diketopurine **106** MtGS class (Fig. 21).

Fig. 18 Inhibitors of the tumour necrosis factor alpha (TNFα)



87 **88**

89 **90**

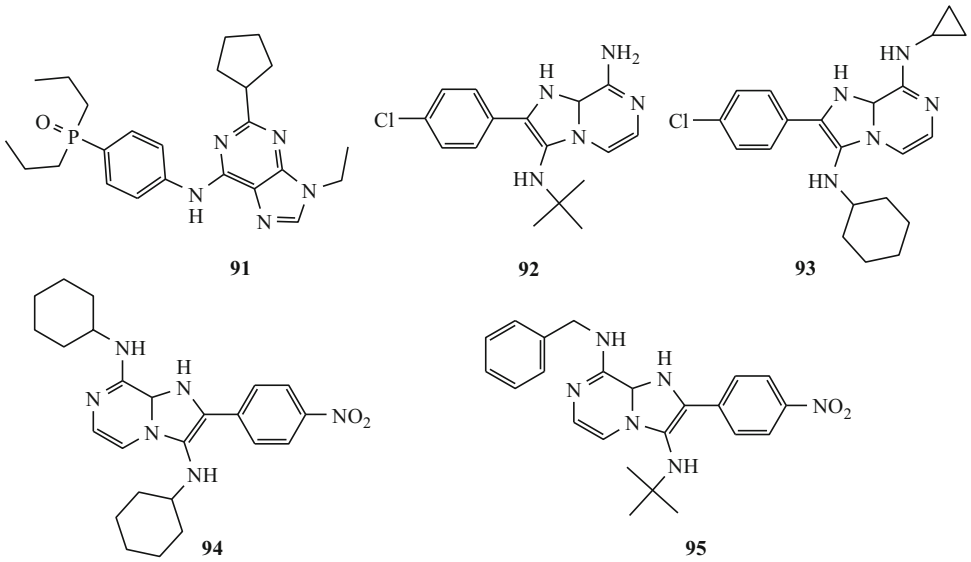


Fig. 19 Imidazo[1,2-a] pyrazines with potent kinase inhibitor activity

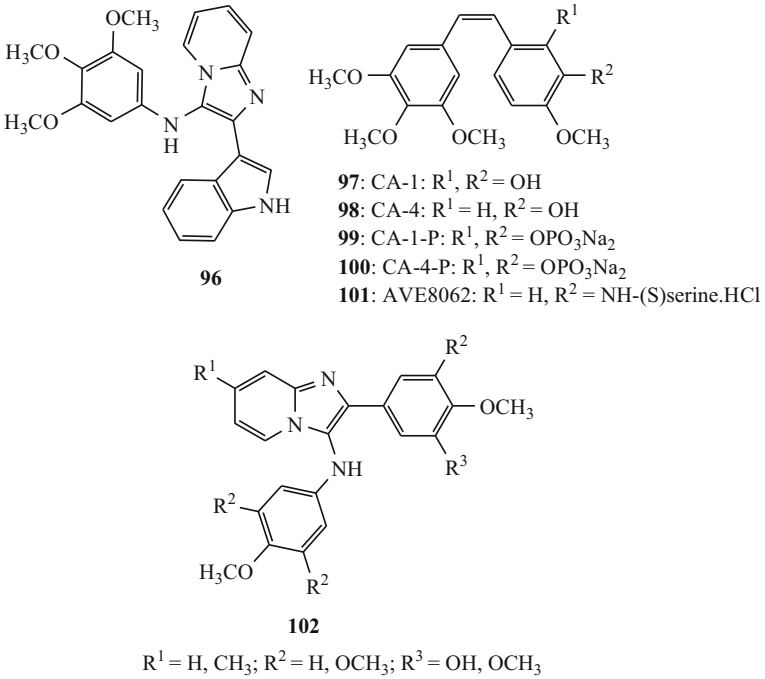


Fig. 20 Synthetic analogues of combretastatin A-4 tubulin polymerization inhibitor

However, it utilizes the same hydrophobic pocket that is adjacent to, but not directly in, the ATP binding site [98].

In 2014, a computational docking multitarget screen of thirty representative imidazo-azines was performed by Kumar et al. [99] in the quest for novel inhibitors against malaria, tuberculosis and Chagas tropical diseases. Well-validated drug targets from literature were selected based on their biological role, selectivity and previous docking history. Computational data (i.e., binding affinity and ligand efficiency) suggested that the chosen set of imidazo-azine scaffolds are selective inhibitors against multiple targets namely; Pf-dihydrofolate Reductase (DHFR), Pf-enoyl acyl carrier protein reductase (Enoyl ACP Reductase), Pf-protein kinase 7 (PK 7), Mt-pentothenate synthetase (Mt-PS) and Mt-thymidine monophosphate (Mt-TMPK). Two compounds namely 2-(4-chlorophenyl)-*N*-cyclohexyl-6-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-amine (MCL011) **107** and *N*-cyclohexyl-2-(4-methoxyphenyl)-6-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-amine (MCL017) **108** have shown the highest binding affinity against the studied targets (except Mt-TMPK) with acceptable ligand efficiency. These compounds can therefore be considered as good hits for the developing of more efficient scaffolds in the future (Fig. 22).

Imidazopyridines and imidazopyrazines **55** and **56** synthesized by Semreen et al. were evaluated for their antibacterial activities against a wide range of hospital-resistant clini-

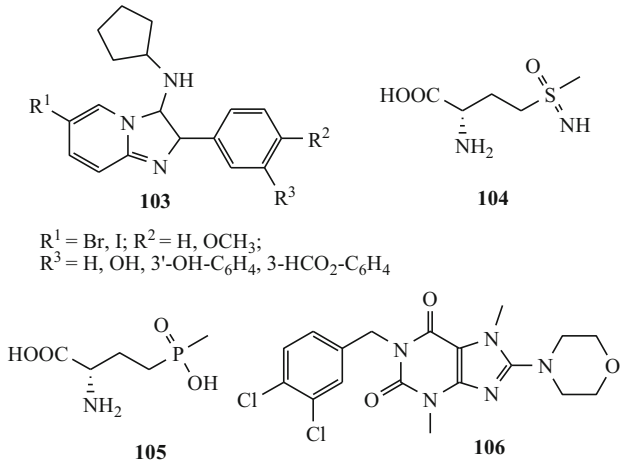


Fig. 21 Novel imidazo[1,2-a]pyridines as potent inhibitors of the MtGS

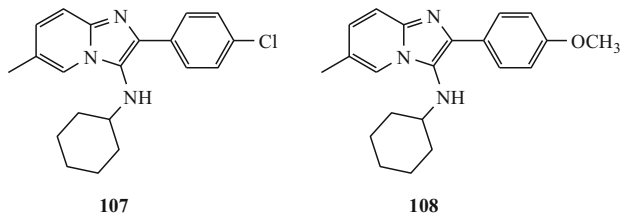


Fig. 22 Structures of suggested inhibitors with highest binding affinity against different targets in malaria and tuberculosis

cal bacterial isolates namely *Staphylococcus epidermidis, Escherichia coli*, *Klebsiella pneuomoniae*, *Pseudomonas aeruginosa* and *Proteus vulgaris* [81]. Some of these compounds were found to be effective against Gram-positive methicillin-sensitive *Staphylococcus aureus* (MMSA; ATCC 25923) and methicillin-resistant *Staphylococcus aureus* (MRSA; ATCC 35591). These findings were in agreements with Shukla et al.'s study on novel GBBR-derived imidazo[1,2-*a*]pyridin-3-amines where these compounds were TLR7/8-inactive, but exhibited bacteriostatic activity against Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA).

Summary and outlook

In summary, MCRs provided a powerful tool to access structural diversity and molecular complexity in the context of DOS. Among the MCRs, IMCRs were developed as a versatile and diverse approach in medicinal chemistry and drug discovery process. Indeed, these reactions were used for the construction of different heterocycles, including bridgehead nitrogen heterocycles, which are of biological and therapeutic relevance. This is where GBBR come to play. The latter is used for the one-pot synthesis of fused imidazoles heterobicyclic compounds from readily available aldehyde, isocyanide and amidine building blocks. According to convergent strategies, low molecular-weight drug-like libraries are obtained in a single synthetic step.

The synthetic scope, variations, secondary transformations and postmodification of GBBR since 1998 were compiled in this review. The reaction included a wide range of catalysts and can be performed either under solvent or solvent-free conditions. This reaction could also be performed under microwave irradiation as an energy-efficient heat source.

Furthermore, the GBBR adducts can be used as a substrate for the synthesis of a variety of more complex scaffolds *via* postmodification reactions. These included cyclization and nucleophilic substitution as well as further MCRs.

The preceding examples showed that this reaction has seen diverse applications in combinatorial and medicinal chemistry and its products are of great use in drug discovery. It is expected that research efforts on this reaction will continue in the search for new, small molecules with drug-like properties.

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