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The Groebke-Blackburn-Bienaymé Reaction

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Abstract

Imidazo[1,2-*a*]pyridine is a well-known scaffold in many marketed drugs, such as Zolpidem, Minodronic acid, Miroprofen and DS-1 and it also serves as a broadly applied pharmacophore in drug discovery. The scaffold revoked a wave of interest when Groebke, Blackburn and Bienaymé reported independently a new three component reaction resulting in compounds with the imidazo[1,2-*a*]-heterocycles as a core structure. During the course of two decades the Groebke Blackburn Bienaymé (GBB-3CR) reaction has emerged as a very important multicomponent reaction (MCR), resulting in over a hundred patents and a great number of publications in various fields of interest. Now two compounds derived from GBB-3CR chemistry received FDA approval. To celebrate the first 20 years of GBB-chemistry, we present an overview of the chemistry of the GBB-3CR, including an analysis of each of the three starting material classes, solvents and catalysts. Additionally, a list of patents and their applications and a more in-depth summary of the biological targets that were addressed, including structural biology analysis, is given.

Keywords

Imidazo[1,2-*a*]pyridine; Multicomponent reactions; Isocyanides; Chemical space; Biological activity

Introduction: Medicinal Chemistry and Multicomponent Reactions

Design and synthesis of biological active compounds are an important field of chemistry as to date there are still many conditions, lacking treatment possibilities. Introduction of novel drugs continuously improve human health despite dramatic increase in world population. The continuous discovery of new biological pathways and the protein targets involved are a great source for medicinal chemist to fill the void in drugs for unmet medical needs. Where the work of structural biologists ends, in elucidating the dynamics and crystallographic structures of large biological structures, medicinal chemists start by the design of agonists and antagonist for those proteins and enzymes. By mimicking the shape and electrostatics of a small natural ligand for example, small molecules can be used to influence those natural processes resulting in inhibition or activation of the associated pathways. Diversity oriented

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synthesis is often applied to discover small molecules and to optimize their binding affinity in receptor binding sites.[1] Introduction of structural diversity is usually accomplished by the stepwise introduction of the individual moieties in the target molecule and each structural variation requires repetition of a part or even whole synthesis route. This divergent and sequential approach for the synthesis of compound libraries can be quite challenging and material and time consuming. A more convenient way would be to assemble a versatile scaffold and obtaining the variations in a single reaction step. With two component reactions the divergent synthesis of very large chemical space and size based on available building blocks is naturally limited. Multicomponent reactions (MCR), however, allow for the concomitant variation of three or more building blocks at the same time and consequently span a very large chemical space. Since the degree of the reaction enters the exponential, the chemical space is naturally much larger the higher the degree of the reaction. E.g. for 2-component and 5-component reaction based on 1.000 building blocks of each variable class, 1.000.000 and 1.000.000.000.000.000 products can be expected, respectively. This exponential explosion of chemical space is key to the philosophy of MCRs.[2] MCRs allow for the introduction of various scaffold shapes introduced through several MCR variants such as Ugi 3-component reaction (U-3CR),[3] Passerini (P-3CR),[4] Gewald (G-3CR),[5] Groebke-Blackburn-Bienaymé (GBB-3CR),[6–8] Biginelli (B-3CR)[9] and many other MCR name reactions. Decorating and derivatization of the scaffolds is simply done by choosing different starting materials (building blocks). For example, in the Ugi-4CR, with 100 different amines, aldehydes, carboxylic acids and isocyanides as reagents, $100 \times 100 \times 100 \times 100 = 10^8$ different compounds can be synthesized, all connected to the dipeptidic Ugi scaffold. Such information rich chemical space has found recently applications in advanced information technology such as molecular steganography.[10] *Clearly, the large chemical MCR space comprise an excellent playground for drug hunters.* Of course there are more different starting materials available, and other MCR reactions, where bi-functional orthogonal starting materials could lead to even more complex (poly)cyclic structures in post modifications, such as UDC-procedures (Ugi-Deprotection-Cyclization) and Passerini-reaction-Amine-Deprotection-Acyl-Migration (PADAM) and giving access to a nearly unlimited number of compounds of most diverse shape and electrostatics and composition of 3D pharmacophores.[11,12] The isocyanide-based multicomponent reactions (IMCR), U-3CR, P-3CR, van Leusen (vL-3CR),[13] GBB-3CR and variations, are nowadays the most popular types of MCR because of the versatile behavior of the isocyanides, carbene-type, α-anion and radical reactivity as well as the excellent atom economy. Examples of marketed drugs and lead compounds made by an MCR approach are Xylocaine (Ugi-3CR),[14] Nifedipine (Hantzsch),[15] Telaprevir (Passerini-3CR)[16] and Crixivan (Ugi-4CR)[17] (Scheme 1). It is estimated that approximately 5 % of the currently marketed drugs can be advantageously assembled by an MCR. Thus MCR scaffolds are clearly “drug-like”.

Here we will focus on one of the youngest IMCRs, the GBB-3CR based on its enormous interest in applied chemistry. The development of the reaction started by Groebke et al. (Hoffman-La Roche), initially published as a side reaction of the U-4CR. While studying the effect of various amine components, it was found that amines with a cyclic H_2N-C=N substructure (2-aminoazines or amidines), such as 2-aminopyridine, 2-aminopyrazine and 2-aminopyrimidine were yielding the corresponding 3-amino-substituted imidazo[1,2-*a*]-

pyridines, -pyrazines and -pyrimidines respectively.[6] In this report, they made the reference to Sugiura et al. and suggests that the very first report of the GBB-3CR methodology was made almost 30 years earlier by condensing 2-aminopyrazine with formaldehyde, the nitrile compound and sodium or potassium cyanide. This was in contrast to the conventional method to access imidazo[1,2-*a*] annulated pyridines, pyrazines or pyrimidines whereby a heterocyclization reaction between α-haloketones with the corresponding amidines was performed.[18,19]

At the very same time Blackburn et al. from Millennium Pharmaceuticals (USA) published their work. The additional value of this work is the use of scandium triflate as Lewis acid catalyst.[20] It follows the finding of Groebke et al. that the presence of an Brønsted acid, such as acetic acid is resulting in higher yields. This pH dependency results from the requirement of proton-assisted activation of the Schiff base to enable attack of the isocyanide component. As a third inventor of the GBB-3CR, Bienaymé et al. (Rhône-Poulenc Technologies (France)) reported in search of new MCR chemistry an approach to apply two covalent bonded or bridged reagents and found a 3-component reaction of 2-aminopyridine or -pyrimidine with aldehydes and isocyanides in the presence of a catalytic amount of perchloric acid in methanol (Scheme 2). This approach was applied to produce 31 examples with variation points in all three components with yields between 33 and 98 %.[8] Due to the nearly simultaneous reports on the discovery of this three component reaction the reaction was called later-on the Groebke-Blackburn-Bienaymé 3-component reaction or in short the GBB-3CR. Interestingly, since its initial description, it took ca. 8 years until an exponential increase in reports was observed using the GBB-3CR methodology broadly in chemistry and also leading to multiple patents (Figure 1).

Quite impressively, so far, more than 200 publications and >100 patent applications have been reported, exploiting the GBB-3CR, with a clear trend of further increasing interest. With this in mind a few reviews were published, dedicated to the GBB-3CR as an MCR approach to access 3-amino-substituted imidazo[1,2-*a*]-heterocycles. Singh et al. were the first to cover the reaction and addressed the used catalysts and the general chemistry behind the GBB-3CR.[21] Abdel/Wahab et al. reported a more comprehensive review, highlighting biological targets the GBB scaffold could be used for, possible post-modifications and to a certain extend the scope and limitations were discussed with some examples of amidines, isocyanides, aldehydes used in the GBB-3CR.[22] In addition Liu published an overview on the Asinger[23] and GBB-3CR, in a historical fashion with emphasis on the possible post modifications and applications of both reactions.[24] Also Liu dedicated a mini review solely on potent applications of the imidazo[1,2-*a*]-heterocycles.[25] To the best of our knowledge patents were never discussed and our review tries to give a complementary twist by giving insight into all the used reactants, all the catalysts and solvents used in the GBB-3CR, detailed discussion of the structural biology, in order to get more insight in how GBB scaffolds interact with therapeutically relevant targets.

Mechanism

Examples of isocyanide based MCR's (IMCR's) are the P-3CR, vL-3CR, U-4CR, Ugi-azide-4CR, U-3CR, and GBB-3CR (Scheme 3). Aside from the P-3CR and the vL-3CR, the

latter 3 IMCR's are mechanistical variations on the U-4CR. The acid component is decisive in how the iminium species will react towards other components, rearrange and ultimately is incorporated into the scaffold.

For example, the U-3CR is only taking the proton of specific acidic reagents (e.g. *p*-toluenesulfinic acid (*p*TsIA)) and eliminating the Mumm rearrangement that otherwise concludes the U-4CR. The Ugi azide-4CR reaction adheres to a similar mechanism as the U-3CR, hydrazoic acid is introduced by using sodium azide or $TMSN_3$. In the GBB-3CR the additional reactivity of the endocyclic nitrogen in the amidine component allows for the formation of a different scaffold, whereas the acid component is not incorporated in the final product and serves only catalytic purposes instead. In the GBB-3CR, the imine intermediate is activated by a Lewis or Brønsted acid, and follows a formal [4+1] cycloaddition sequence concluding with aromatization via a 1,3-H shift (Scheme 4 Pathway A) to form the imidazo[1,2-*a*]pyrimidine when 2-aminopyridine is used. The GBB-3CR could follow two possible pathways leading to regioisomers as indicated in Scheme 4. Pathway A is the most common and is referred to as the GBB-3CR and pathway B as the "inverse" GBB-3CR.

2-Aminopyrimidines tend to form both regioisomers as it was first described by Bradley et al., trying to explain the low yields of some of their reactions while the starting materials were fully consumed.[26] Isolation of a second product having nearly identical TLC-R_f values, mass and ^1H NMR spectra gave reason to perform an X-ray structure analysis, uncovering the two regioisomers **1** and **2** depicted in Scheme 5. Luckily, the normal GBB product is the major product for most cyclic amidine building blocks, thus rendering it a quite useful synthetic reaction. In fact, in most cases not even traces of inverse GBB products can be observed.

Proceedings in the Development of the GBB-3CR

Based on the pharmacological relevance of imidazo[1,2-*a*]-heterocyclic compounds and their easy access through the GBB-3CR, many scientists explored the scope and limitations of this reaction, trying a large variety of catalysts, solvents and temperature conditions, resulting in a wide variety of publications with a confusing high number of different conditions. Herein, some of the more relevant reports are discussed, showing important developments, noteworthy applications and several reaction conditions used are described to fully comprehend the versatile character of the GBB-3CR. For example, Varma et al. showed that a microwave (MW) assisted solvent-free method could be applied by the aid of montmorillonite K-10 clay.[19] The conditions were quite unusual that time since microwave assisted procedures were not yet broadly applied in 1999. Here a household microwave was used with an unsealed test tube irradiated at 900 W for 3 minutes. Together with the clay catalyst and variations of simple aromatic aldehydes, various isocyanides and 2-amino-pyridine (**3**), pyrazine (**4**) or pyrimidine (**5**) yields of >80 % were obtained (Scheme 6).

Whittaker et al. showed a very similar scandium triflate catalyzed reaction via a microwave assisted GBB-3CR in 10 minutes with yields between 33–93 % and using substituted benzaldehydes and mostly aminopyridines, interestingly also a 5-membered aminothiazole substrate was introduced, giving lower yields mostly related to side products (**6**) formed by

the addition of methanol to the intermediate Schiff base (Scheme 7).[8,27] The side product formation could, however be suppressed by the use trifluoroethanol as a less nucleophilic solvent.

Hulme et al. showed TMSCN as an equivalent to the simplest isocyanide HNC, to directly access 3-aminoimidazo[1,2-*a*]pyridines **7–8**, which otherwise would require an additional deprotection step when a convertible isocyanide such as the Walborski's reagent (1,1,3,3-tetramethylbutyl isocyanide) is used in the GBB-3CR (Scheme 8).[28]

Some side product was found to be the Schiff base **9**, formation could be prevented by using an excess of amidine. After the reaction the residual catalyst $Sc(OTf)_3$ was removed using 5 equivalents of Si-trisamine, which is a powerful scavenger of electrophiles as well as an effective scavenger for transition metals.

GBB-3CR products are often observed as being strongly fluorescent. Balakirevet al. introduced "Flugis"; fluorescent Ugi products as drug-like probes for the identification and visualization of potential targets.[29] The compounds described as U-3CR compounds arise from the GBB-3CR and were used with the rationale to incorporate drug-like scaffolds into fluorescent molecules. *The often fluorescent nature of GBB products should be kept In mind during biophysical receptor-ligand screens based on fluorescence principles!* For example, in a recent screen for inhibitors of the NS3/4A serine protease of the hepatitis C virus, some of the compounds with the [1,2-*a*]pyridine scaffold were found to exhibit auto-fluorescence in UV that interfered in the enzymatic fluorescence detection assay.[29] This led to their approach to incorporate this scaffold that is synthesized using the GBB-3CR in their search of fluorophores in a 1600 compound containing microarray, resulting in fluorescent imidazo[1,2-*a*]-pyridine compounds, which are known to interact with the peripheral benzodiazepine receptor (known as the translocator protein TPSO) and $GABA_A$ benzodiazepine receptors. The compounds were tested for their affinity with, and use as TPSO imaging probes (Scheme 9).

The introduction of a ^{18}F-label to PET radiotracers via ^{18}F-labelled prosthetic groups using MCR chemistry was discussed by Gouverneur et al.[30] Labeling of ^{18}F requires reaction conditions which might not always be compatible with the substrate. By using ^{18}F-benzaldehydes in MCR assisted radiochemistry, mild conditions could easily be performed in the U-4CR, P-3CR, B-3CR and GBB-3CR while maintaining a swift reaction necessary for the rather short half-life time of 110 min for ^{18}F.

The "hot" GBB-3CR was performed in 3-methyl-1-butanol under conventional heating in most cases and some under MW conditions, where 150–170 °C was found to give the highest yields; 64–85 %.

The use of hydrazines in the GBB-3CR has not been explored until 2014. A variation in which 2-hydrazinopyridine is used to obtain bicyclic pyridotriazines was introduced by Hulme et al.[31] The proposed mechanism is quite similar to that of the GBB-3CR reaction, it involves a non-concerted [5+1]-cycloaddition of the Schiff base and isocyanide.

Comparable to the example of ketones (Kumar et al. example in chapter 3.2) in the GBB-3CR discussed below, there is no rearomatization seen with both aldehydes and ketones, which otherwise concludes the GBB-3CR. The appendant moiety originating from the isocyanide component remains in the product as a stable imine (**10**). The reactive nature of the Schiff base intermediate **11** allows introduction of not only isocyanide, but isocyanates, acyl chlorides and cyclic anhydrides as well (Scheme 10).

Hulme et al. reported the use of acyl cyanide (**14**) as isocyanide replacement in the GBB-3CR. The resulting primary amine (**15**) subjected to the excess of aldehyde (4 eq.) and acyl cyanide (3 eq.) undergoes a domino/tandem acyl-Strecker reaction.[32] A great example of a modified GBB-3CR: on one hand the acetyl cyanide serves as a less toxic replacement for TMSCN, on the other hand a great catalyst, acetic acid is freed during the course of this one-pot 3-step cascade reaction (Scheme 11).

In situ generation of amidines for use in the GBB-3CR was demonstrated by Mahdavi et al., using 2-bromopyridine **16**, sodium azide, and aldehyde and isocyanide in a copper-catalyzed 4CR.[33] The activated bromine is converted to amine **17** via a reductive amination as depicted in Scheme 12, prior to take part in the GBB-3CR. The reaction sequence is described a one pot four component reaction, the reaction could as well be considered as a three-component reaction with in situ generated 2-aminopyridine.

Procedures in process chemistry are necessarily studied in depth for optimal conversion to the desired products. In this respect the report of Mathes et al. is very useful, as it investigates the driving forces of the GBB-3CR, introducing alternative purification methods that circumvent labor-intensive chromatography.[34] Apart from the usual reagents, the Schiff base preformation was promoted by adding a catalytic amount of *p*TsA. The following cycloaddition was in turn catalyzed by borontrifluoride-acetonitrile complex (BF_3·MeCN) and two equivalents of trimethyl orthoformate as dehydrating agent was added to increase the rate of the reaction significantly, giving good yields in less than a day of reaction time (Scheme 13). Purification was done by adding 1,3 equivalents of sulfuric acid to precipitate the GBB-3CR products from *i*-PrOH as sulfate salts in high purity. From the optimized method, a large scale reaction was performed at 100 mmol scale, yielding the GBB product **18** in 82 % yield, against 85 % on 1 mmol scale, proving the scalability of the reaction.

Using bis- (**19–20**) or tris amidines in the GBB-3CR allows for multiple MCRs in a single transformation as demonstrated by Lavilla et al.[35] The position of each amidine when applying asymmetric bis-amidine **19** determines the reactivity and therefore the selectivity of the first GBB-3CR and enables introduction of different aldehyde and isocyanide components in the second GBB-3CR. This regioselectivity is also seen in symmetric bis-amidines, but require stoichiometric amounts of the aldehyde and isocyanide components. Reactions with the tris-amidine melamine **21** exclusively yielded symmetric products. The fluorescence abilities of the synthesized compounds was highlighted and through introduction of EWG or EDG functionality at specific locations, the fluorescence emission wavelengths could be tuned. Additionally BODIPY (**93**) like fluorophores were made by reacting α-pyridyl GBB-3CR compounds with BF_3OEt_2, to create a BF_2 bridge between the

pyridine and imidazo rings. This bridged compound (**23**) showed a shift in the emission wavelength by 60 nm, a 40-fold emission increase and pH insensitivity as compared to unbridged (**22**) (Scheme 14).

Scope and Limitations of the GBB-3CR

Immediately after the introduction of the GBB-3CR approach to access imidazo[1,2-*a*] heterocycles, the scope and limitations were elaborated. However, in each of the attempts only a small selection of variables was assessed. This went from solvent screening, varying reaction conditions, catalysts and reagent use to solid phase approaches. A good example is the use of glyoxylic acid to obtain an uncatalyzed formaldehyde-based product. In the general scope and limitation of the GBB-3CR it was found that the reaction is best performed at room temperature in MeOH, with a concentration ranging between 0.3–1.0 M, using arylaldehydes, 2-aminopyridines, and aliphatic isocyanides in stoichiometric amounts, in the presence of a catalytic amount of 10 mol-% $Sc(OTf)_3$. Difficulties in predicting reactivity were found with some combinations of starting materials and cannot always be attributed to electronic factors, as steric effects have a significant effect as well, illustrated in Figure 2.[35]

Aliphatic aldehydes give good yields when aromatic isocyanides are used, however, when both aldehyde and isocyanide are both electron rich, a reduction in yield was described recently.[34] Although such findings are valuable starting point for better understanding the GBB-3CR, we've tried to illustrate the scope and limitations in a broader sense, including the effect of substituents on each of the reported starting materials. Therefore, a tabular summary of amidines, aldehydes, isocyanides and catalysts used in the GBB-3CR is presented in the following. Additionally, the tables act as reference guide to which components are suitable, including every report the component was successfully used in. The benefit here is a complete and simple access to the possible starting materials, grouped according to aromatic, hetero aromatic and aliphatic nature and electron donating or withdrawing substituents (EDG and EWG respectively) and bulkiness. Thus a quick look in the tables can reveal unambiguously which component has been used previously and will likely work in other instances.

Cyclic Amidines in the GBB-3CR

The amidines are key to give the scaffold its typical imidazo-[1,2-*a*] heterocyclic form, whereas the aldehyde and isocyanide components are more appendant substituents, sometimes called scaffold decoration. Nearly 90 different amidines were used in GBB-3CR, of which 22 are five membered and 66 are six membered amidines. All of them were sorted in Table 1 according to ring size, type and additional substituents. The most abundant amidine in the Table 2-aminopyridine is where the GBB-3CR was discovered with and is not surprisingly used in many model reactions to test other solvents and catalysts. Substituted 2-aminopyridines also show good reactivity, giving products in good yields. Electron withdrawing substituents, mostly halogens seem to increase the yield, with the exception of nitro-groups. Alkyl groups and other more EDG generally give lower yields. More electron deficient pyrimidines give lower yields in the GBB-3CR, both 2- and 4-aminopyrimidine

with EWG substituents were reported as low yielding. Aminopyrazines are overall reported as good yielding. A broad range of 5-membered amidines appears often with other hetero atoms, such as oxazoles and thiazoles, and are not very reactive resulting in less good yields. 3-Amino-1,2,4-triazole, on the other hand, is reported as good yielding amidine. Nucleobase derived compounds are popular as they possess good hydrophilicity and solubility, which are therefore potentially therapeutically relevant heterocycles. Adenine **26**, guanine **27** and cytosine **28** are nucleobases that bear an amidine moiety which was exploited in the GBB-3CR by Madaan et al. to furnish aminoimidazole-fused nucleobases.[36] The polar nature of these amidines required a more polar solvent than methanol, as this solvent did not yield any product at all. The screened solvents PEG-400, ethylene glycol, DMSO, DMA and DMF all give product, with yields varying between 23 to 68 % with $ZrCl_4$ in DMSO as a catalyst (Scheme 15). Even the otherwise difficult to modify guanine is giving GBB-3CR products albeit in rather low yields.

A feature which can be generally observed with many MCRs is their great functional group compatibility. Thus, heteroaromatic amidines can comprise all halogens, and pseudo halogens such as nitrile, nitro, methoxy, free carboxylic acids, esters, unprotected primary and secondary amines, unprotected phenolic and aliphatic hydroxyl, amides, alkynes, alkenes, and boronic acid esters. This great functional group compatibility is important for further reactivity of the initial GBB-3CR products and also for optimal interaction within a receptor pocket.

Aldehydes

Aldehydes are common building blocks which are cheap and have good commercial availability and with 180 different records they are very broadly applicable in the GBB-3CR reaction with great variability (Table 2). The diversity of aldehydes found is broad, from aromatic to aliphatic aldehydes with many different substituents, both electron withdrawing and donating and bulky and small groups and also aldehydes containing reactive to labile protective groups that allow secondary modifications. Aromatic aldehydes generally form stable Schiff bases, where an effective conjugation system is beneficial for its stability. Schiff bases from aliphatic aldehydes are found to be less stable and readily polymerize, which translates to reduced yields of subsequent transformations. Benzaldehyde is the mostly used aldehyde for reasons such as detectability on TLC for reaction monitoring and good reactivity. Substituents on benzaldehydes do affect their reactivity. Using substituted benzaldehydes bearing an electron donating group usually increases the yields, whereas withdrawing substituents reduce the yields.

It would be an extensive exercise to discuss every variant in detail, therefore the more interesting examples were highlighted. The use of formaldehyde in order to obtain 2-unsubstituted-3-amino-imidazoheterocycles in the GBB-3CR was not reported until 2004 by Kercher et al.[42] Successful preparations of the unsubstituted imidazole were actually scarce and the few reports that did, showed low yields in non-efficient synthetic routes.[173–175] In this report formaldehyde (aqueous) and paraformaldehyde were used, resulting in poor yields of 36 and 44 % respectively. Other formaldehyde substitutes were screened, showing that glyoxylic acid is giving good yields up to 71 % with glyoxylic acid immobilized on

macroporous polystyrene carbonate (MP-CO_3) **29** in an uncatalyzed GBB-3CR reaction (Scheme 16).

Kennedy et al. reported three examples with the successful use of paraformaldehyde with varying yields between 68–78 % in a microwave assisted GBB-3CR in MeOH, catalyzed with 4 mol-% $MgCl_2$ at 160 °C in just 10 minutes.[136]

The first ketone example in a tetracyclic fused imidazo-[1,2-*a*]pyridines from isatin **30** was reported by Che et al.[119] The special multi-reactive nature of isatin is allowing for a formal [4+1] cycloaddition with different isocyanides and subsequent rearomatization via [1,5]-H shift through a retro-aza-ene reaction compound **31** (Scheme 17).

Using other ketones, Kumar et al. reports the synthesis of spiro-heterocycles catalyzed with TiO_2 nanoparticles in excellent yields.[170] The quaternary spiro carbon lacks, however, the proton required for [1,3]-H shift, therefore rearomatization of the unstable [4+1] adduct could not take place. These adducts were reported as the products and also contains an example of an isatin containing product **32**, wherein the structure was found to be surprisingly different from the isatin products described by Che et al.[119] The conflicting structures are not likely to be attributed to the amidine and isocyanide components and the right structure is without appropriate structure elucidation such as X-ray diffraction spectroscopy difficult to confirm.

The aldehyde pyridoxal **76** has a different outcome and will not result in the typical GBB-3CR scaffold when reacted with an amidine and isocyanide. The resulting product formed instead, a furo[2,3*c*]pyridine **78**, is shown in Scheme 32 and discussed further in the biologically active compounds section.

Interestingly, 2-siloxypropanecarboxylates were applied as aldehyde substitutes to obtain GBB-3CR compounds with a δ-amino acid backbone.[45] The siloxanes go through a ring opening pathway and behave as the aldehyde component **33**, together with 2-aminopyridine and p-methoxyphenyl isocyanide **34**, catalyzed with acetic acid in MeOH to give methyl (3-aminoimidazo[1,2-*a*]pyridin-2-yl)propanoates in moderate to good yields (Scheme 18).

Again the functional group compatibility of the GBB-3CR aldehyde component is amazing and comprises aromatic benzaldehydes include substitutions on all positions with alkyl, aryls, alkoxy groups, alcohols, acids, nitro groups, cyano groups, tertiary amines, polyaromatics and fused heterocycles. Aliphatic aldehydes are also widely represented, including saturated and unsaturated alkyl groups (1°, 2° and 3°), substituted with alcohols, esters, adjacent carbonyls, thiols and cyclic alkyl groups. Thus, heteroaromatic amidines can comprise all halogens, and pseudo halogens such as nitrile, nitro, methoxy, free carboxylic acids, esters, unprotected primary and secondary amines, unprotected phenolic and aliphatic hydroxyl, amides, alkynes, alkenes, and boronic acid esters. This great functional group compatibility is important for further reactivity of the initial GBB-3CR products and also for optimal interaction within a receptor pocket.

Isocyanides Used in the GBB-3CR

The commercial availability of isocyanides is limited and those available are often expensive, likely because of the stability, applicability and the undesirable smell of most liquid isocyanides. Therefore only a few dozen of isocyanides are commonly used in many isocyanide-based MCRs. Due to the pricing and availability isocyanides are often prepared in house. Preparation of isocyanide from primary amines via the Hoffman- or Ugi route (formylation & dehydration) is most common and recently the substrate scope has been broadened by conversion of cheap and broadly available oxo-compounds (aldehydes and ketone) to isocyanides by the repurposed Leuckart-Wallach reaction as described by Dömling et al.[178] Altogether an astonishing 100 different isocyanides were reported in the GBB-3CR, proving that the isocyanide variation point is broadly exploited and is hardly to be considered as a limitation of variability in this three component reaction (Table 3). Aromatic and aliphatic isocyanides participate with equal ease in the GBB-3CR, although it must be noted that combinations of bulk substituents affect the yield when bulky amidines and aldehydes are used simultaneously. Not surprisingly, there is again a great functional group compatibility. This includes aliphatic isocyanides widely substituted, heterocycles, substituted with esters, alcohols and ethers. Also a broad selection of substituted phenyl isocyanides are compatible, with substitutions on all positions with alkyls, halogens, ethers, esters and thiols.

Catalysts in the GBB-3CR

From the moment the GBB-3CR was discovered, Lewis and Brønsted acid catalyst were used for an efficient transformation. Saying this, it is possible to run the GBB-3CR without the aid of a catalyst, it generally depends on the nature of the reagents. Low electrophilic aldehydes such as various benzaldehydes are suspected to be unable to condensate with electron deficient amidines, whereas the addition of Lewis acids would increase the reactivity of the imine formation considerably.[145] In Figure 3 the occurrence of the catalysts used in the GBB-3CR are mapped. Clearly scandium triflate has the highest success rate followed by the Brønsted acids $HClO_4$, *p*TsA and acetic acid. However, when taking into account that early adaptors of the GBB-3CR were basically reproducing reaction conditions, the frequency of some of the applied catalysts is artificially higher and are possibly not the best catalysts in the given reactions. Examples of such catalysts are acetic acid and Montmorillonite k-10 clay which appear mostly in the first few years after the discovery of the GBB-3CR. Additionally some catalysts were reported multiple times, however from the same research groups, introducing a biased success rate.

Table 4 summarizes the catalysts applied in the GBB-3CR, which give the highest yield in the described model reaction. Surprisingly not every catalyst screening includes the often excellent performing catalysts ($Sc(OTf)_3$, $HClO_4$, and *p*TsA). Nearly 50 different catalysts were described as high yielding, indicating a great scope and freedom for selecting the catalyst of choice. There are some reports of catalyst free GBB-3CR's, that run perfectly fine without any additional reagent. An uncatalyzed GBB-3CR was first reported by Lyon et al. employing immobilized glyoxylic acid on macroporous polystyrene carbonate (MP-glyoxylate) as a formaldehyde equivalent. The decarboxylation leaves a 2-unsubstituted 3-

amino-imidazo[1,2-*a*] heterocycle without use of any catalysts in a yield of 71 % (Scheme 16).[42] Further reports of catalyst free GBB-3CR's employ bifunctional building blocks that hold a carboxylic acid which probably catalyzes the reaction. Truly catalyst free reactions are only recently reported by Sharma et al., but seem to work exclusively in a reaction using 2-aminothiazole under microwave conditions.[160,161,171,172,196] In some of the catalyst-free reactions, a carboxylic acid functional group was found in one of the three components that facilitated the reaction in good yields, although it must be noted, that the use of carboxylic acids will show Passerini poisoning. This side reaction is driven by the presence of 3 components; aldehyde, isocyanide and carboxylic acid that allow for the P-3CR to happen (Scheme 19).

As most Lewis acids rapidly decompose or get deactivated when they come in contact with water, anhydrous conditions are usually required when running a Lewis acid catalyzed GBB-3CR. $Sc(OTf)_3$ is, however, more stable and even applied in aqueous media as an Lewis acid.[197] The GBB-3CR is a condensation reaction, the formation of a water molecule would explain why scandium triflate is such a successful catalyst in this reaction. The only disadvantage noteworthy is that scandium triflate has the ability to polymerize isocyanides, explaining the darkening of some reaction mixtures when this catalyst is applied.[141] Phenyl isocyanides are prone to polymerization and amongst them unsubstituted phenyl isocyanide most.[198–200]

Base Catalyzed GBB-3CR

Sun et al. reported in 2013 the first application of piperidine (**35**) as a Brønsted base catalyst for the GBB-3CR, which was applied to overcome the need to run a deprotection-cyclization-alkylation sequence to obtain their tetracyclic compound. Later in 2013, Sun et al. reported the same strategy without the post modifications and therefore these base catalyzed conditions could be applied for the standard GBB-3CR.[162,163] In the plausible mechanism, piperidine is initially involved in the formation of the Schiff base, then with the introduction of the isocyanide component, the [4+1] cycloaddition takes place, where piperidine facilitates the 1,3-H shift resulting in rearomatization, giving the GBB-3CR product as depicted in Scheme 20.

Sun et al. reports the first Brønsted base catalyzed GBB-3CR of 2-aminobenzimidazoles **37**, methyl 2-formylbenzoate **38** and isocyanides, piperidine was herein used as catalyst.[163] In their search for a post modification on the MCR product, an intramolecular cyclization of the secondary amine with the methyl ester was performed. The secondary amine was arising from the isocyanide input as mostly cleavable isocyanides were utilized. They envisioned a tandem GBB-3CR and post modification sequence in a single step resulting in 20 compounds with a yield varying between 34–95 % (Scheme 21). The heterocyclic benzimidazole and dihydropyrimidine fragments combined are promising compounds as these are associated with PARP, topoisomerase I, INOS, PI3K and PrCP inhibition.

Solvents Used in the GBB-3CR

Around 30 solvents and solvent mixtures used in the GBB-3CR were analyzed and discussed. Looking at the occurrence, methanol is by far the most popular solvent for the GBB-3CR reaction. This is largely attributed to the fact that the highest yields without many side products can be achieved with this solvent, the ease of removal and the ability to dissolve quite some polar catalysts and starting materials as well as more apolar reactants. Discussion of the solvents such as methanol trapping and methanol mediated intermediates rise the question on how broad the solvent range is and whether other solvents than methanol should be applied in the GBB-3CR. Furthermore, the stability of the intermediates from pathway A and B (Scheme 4) are predicted to have different stabilities that vary with the used solvent and therefore would yield either one of the two isomers or the trapped side product.[43] While focusing on solvent screens and suitable solvents for the GBB-3CR, it is remarkable that the 2nd most frequent applied reaction conditions is actually solvent-less. The solvent-less reports show that neat reactions with simple stirring or mechanical mixing such as ball-milling will yield the GBB-3CR compounds as well, but often require more exotic catalysts such as zeolite HY, Montmorillonite K-10 clay and nano-magnetically modified sulfuric acid.[19,71,195] The use of water in a catalyst free GBB-3CR is not only working, but also affords GBB-3CR products in high yields. The aforementioned mechanism should be different from the reaction usually following the concerted [4+1] cycloaddition through iminium ions but rather a non-concerted 5-exo-dig pathway. The protonation of the imine is in general performed with Brønsted acids, in the case of water without catalysts this is unlikely to happen since the pKa of water is higher than pKa's found for iminium ions.[171] Additionally the Woodward-Hoffmann rules which indicates that the uncatalyzed concerted [4+1] cycloaddition is in fact symmetry-forbidden. The GBB-3CR is, however, mostly performed with a catalyst, which disrupts the symmetry and therefore allowing the [4+1] cycloaddition.[201] Considering the possibility of using water or a percentage of water in EtOH; it might be odd that several reports, indicate that anhydrous conditions (dry methanol, dry MeCN and so on) are required for the GBB-3CR while the individual starting materials and catalysts aren't sensitive to water, with the exception of some Lewis acids catalysts. Water, however, has the downside to negatively affect the speed of the reaction, anhydrous solvents and the use of a dehydrating agent could greatly increase the reaction rate.[34] The use of non-protic apolar solvents would suppress the intermediate in pathway B, yielding exclusively the product of pathway A; imidazo[1,2-*a*]-pyrimidines. Toluene is such a solvent and is found quite often to be used together with ammonium chloride as catalyst with heating between 80 °C toward reflux temperatures, ruling out formation of any regioisomers getting exclusively the pathway A product (Scheme 4). Interestingly, while attempts were made to find conditions to control the regioselectivity towards pathway B, Stephenson et al. reported an alternative route, applying a base assisted Dimroth rearrangement giving access to the inverse GBB-3CR regioisomer with full conversion as depicted in Scheme 22.[47] The stability of the regioisomer is the driving force behind this rearrangement, resulting in a preferred single isomer.[202]

Solvents such as DMSO, DMF and PEG-400 are in general not the solvents of choice because of their high boiling points and difficulties to remove during workup (Table 5). They

prove, however, to be quite useful when solubility issues with highly polar starting materials are present such as the aforementioned amidine containing nucleobases.[36,146]

Biologically active Compounds

Quite often the imidazo[1,2-*a*]-heterocycles that arise from the GBB-3CR are linked to known drugs such as Minodronic acid (**40**), Saripidem (**41**) Zolpidem (**42**) and other members of the so-called Z-drug group of tranquilizers. There are however no reports that GBB-3CR compounds act in a similar way as Z-drugs on the $GABA_A$ receptor. The difference between Z-drugs and GBB-3CR compounds is found in the exocyclic secondary amine, originating from the isocyanide component. This amine enables ionic or hydrogen bonding, thus having its own influence on the binding affinity with various protein targets. As a whole it might be better to address real examples of the GBB-3CR scaffold and their associated biological activity. Examples of 3-aminoimidazo[1,2-*a*]pyridines are shown in multiple pharmaceutical drugs or candidates **43–45** (Scheme 23).[205] Most notably, the late stage autotaxin inhibitor GLPG-1690 (**45**) for the treatment of idiopathic pulmonary fibrosis (IPF) which has been discovered and developed whereby the GBB-3CR chemistry played a key role.[186,194]

Only in 2009 the first biological target was addressed and published by using a true GBB scaffold as reported by Fraga et al.[184] In their efforts to combine the structural features of (**46**), a selective p38 MAPK inhibitor, (**47**) celecoxib a PGHS-2 inhibitor and (**48**) also a p38 MAPK inhibitor a GBB-3CR scaffold was used. The main target was to obtain polypharmacological 3-arylamine-imidazo[1,2-*a*]pyridine derivatives with anti-inflammatory and analgesic MOA (Scheme 24).

This approach resulted in compound **49** which was identified as PGHS-2 inhibitor (IC_{50} = 18.5 μM) and acts similar to the p38 MAPK inhibitor SB-203580, reverting capsaicin-induced thermal hyperalgesia, a pain model to assess analgesic properties. Compound **50** is a novel PGHS-2 inhibitor, with an ED_{50} = 22.7 μmol·kg^{-1}, 10-fold more potent than celecoxib.

During a study on the TB targets *M. tuberculosis* glutamine synthetase (*Mt*GS) inhibitory effect, a hit to lead exercise was performed on 3-amino-imidazo[1,2-*a*]pyridines as these were identified as *Mt*GS inhibitors after a high-throughput screening.[193] Two libraries were synthesized the first via a microwave assisted GBB-3CR sequence for 20–30 min at 160 °C and the second via a post-modification on the pyridine 6-position halogen under Suzuki coupling conditions to study the effect of hydrophobic groups such as aryl moieties **52** (Scheme 25). Unfortunately, the Suzuki coupling did not lead to an improvement in IC_{50} value, leaving the aryl halides **51** themselves as potent inhibitors for this target. In a subsequent paper, lead optimization did result in a series of potent compounds, **53** was showing a five-fold improvement with an IC_{50} = 1,6μM.[134] The mode of binding of **53** was discussed according to its co-crystalstructure with MtGS in the structural biology section.

Three years after their patent application, Djuric et al. published the work of 5-substituted indazoles as kinase inhibitors such as Gsk3β, Rock2, and Egfr,[61] by using MCR

methodologies such as the GBB-3CR with pyrimidines for imidazopyrimidines, thioamides for thiazolyl-indazoles and van Leusen TosMICs for imidazole substituents.

Introduction of the indazole was achieved through the use of indazole-5-carbaldehyde as reactant in different multicomponent reactions and afforded compounds as **54**–**56**. The imidazole[1,2-*a*]pyrimidine **54**, GBB-3CR product, showed the highest inhibition against Gsk3β, imidazopyridine **55** was however, much less potent. Choosing different substituents on the amino group, coming from the isocyanide input (**56**), selective inhibition for Rock2 could be fine-tuned as well (Scheme 26).

Al-Tel et al. described the synthesis of a series of imidazo-[1,2-*a*]pyridine and imidazo[2,1-b][1,3]benzothiazole carrying quinolone and indole moieties introduced via the aldehyde component. Many of the synthesized compounds showed both antibacterial and antifungal activities. A very potent broad-spectrum antibiotic was identified as compound **57** depicted in Scheme 27.[138]

The effect of imidazo[1,2-*a*]pyridines was studied on colon cancer cell lines by Koning et al. by showing apoptosis inducing effects in HT-29 and Caco-2 cancer cells.[65] Compounds **58** and **59** showed a cytotoxic effect towards the Huh7 cell line at low μM concentrations and interestingly minimal cytotoxicity against white blood cells.

Schneider et al. performed a chemical advanced template search (CATS) for target profiling. CATS use topological descriptors generated from known binders and to these descriptors it assigns features such as lipophilic, aromatic, hydrogen-bond donors and hydrogen-bond acceptors to find new chemotypes. This virtual target screening yielded a library in which the starting point was the GBB-3CR. From the results, 3840 virtual products, the top 9 compounds were synthesized for PI3Ka inhibition.[78] Four out of nine exhibited activity, with the most active compound **60** showing an IC_{50} = 131 μM confirming CATS usefulness as a tool to predict targets of virtually generated compounds. In addition, a set of 57 predicted compounds, with highest joint prediction scores for PI3K and DNA topoisomerases, were synthesized using a microwave assisted approach with perchloric acid as catalyst. Although no human DNA topoisomerase II inhibition was observed, four new compounds showed inhibitory effects on bacterial DNA gyrase such a compound **61**, a bacterial type II topoisomerase.

In silico screening was initiated by Brenk et al. to produce a library of novel kinase inhibitors derived from commercially available fragments.[151] As a core structure they've chosen a ring system with heteroatom containing functional groups. After applying several selection steps, the number of hits was brought down from over two million compounds to 265 that yielded in 186 compounds being successfully synthesized. 17 of those were prepared using the GBB-3CR, starting from 3-amino-1,2,4-triazole, aldehydes and isocyanides, catalyzed with $HClO_4$ in MeOH at room temperature. One of the obtained compounds **62** showed activity against the kinases EPH-B3 (158μM) and FGF-R1 (469 μM).

Similar imidazo[2,1-*c*][1,2,4]triazoles derivatives were reported to possess antimicrobial and antioxidant activities by El Kaim et al.[168] The reaction conditions were different as compared to the method described by Akbarzadeh.[158] A $Sc(OTf)_3$ catalyzed reaction with

substituted benzaldehydes, various isocyanides and substituted 5-amino-1,2,4-triazoles was performed in DMF (80 °C, 30h) to produce a small collection of compounds with yields between 54 and 72 %, the best performing compound **63** possesses both antifungal and microbial activity.

Another report from 2011 by Al-Tel et al. describes the identification of imidazopyridines derivatized with benzimidazole and/or arylimidazole as potent β-secretase inhibitors.[62] In multiple rounds the GBB-3CR compound **64** gave a sub micro molar activity, post modification by removal of the *tert*-butylamine group, a 40-fold increase in activity was achieved. The best compound **65** showed nanomolar potency for the BACE1 enzyme associated with Alzheimer's disease (Scheme 28).

Baviskar et al. published in 2011 their work on novel topoisomerase IIα inhibitors as anticancer agents. With the aid of molecular docking studies they predicted bicyclic N-fused aminoimidazoles as potential human topoisomerase IIα (hTopoIIα).[63,94] Based on the previous reported topo II inhibitors in combination with known drugs containing an imidazo[1,2-*a*] scaffold, a library was synthesized using the GBB-3CR. The result is a GBB-3CR scaffolds, by heating the corresponding heterocyclic amidine, aldehyde and isocyanide with a catalytic amount of $ZrCl_4$ at 50 °C in PEG-400 or under MW conditions at 140 °C in *n*-butanol. In some examples the *tert*-butyl group was cleaved using HBF_4 yielding primary amines exhibiting similar activities, multiple compounds **65–70** shown higher potency anticancer activity as compared to 5-fluorouracil and etoposide in kidney cancer cells. Introduction of C2-biaryl and C6-aryl substitutions on the same imidazo[1,2-*a*]-pyridine/pyrazine scaffold resulted in compound **69** which showed inhibitory effects in the catalytic cycle of hTopoIIα, additional studies suggests that its binds similar as compared to merbarone (a known catalytic inhibitor of hTopoIIα) overlapping the etoposide binding domain (Scheme 29).

Callejo et al. reported a new cancer therapeutic approach by inhibition of the kinase B-Raf.[149] In a virtual screening they identified imidazo[1,2-*a*]pyrazines as a binder of B-Raf, in a subsequent synthesis of a small library they found the derivative with an indanone oxime substituent **71** to be highly potent with an IC_{50} of 4 nM. Exchange of the furfural moiety lead to compounds **72** and **73** showing improvement on B-Raf with an inhibition <2 and 0.2 nM respectively.

Further SAR optimizing led to replacement of the imidazo[1,2-*a*]pyrazine moiety by thienopyridines **72** with improved inbibition (<2nM) and ultimately with furopyridines **73** bearing superior sub-nanomolar activity (Scheme 30).

Chatterjee et al. described a screening campaign using the public malaria database for the discovery of novel chemotypes that could inhibit *Plasmodium falciparum*, a selection was made of compounds that matched criteria such as good potency (IC_{50} of <1μM), good safety index, (>20-fold in a six-cell line toxicity panel) and easy synthesis. The imidazolopiperazine moiety was found to be an attractive hit, based on the aforementioned criteria.[150]

The imidazolopiperazines **74** were accessed by performing a GBB-3CR in MeOH at r.t. catalyzed with $HClO_4$, followed by reduction with PtO_2 under hydrogen atmosphere. The most potent compound **75** exhibited an IC_{50} of 4 and 3 nM on the *P. falciparum* strains W2 and 3D7 respectively (Scheme 31).

David et al. reported the use of pyridines, isocyanides and benzaldehydes in a microwave assisted GBB-3CR. Some analogues of the imidazo[1,2-*a*]pyridine products were found to exhibit activation of the TLR8-dependent NF-κB signaling. As the GBB-3CR was discovered by using pyrimidines as a variation of the amine component in the U-4CR, a similar phenomenon that was observed when performing a GBB-3CR with pyridoxal **76** as aldehyde component. Surprisingly the use of pyridoxal **76** as benzaldehyde component did not yield imidazo[1,2-*a*]-pyrazines/pyridine **77**, but the unexpected furo[2,3*c*]pyridine scaffold **78**. Beyond the scope of this paper, they proposed a mechanism and explored scope and limitation of this reaction. The reaction follows the typical GBB-3CR mechanism of the imine formation and attack of the isocyanide, but the otherwise [4+1] cycloaddition concerning the nucleophilic attack of the endocyclic amine with the carbene of the isocyanide does not take place. The proposed mechanism rather proceeds in attack of the phenolic hydroxyl directed by steric hindrance of the apposing benzylic hydroxyl group. The use of anilines together with pyridoxal resulted in formation of the furo[2,3*c*]pyridine as well. Replacement of pyridoxal with the very similar salicyl aldehyde did however yield the usual GBB-3CR scaffold **79**, likely due to the absence of the bulky hydroxymethylene group in this otherwise similar aldehyde (Scheme 32). The obtained imidazo[1,2-*a*]pyridin-3-amines were TLR7/8 inactive, but showed bacteriostatic activity against Gram-positive bacteria. SAR studies led to the synthesis of a library of 24 compounds with the emphasis on the size of aryl aldehydes, difference between 2-aminopyridines vs. 2-aminopyrazines and aliphatic or aromatic isocyanides.[73] The aim was to assess whether modifications were possible without loss of antibacterial activity, resulting in **80** as best compound.

Anabasine **81** a natural product was used by Krasavin et al. as a template to prepare hydrazo-Ugi and GBB-3CR derivatives were evaluated as agonists and antagonists of nAChR. Targeting this family of neurotransmission receptors could lead to drugs for the treatment of associated with PD, AD, schizophrenia and depression.[176]

The five GBB-3CR products were synthesized in low to moderate yields 20–53 %, employing various isocyanides, modified anabasine 2-aminopyridine and substituted benzaldehydes in MeCN, 70 °C using an stoichiometric amount of TMSCl as Lewis acid promoter (Scheme 33).

The use of a alkynylbenzaldehydes **83** in the GBB-3CR allows for post modifications such as metal catalyzed intramolecular cyclization yielding a library of compounds, some with strong cytotoxicity against the HeLa cell line, due to binding affinity with the G-quadruplex DNA motif, thus exhibiting anti-proliferative activity as described by Shen et al.[206] The cyclization to the tricyclic compounds, such as **84**, was performed in a domino one pot approach of the $Yb(OTf)_3$ catalyzed GBB-3CR between 2-aminopyridines, isocyanides and 2-alkynylbenzaldehyde followed by a AgOTf catalyzed intramolecular cyclization (Scheme 34).

Proschak et al. reports hybrid imidazo[1,2-*a*]pyridine and an urea moiety as dual soluble epoxide hydrolase (sHE)/ 5-lipoxygenase (5-LOX) inhibitors.[128] A three or four step approach was used to introduce both the urea and imidazo[1,2-*a*]pyridine elements. In total a library of 22 compounds were synthesized in an AcOH catalyzed GBB-3CR approach in MeOH in yields varying between 7–64 % and showing good inhibition potential on recombinant enzyme on both targets. The best 5-LOX inhibitor **85** was not the best sHE inhibitor (**86**), and it is to be evaluated whether equipotent inhibition is favored over higher inhibition of one of the two targets (Scheme 35).

In 2011 Al-Tell et al. described the application of various subsequent MCR's.[58] The carboxylic acid group attached to one of the three typical GBB-3CR starting materials would not participate in this MCR reaction, but is useful for follow up MCR chemistry via for example the U-4CR to synthesize antibiotics.[80] The six components introduced in two sequential reactions, yielded 40 polyfunctionalized imidazopyridine, pyrimidine and pyrazine derivatives and were screened against multiple bacterial strains such as *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and screened against two human cancer cell lines; breast carcinoma (MCF7), A549 (lung cancer cell line) and melanoma (M8).

Five of the synthesized compounds **87–91** were found to exhibit lower IC_{50}values compared with the internal standard doxorubicin, against A549, M8 and MCF7 cell lines. Moreover, compound **92** exhibits a high potency against breast cancer (Scheme 36).

Vendrell et al. reported the synthesis of functionalized BODIPY probes to introduce fluorescence in otherwise difficult accessible structures.[82] While BODIPY dyes were previously derivatized via BODIPY containing an amine or carboxylic acid substituent respectively, this paper focuses on the preparation of isocyanide functionalized BODIPY (**93**).[207–211] The application of this dye was found through isocyanide-based MCR chemistry for the aid of in vivo imaging of phagocytic macrophages. Different IMCR compounds were synthetized as the GBB-3R variant **94**, and incubated with A549 cells and although all the adducts readily entered cells at concentrations in the nanomolar range, the Ugi adduct **95** exhibited the best coloured images (Scheme 37).

Glyoxylic acid based GBB was employed by Li el al. to obtain a series of mono-substituted imidazopyridines that target the RET kinase class, a known oncogene.[212] In their first series, 100 MCR fragments were synthesized by a acetic acid catalyzed GBB-3CR using substituted 2 aminopyridines, isocyanides and glyoxylic acid. Screening resulted in a hit **96** which was subjected to computational binding analysis in the RET kinase. The phenyl moiety accesses a lyophilic pocket that could be extended from the allosteric pocket. Another non-MCR series of compounds were synthesized to engage this adjacent lipophilic pocket, resulting in an increase of inhibitory potency as shown by two compounds (**97** = 0.21 μM and **98** = 0.75 μM) thus identified as novel RET kinase inhibitors (Scheme 38).

Imidazo[1,2-*a*]pyridine-N-glycinylhydrazone derivatives were applied as inhibitors of tumor necrosis factor alpha (TNF-α) by Fraga et al.[84] The design of the scaffold was performed by combining two earlier described TNF-α inhibitors wherein the N-phenyl-pyrazole

nucleus **99** was replaced with the heterocyclic imidazo[1,2-*a*]pyridine isoster, easily accessible by the GBB-3CR.

Via an acetic acid catalyzed reaction of benzaldehyde or pivaldehyde, 2-aminopyridine and ethyl 2-isocyanoacetate two GBB-3CR products were obtained with yields of 65 and 75 % respectively. Post modification with hydrazine and subsequent hydrazone formation yielded 11 products that were screened in a TNF-α production assay, ultimately leading to the most active **100**, equipotent with SB-203580 (**101**) a known p38 MAPK inhibitor herein applied as anti TNF-α agent (Scheme 39).

Inhibition of the BET bromodomain is a promising approach as anti-cancer therapy. In a fragment based optimizing strategy, Bradner et al. used the dimethylisoxazole biasing element as a key fragment and screened on BRD4 and BRD4-dependent lines, using different heterocyclic substituents to gather information on preferred regiochemistry.[86] Bromo substituted benzaldehydes were employed in the μW assisted, $Sc(OTf_3)$ catalyzed GBB-3CR to perform a follow-up Suzuki coupling in order to introduce the 3,5-dimethylisoxazole warhead. The best compound is built around the *para*-substituted phenyl-imidazo-[1,2-*a*]pyrazine scaffold and a small library of 29 compounds was synthesized for SAR optimizing, resulting in lead compound **102** (Scheme 40).

In continuation of Shen et al.[206] another HeLa cytotoxic series of 6H-pyrido[2′,1′:2,3]imidazo[4,5-c]isoquinolin-5(6H)-ones was reported by the same research group[87] In this report the tetracyclic profile was maintained, however the alkynyl moiety was replaced with a carboxylic acid (phthaldehydic acid) which direct reacts with the secondary amine, formed in the GBB-3CR (Scheme 41).

Shen et al. published, more work on cytotoxic compounds while abandoning the tetracyclic scaffold, switching to a bicyclic scaffold exhibiting intramolecular hydrogen bonding to form pseudo-tetracycles.[177] A more straightforward methodology, as it only comprises a single GBB-3CR step. The library was step by step optimized with variations of all three components. The hydrogen bonding ability was most successful when an ortho substituted hydroxyl- or methoxybenzaldehyde component was used. A 100-fold activity increase over compound **104** was realized with compound **105**.

Foroumadi et al. reported novel anticancer agents based on N-fused aminoimidazole derivatives with triazine analogs.[158] The basis of this compound were a combination of potent topoisomerase IIα inhibitors[63] and triazines[213] to yield the N-cyclohexyl-3,4-diphenylimidazo[2,1-*c*][1,2,4]triazin-6-amine scaffold **109** (Scheme 42). The aminotriazine **108** was prepared from condensation of benzil **106** with aminoguanidine **107**. Noteworthy are the conditions that were found whilst optimizing the GBB model reaction. The reaction with toluene under reflux conditions gave the highest yield of 70 % in the presence of 1 equivalent ammonium chloride as compared to 45 % without.

A small library of 20 compounds was prepared and their cytotoxicity was assessed on HL60, MCF-7 and MOL-4 by the MTT reduction assay against cisplatin and doxorubicin. The highest potency of compounds **110** and **111** was observed on MCF-7 and HL60 cells

respectively. SAR optimizing showed that replacing the 7-aryl moiety with pyridyl or furan-2-yl (compounds **112** and **113**) gave improvement of the potency against MOLT-4.

In a substrate activity screening, Veken et al. decorated an imidazo-[1,2-*a*]pyridine scaffold with a library of fragments that bind to the urokinase plasminogen activator (uPA) S1 pocket.[96] This target is a biomarker and therapeutic target for cancer types such as breast, ovarian and pancreatic cancer. In two rounds the imidazopyridine scaffold was optimized. The first round focused on mono-substitution with fragments on the 3 position of the imidazopyridine scaffold using a GBB-3CR to identify fragments that bind to the S1 pocket. In a second round structural optimization was performed by introducing substituents through the aminopyridine and aldehyde component. This resulted from an IC_{50} (uPA) value (**114**) of 9.04 μM towards 0.097 μM (**115**) improvement between the first and second round respectively (Scheme 43).

The imidazo[1,2-*a*]pyrazine scaffold is found in Heat shock protein 90 (Hsp90) inhibitor PU-H71, using the Zolpidem rationale that absence of the amine moiety in the 3 position wouldn't affect the inhibitory effects, Shen et al. synthesized a library of substituted 3,8-diaminoimidazo[1,2-*a*]pyrazines to target this protein.[153] The biggest challenge in these compounds was the incorporation of the adenine motif with an amine in the 8 position, which will in unprotected form participate in the GBB-3CR. Introduction of a chlorine at position 8 followed by aminolysis as well as protected amines were tried by the authors. The resulting lead compound **116** exhibits moderate Hsp90 inhibition as compared to PU-H71 (**117**), however, the co-crystallization of the reported 3,8-diaminoimidazo[1,2-*a*]pyrazines have shown to bind in the same way as the known inhibitor (Scheme 44).

Coelenterazione **118** is a bioluminescent imidazopyrazine and can be found in several marine organisms. The properties such as bioluminescent and antioxidant are useful and utilized as optical signaling agents for cancer behavior studies. Vuocolo et al. reports the synthesis of 3 deoxy- derivatives of coelenterazine to improve some of its properties, such as its low stability.[154] The 3 deoxy approach brings room to apply the GBB-3CR with substituents on the C-3 position.

In this report only *tert*-butyl isocyanide was used in a acetic acid catalyzed GBB-3CR under dry conditions (3Å molecular sieves) yielding compound **119** in 64 % and in follow up reactions a deprotection and reductive deamination ($NaNO_2/H_2SO_4$) routine was used to obtain compound **120** (Scheme 45).

Liu et al. describes a library of imidazopyridine and quinoxaline derived compounds and introduces ferrocene incorporation via the aldehyde or isocyanide component through the GBB-3CR, with the aim of developing new antioxidants to reduce oxidative stress/DNA damage due to reactive oxygen species.[104]

The $LaCl_3{\cdot}7H_2O$ has proven to be an excellent catalyst with yields >84 % at a reaction temperature of 60 °C in EtOH for 2h. Compounds **121** and **122**, the ferrocene bearing compounds, were the best in inhibiting DNA oxidation. More improvement was made by derivatization of the imidazo[1,2-*a*]quinoxaline scaffold.[155] Decoration with ferrocenyl and

p-methoxyphenyl (**123**) or flavonyl (**124**) groups on either the 2 or 4 position boosted the radical suppression/inhibition of DNA oxidation (Scheme 46).

A hybrid structure between imidazo[1,2-*a*]pyridine and coumarins were synthesized by Shah et al. as potential Hepatitis C virus replicator inhibitor.[110] The 20 compounds were synthesized using a AcOH (20 mol-%) catalyzed GBB-3CR in MeOH at 70 °C for 2h in yields between 67–92 %. Molecular docking studies indicate good binding interactions of compound **125** with nonstructural protein 5B.

Trivedi et al. combined the structural properties of anticancer agents that commonly have a coumarin structure and anti-osteoporotic agents holding pyridine or imidazole heterocycles into coumarin-imidazo[1,2-*a*]pyridine hybrids for the treatment of cancer induced osteoporosis.[113] 18 GBB-3CR products were obtained using ethanol reflux conditions and 20 mol-% AgOTf with excellent yields (71–88 %), including compound **126**. Compound **127** was found to possess anti-breast cancer activity (MDA-MB-231 IC_{50} = 14.12 + /− 3.69 μM) as well as disrupting the differentiation of osteoblast and osteoclast cells and therefore indicating the compound as promising hybrid for both aforementioned diseases (Scheme 47).

The first-in-class autotaxin (ATX) inhibitor GLPG1690 was described by Heckmann et al. and was discovered and optimized through the synthesis of a 2,3,6 trisubstituted imidazo[1,2-*a*]-pyridine series, identified by HTS.[186,194] Approximately 100.000 compounds were subjected to screening in which ATX activity is promoting release of the fluorophore FS-3, an HTS suitable substitute of LPC, thus easily identifying inhibitors by a fluorescence detection assay. The N-benzyl-2-ethyl-N-methyl-imidazo[1,2-*a*]pyridin-3-amine hit series **128** displayed a IC_{50} around 30 nM in the FS-3 assay (Scheme 48).

The metabolic stability of this series was however poor and a second series with improved pharmacokinetic properties was developed, resulting in an early lead compound **129** (IC_{50} = 122 nM (FS-3 assay). The reduced potency gave reason to continue SAR analysis and synthesis. Furthermore the ATX activity could not be reproduced with biochemical assays; using the natural substrate LPC displayed only micromolar activity. Extensive optimizing on all substituents, assisted by analysis of the binding mode using compound **129**, resulted in lead compound **130** with a potency of 27 nM in the biochemical assay and 22 nM in a rat plasma assay. The improved potency was achieved through the 6 position by extending the substituent and the addition of a basic amine and an H-bond donor or acceptor. The addition of a nitrile group on the thiazole moiety pushes out a high energy water by full occupation by the ligand, increasing the potency even more. In a second report Heckmann et al. describes improvement of lead compound **130**, focusing on ADMET (hERG and CYP3A4) and PK properties (clearance and bioavailability), ultimately resulting in the clinical candidate GLPG1690 (**131**) (IC_{50} = 131 nM). The five-fold loss in activity of **131** was outweighed by the absence of CYP3A4 TDI and the compound is overall the best combination of activity, pharmacokinetic, ADMET and PK properties. The ATX inhibitor was further discussed in the structural biology section.

Structural Biology

Farnesoid X receptors (FXRs) are nuclear hormone receptors expressed in high concentration in tissues that participate in bilirubin metabolism including the kidneys, intestines, and liver. In animal models of nonalcoholic fatty liver disease (NAFLD), FXR activation protects against fatty liver injury and nonalcoholic steatohepatitis (NASH), and improved hyperlipidemia, glucose intolerance, and insulin sensitivity. Thus, FXR agonists could potentially be used as drugs to treat nonalcoholic fatty and cholestatic liver diseases. A GBB product **132** was described in a cocrystal structure bound to FXR (Figure 4A).[214] Remarkably, **132** fits tightly in the pocket undergoing a range of hydrogen, pi-stacking and van der Waals interactions (Figure 4. C–E).[214] The 2,6-dimethyl phenyl moiety (derived from the isocyanide) ensures an out-of-plane orientation of the two phenyl substituents with regard to the imidazopyridine bicycle through sterically repulsion which can help to increase binding affinity through preorganisation of the binding conformation (Figure 4B).

The protein bromodomain (BD) serves the recognition of acetylated lysine as in histones and is composed of approximately 110 amino acids. In the context of signal transduction, the bromodomain function as a “reader” of the lysine acetylation. For a family of bromodomains, the BET (bromodomain and extra terminal domain) family, several compounds are in clinical evaluation. Members of the BET family are targets in both human cancer and multiple sclerosis. The bromodomain has also been investigated as antifungal target. Screening a library of ca. 80.000 chemically diverse compounds by a HTRF inhibition assay revealed GBB **133**.[215] Compound **133** inhibits the *Ca*Bdf1 BD2 with high selectivity: HTRF and ITC assays yielded IC_{50} and K_d values of 1.1 and 2.1 μM, respectively, whereas human Brd4 BD2 and *Ca*Bdf1 BD1 were only weakly inhibited (IC_{50} ≥ 40 μM). Moreover, no significant inhibition of any human BDs was observed for compound **133** by BROMO-scan profiling and by an ITC assay on the two most sensitive BDs identified by this screen. Only mild cytotoxicity was observed towards mammalian cells (EC_{50} ca. 60 μM) for compound **133**. A cocrystal structure of **133** in Candida albicans Bdf1 reveals shape complementarity to the receptor and a network of hydrogen bonding, pi-stacking, van der Waals interactions (Figure 5).

Autotaxin (ATX) is a secreted lysophophospholipase D that converts lysophosphatidyl choline (LPC) into the bioactive phospholipid derivative lysophosphatidic acid (LPA). LPA exerts its biological activities through activation of the LPA receptors: LPA1–6. The ATX/LPA axis is involved in numerous physiological and pathophysiological processes. Autotaxin inhibitors have been proposed to be useful in various pathologies such as cancer, pain, and cholestatic pruritus, as well as fibrotic, inflammatory, and cardiovascular diseases.

Appropriate structural modifications of the initial GBB hit lead to 134 with improved ADMET (hERG and CYP3A4 TDI) and PK properties (bioavailability and clearance).[186] Compound **134** was able to decrease LPA levels in mouse plasma. Additionally, compound **134** demonstrated significant activity in a mouse fibrosis model at doses of 10 and 30 mg/kg twice a day, with an efficacy comparable or superior to that of the reference compound pirfenidone. Compound **134** is currently being evaluated in an exploratory phase 2a study in

idiopathic pulmonary fibrosis patients. Compound **134** was also cocrystallized with its target to better understand the molecular basis of its disease modifying activity (Figure 6).

Heat shock protein 90 (HSP-90) is a so-called chaperone protein that assists other proteins to fold properly, stabilizes proteins against heat stress, and aids in protein degradation. It has shown to stabilize proteins during cancer development. The natural product geldanamycin and derivatives and totally synthetic compounds show promising antitumor activity in clinical trials and therefore HSP-90 is a validated cancer target. The GBB compound **135** was synthesized based on the observation of ATP-competitive Hsp90 inhibitors containing the 8,9-disubstituted adenine motif, which might be replaced with the 2,3-disubstituted 8-aminoimidazo[1,2-*a*]pyrazine scaffold (GBB).[153] Additionally, computational scaffold hopping exercises suggested that a similarly substituted 8-aminoimidazo[1,2-*a*]pyrazine might possess Hsp90 inhibitory activity due to the remarkable resemblance to PU-H71, an Hsp90 inhibitor in Phase I clinical trial. The hypothesis proved to be trough and multiple GBB compounds with this adenosine mimicking patterns showed competitive binding to HSP-90.**135** has been cocrystallized with HSP-90 (Figure 7) and shows multiple contacts to the ATP binding site including hydrogen bonding, pi-stacking of the piperonyl moiety and van der Waals interactions.

Glutamine synthetase catalyzes the synthesis of glutamine from glutamate and ammonia under hydrolysis of adenosine 5′-triphosphate (ATP). The enzyme is involved in nitrogen metabolism and cell wall biosynthesis in pathogenic mycobacteria and thus comprise a potential anti tuberculosis target. ATP-competitive MtGS inhibitors were identified in a high-throughput screening (HTS). One hit compound was a GBB 3-amino-imidazo[1,2-*a*]pyridines. This was an ideal candidate class for structure–activity relationship (SAR) studies, because diverse analogs can easily be obtained in one step via GBB-3CR.[134] The best compound showed an IC50 of 0.6 μM. Co-crystallization of one of the best inhibitors with MtGS **136**, helped to rationalize the observed SAR (Figure 8).

Patents

The first appearance of the GBB-3CR in patents took roughly 3 years when a nitric oxide synthase inhibitor was reported by Gruenenthal GmbH.[216] About 100 patents were filed in the course of 18 years, in which some had the imidazo[1,2-*a*]pyridine/pyrazine as main decorated scaffold obtained using the GBB methodology, while others reported the scaffold either by sequential synthesis and as one of many different claimed structures. The GBB-3CR was found in the pharmaceutical industry and shortly after its discovery patents concerning the [1,2-*a*]-imidazo scaffold appeared in patent applications, either directly or indirectly as seen in the 2004 Patent from Merck & Co. Inc.[217] where the double bonds in the originating pyrazine were reduced to obtain a piperazine. The drug was with various structural modifications brought to the market as Sitagliptin, also known under the tradename Januvia. As many patents were reported in the last decades, not many true GBB-3CR scaffolds were marketed as actual drugs. Recently compound KAF156in development by Novartis AG, completed phase 2 clinical trials (NCT01753323), being effective against the *Plasmodium falciparum* and *Plasmodium vivax* forms of the malaria

parasite with clearance of the parasites within 2 days.[218,219] More examples of patents that leverage the GBB scaffold were listed in Table 6.

AnchorQuery

The scaffold of the GBB-3CR is one of the 27 MCR scaffolds that is included in the AnchorQuery library which was recently introduced as powerful tool for rational structure-based design of protein-protein interaction (PPI) inhibitors.[261] The often deeply buried amino acids comprise a major energetic hotspot which is leveraged in a pharmacophore model search that rapidly screens libraries yielding a possible 31 million synthesizable compounds, each containing an anchor motif that is bioisosteric to amino acid residues, including D, W, Y, F, V and E anchor side chains. Important examples of the power of AnchorQuery are demonstrated through the role it played in the development of novel p53-MDM2 inhibitors and an allosteric inhibitor.[262–264] In the virtual screening the suggested scaffolds are amenable in one to maximal three reaction steps. More specifically, the screening platform contains xyz GBB in xyz different conformations. Using AnchorQuery as a tool is free of charge, accessible via http://anchorquery.csb.pitt.edu and will provide all the tools necessary to interactively perform online virtual screening, rapidly going through millions of compounds with pharmacophore elucidation and enrichment analysis queries. A great benefit of the screening platform is obviously that a binding hypothesis can be immediately tested by resynthesizing the virtual hit (Figure 9).

Conclusions

The GBB-3CR has been described the first-time 20 years ago and is currently one of the mostly used MCR reactions. According to the definition of the Ugi reaction as an α-addition of a Schiff base and a suitable acid component and a rearrangement reaction it belongs formally to the same class of reactions. Similar to the classical Ugi MCR the GBB-3CR also shows a great scope in terms of diversity of starting materials. For mostly any combination between aldehydes, isocyanides and heterocyclic amidines, with the help of a suitable catalyst, the reaction is giving the expected products. Not surprisingly the GBB scaffold is described in multiple publications and patents. The first derivatives of GBB products have entered clinical trials. This is very well in line with the saying that after 15–20 years since the discovery of a new reaction first products based on new reactions will enter the market. It can be predicted that several more bioactive compounds will enter the market in the future. An interesting freely accessible virtual screening platform will be useful in the discovery of tool compounds against difficult to drug targets. Currently still underdeveloped are materials science application of the GBB-3CRs, such as functional polymers or organic conductors or light to energy transformers. Clearly the GBB scaffold has the potential that many interesting electronic and optical applications will be described in the future.

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Biographies

André Boltjes was born in the Netherlands. He received his Bachelor's Degree in chemistry in 2007 from Hanze University and started working at the University of Groningen, developing dopamine agonists, HAT inhibitors, doxorubicin prodrugs, and performing various contract synthesis projects. In 2011 he joined Dömling's group as a technician in University of Groningen. Over the years he was heavily involved in many research projects and is expecting to obtain his Ph.D. at the end of 2019.

Alexander Dömling studied chemistry & biology at the Technical University Munich. After performing his Ph.D. under the supervision of Ivar Ugi he spent his postdoctoral year at the Scripps Research Institute in the group of Barry Sharpless under a prestigious Feodor Lynen research fellowship from the Alexander von Humboldt society. He is founder of several biotech companies, including Morphochem, Telesis and SMIO. In 2004 he performed his habilitation in chemistry at the Technical University of Munich. Since 2006 he was Professor at the University of Pittsburgh in the Department of Pharmacy and Chemistry and in 2011 he became Chair of Drug Design at the University of Groningen. He is author of more than 200 papers, reviews, book contributions and patents. His research interest focuses on novel aspects of multicomponent reaction chemistries and its applications to drug design.

Abbreviations

A list of abbreviations is given in Table 7.

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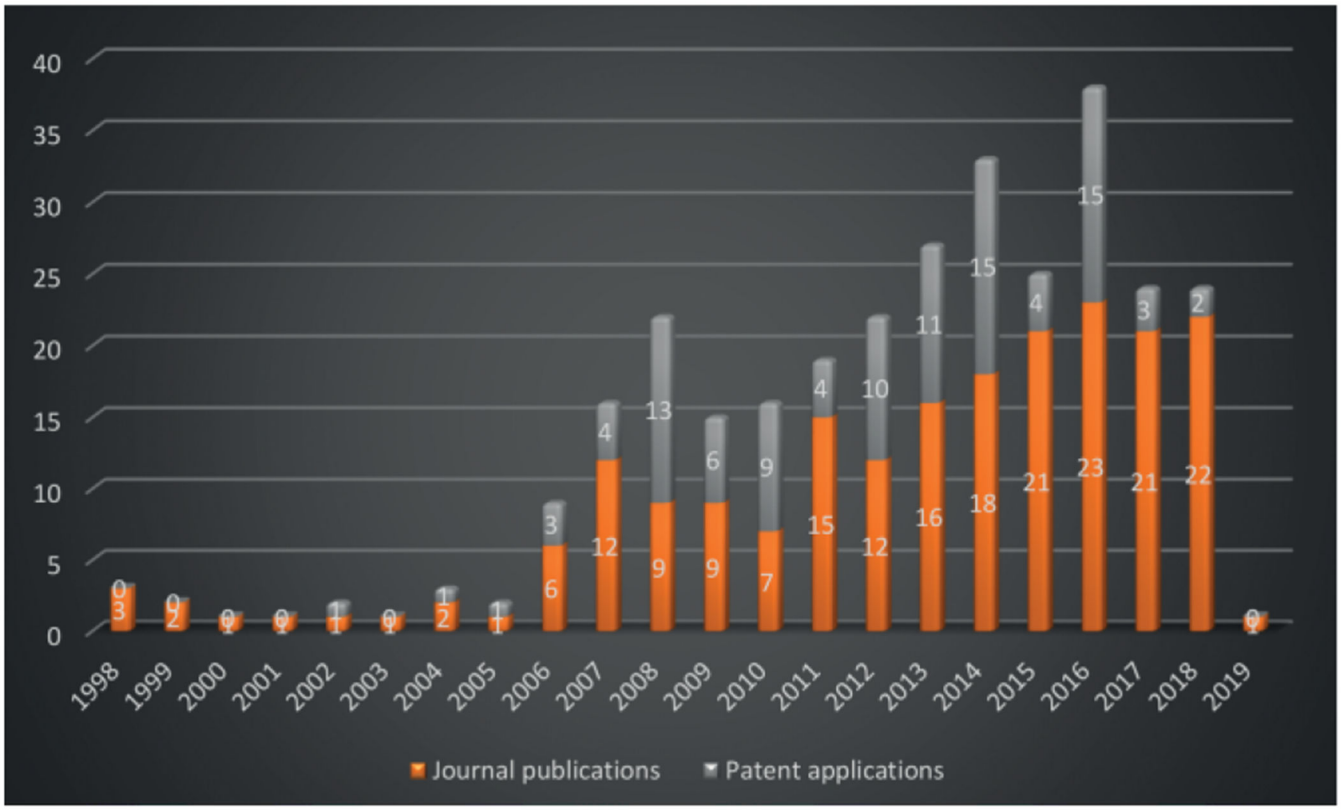


Figure 1.

Development of the GBB-3CR over the last two decades as indicated by increasing number of publications and patents. The numbers were collected through a SciFinder search (April 2019) using GBB-3CR related keywords and structure search of 5- or 6 membered GBB-3CR products including all variations of hetero atoms of the amidine component, corrected for the non GBB-3CR originated 3-amino-substituted imidazo[1,2-*a*]-pyridines, -pyrazines and -pyrimidines.

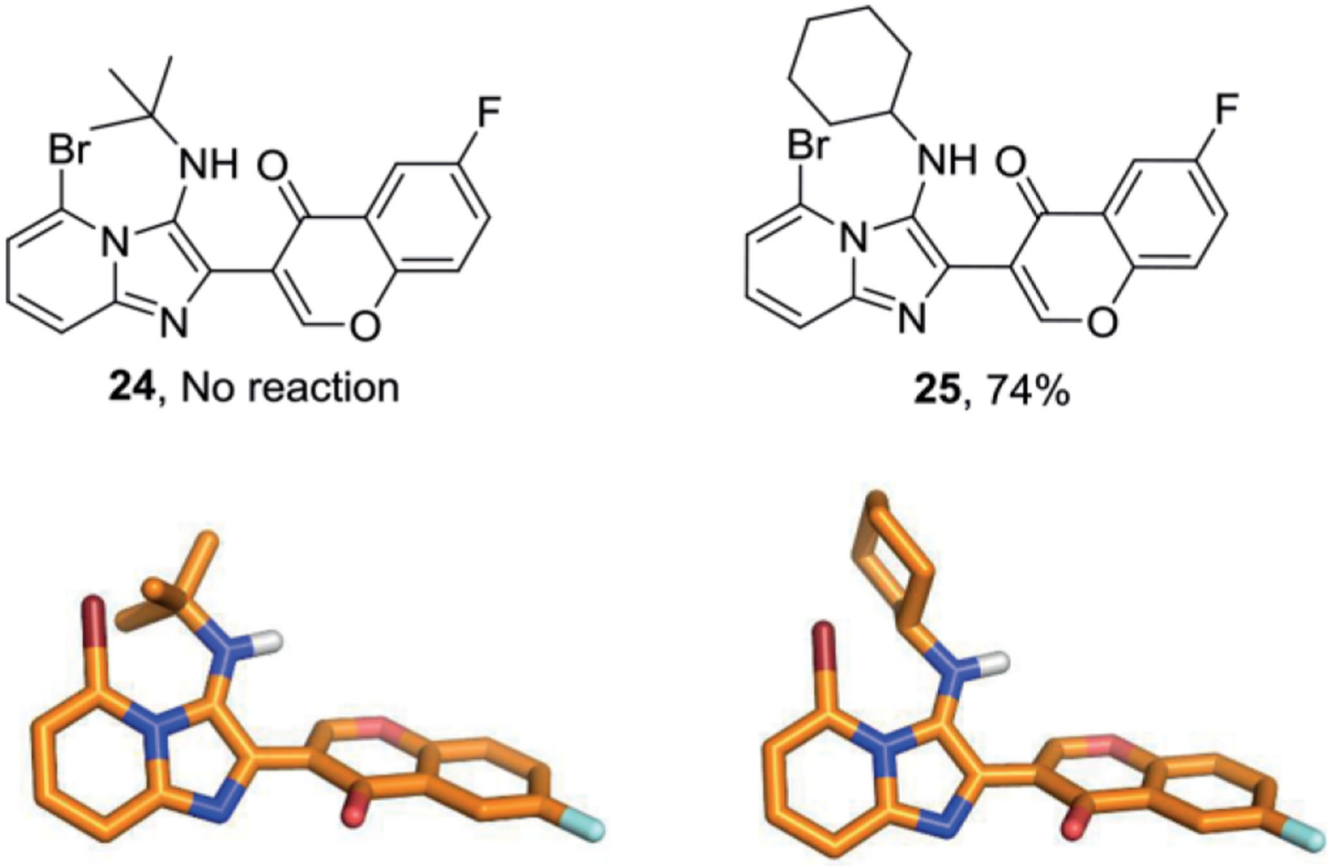


Figure 2.

Steric effects in the GBB-3CR. The bulk effect of *tert*-butyl prevents the reaction from happening, the optimized geometry was calculated for compound **24**, exchanging the *tert*-but- for a cyclohexyl moiety, affording compound **25** in a good yield.

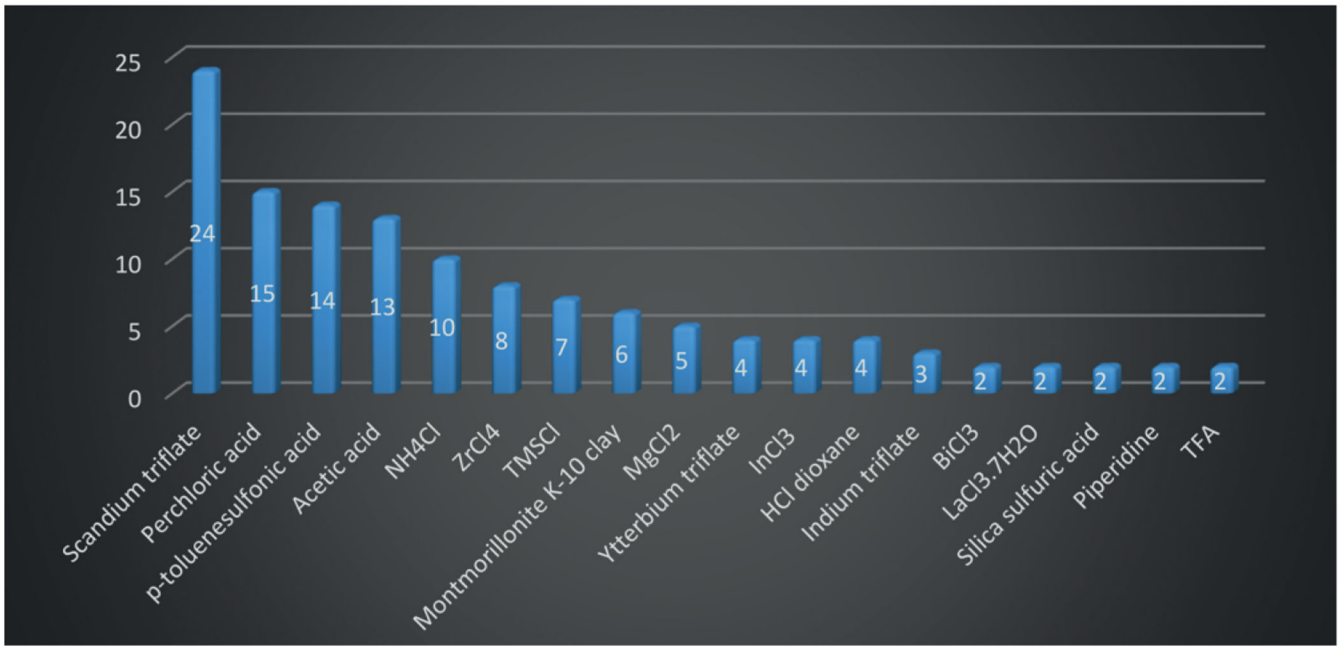


Figure 3.
Overview of GBB catalysts that performed best in reported catalyst screenings (single hits were omitted for clarification).

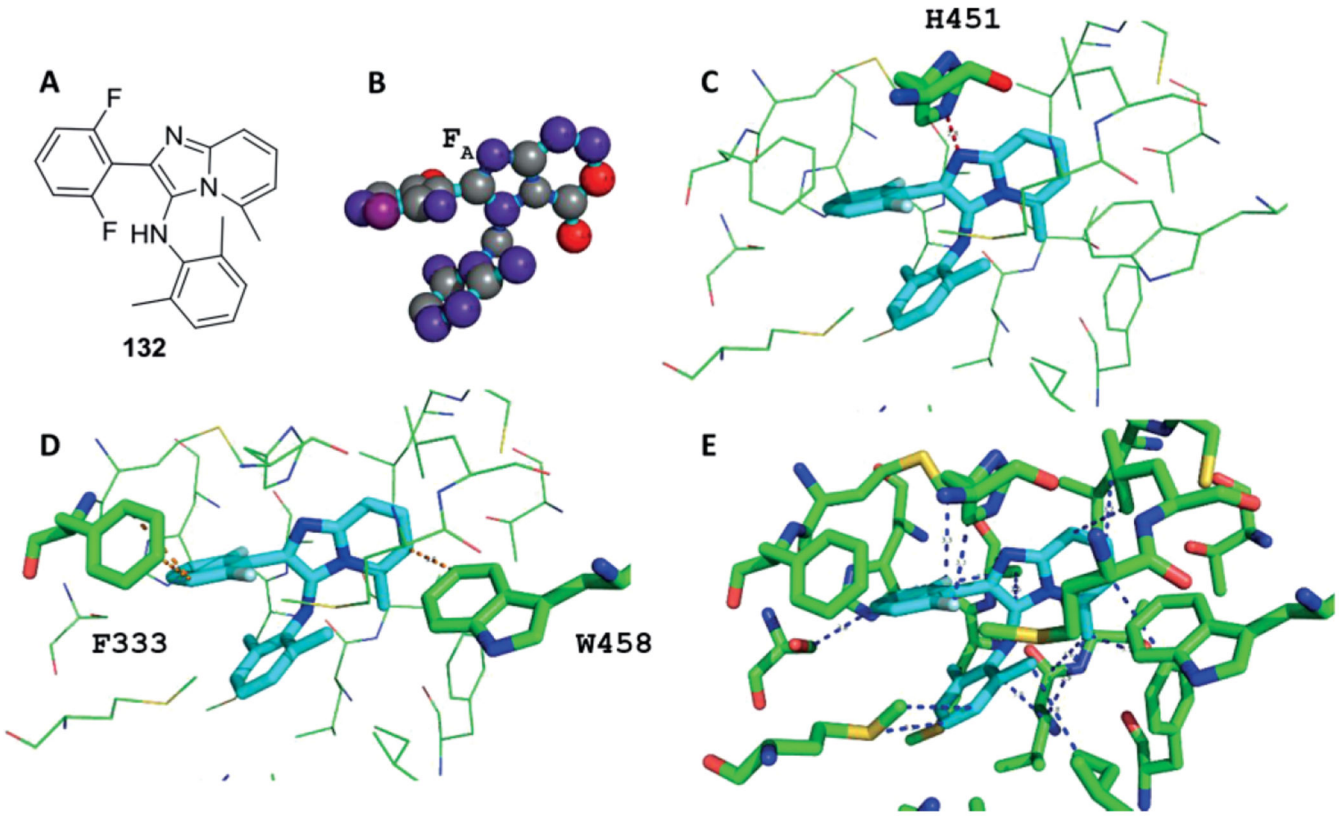


Figure 4.

GBB product **132** bound to farnesoid X receptor (FXR, PDB ID 5Q12). A) 2D structure of **132**; B) scorpion score (14.0) and its heavy atom distribution on **132** (color code: red strong to purple weak contribution, grey minor contribution); C) the imidazole-N of **132** acts as a hydrogen-bond acceptor towards the His451 (2.8 Å); D) **132** forms two pi-stacking interactions between Phe333 and the 2,6-difluorophenyl moiety and the Trp458 and the 2-methyl pyridine moiety; E) multiple hydrophobic interactions can be found between all parts of **132** and the surrounding hydrophobic receptor amino acids; specifically to mention is F_A (red in B) which makes multiple contacts with His298, Met332 and Ala295.

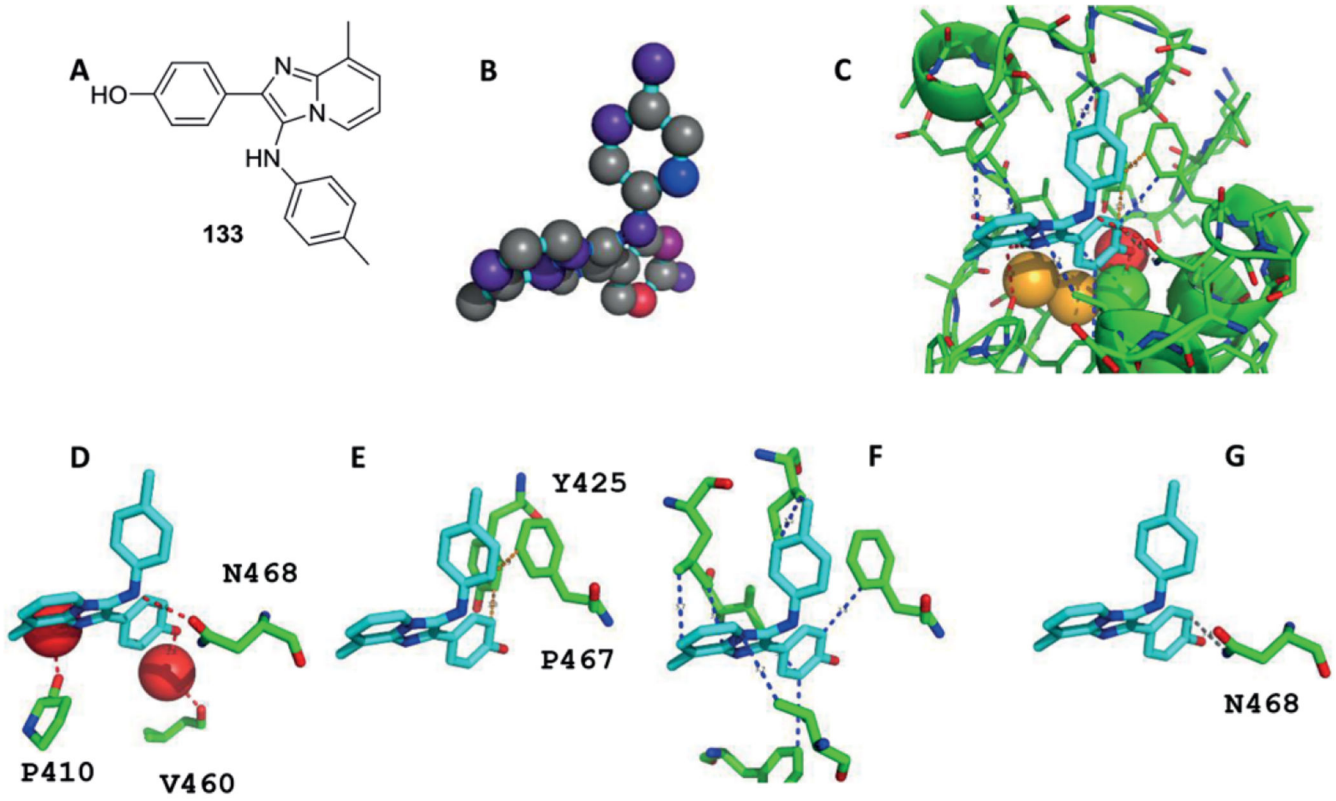


Figure 5.

Second Bromodomain (BD2) from Candida albicans Bdf1 binding to an GBB imidazopyridine (PDB 5N18). A) 2D structure of **133**; B) scorpion score (5.6) and its heavy atom distribution on **133** (color code: red strong to purple weak contribution, grey minor contribution);; C) overall GBB receptor binding site featuring multiple electrostatic interactions and a string of four signature structural waters (green, yellow and red balls); D) two water mediated hydrogen bondings including Pro410 carbonyl-H2O-N imidazole and Val460 carbonyl-H2O-p-hydroxyphenyl and Asn468 side chain amide-CO and exocyclic NH of isocyanide moiety; E) T-shaped pi-pi interactions between Phe467 and Tyr425 and the phenyl groups of the isocyanide and aldehyde components; F) multiple van der Waals interactions involving Phe467, Val415, Ph411, Val474 and Leu420; G) a H-bond donor-pi interaction involving the side chain amide NH of Asn468 and the aldehyde phenyl.

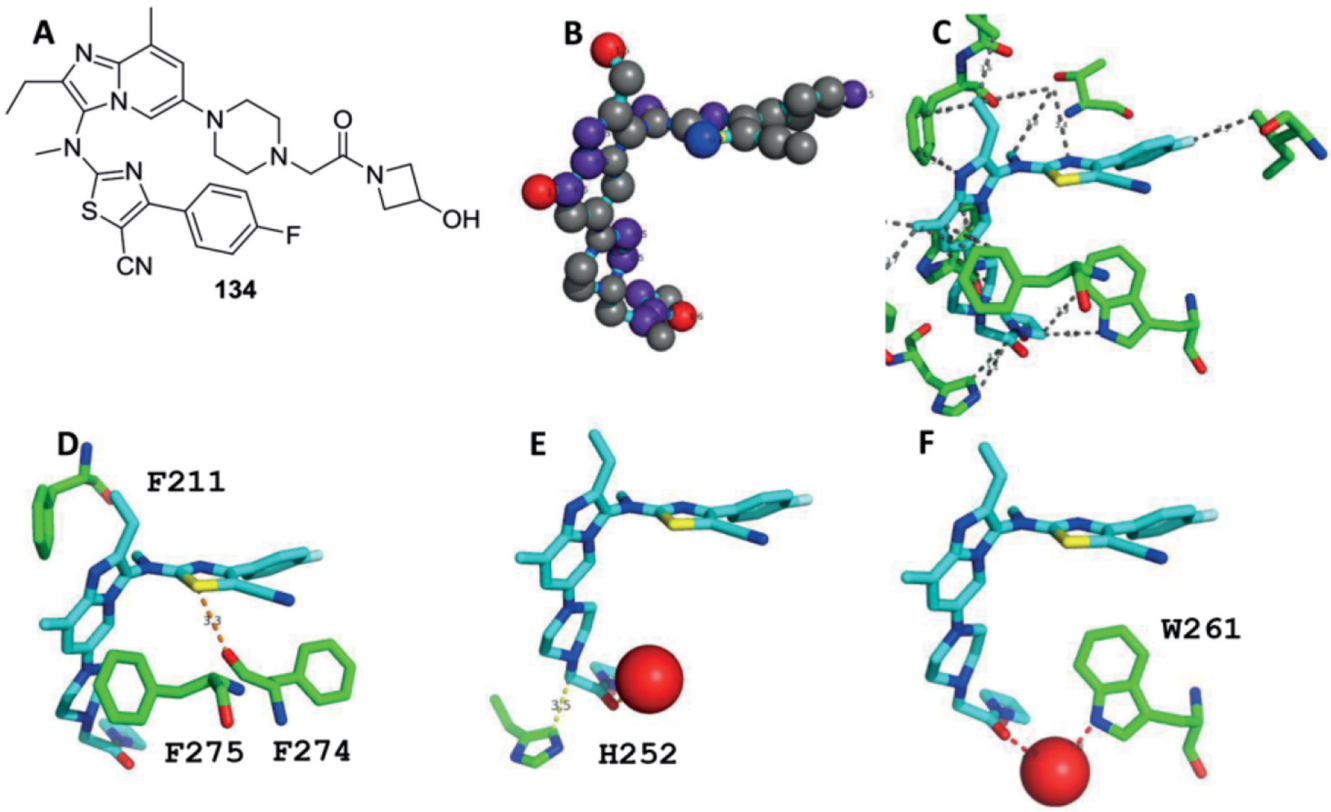


Figure 6.

GBB Imidazo[1,2-*a*]pyridine derivatives with potent autotaxin/ENPP2 inhibitor activity (PDB ID 5MHP). A) 2D structure of 134; B) scorpion score (10.6) and its heavy atom distribution on 134 (color code: red strong to purple weak contribution, grey minor contribution); C) overall topology of the interaction of 134 with its receptor featuring multiple hydrophobic, hydrogen bonding and stacking interactions; D) x is embedded in a aromatic cage including Phe's211, 275, 274, Trp261 and His252; Phe274 carbonyl forms a pi-pi interaction with the thiazole sulfur; E) two H bond donor pi interactions involve His252 and a structural water molecule; F) a water mediated hydrogen bond involves the azetidine carbonyl and the NH of Trp261.

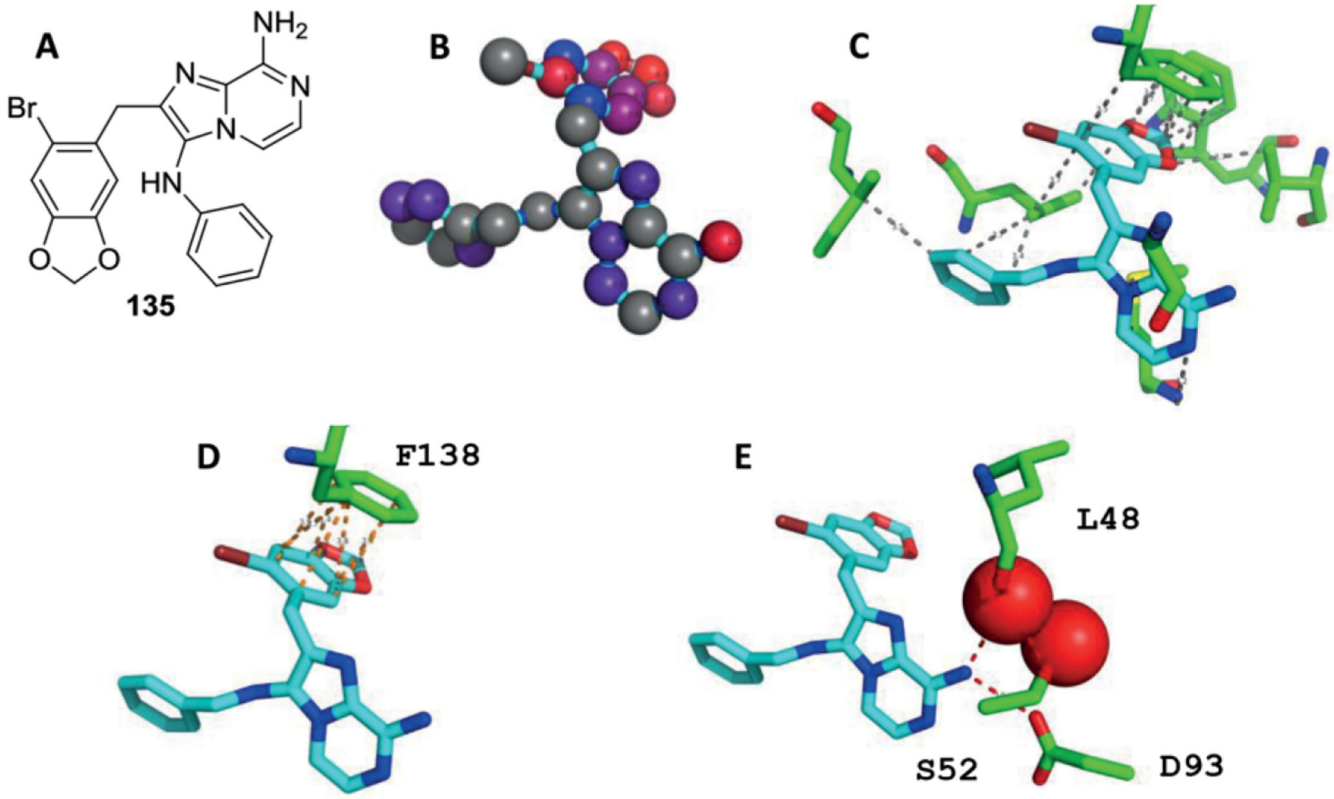


Figure 7.

GBB compound **135** binding to HSP-90 (PDB ID 4R3M). A) 2D structure of **135**; B) scorpion score (14.8) and its heavy atom distribution on **135** (color code: red strong to purple weak contribution, grey minor contribution); C) overall receptor ligand interaction involving multiple van der Waals, stacking and hydrogen bonding interactions; D) a parallel pi-pi stacking interaction between Phe138 and the moiety 1,2- methylenedioxybenzen e moiety is a strong affinity contributor; E) the adenine-NH_2 forms a direct hydrogen bond towards Asp93 carboxylate and a tripartite hydrogen bond Leu48 backbone carbonyl and Ser52-OH mediated by two structural water molecules accounting for the adenine-NH_2 importance for binding.

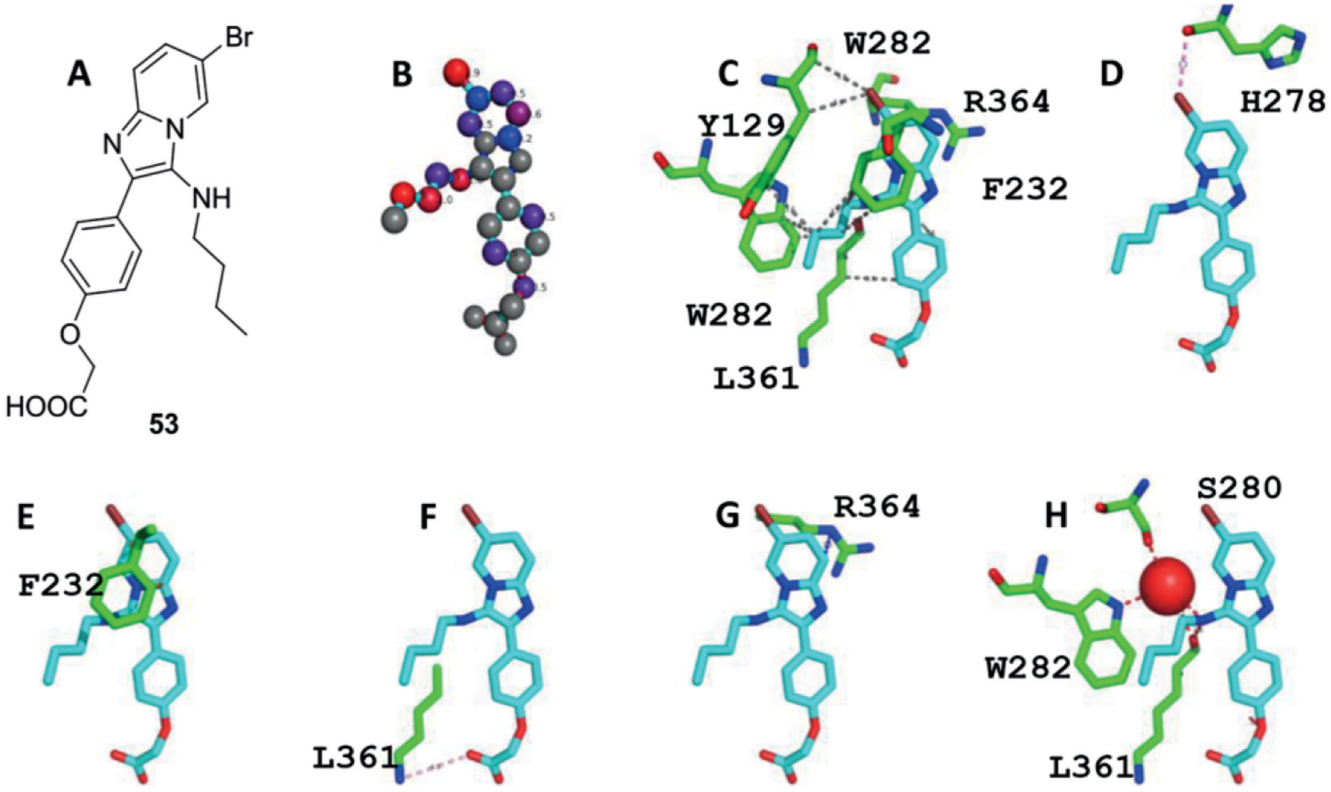


Figure 8.

Crystal structure of Mycobacterium tuberculosis glutamine synthetase in complex with GBB **53** (PDB ID 4ACF). A) 2D structure of X; B) scorpion score (10.3) and its heavy atom distribution on **53** (color code: red strong to purple weak contribution, grey minor contribution); C) **53** is embedded in a hydrophobic site involving Arg364, Phe232, Lys361, Trp282 and Tyr129; D) a halogen bonding between Hi278 backbone carbonyl and the Br is identified; E) a parallel pi-pi stacking interaction between Phe231 and the pyridine central part of GBB backbone is formed: F) a ionic interaction is spotted between the ligands carboxy group and the Lys361; G) a cation-pi interaction is formed between Arg364 and the pyridine part of the GBB backbone; H) the aminobutyl side chain-NH is involved in a direct hydrogen bonding with Lys361 carbonyl and a tripartite water mediated network with Trp282 indole NH and Ser280-OH.

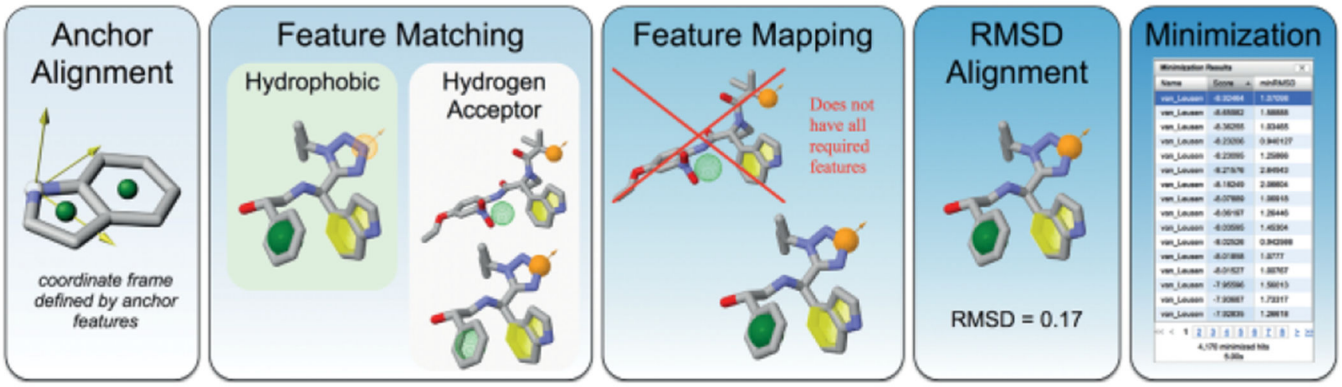
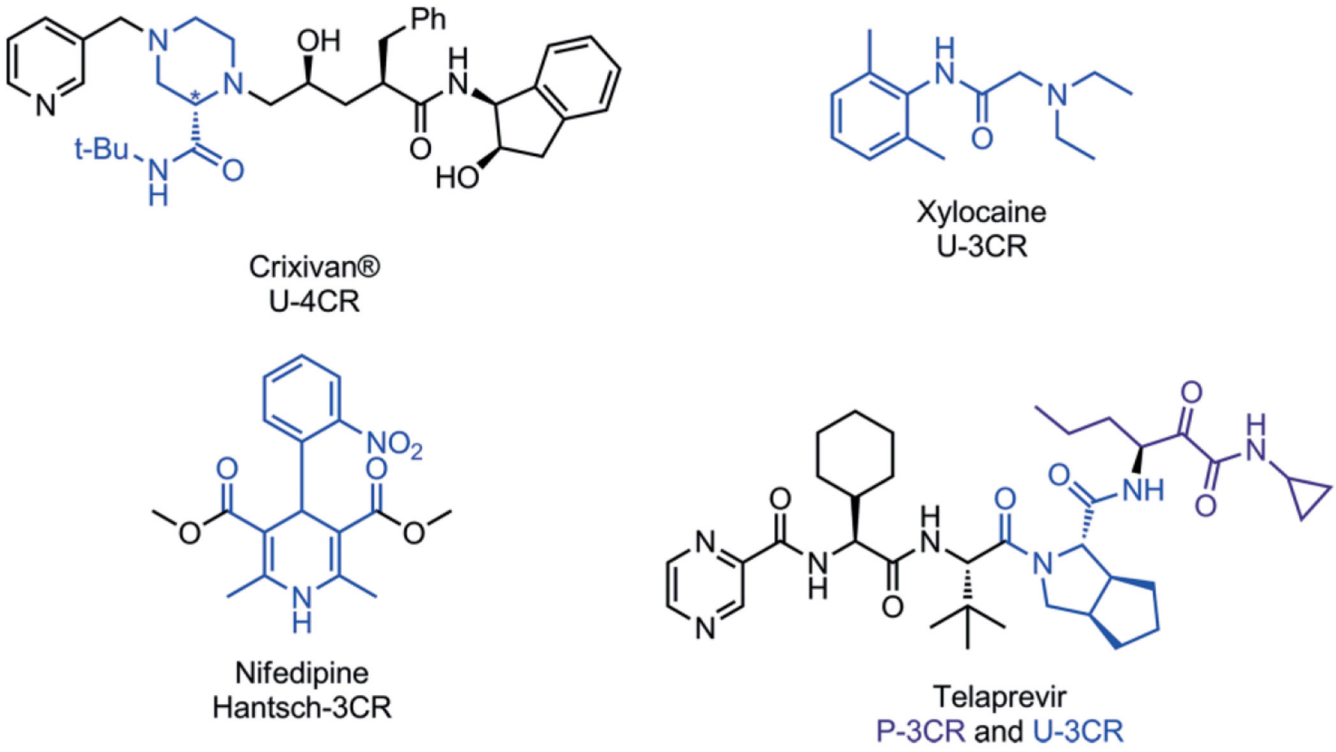
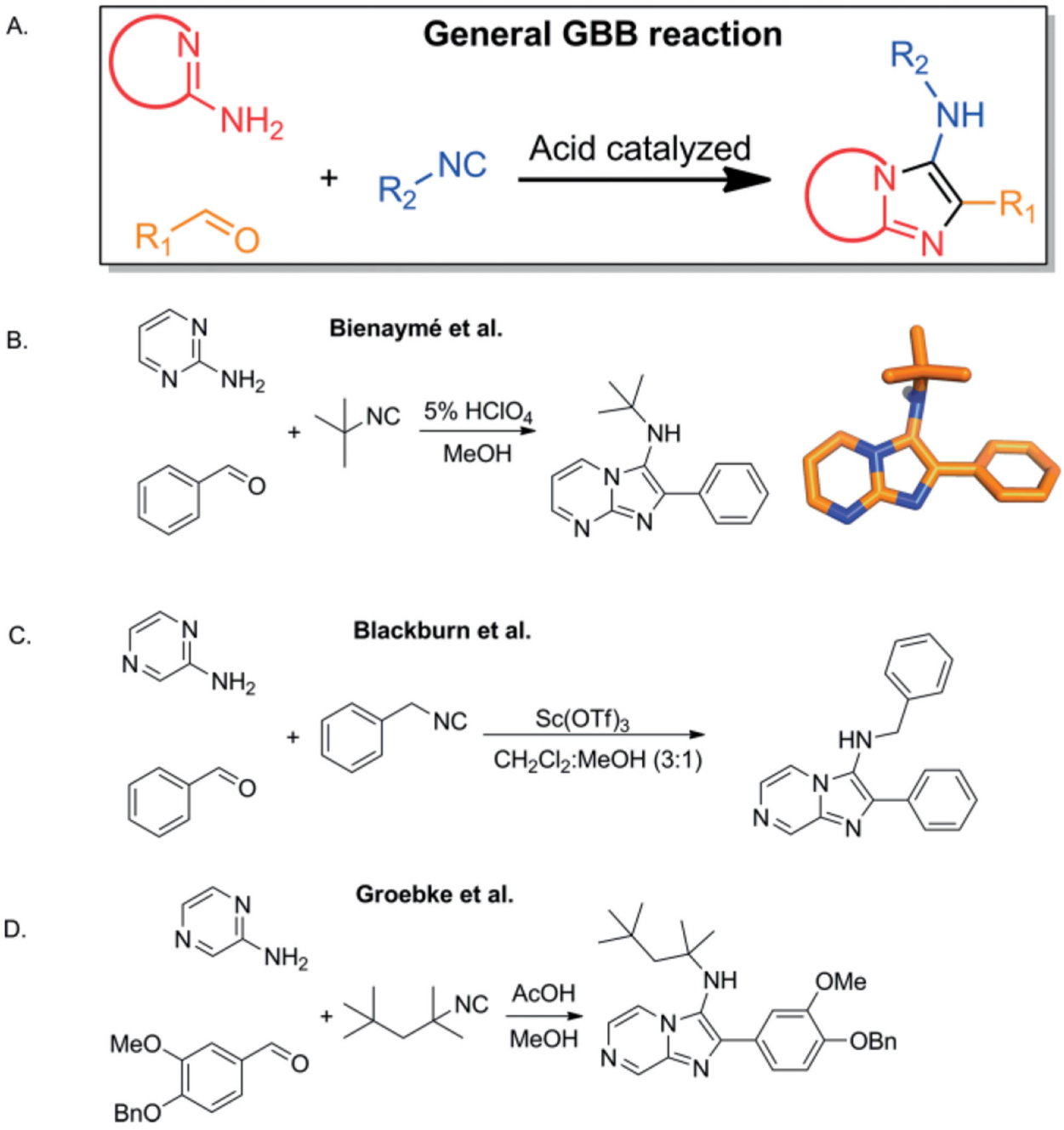


Figure 9.
Workflow of the online virtual screening platform ANCHOR.QUERY.



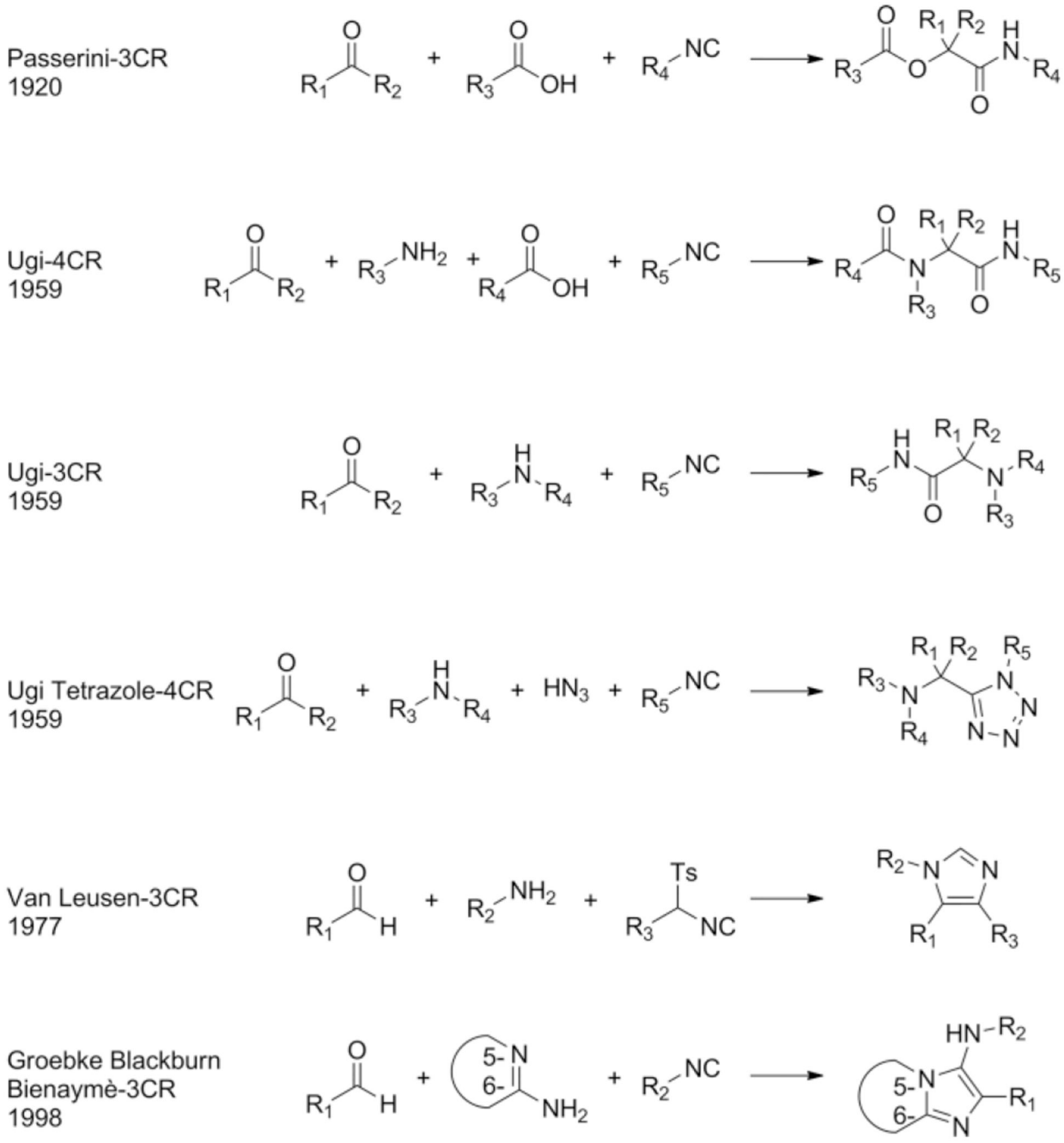
Scheme 1.

Drug synthesized using MCR reactions. The scaffold originating from the MCR is marked in blue or purple. The central piperazine element of the HIV protease inhibitor Crixivan was enantioselectively synthesized by U-4CR, the local anesthetic Xylocaine can be advantageously synthesized in one step using U-3CR, the cardiovascular blockbuster drug Nifedipin by a Hantzsch-3CR and the stereochemical complex HCV protease inhibitor Telaprevir by a combination of P-3CR (purple) and U-3CR (blue) thus reducing the total number of steps by half.

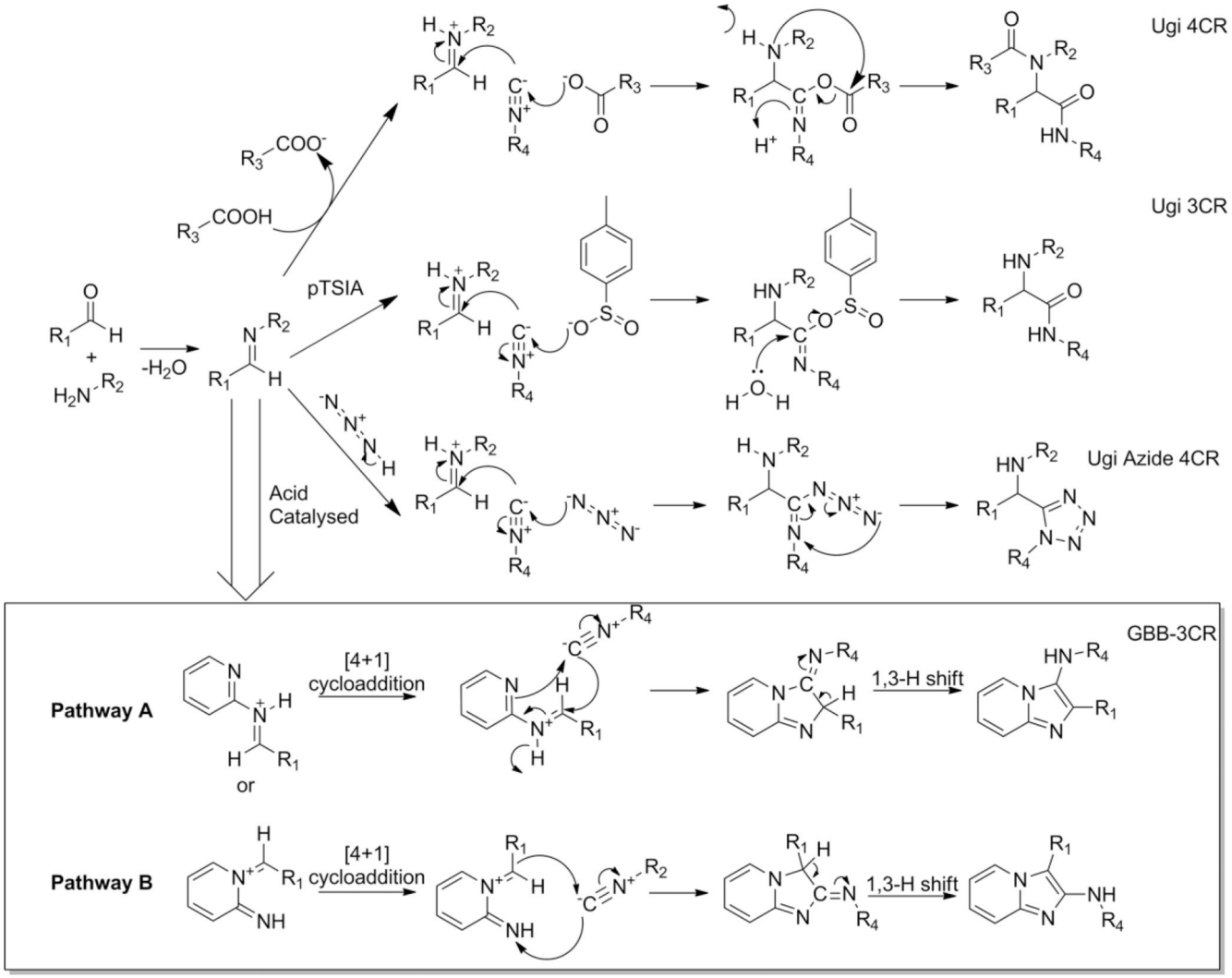


Scheme 2.

The discovery of the GBB-3CR: **A**, General description of the GBB-3CR using amidines, aldehydes and isocyanides. **B**, one of the examples of Bienaymé using 2-aminopyrimidine, benzaldehyde, *tert*-butyl isocyanide and perchloric acid as catalyst, the formation was verified by X-ray structure refinement (CCDC-101255). **C**, Blackburn et al. reporting scandium triflate as optional catalyst. **D**, one of the Groebke examples; with 2-aminopyrazine, catalyzed with acetic acid.

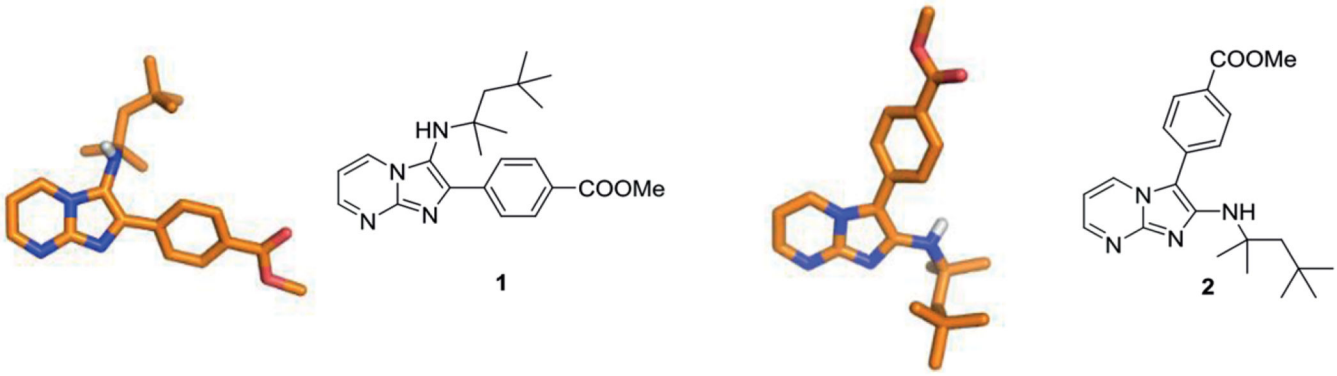


Scheme 3.
Overview of the most common IMCR's.



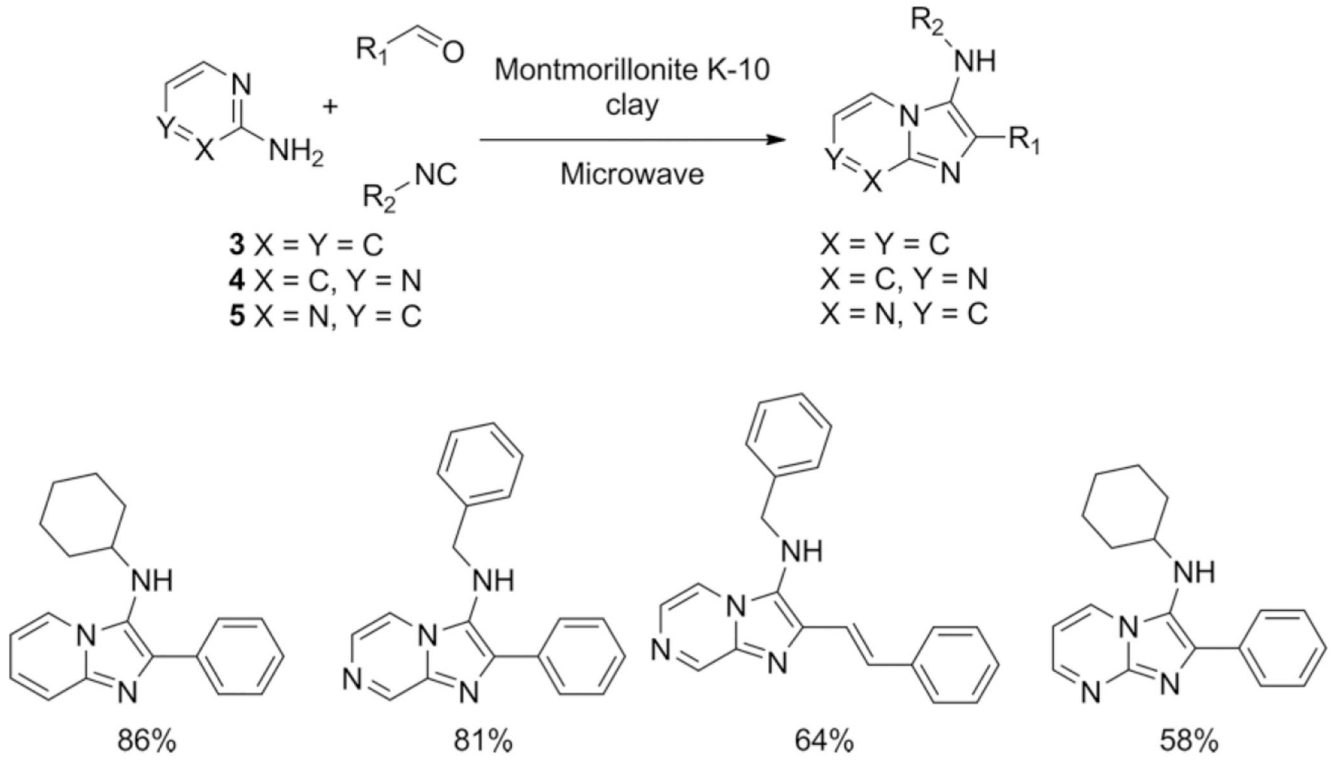
Scheme 4.

Variations of the Ugi reaction and the Groebke Bienaymé Blackburn reaction. In the GBB mechanism one of the most commonly used amidines; 2-aminopyridine as R_2-group was used in the mechanistic overview to simplify the scheme.

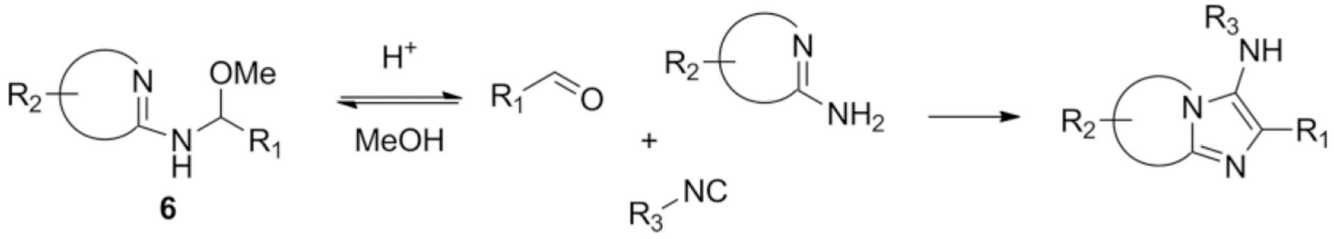


Scheme 5.

Two possible regioisomers of the GBB-3CR. Left **1** (CCDC-189548) a typical GBB-3CR imidazo[1,2-*a*]pyrimidine and on the right **2** (CCDC-189549) its inverse GBB regioisomer.

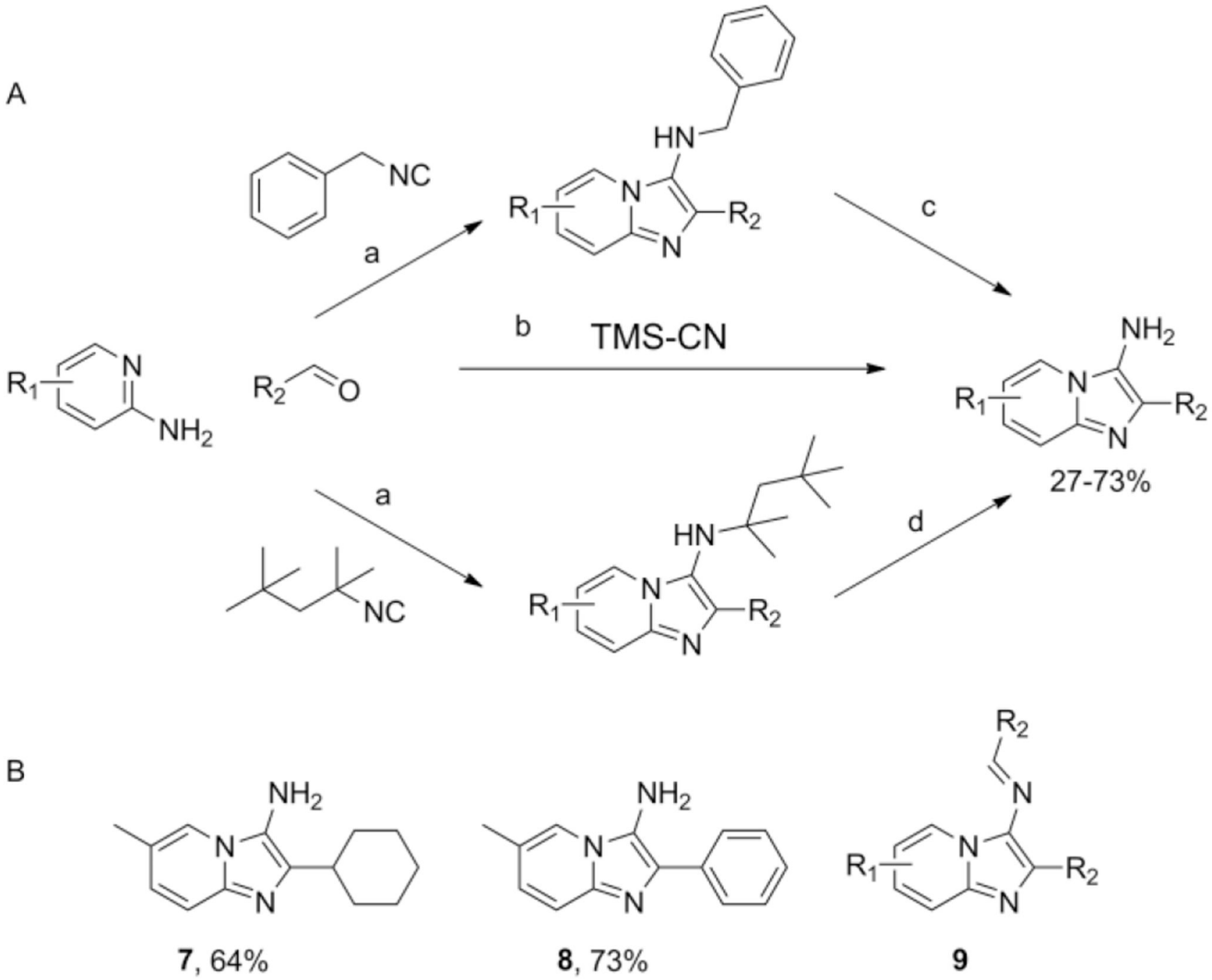


Scheme 6.
Montmorillonite K-10 clay-catalyzed and solvent free GBB-3CR.



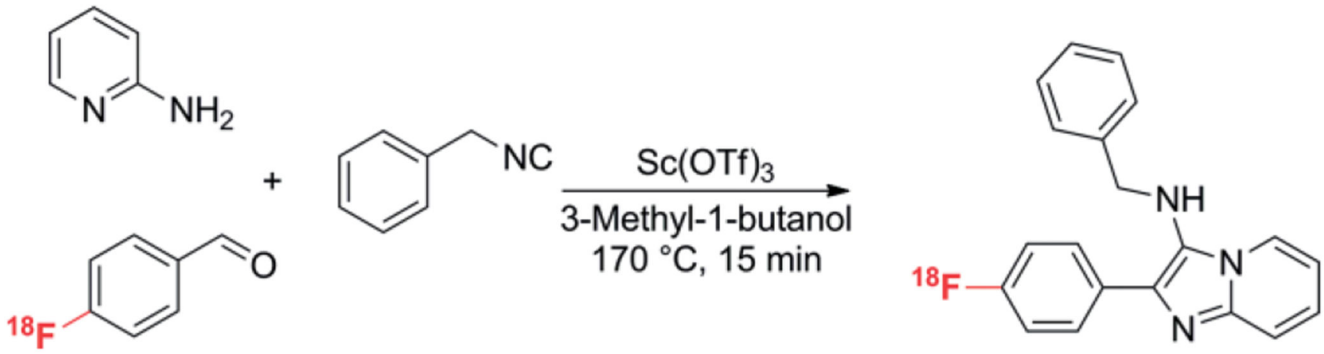
Scheme 7.

Application of electron-poor cyclic amidines in the GBB-3CR results in poor conversion and side reactions such as addition of MeOH to the Schiff base intermediate.

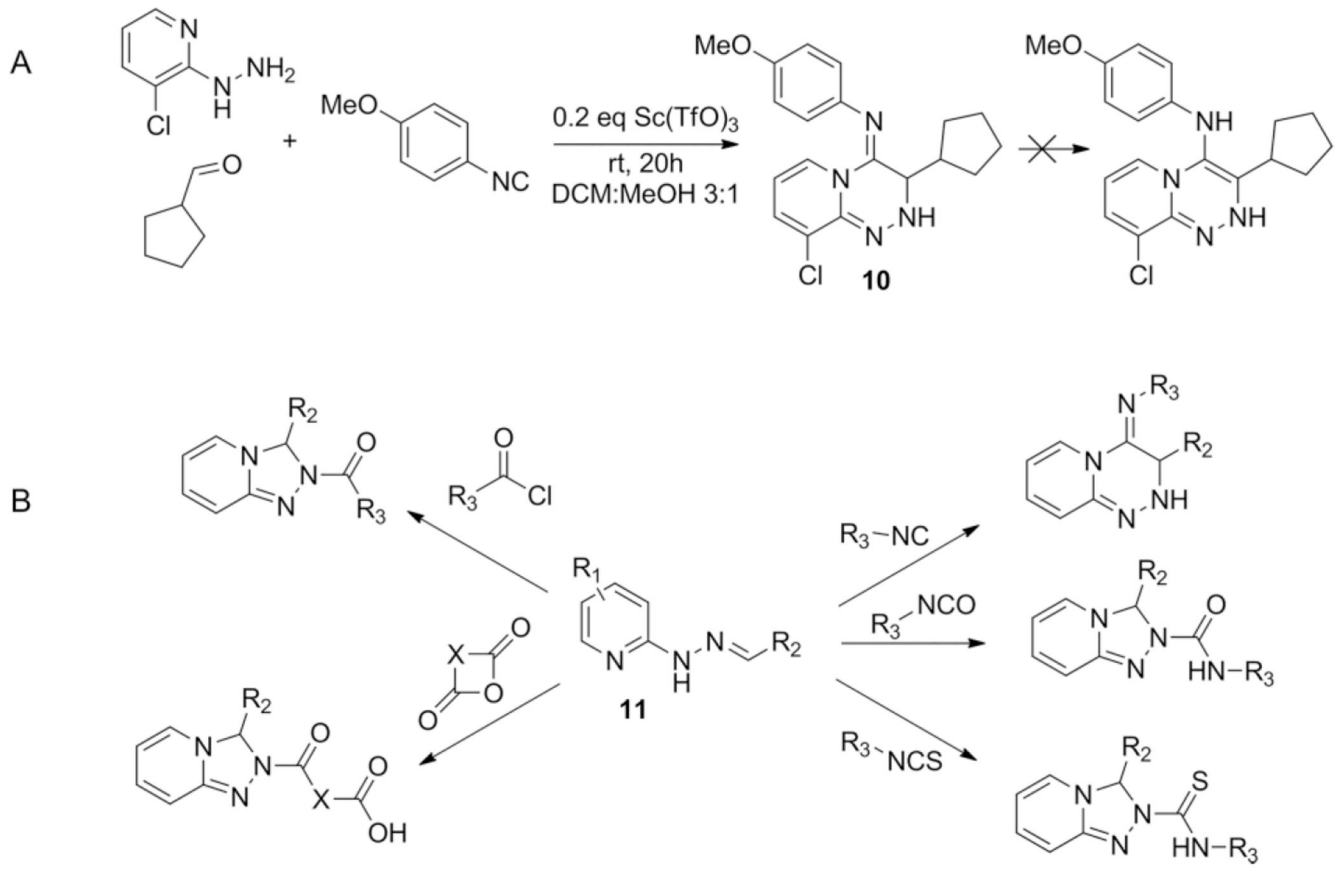


Scheme 8.

Access to N-exocyclic unsubstituted GBB products. A: reagents and conditions: a) aminopyridine (1 equiv.), R_2CHO (1 equiv.), 2 (1 equiv.) or benzyl isocyanide (1 equiv.), $Sc(OTf)_3$ (5 mol-%), 16 h; b) aminopyridine (1.2equiv.), R_2CHO (1 equiv.), TMSCN (1 equiv.), $Sc(OTf)_3$ (5 mol-%), MeOH, microwave, 10 min, 140 °C. Followed by Si-trisamine (5 equiv.); c) H_2, EtOAc, 24 h; d) 10 % TFA/CH_2Cl_2, 18 h B: representative examples and their yields and the observed Schiff base as side product.

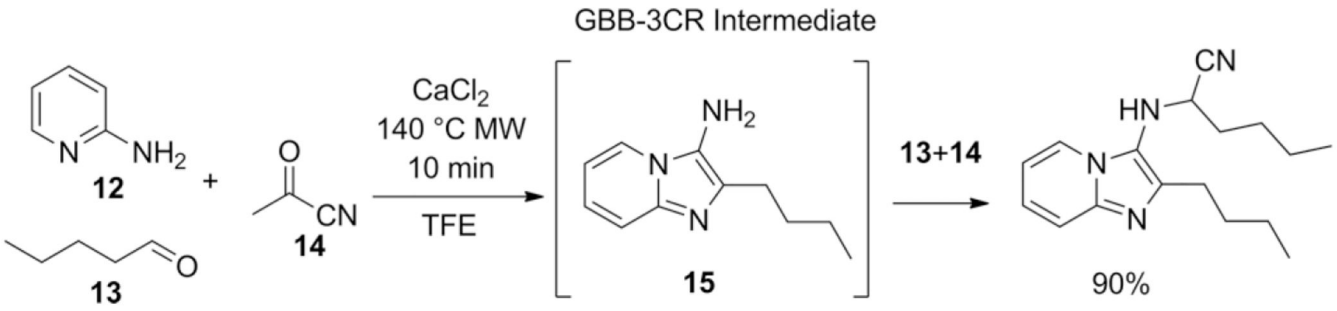


Scheme 9.
^{18}F introduction in GBB-3CR products.

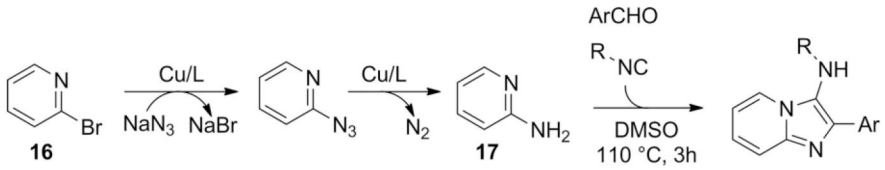


Scheme 10.

A: hydrazines undergo a GBB-like [5+1] cycloaddition to furnish bicyclic triazines. This given example was obtained in 85 % yield, aromatic aldehydes will not result in product formation B: The reactivity of the hydrazine derived Schiff base could be exploited for other transformations with various electrophiles.

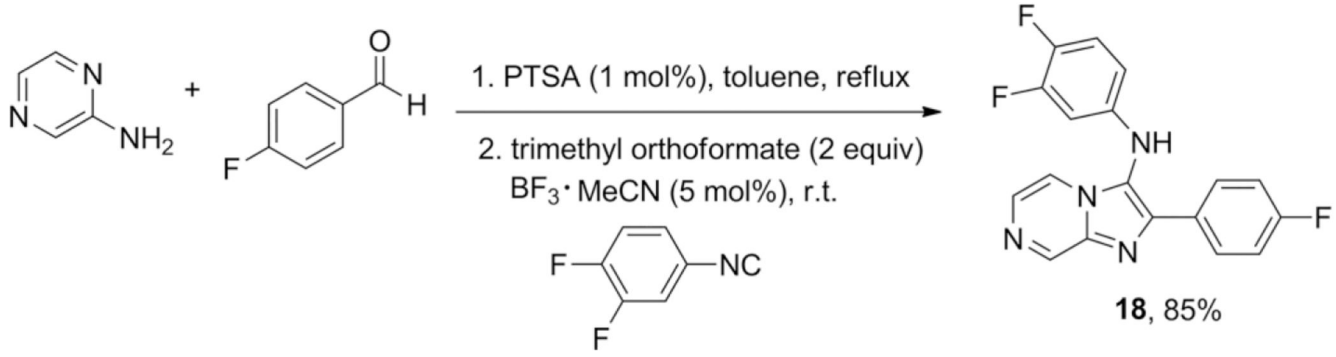


Scheme 11.
Acetyl cyanide assisted one-pot three-step GBB-Strecker cascade.

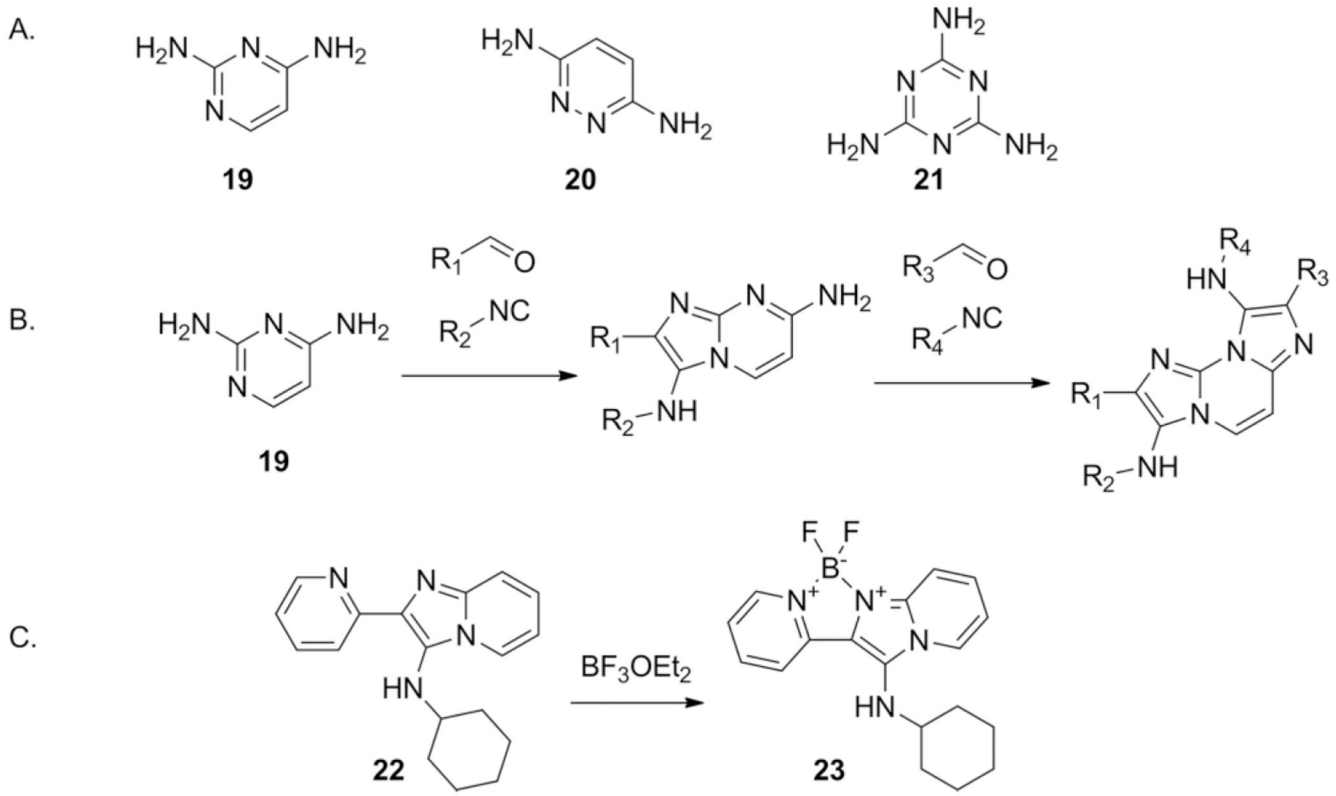


Scheme 12.

The scope of the GBB-3CR was expanded by the use of 2-bromopyridine, in situ converted into the essential amidine.

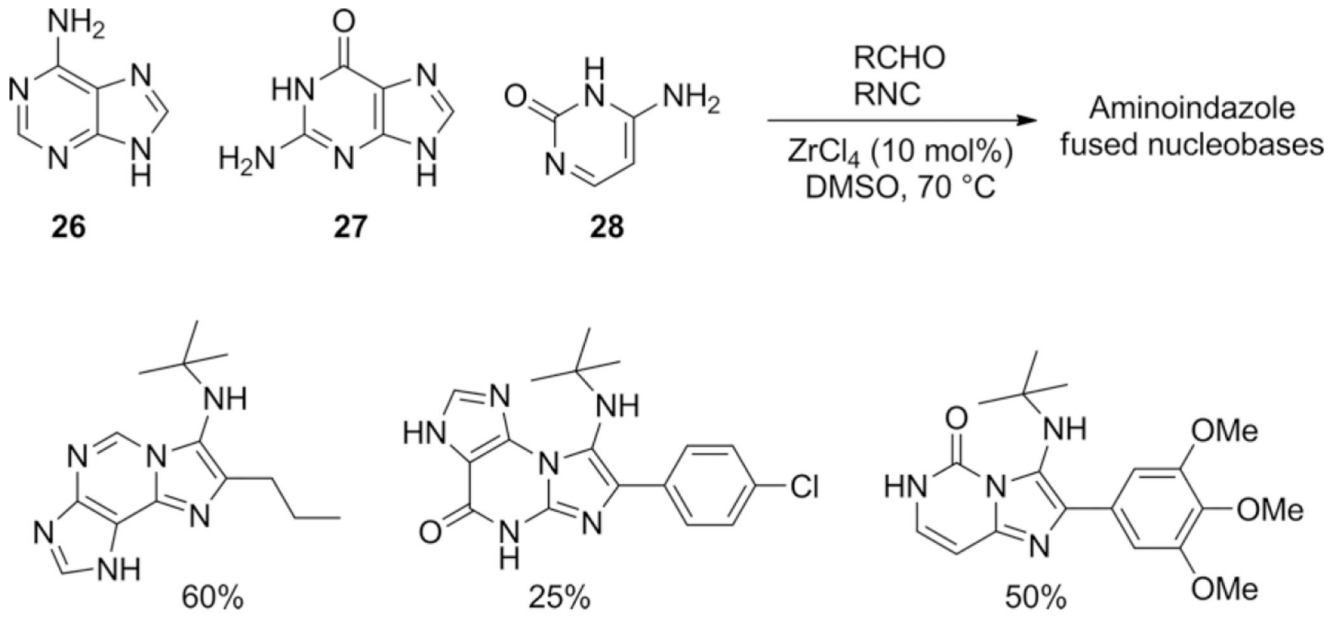


Scheme 13.
The optimized one-pot two-step process of a BF_3·MeCN catalyzed GBB-3CR.

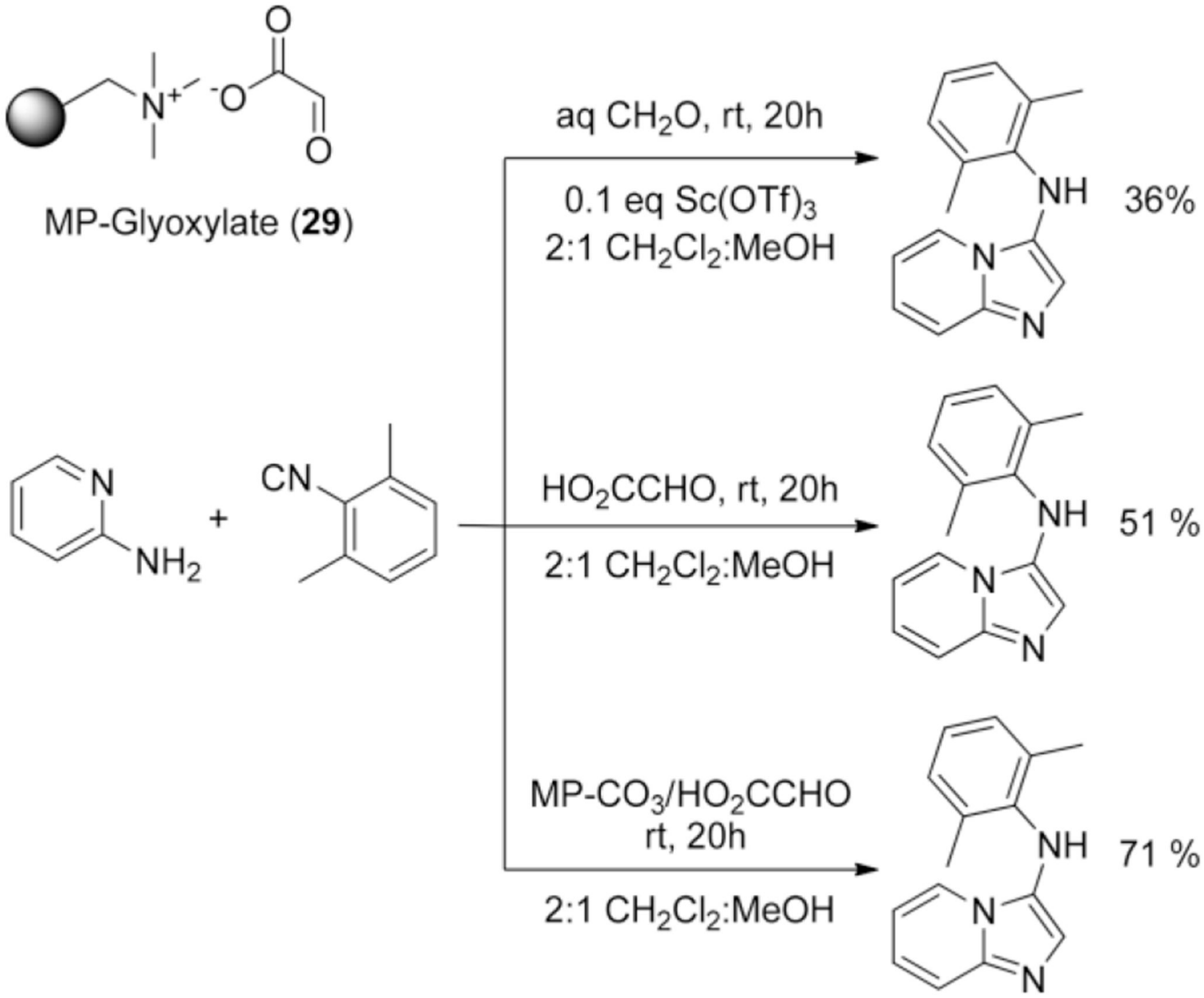


Scheme 14.

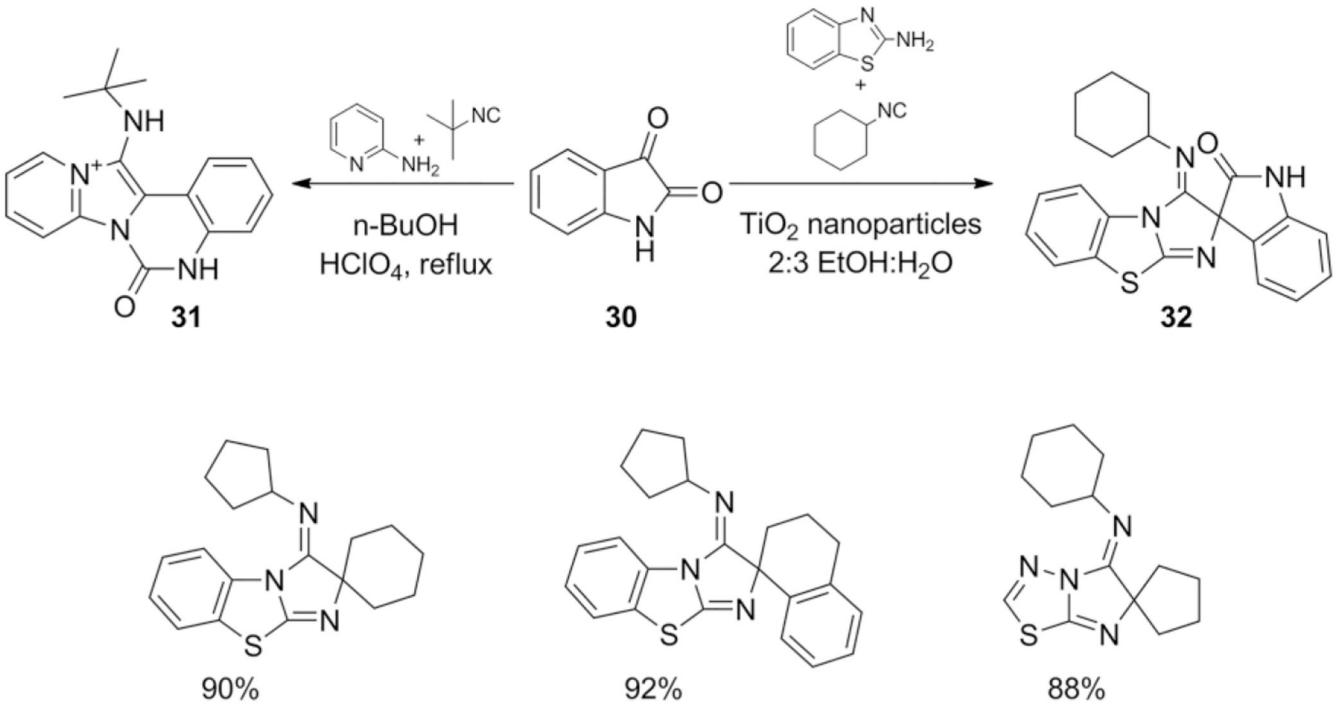
Bis-amidines in the GBB-3CR: A. The bis- and tris amidines reacted in the GBB-3CR. B. Asymmetric product formation using different aldehydes and isocyanides in two separate MCRs. C. Enhancement of fluorescent properties by introduction of a BF_2 bridge.



Scheme 15.
Synthesis of aminoimidazole-condensed nucleobases.

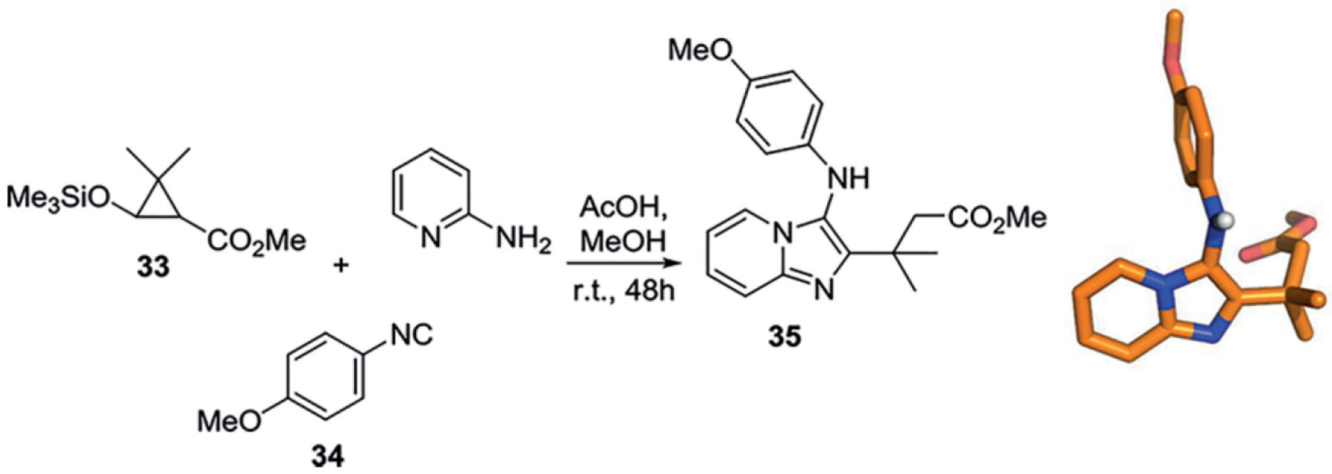


Scheme 16.
Formaldehyde and formaldehyde surrogates in the GBB-3CR and their associated yields.



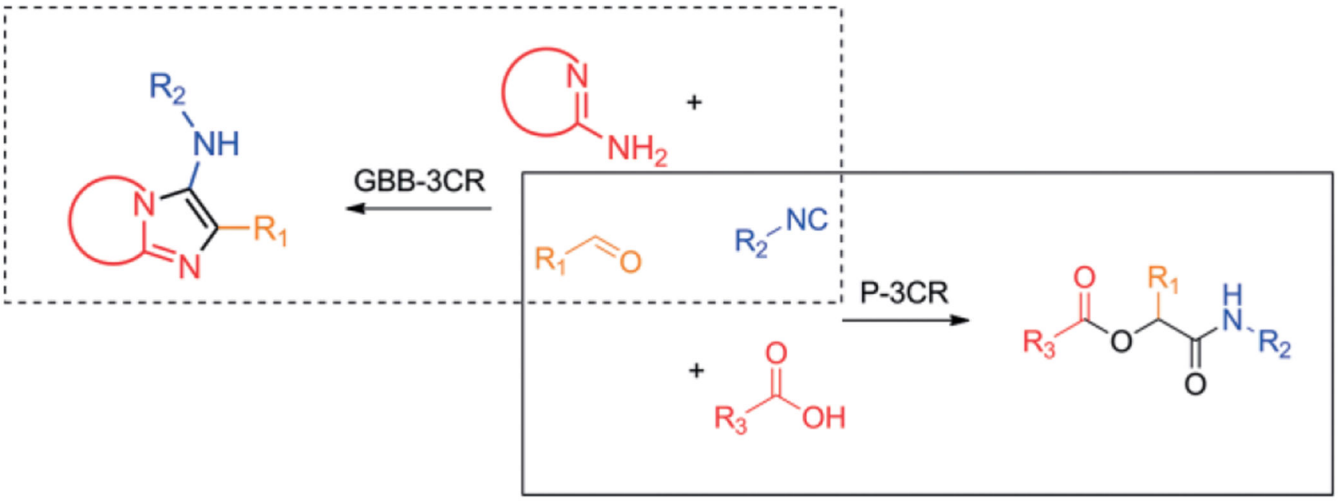
Scheme 17.

Two possible reaction pathways with the α-ketoamide isatin and some examples of the GBB-3CR ran with other ketones.



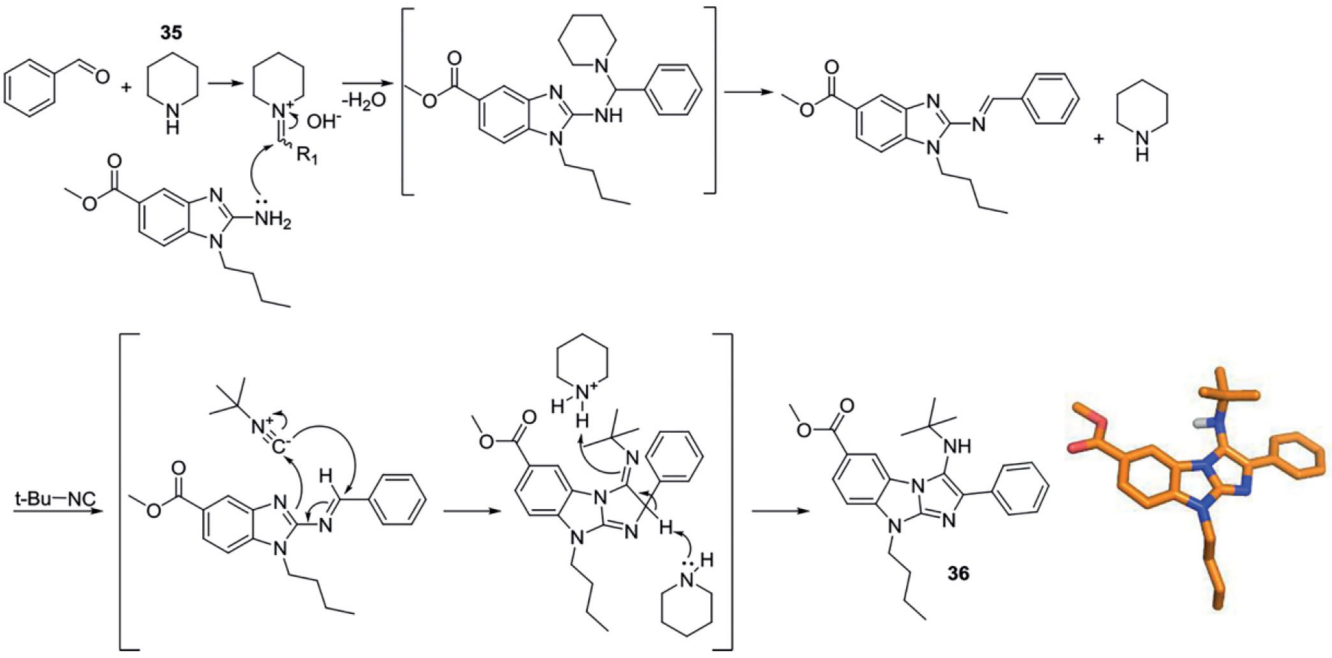
Scheme 18.

2-Siloxycyclopropanecarboxylates as aldehyde substitutes in the GBB-3CR. One example of a GBB product **35** synthesized from 2-siloxypropanecarboxylates and its resolved X-ray structure (CCDC-601760), in total 8 products were synthesized with variations on the amines, isocyanides with yield varying 40–79 %.



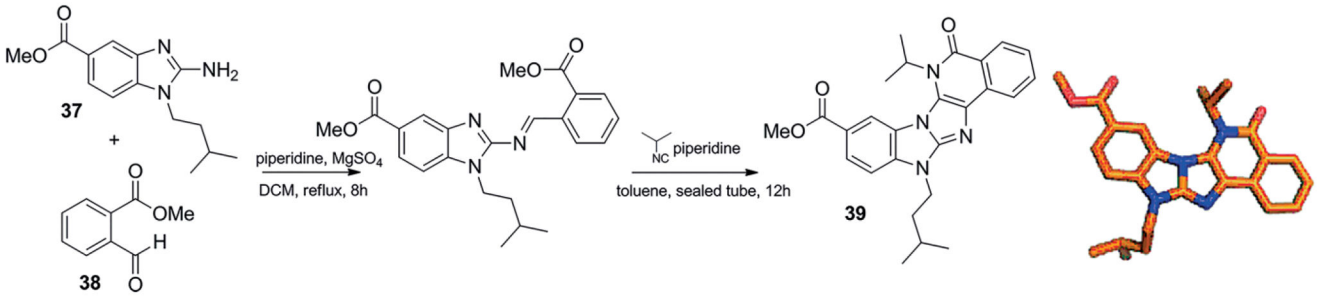
Scheme 19.

The P-3CR is competing with the GBB-3CR when carboxylic acids are used as catalyst, consuming the aldehyde and isocyanide components that otherwise would be consumed by the GBB-3CR.



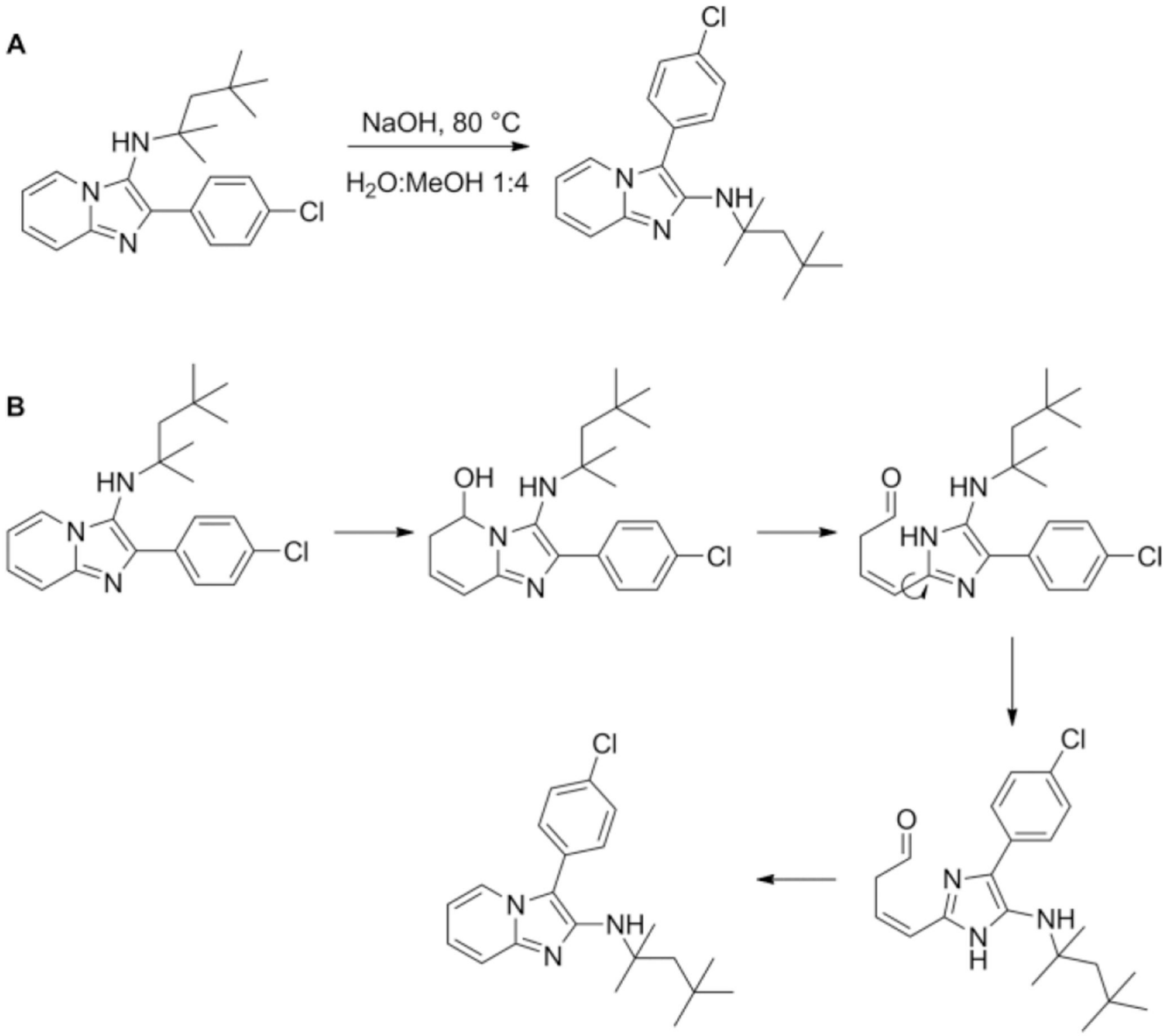
Scheme 20.

Plausible mechanism for the piperidine catalyzed GBB-3CR projected on methyl 9-butyl-3-(*tert*-butylamino)-2-phenyl-9H-benzo[d]imidazo[1,2-*a*]imidazole-6-carboxylate (**36**) and its corresponding X-ray structure.



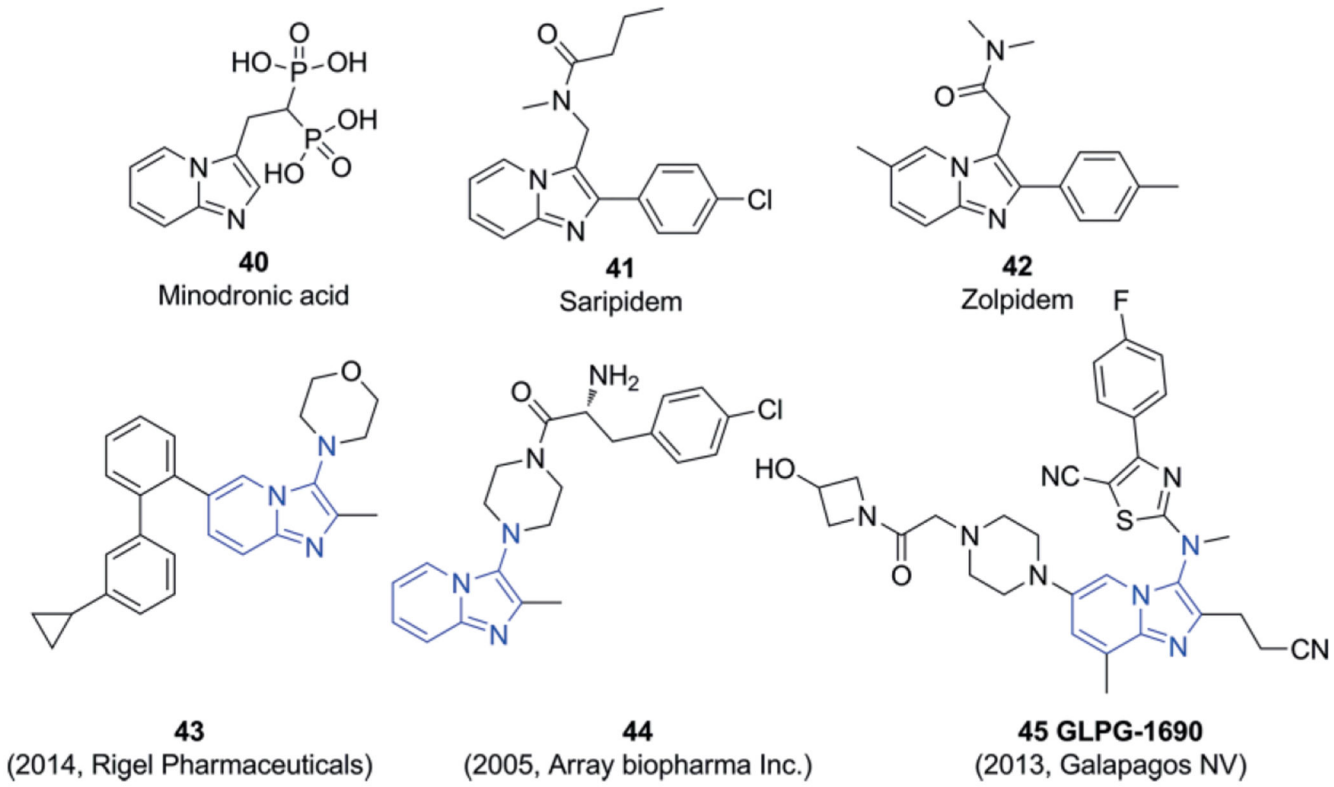
Scheme 21.

Preparation of polyheterocyclic **39** unambiguously confirmed by X-ray structure analysis (CCDC 850793).



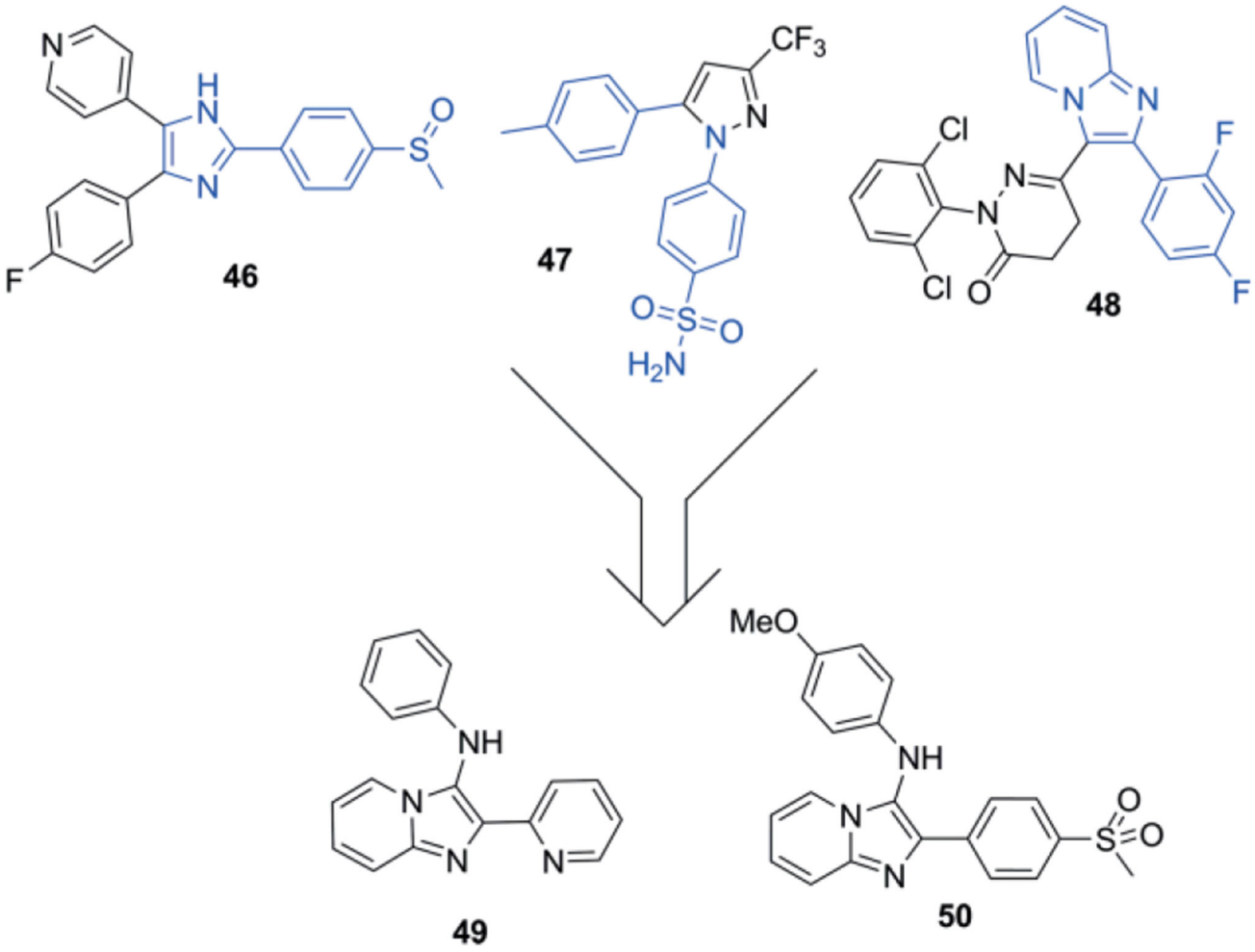
Scheme 22.

The Dimroth rearrangement gives access to both regioisomers. A: the rearrangement is performed under basic conditions while heating. B: the proposed mechanism, driven by the stability of the product and properties of the initial starting material, such as aromaticity of the ring, bulkiness of substituents and solvent.



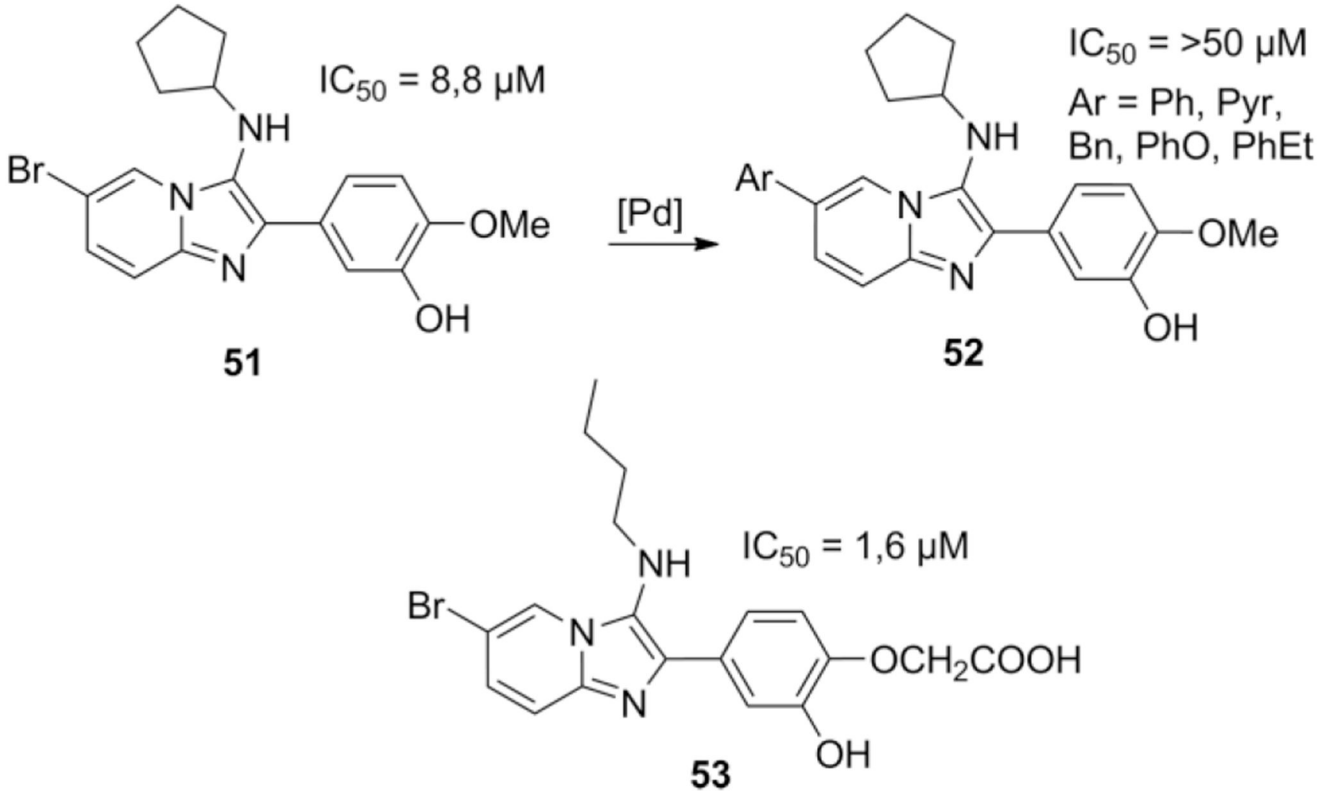
Scheme 23.

Examples of imidazo[1,2-*a*]pyridines **40–42** and 3-aminoimidazo[1,2-*a*]pyridines, containing the GBB-3CR scaffolds (blue) reported as bioactive leads; **43** anti-inflammatory **44** anticancer, **45** anti-fibrosis.

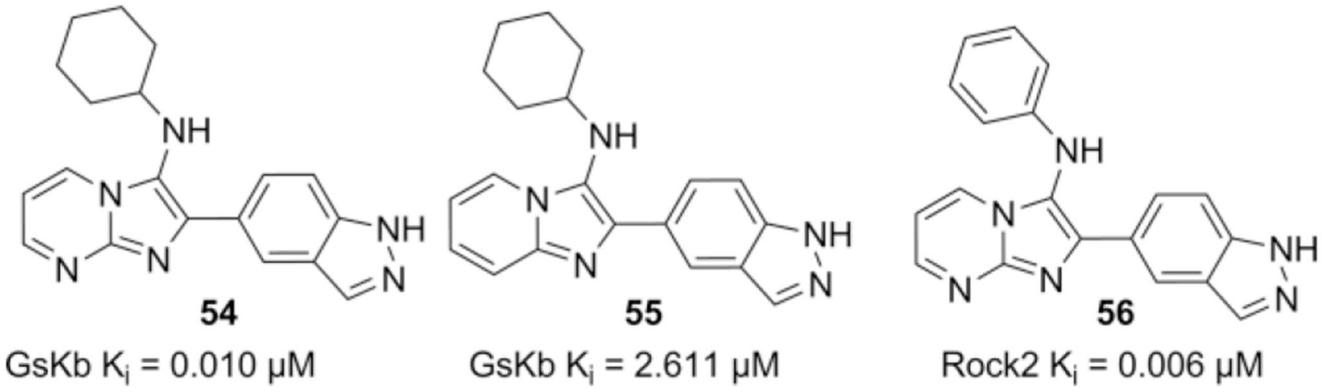


Scheme 24.

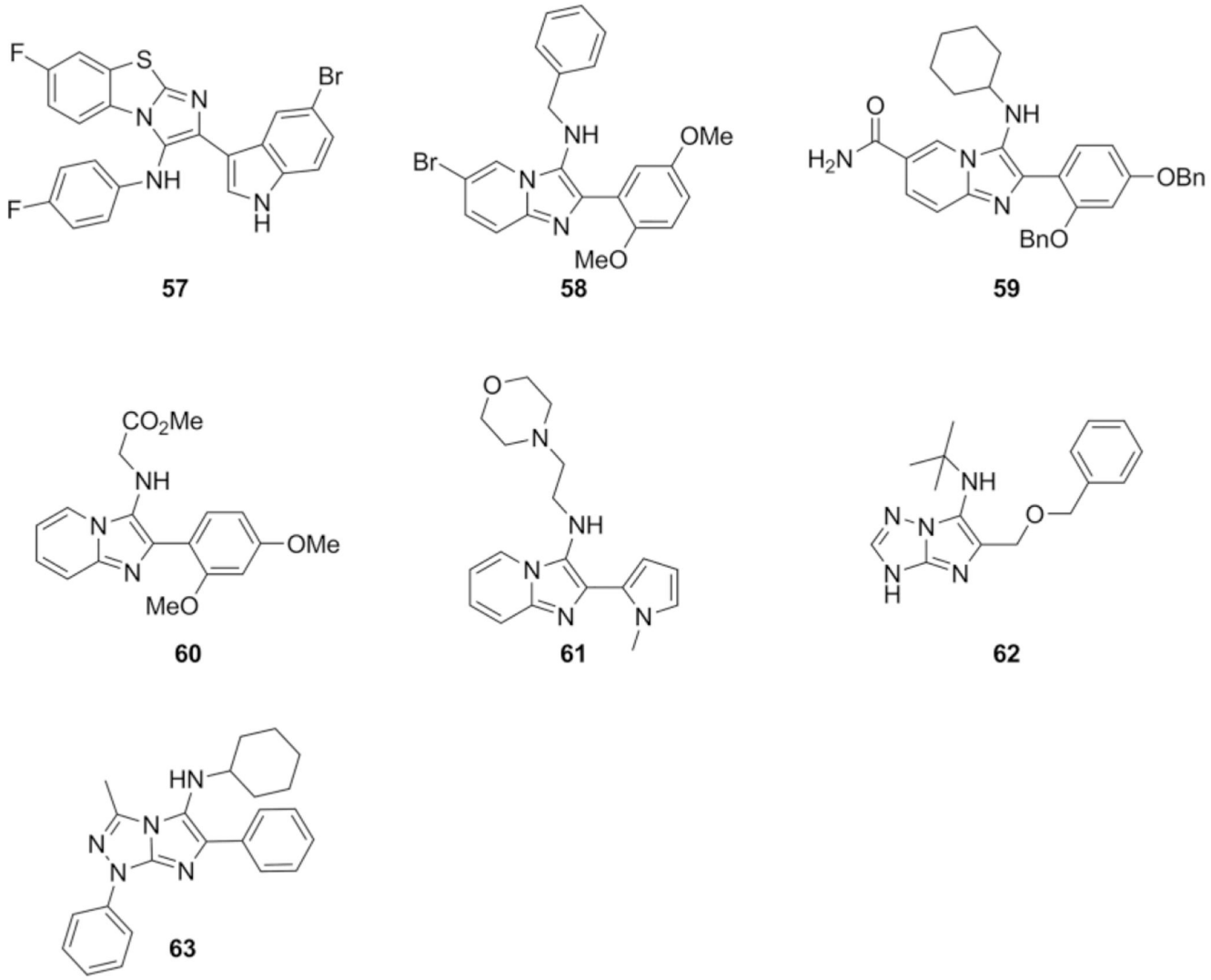
Synthesis of substituted imidazo[1,2-*a*]pyridine derivatives as anti-inflammatory and analgesic drugs.



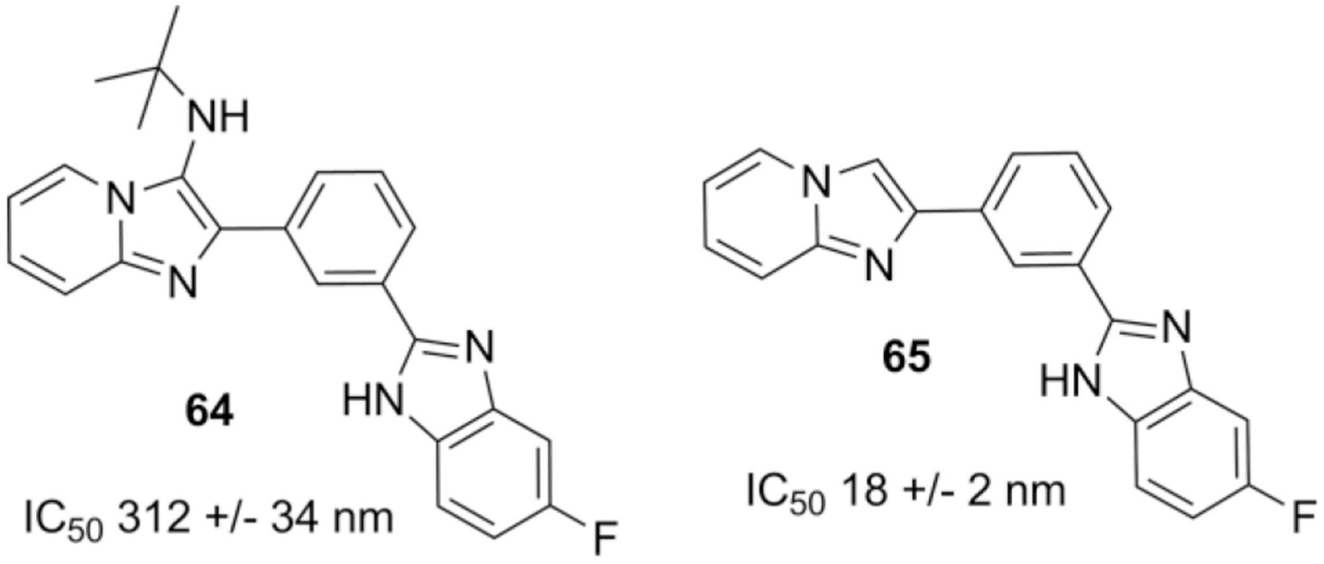
Scheme 25.
Synthesis and optimizing of *MtGS* inhibitors.



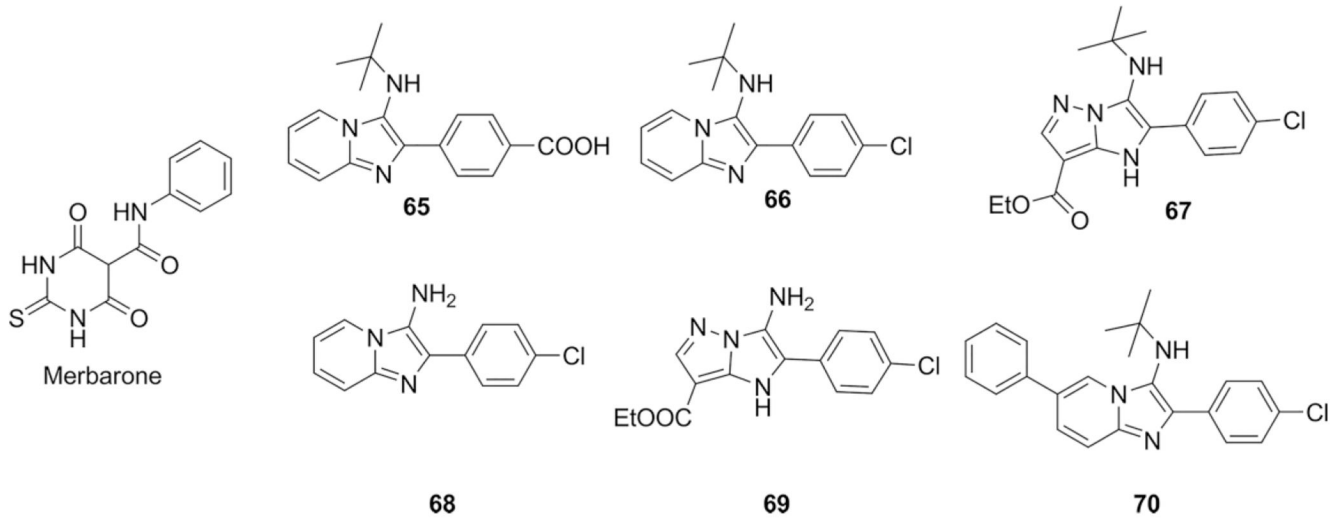
Scheme 26.
5-substituted indazoles as kinase inhibitors.



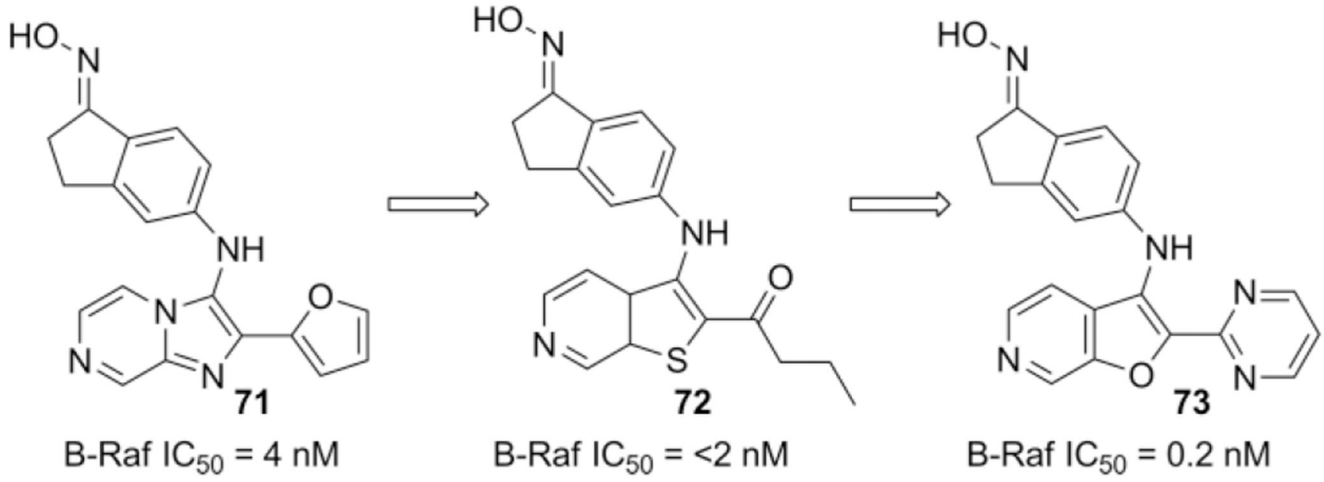
Scheme 27.
Various GBB-3CR bioactive compounds.



Scheme 28.
Highly selective β-Secretase inhibitors of the BACE1 enzyme.

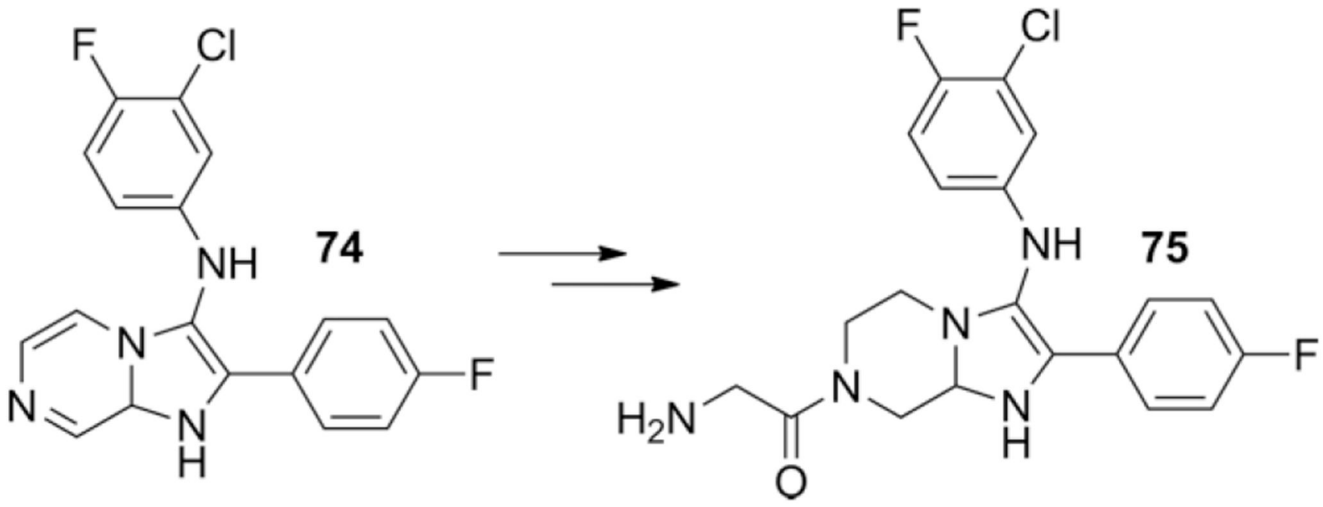


Scheme 29.
Synthesis, screening and optimizing of hTopoIIα inhibitor.

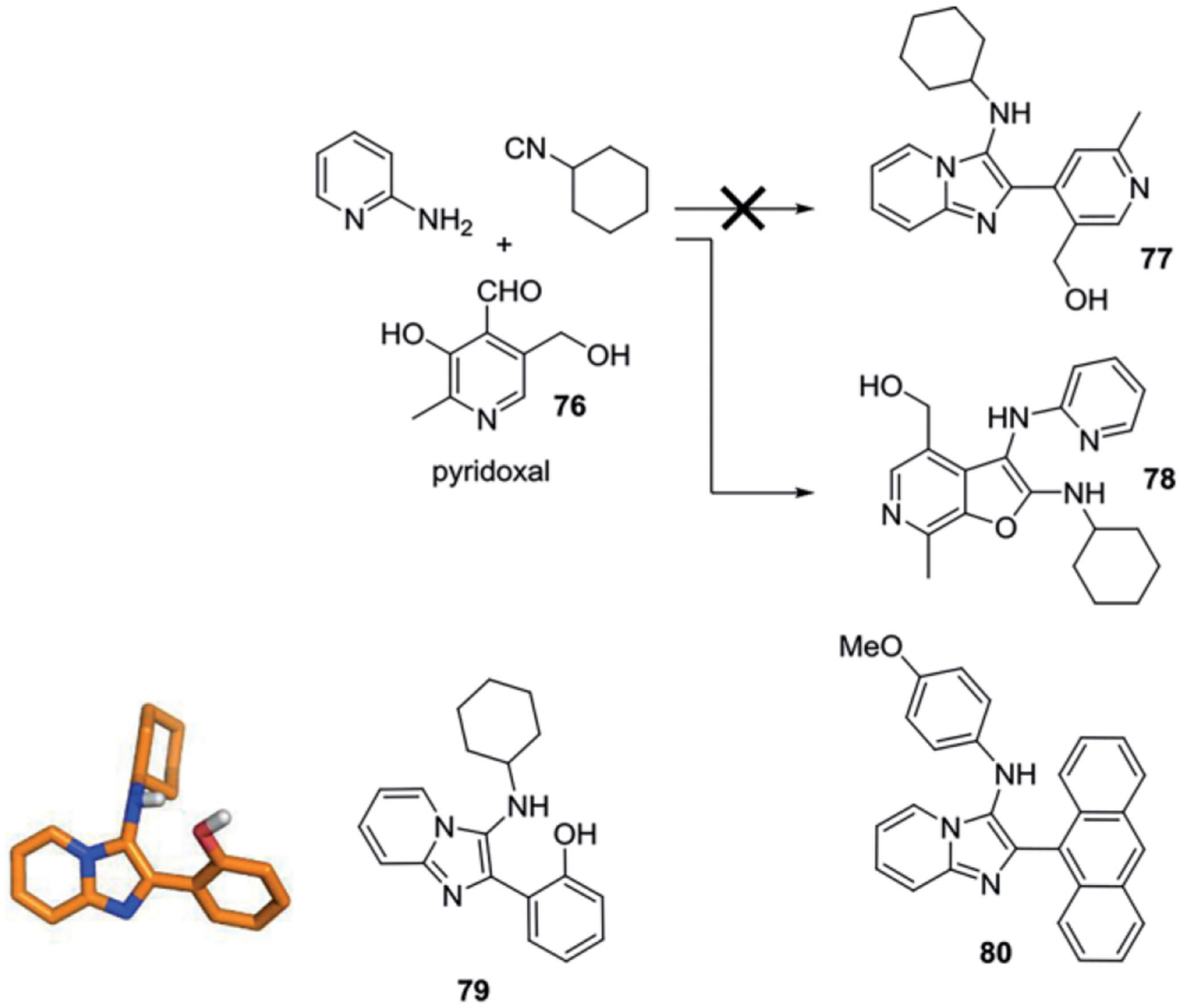


Scheme 30.

Imidazo[1,2-*a*]pyrazine based B-Raf inhibitors and its SAR assisted evolution towards sub-nanomolar inhibitors.

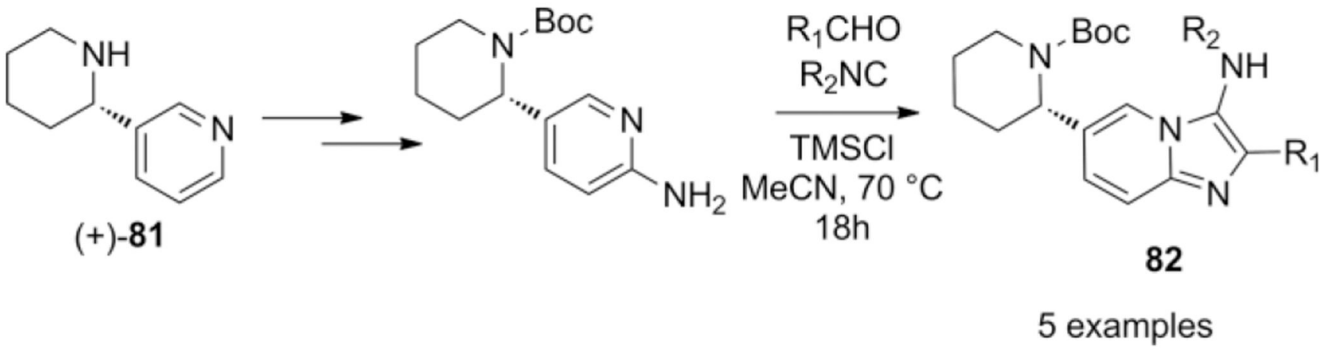


Scheme 31.
Post modifications of GBB-3CR product **74** lead to potent anti-malarial compound **75**.

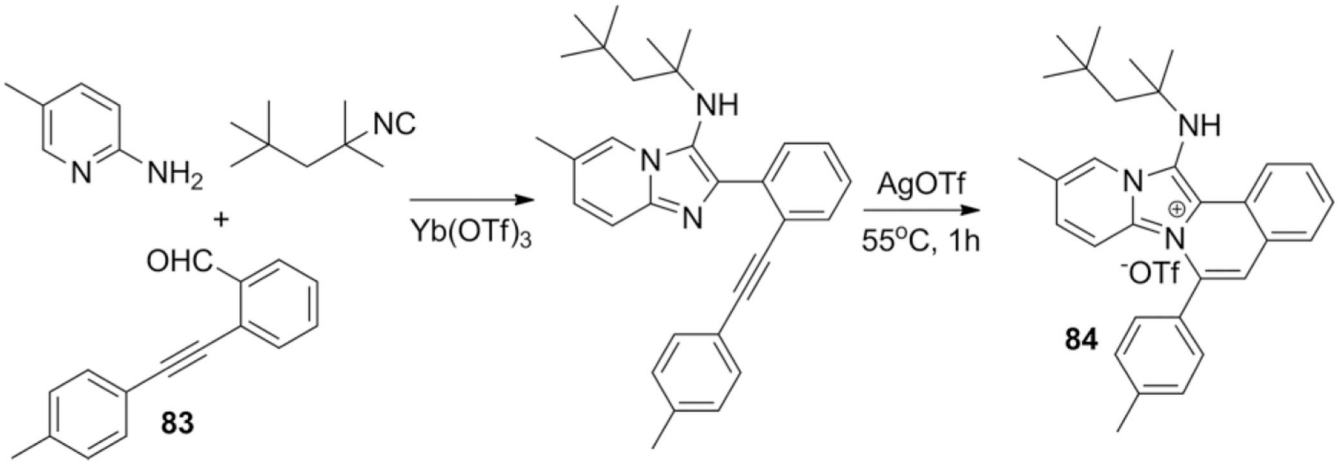


Scheme 32.

Discovery of side reactions accompanied with use of pyridoxal as aldehyde component, compound **79** (CCDC-893566) confirmed by X-ray structure analysis.

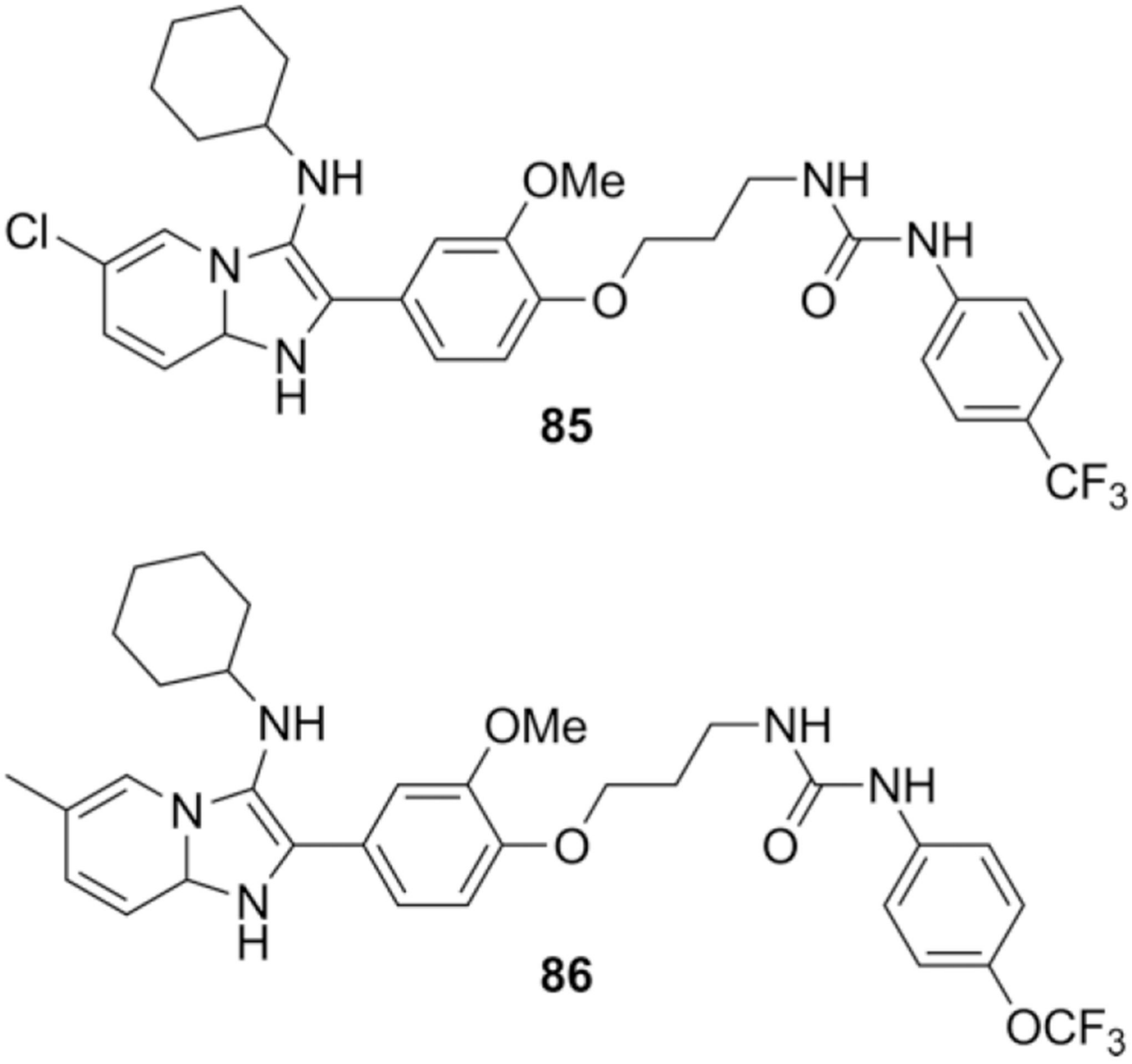


Scheme 33.
Anabasine derived GBB-3CR products as binders of nAChR.

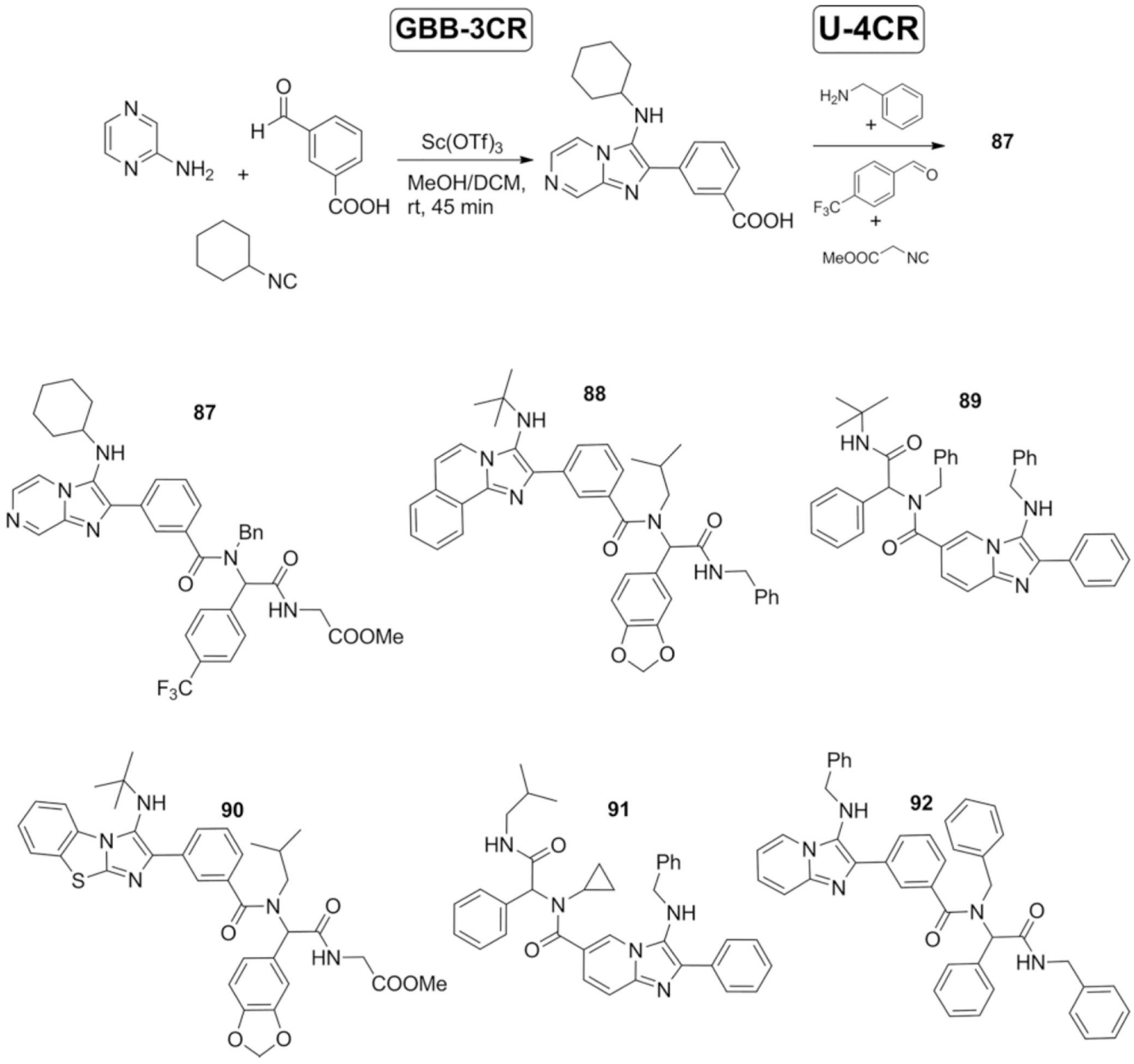


Scheme 34.

In total a library of 23 compounds was synthesized, in which **84** showed the best HeLa cell potency (IC_{50} = 0.58 μM).

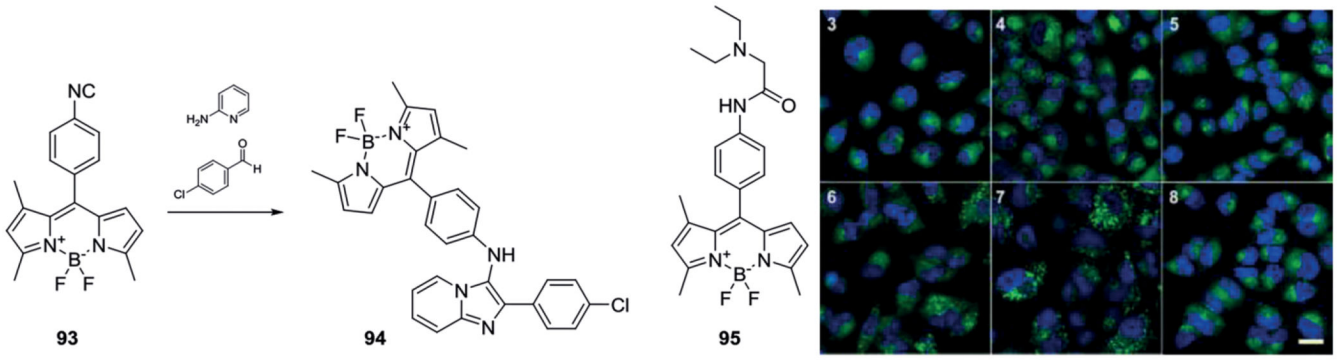


Scheme 35.
Combined urea and GBB-3CR products synthesized in an 8-step sequence.



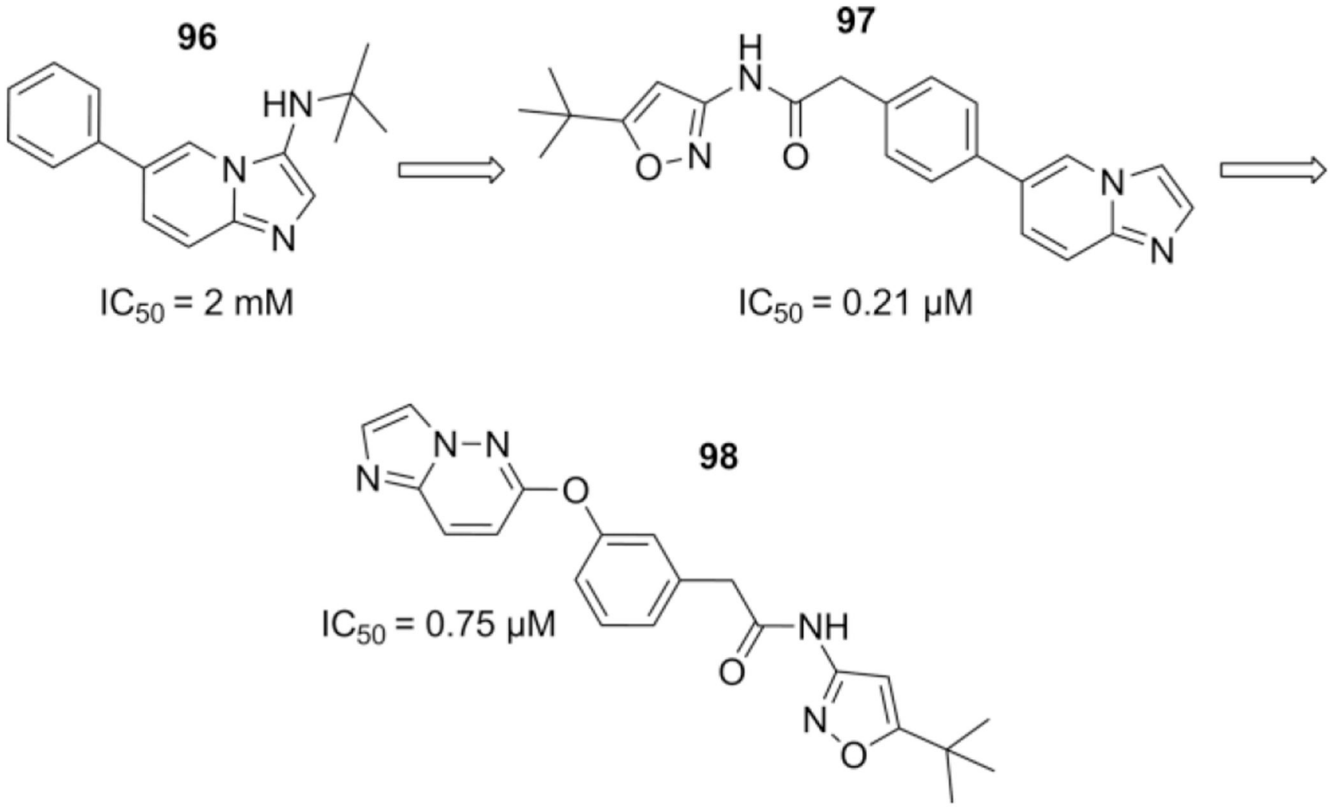
Scheme 36.

Application of a subsequent MCR approach to conveniently obtain complex compounds, exhibiting both antibacterial and anticancer properties.

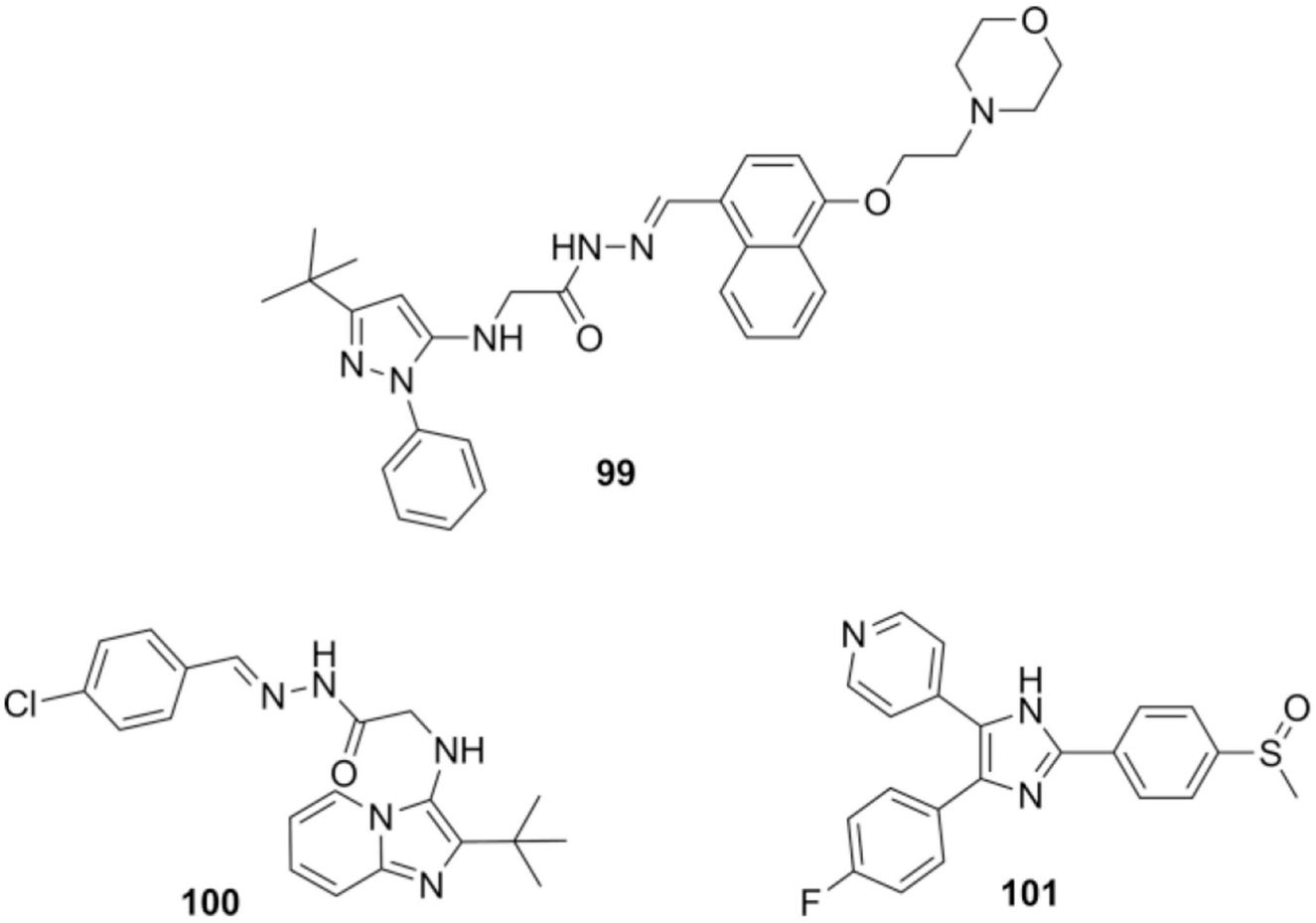


Scheme 37.

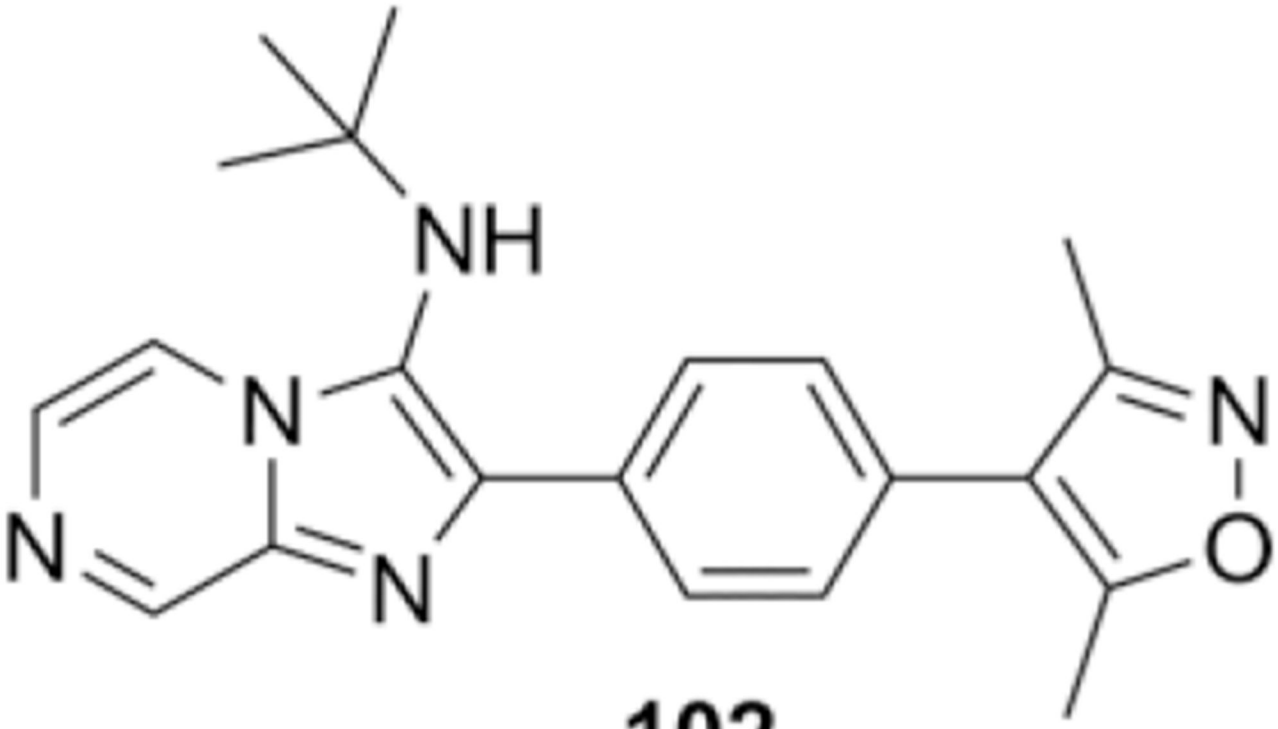
BODIPY isocyanide **93** used as fluorescent tag. Compound **95** exhibit fluorescence in A549 cells as depicted in image 7 on the right. Reprinted (adapted) with permission from reference[82] Copyright 2013 American Chemical Society.



Scheme 38.
Initial GBB-3CR hit design towards novel non-MCR RET inhibitors.



Scheme 39.
Imidazo[1,2-*a*]pyridine-N-glycinylhydrazone derivatives as TNF-α inhibitors.



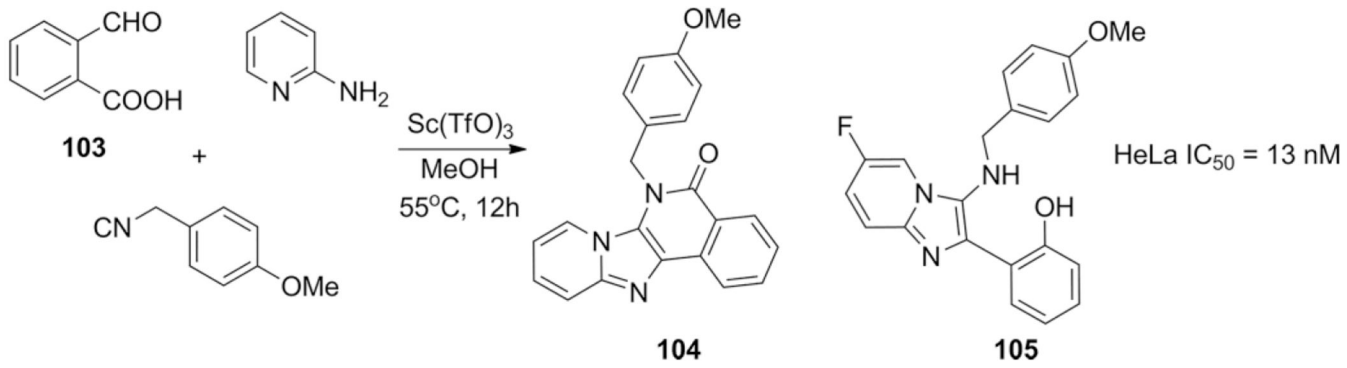
102

Found K_d values

BRD4 = 550 nM

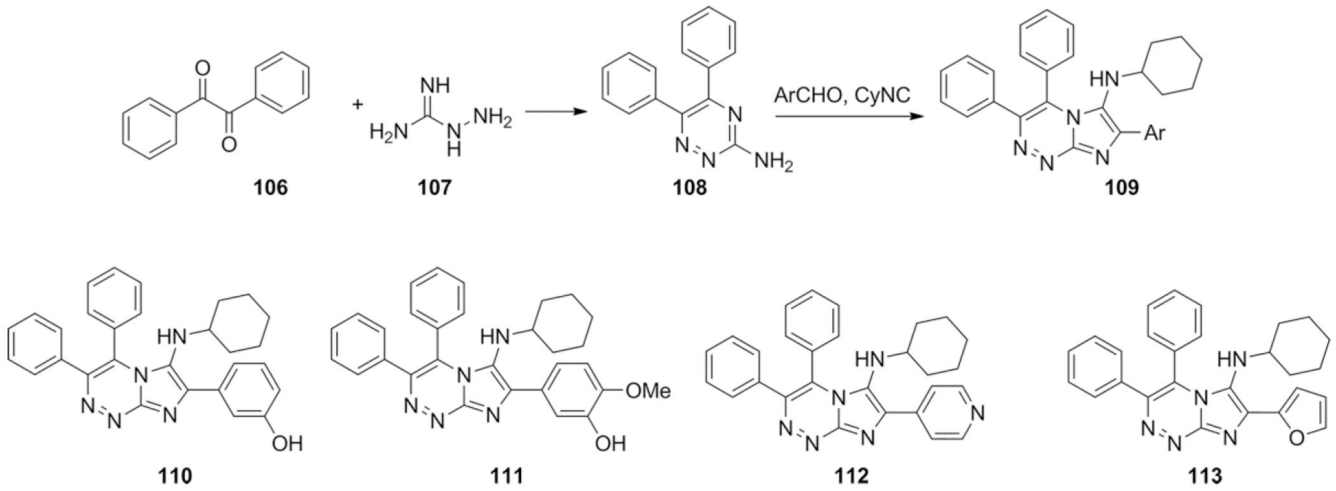
TAF1 = <1 μM

Scheme 40.
GBB-3CR compound **102** as potent BET bromodomain inhibitor.



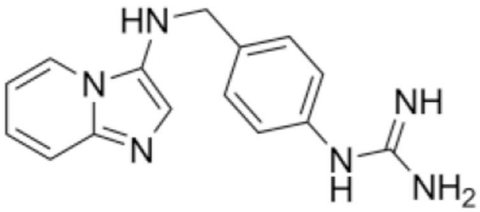
Scheme 41.

Application of the bi-functional phthaldehydic acid **103** giving access to tetracyclic heterocycles with example **104** exhibiting HeLa toxicity (IC_{50} = 1.8 μM).

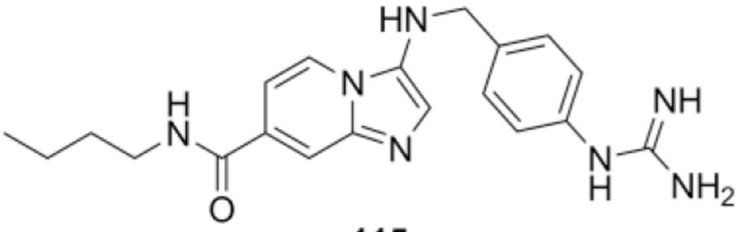


Scheme 42.

A series of anticancer agents, through the clever condensation benzyl **106** and aminoguanidine **107** and subsequent GBB-3CR.



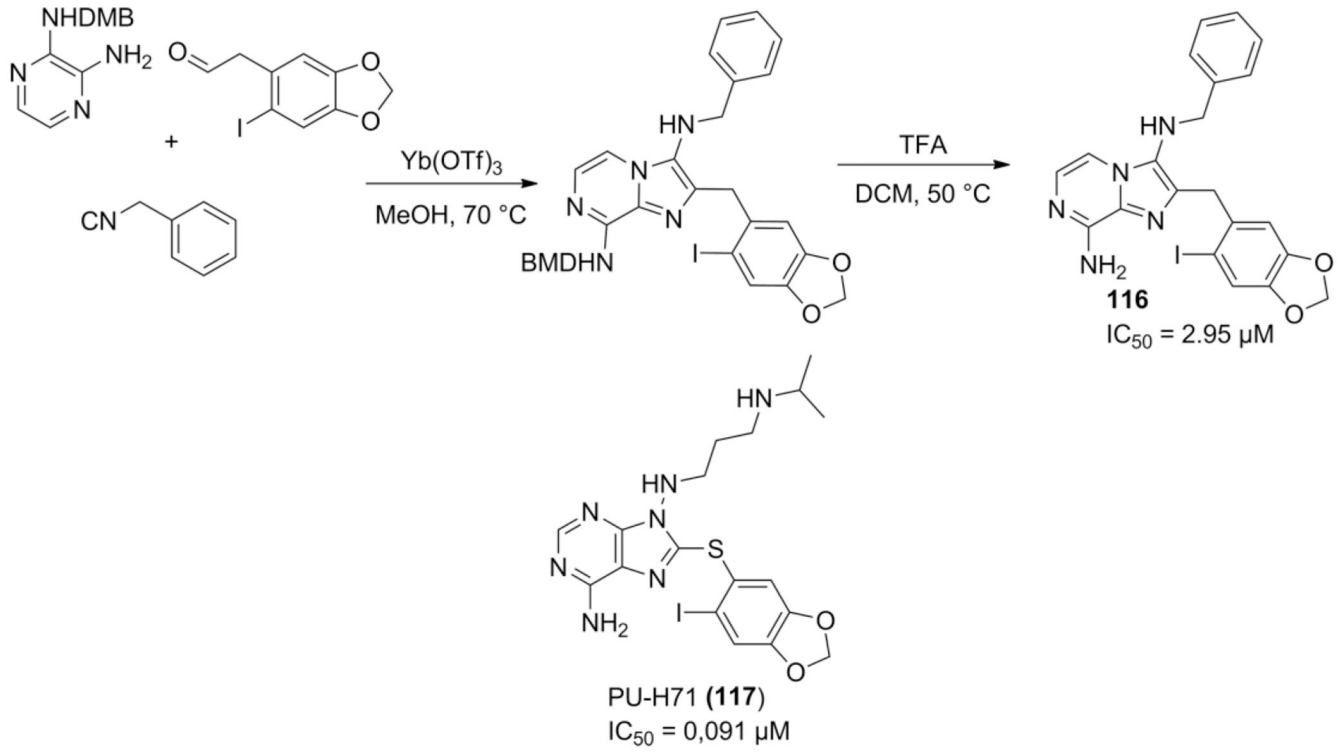
114



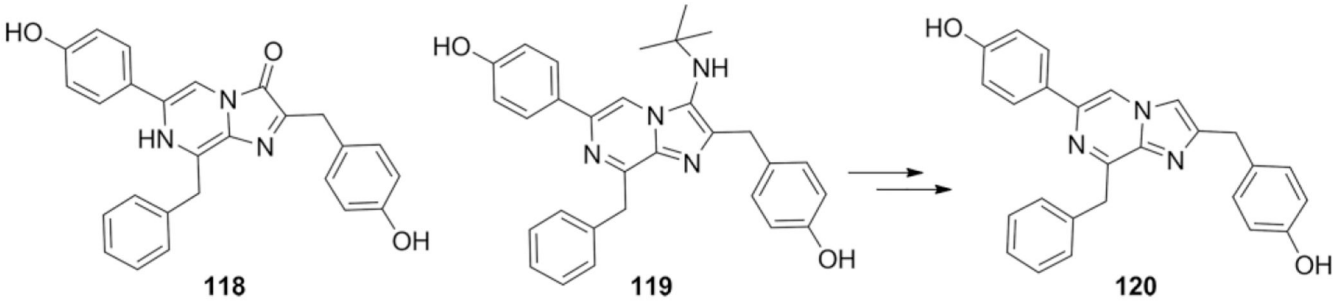
115

Scheme 43.

Binders of the urokinase Plasminogen Activator (uPA) S1 pocket, round 1 and 2 top performing products.

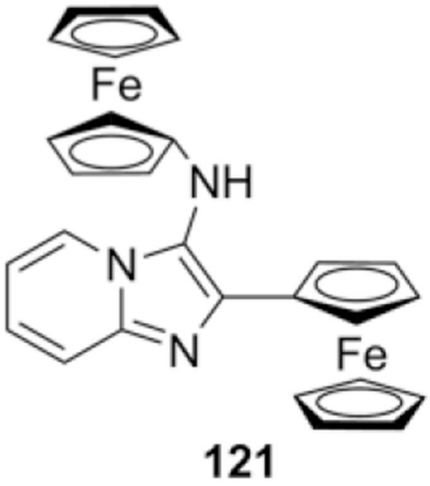


Scheme 44.
Development of novel imidazo[1,2-*a*]pyrazine based Hsp90 inhibitors.

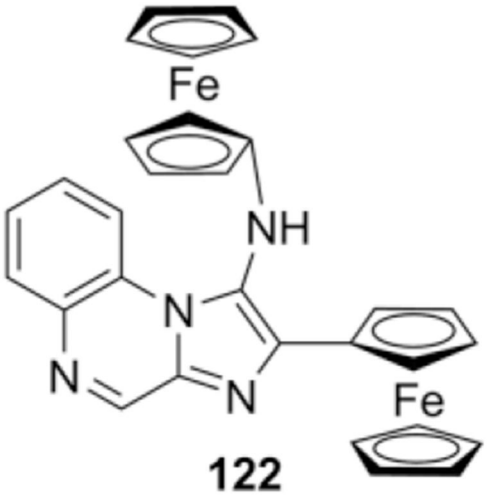


Scheme 45.

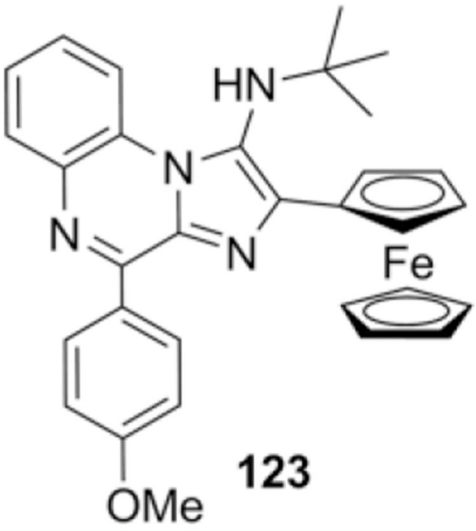
3 deoxy- derivatives of coelenterazine as bioluminescent and antioxidant.



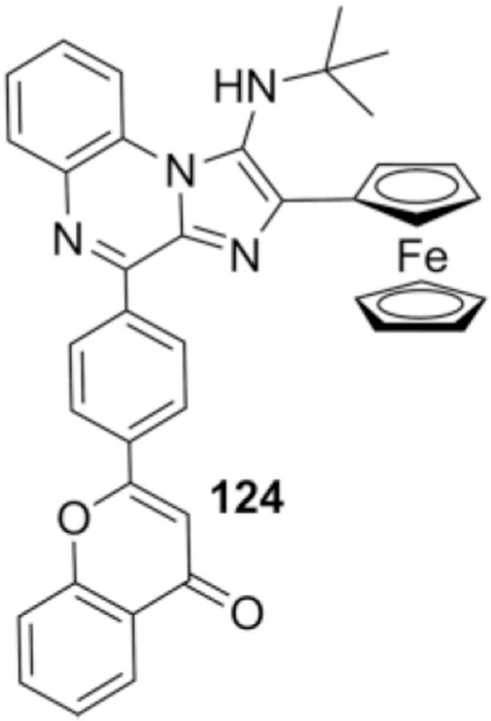
121



122

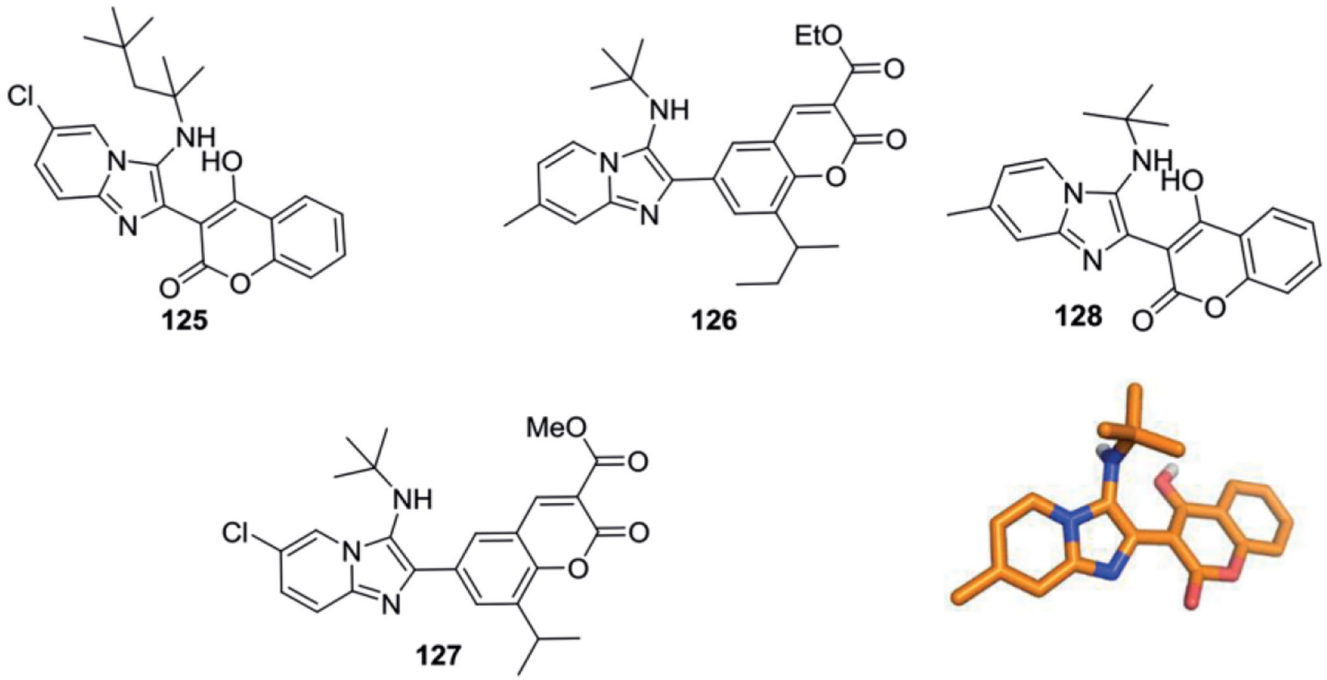


123



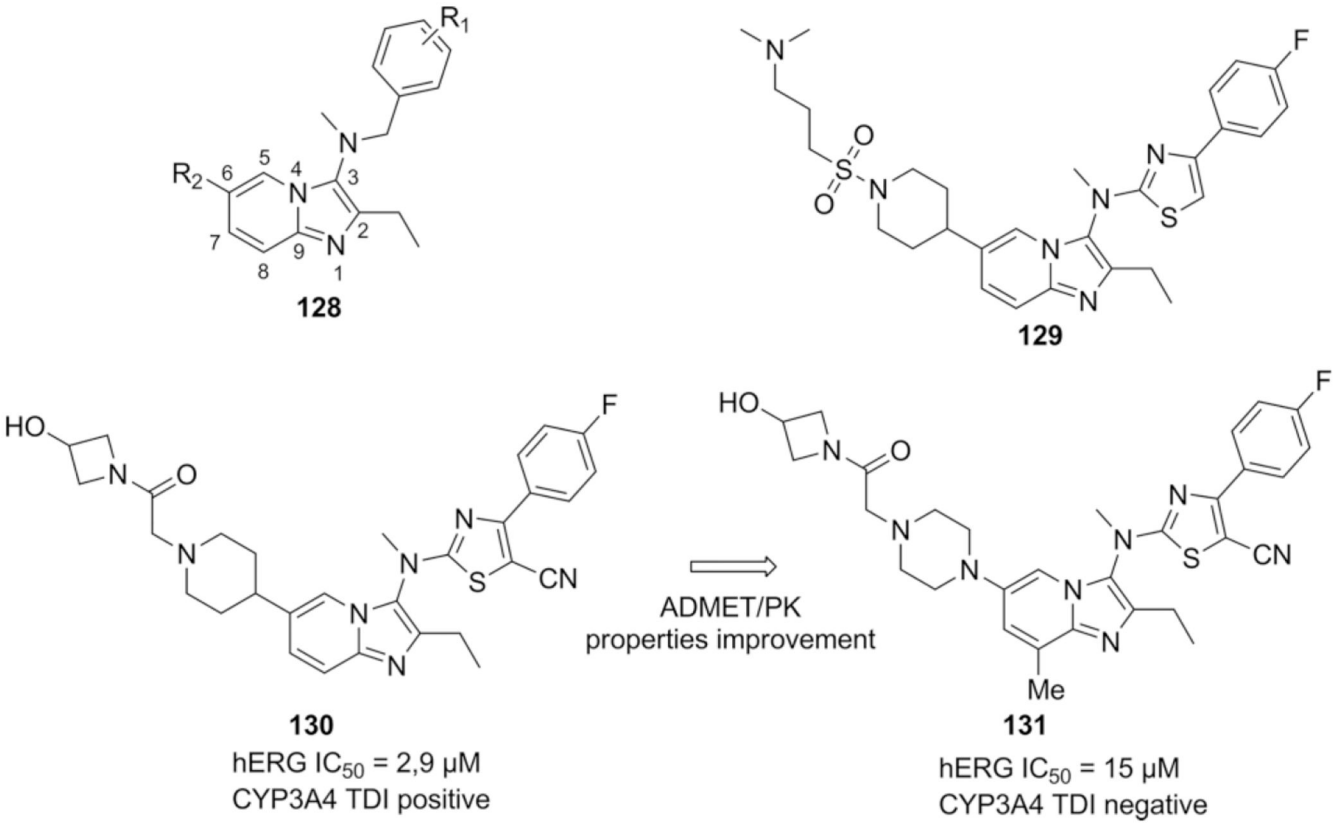
124

Scheme 46.
Ferrocene based anti-oxidants.



Scheme 47.

Coumarine based GBB-3CR products, compound **128** was crystallized and the structure was unambiguously verified by X-ray analysis (CCDC-1053723).



Scheme 48.
Autotaxin inhibitors; from hit to lead.

Table 1.

Amidines applied in the GBB-3CR. Those with R groups have multiple similar substitutions, used for producing derivatives. *This amidine has 10 more examples of N substituted piperazines.[37,38]

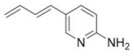
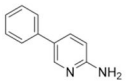
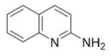
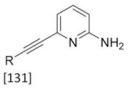
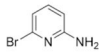
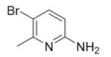
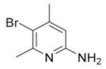
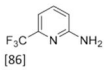
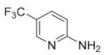
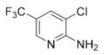
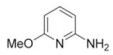
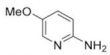
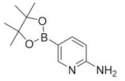
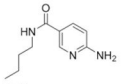
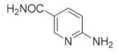
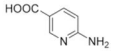
 [8, 19, 30, 33, 38-122]		 [28, 34, 57, 64, 68, 71, 79, 81, 87, 91, 93, 97, 101, 107, 110-112, 114-115, 123]	 [27-28, 41-42, 46, 51-52, 54-57, 60, 64-65, 68-69, 71, 75-76, 85-87, 96, 100-101, 103, 108-109, 116, 119, 122, 124-129]	 [41, 57, 63-64, 74-75, 90, 92, 95, 101-103, 105, 107-110, 112-113, 115-116, 122-123, 125, 130]	 [59, 64, 68-70, 87, 95-97, 108, 112, 115-116]	 [28, 52]
 [42, 52, 117]	 [8]	 [64]	 [28, 42]	 [8, 27, 104]	 [58, 80]	 [131]
 [64, 75, 98, 118, 120-121, 132-133]	 [27, 51-52, 54-57, 59-60, 63-66, 68, 70, 73-76, 85, 94, 97, 100, 102, 105, 108-110, 113-116, 119, 121-122, 124-127, 130, 134]	 [100, 117]	 [66, 108-109, 115-116, 122-123]	 [64, 87]	 [69]	 [87]
 [123]	 [8]	 [8, 30, 41, 52, 59, 63-64, 66, 68, 75, 86, 95, 102-103, 108-110, 112-113, 116, 119, 121-123, 125, 128, 130, 135]	 [29, 66, 105, 112, 117]	 [108]	 [64, 96, 107, 128]	 [62]
 [86]	 [75, 96, 103, 107, 130]	 [107, 117]	 [110]	 [64]	 [102]	 [86]
 [29]	 [8, 40, 42, 52, 75, 93, 112, 118, 120]	 [136]	 [96]	 [8, 65, 96]	 [58, 80, 86, 137-138]	[139]
[29]	[29, 75, 86, 89, 102-103]	[29, 78, 96]	[29]	[65, 81, 92, 103, 110]	[73]	[64]

Table 2.

The large variety of aldehydes sorted by origin and substituents.

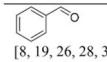
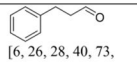
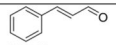
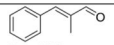
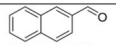
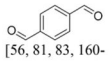
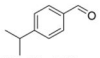
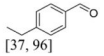
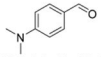
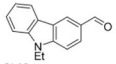
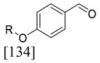
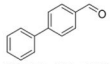
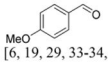
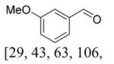
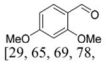
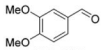
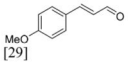
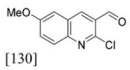
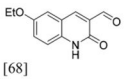
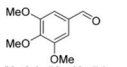
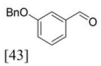
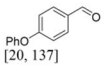
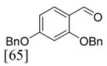
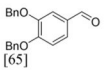
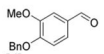
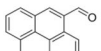
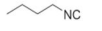
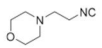
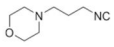
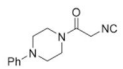
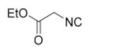
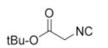
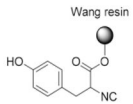
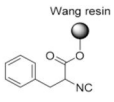
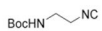
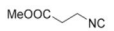
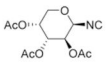
 [8, 19, 26, 28, 33-34, 37-40, 43, 46-47, 50-51, 53-55, 58, 60, 63, 70-73, 76, 79-80, 83-85, 89-90, 92-93, 96, 100, 104-107, 109, 111, 114, 117, 124, 126-127, 131-133, 136, 140, 143, 145, 148-150, 152, 155-156, 158, 162, 164-167, 172, 176]	 [96, 136]	 [6, 26, 28, 40, 73, 83, 107]	 [6, 19]	 [29, 165]	 [27, 114, 162]
 [56, 81, 83, 160-161]	 [37, 144]	 [19-20, 33-34, 36-37, 43, 46, 51, 54-55, 60, 76, 90, 100, 105, 109, 114, 124, 126-127, 132-133, 137, 139-140, 143, 164-165]	 [29]	 [90]	 [166]
 [92-93, 141]					
 [37, 96]	 [8]	 [29, 36, 63, 68, 169]	 [29]	 [61]	 [59, 63, 70, 83, 162, 164, 169]
 [134]					
 [72-73, 133, 152]	 [92-93, 133, 144, 148, 158, 167, 177]	 [6, 19, 29, 33-34, 36, 39, 43, 50, 54-55, 59, 63, 68, 74, 77, 83, 90, 94, 100, 105-107, 114, 117, 126, 131-133, 136, 140, 143, 145-148, 150, 152-153, 155, 157-158, 166-167, 172]	 [29, 43, 63, 106, 158]	 [29, 65, 69, 78, 89, 153, 158]	 [50, 117, 141, 158, 166, 176]
 [29]					
 [130]	 [68]	 [8, 36, 59, 69, 74, 83, 141, 147, 158]	 [43]	 [20, 137]	 [65]
 [65]					
 [6]	 [43, 117, 166]	 [73, 83, 99]	 [73]	 [73]	 [73]
[131]					
[41]	[41]	[41]	[41]	[140, 162]	[162, 168]
[56]					
[29]	[156]	[130]	[134, 144, 158]	[85, 134, 142, 155, 169]	[142]
[134]					
[108]	[121]	[121]	[122]	[68]	[88, 92-93, 109]
[96]					

Table 3.

Nearly 100 reported isocyanides used in the GBB-3CR and sorted by type and substituents.

 [8, 19, 26, 29, 33, 36-38, 45-46, 49-51, 54-60, 62-63, 66, 69, 71-74, 76, 79-81, 85-86, 89, 91-93, 95, 97-98, 100-105, 109-116, 118-120, 122, 124, 126-127, 135-136, 139-140, 144, 146-147, 152-157, 159-162, 164-165, 167, 169, 171-172, 176]	 [8, 19, 26, 28, 36, 42, 45-47, 53, 56, 63, 73, 76, 95, 97, 100, 102, 104-105, 110, 117, 127, 136, 143, 156, 160-161, 164-165]	 [29, 34, 52, 61, 73, 86, 128, 134, 140, 163]	 [145]	 [41, 52, 61, 66, 73-74, 125, 134, 156, 170]	 [73, 128, 134, 152, 159, 162-163]
 [66, 73, 131]	 [176]	 [37, 66, 128, 134, 140, 145]	 [8, 19, 29-30, 33-34, 36, 41, 46, 49-52, 54-57, 60-61, 64-65, 67, 69-74, 76, 79-81, 85-86, 90-93, 95, 97-98, 100, 105-106, 111-112, 114, 117-121, 124, 126-128, 131, 136, 139-140, 144, 146-148, 150, 152-153, 156, 158-159, 162-165, 168, 170-172]	 [43]	 [142]
 [73, 117, 121]	 [48, 132, 169]	 [42]	 [48]	 [169]	[169]	TMSCN [73, 102, 159]
 [29, 50, 69, 74, 78, 89, 114, 159]	 [8, 48, 77]	 [8]	 [42, 48, 52, 58, 78, 87, 89, 105, 108, 115-116, 122, 132, 165]	 [27, 84, 86, 104, 112, 115-116, 121-122, 125, 131-132]	 [8, 29, 86]	 [40]
 [40]	 [40]	 [48]	 [86]	 [87]	 [34, 87]	 [99]
 [48]	 [143]	 [87]	 [48]	 [43, 47, 77, 92, 105, 125, 145, 166, 176]	 [142]	 [34, 43, 142, 145, 150]
 [8, 42, 48, 50, 55, 57, 65-66, 97, 100-101, 124, 126-127, 136, 141-142, 156, 160-161, 172]	[142]	[142]	[43, 166]	[34, 36, 42, 45, 66, 72-73, 75, 86, 101, 118, 120, 130-131, 141-142, 145, 150, 159]	[48, 145]	[6, 141]

[77]	[48, 142, 150]	[142]	[29, 43, 77, 134, 150, 166, 176]	[145, 150]	[150]	[150]	[48, 77]	[150]	[150]
[150]	[143]	[73]	[150]	[42, 61, 77, 125, 149, 168]	[48]	[150]	[49, 77]	[42]	[132]
[142]	[142]	[70, 123]	[8]	[141]	[44]	[129]	[150]	[48]	[143]
[66]	[149]	[156]	[20, 141]	[129]	[87]	[87]	[132]	[132]	[98, 120, 171]
[86]	[19-20, 27-29, 41-42, 45, 47-49, 52, 58, 65-66, 70, 72-73, 77, 80, 86, 89, 97-98, 100, 112, 118, 120-121, 125, 129-130, 132, 136, 140, 153, 156, 159, 162-163, 171]	[77, 104, 129, 145]	[129]	[87]	[87]	[129]	[87]	[104]	[107]
[98, 129, 132, 168, 171, 177]	[87]	[34, 88]	[48]	[87]	[96]	[107]			
[87]	[82]								

Table 4.

Every catalyst previously used in the GBB-3CR arranged by occurrence.

Catalysts (formula)	Occurrence	Reference	Catalysts (formula)	Occurrence	Reference
Scandium triflate ($Sc(OTf)_3$)	24	[20,26–30,39,41,47,48,58,61,62,67,77,86,125,137,138,140,146,149,168,177]	Calcium chloride ($CaCl_2$)	1	[32]
Perchloric acid ($HClO_4$)	15	[8,44,66,75,78,89,96,102,103,119,123,150,167,179,180]	Cellulose sulfuric acid	1	[51]
p-toluenesulfonic acid, PTSA, *p*TsOH	14	[34,40,55,56,74,85,88,97,107,130,141,164,181,182]	Cellulose@Fe_2O_3	1	[183]
Acetic acid (AcOH)	13	[6,45,68,110,128,129,142,154,184–188]	$CuFe_2O_4$@SiO_2–SO_3H	1	[115]
Ammonium chloride (NH_4Cl)	10	[43,49,54,95,144,147,156,158,166,189,190]	(MWCNTs)	1	[100]
$ZrCl_4$	8	[36,55,59,63,94,99,143,191]	TiO_2 NPs (nanopowders)	1	[170]
TMSCl	7	[37,38,53,152,155,169,176]	ZnO NPs	1	[116]
Montmorillonite K-10 clay	6	[19,64,65,70,121,192]	Methanesulfonic acid	1	[52]
Magnesium chloride ($MgCl_2$)	5	[134,136,193,194]	Zeolite HY	1	[195]
Ytterbium triflate ($Yb(OTf)_3$)	4	[105,131,132,153]	$SnCl_2 \cdot 2H_2O$	1	[127]
$InCl_3$	4	[57,98,122,145]	Heteropolyacid $H_3PMo_{12}O_{40}$	1	[60]
HCl dioxane	4	[72,73,84,117]	Bromodimethylsulfonium bromide (BDMS)	1	[69]
Indium triflate ($In(OTf)_3$)	3	[108,109,122]	γ-Fe_2O_3@SiO_2-OSO_3H	1	[71]
Trifluoroacetic acid (TFA)	2	[82,165]	Cationic polyurethane dispersions (CPUDs)	1	[76]
Bismuth chloride ($BiCl_3$)	2	[81,91]	*p*TsCl	1	[77]
Silica sulfuric acid	2	[126,148]	Iodine	1	[135]
Lanthanum chloride ($LaCl_3 \cdot 7H_2O$)	2	[92,104]	(TBBDA)	1	[83]
Piperidine	2	[162,163]	(PBBS)	1	[83]
Silver triflate (AgOTf)	1	[113]	nano-LaMnO3	1	[90]
Ionic liquid [bmim]Br	1	[124]	NH2-MIL-53(Al)	1	[111]
Ionic liquid [bmim]BF_4	1	[70]	CuI L-Proline	1	[33]
Aluminum chloride ($AlCl_3$)	1	[136]	BF_3·MeCN	1	[34]
Ruthenium chloride ($RuCl_3$)	1	[79]	2-chloroacetic acid ($ClCH_2COOH$)	1	[120]

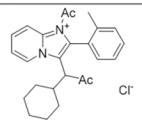
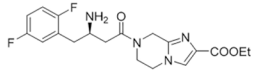
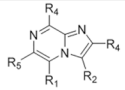
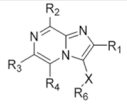
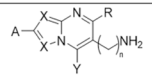
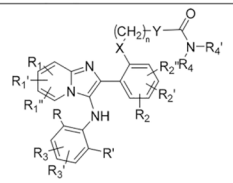
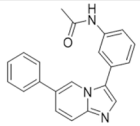
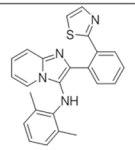
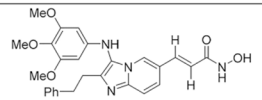
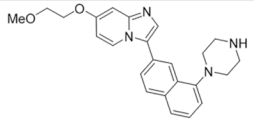
Table 5.

All the solvents used in the GBB-3CR.

Solvent	References	Occurence	Solvent	References	Occurence
MeOH	[6,8,26–28,30,39,45,51,54–56,61,66,68,74,75,78,87,96–100,103,108,110,118,120,123,125,126,128,130,136,141,142,150,153,154,156,166–168,177,181,183–185,187,188]	51	1:1 EtOH:H_2O	[165,180]	2
No solvent	[19,60,71,79,81,83,85,90,92,93,101,105,111,112,127,133,140,147,148,161,172,192,195]	23	Water	[46,76]	2
Toluene	[43,49,52,70,95,109,144,145,158,159,163,164,171,186,189,190]	17	DMSO	[33,36]	2
EtOH	[57,84,89,104,113,115,116,121,122,131,132,134,135,139,160,193]	16	DMF	[146,180]	2
MeCN	[53,69,72,73,77,117,152,155,169,176,182]	9	MeOH:DCE	[42]	1
2:3 MeOH:CH_2Cl_2	[58,62,80,137,138]	5	TFE/DCE 1:1	[67]	1
*n*BuOH	[59,94,119,194]	4	DCE	[162]	1
3:1 MeOH:CH_2Cl_2	[20,39,41]	3	1:1 MeOH:CH_2Cl_2	[129]	1
1:3 MeOH:CH_2Cl_2	[31,86,143]	3	1:4 MeOH:CH_2Cl_2	[47]	1
Ionic liquid [bmim]Br; DES	[106,114,124]	3	1:2 MeOH:CH_2Cl_2	[48]	1
1,4-Dioxane	[50,64,65]	3	1:1 EtOH:CH_2Cl_2	[107]	1
MEOH/MeCN	[37,38,203]	3	2:3 ethanol/H_2O	[170]	1
PEG-400	[63,191,204]	3	1:1:1 $CHCl_3$/ TMOF/MeOH	[40]	1
TFE	[32,180]	2	DMSO:H_2O 1:1	[29]	1
CH_2Cl_2	[34,102]	2	Et_2O	[88]	1

Table 6.

The structures found in the patent were found as GBB products, whereas the listed structures comprise the in general most active compound, shown as the active component of interest.

Assignee	Year	Structure	Target/Condition	Class	Patent number
Gruenenthal GmbH	2002		CNS, Ischemia, Brain disease, Shock, Septicemia		WO2002030428[216]
Merck & Co., Inc.	2004		Diabetes Melitus type II	DPP-4	WO 2004058266[217]
Esbatech A.-G	2005		RTK	Kinases	WO2005120513A1[220]
Array BioPharma Inc.	2006		RAF	Kinases	WO2006125101A2[221]
Bristol-Myers Squibb company	2006		GLPP-1(7-36) Diabetes II	Peptidase	WO2006071752A1[222]
Merck Patent GmbH	2007		SGLT I, II (Diabetes I, II)		WO2007147478A1[223]
Astex Therapeutics Limited, UK	2008		FGFR3, PDGFR	Kinases	WO 2008078091[224]
Merck Patent GmbH, Germany	2008		SGLT1, Diabetes	Transport proteins	DE 102006048728[225]
S bio Pte. Ltd., Singapore	2008		HDAC	Epigenetics	US 20080085896[226]
Array BioPharma Inc., USA	2008		PDGFR	Class 3 and 5 Kinases	WO 2008121687[227]

Cytokinetics, Incorporated, USA	2008		SKM Myofibril AC1.4	Skeletal muscle myosin modulators	WO2008016648A2[228]
ACADIA Pharmaceuticals Inc., USA	2008		CB2 receptors	Cannabinoid CB2 receptors	WO2008141239A1[229]
Schering Corporation, USA	2008		JNK1, ERK	Kinases	WO2008082490A2[230]
Merck Sharp & Dohme Ltd., UK	2008		GABAA	GABAA	GB2448808A[231]
Fuji Film RI Pharma Co., Ltd., Japan; Daiichi Sankyo Co., Ltd.	2009		amyloid β (1-40)	Alzheimer's disease, Down's syndrome,	JP2009007348A[232]
Universidade Federal do Rio de Janeiro - UFRJ, Brazil	2007		MAPK p38 and PGHS-2	Anti-inflammatory and analgesic activity	BR 2007011519 [233]
Bristol-Myers Squibb Company, USA	2009		CK2	Protein kinase, cell proliferation	WO2009100375[234]
Merck Patent GmbH, Germany	2009		SGLT1	Sodium-dependent glucose transporter	WO2009049731A1[235]
Oncalis AG, Switz.	2010		Ser, Thr, Tyr kinases; c-src, EphB2/4 HER-1, PDGF, RET	Protein kinase inhibitors	WO2010083617A1[236]

University of the Witwatersrand, Johannesburg, S. Afr	2010		Caco-2, HT-29 (Colon cancer)	Anticancer activity	WO2010116302A1[237]
Ortho-McNeil-Janssen Pharmaceuticals, Inc, USA	2010		(AD) Gamma secretase complex	Gamma secretase inhibitors	WO2010089292A1[238]
Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Peop. Rep. China	2010		HeLa	Mitosis inhibitors	CN101717397A[239]
IRM LLC (Novartis), Bermuda	2011			Antimalarial activity	WO2011006143A2[218]
EQUISnZAROO Co., Ltd., S. Korea	2011		H1N1, H3N2	Influenza virus	KR20110974484[240]
Centro Nacional de Investigaciones Oncologicas (CNIO), Spain	2011		PI3	Kinase inhibitory activity	WO2011036461A1[241]
Schering Corporation, USA; Merck Sharp & Dohme Corp	2012		Edwarsiella spp	Microbial infections	WO2012018662A2[242]
Supergen, Inc., USA	2012		Pim-1	Kinases	US20120058997A1[243]
GlaxoSmithKline LLC, USA	2013		HCV	Innate immune responses	WO2013059559A2[244]

National Institute of Pharmaceutical Education and Research (Niper), India	2011		Topoisomerase IIα	Anticancer agents	IN2011DE00091A[245]
F. Hoffmann-La Roche AG, Switz.; Hoffmann-La Roche Inc	2014		h-TRPA1	Respiratory disorders	WO2014076021A1[246]
UCB Pharma S.A., Belg.	2014		TNFα	TNFα	WO2014009295A1[247]
Galapagos NV, Belg.	2014		Human LPC hENPP2	Prophylaxis	WO2014202458A1[248]
Kyowa Hakko Kirin Co., Ltd., Japan	2014		CaV3.2 T-type Ca2+ channel	Pruritus	WO2014021383A1[249]
Bristol-Myers Squibb Company, USA	2014		CKIε, CKIδ	Kinase I	WO2014100533A1[250]
Heesung Material Ltd., S. Korea	2015		Non medical	Organic light-emitting device materials	KR20150751694A[251]
HDI Foundation, Inc., USA	2016		Imaging	Huntington protein	WO2016033440A1[252]
Bristol-Myers Squibb Company, USA	2016		TNFα		WO2016149439A1[253]
Janssen Pharmaceutica NV, Belg.	2016		pAkt-S473, pAkt_Thr308	PI3Kβ kinase inhibitors	WO2016097347A1[254]

Janssen Pharmaceutica NV, Belg.	2016		PI3Kα, PI3Kδ, PI3Kγ and MTOR	PI3Kβ kinase inhibitors	WO2016097359A1[255]
NEOMED Institute, Can.	2017			Bromodomain inhibitors	WO2017066876A1[256]
University of the Witwatersrand, Johannesburg, S. Afr.	2017			Anticancer activity	WO2017178992A1[257]
Albert Einstein College of Medicine, Inc., USA.	2017		Pak1 inhibitors	Kinases	WO2017192228A1[258]
Dana-Farber Cancer Institute, Inc., USA.	2017			Anticancer activity	WO2018058029A1[259]
Dana-Farber Cancer Institute, Inc., USA.	2018		TRIM33	E3 ubiquitin-protein ligase	WO2018200988A1[260]

Table 7.

List of abbreviations.

AcOH	**Acetic acid**
AD	Alzheimers disease
ADMET	Absorption, distribution, metabolism, and excretion
ATX	Autotaxin
3CR	3-component reaction
BODIPY	Boron-dipyrromethene
CB2	Cannabinoid receptor type 2
CH2Cl2	Dichloromethane
CK2	Casein Kinase II
DMA	Dimethylaceetamide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
ERK	Extracellular signal-regulated kinases
FDA	Food and Drug Administration
FGFR3	Fibroblast growth factor receptor 3
GABA	Gamma aminobutyric acid
GLP1	Glucagon-like peptide-1
h-TRPA1	Transient receptor potential cation channel, subfamily A, member 1
HClO4	Perchloric acid
HCV	Hepatitis C
HDAC	Histone deacetylase
hENPP2	Ectonucleotide pyrophosphatase/phosphodiesterase family member 2 (ATX)
HTS	High throughput screening
IMCR	Isocyanide-based multicomponent reactions
JNK1	See MAPK8
LPC	Lysophosphatidylcholine
MAPK8	Mitogen-activated protein kinase 8
MCR	Multicomponent reactions
MDM2	Murine double minute 2
MeCN	Acetonitrile
MeOH	Methanol
MP-CO_3	Macroporous polystyrene carbonate
MTOR	Mammalian target of rapamycin
MW	Microwave
NMR	Nuclear magnetic resonance
P-3CR	Passerini 3-component reaction
PADAM	Passerini-reaction-Amine-Deprotection-Acyl-Migration
PD	Parkinsons Disease
PDGFR	Platelet-derived growth factor receptor
PEG	Polyethylene glycol

AcOH	**Acetic acid**
PET	Positron emmision tomography
PGHS-2	Prostaglandin-endoperoxide synthase 2
PI3	Phosphoinositide 3-kinase
Pim-1	Proto-oncogene serine/threonine-protein kinase
PK	Pharmacokinetic
PTSA	para-Toluenesulfonic acid
*p*TsIA	para-Toluenesulfinic acid
RET	Rearranged during transfection
SAR	Structure-activity relationship
$Sc(OTf)_3$	Scandium triflate
SGLT	Sodium-glucose transport proteins
SKM	Leukemic cell line
TDI	Time-dependent inhibition
Tf	Triflate
TFE	Trifluoroethanol
TLC	Thin Layer Chromatography
TMOF	Trimethyl orthoformate
$TMSN_3$	Trimethylsilyl azide
TNFa	Tumor necrosis factor alpha
TPSO	Translocator protein
TRIM33	Tripartite motif-containing 33
U-3CR	Ugi 3-component reaction
U-4CR	Ugi 4 component reaction
UDC	Ugi-deprotection-cyclize
vL-3CR	van Leusen 3 component reaction