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Recent advances in the trifluoromethylation methodology and new CF_3-containing drugs

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ABSTRACT

This review provides a brief assessment of the methodological field of trifluoromethylation and its possible impact on the development of new CF_3-containing pharmaceuticals. Structural aspects of five new drug-candidates, [tafenoquine (aromatic CF_3), roniciclib (heteroaromatic CF_3), BAY-38-7271 (aliphatic CF_3), sonidegib (O–CF_3) and navitoclax (S-CF_3)] currently under the development in phase II and III clinical studies, and their biological properties, therapeutic area and synthesis are critically discussed.

1. Introduction

Fluorine chemistry has quite a few success stories of truly historic proportion in shaping up the modern-day science and technology [1]. The most recent one is the impact that fluorine is currently making on the development of contemporary pharmaceutical industry [2]. Considering the fact that fluorine, among light elements, is the most xenobiotic, its rise to the prominence as key designer component in the structure of modern biologically active compounds is rather incredible and fascinating scientific progress. It is generally known that introducing fluorine atoms and/or fluorine-containing groups into bioactive molecules can have a range of overall positive effects, such as rendering them more selective, potent, increasing efficacy, or making them easier to administer [3]. Some of the fluorine effects on the molecules' properties are well understood [4], however, in most of the cases the development of a fluorine containing drug is a tedious trial-and-error process. As one can assume, the fluorine-scan approach, placing fluorine in various structural positions, is strictly limited by the availability of the corresponding synthetic methodology allowing preparation of the fluorinated target molecules. Thus, it is obviously clear that the emergence of certain fluorinated drugs on the pharmaceutical market [2] comes after the development of the suitable methodology allowing a desired particular type of fluorination on a commercial scale. Connecting this trend with the recent methodological "revolution" in the area of trifluoromethylation [5], it seems apparent that future generations of pharmaceuticals will have increasing number of CF_3-bearing molecules. Drawing inspiration from this prospect, we have designed the present review article providing a brief outline of the recent advances in the trifluoromethylation methodology in connection with some CF_3-containing drug candidates currently under the development by the pharmaceutical industries. We believe this innovative treatment of synthetic and medicinal chemistry literature will be of general interest to all practitioners working in this most exciting multidisciplinary area.

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2. Brief appraisal of the current trifluoromethylation methodology

In the last several years the trifluoromethylation methodology has been extensively and comprehensively reviewed [6], focusing on a particular source of CF_3 group, mechanistic or structural considerations. To avoid any overlap with these excellent reviews, we present herein a brief outline of the most recent literature highlighting advances in preparation of trifluoromethyl-containing compounds based on a structural type of C–CF_3 or heteroatom–CF_3 bond, which can be found in the drug-candidates profiled in this article.

2.1. Trifluoromethylation of aromatic compounds

Trifluoromethyl arenes have been traditionally prepared using the procedure developed by Swarts at the end of 19th century [7]. However, this involves very harsh reaction conditions in order to transform toluene to (trichloromethyl)benzene and then to (trifluoromethyl)benzene, and therefore it is obvious that new synthetic protocols are in great demand, especially for late stage introduction of CF_3 groups into already functionalized aromatic rings. In addition, special attention has been recently dedicated to the discovery of catalytic processes [6b].

In principle, replacement of a halide atom by a CF_3 group is the most reliable method in terms of selectivity [6a,6d]. For many years, the reaction of aryl iodides with a stoichiometric amount of $CuCF_3$ species has been the method of choice, most of the times using CuI and the Ruppert–Prakash reagent (CF_3SiMe_3) or its analogs as the Cu(I) and trifluoromethyl sources, respectively [8] (Scheme 1, path a). As a consequence, a substantial amount of metal waste was always produced. Furthermore, relatively high temperatures and long reaction times were usually required. These shortcomings led to the development of room temperature protocols employing isolable Cu–CF_3 complexes, either preformed or used *in situ*. These reagents also display a broader substrate scope and higher compatibility with other functional groups, especially carbonyl moieties [9].

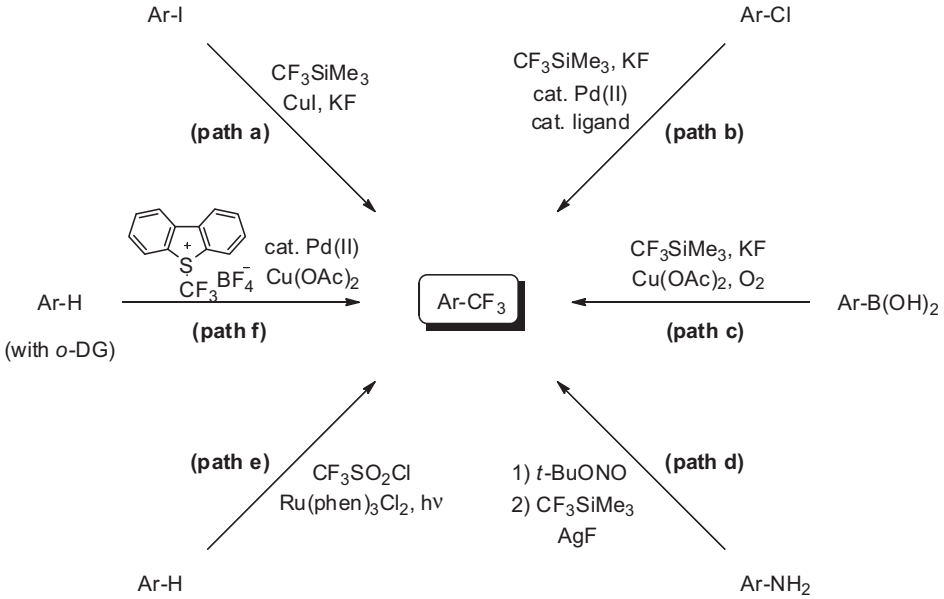
The development of a catalytic method in copper constituted a landmark in the trifluoromethylation of arenes. This involved the reaction of electron-deficient aryl iodides with CF_3SiEt_3 and a catalytic amount of CuI in the presence of a chelating diamine ligand, 1,10-phenanthroline (phen) [10]. Subsequently, other procedures have been reported based on more stable or cheaper sources of CF_3, such as potassium (trifluoromethyl)trialkoxyborates [11], trifluoroacetaldehyde (fluoral) [12] or environmentally friendly fluoroform [13].

Pd(II) and Pd(IV) complexes containing an aryl and CF_3 groups can act as intermediates in the trifluoromethylation of aryl iodides by a reductive elimination step leading to Ar–CF_3 bond formation [14]. These discoveries paved the way for a major advance in this area: the development of a Pd(II)-catalyzed trifluoromethylation method by way of the correct choice of ligands, that allowed using the much cheaper and available aryl chlorides as substrates with amounts as low as 3 mol% of palladium catalyst [15] (Scheme 1, path b).

Aryl boronic acids are a suitable alternative to aryl halides as substrates in trifluoromethylation processes, due to their higher reactivity and easy synthetic access. The first examples reported consisted in the copper-mediated reaction with CF_3SiMe_3, in the presence of oxidants such as Ag_2CO_3 [16] or oxygen [17] (Scheme 1, path c). Soon afterward, a plethora of related protocols have increased the potential of aryl boronic acids employing different sources of CF_3, which include other nucleophilic (potassium (trifluoromethyl)trialkoxyborates [18]), electrophilic (trifluoromethyl sulfonium salts [19]), or radical reagents ($NaSO_2CF_3$/TBHP [20]) as well as fluoroform [21]. From these findings, catalytic procedures have also been developed, by using CF_3SiMe_3 [22], Togni's reagent [23], Umemoto's reagent [24], CF_3I/visible light [25] or again $NaSO_2CF_3$/TBHP [26].

Anilines can be converted into trifluoromethyl arenes by means of a Sandmeyer-type process. Two synthetic protocols have been recently described to perform this transformation, consisting in the reaction of the derived diazonium salts with Umemoto's reagent and Cu metal [27], or with CF_3SiMe_3 and AgF [28] (Scheme 1, path d).

In the absence of a pre-positioned and replaceable functional group, trifluoromethylation of arenes can be achieved by C–H activation, although regioselectivity issues may then arise. This strategy has been pursued employing CF_3SiMe_3/AgOTf at 80 °C [29], or more efficiently at room temperature with CF_3SO_2Cl in the presence of visible light and $Ru(phen)_3Cl_2$ as photocatalyst [30]



Scheme 1. Selected methods for the synthesis of Ar–CF_3 compounds.

(Scheme 1, path e). In this manner, the need of an underlying pre-functionalization step is avoided, even if application of these protocols on substituted benzenes usually produced mixtures of regioisomers.

A simple way to overcome the selectivity problems is the use of *ortho*-directing functional groups that may or may not be removed after the trifluoromethylation step. For instance, a Pd(II)-catalyzed C–H trifluoromethylation method was described taking place in the *ortho*-position of heterocyclic-functionalized benzenes, using Umemoto's reagent as the CF_3 source and a Cu(II) salt as oxidant [31] (Scheme 1, path f). Some related procedures have been applied to benzamides [32] or *N*-acetylanilines [33]. Also, a silver-promoted *ortho*-trifluoromethylation of aryl triazenes has been reported, with the added value of the synthetic versatility of the triazene moiety [34].

A complementary approach consisted a two step protocol, namely iridium-catalyzed borylation of aromatic rings, followed by copper-catalyzed trifluoromethylation [35]. This method benefits from the high regioselectivity usually observed in the arene borylation step, which depends mostly on steric effects rather than electronic ones.

Finally, it should be mentioned the possibility of introducing CF_3 groups into arynes, by reaction with $AgCF_3$ (in turn prepared from CF_3SiMe_3 and AgF) and an electrophile, in practice consisting in a difuncionalization of the aromatic ring [36].

2.2. Trifluoromethylation of heteroaromatic compounds

In general, most of the methods discussed above for the trifluoromethylation of aromatic compounds have been applied or potentially could be used for the preparation of trifluoromethyl heteroarenes [6g,37]. Nevertheless, the need for new CF_3-substituted heterocycles has inspired new synthetic procedures, more environmentally friendly and without any metal, taking advantage of the inherent reactive positions of a variety of heterocyclic rings explored, and also displaying a high functional group compatibility [38] (Scheme 2).

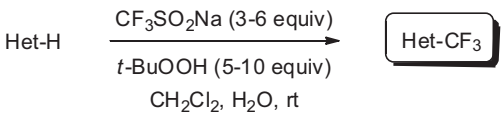
An illustrative example is provided by the regioselective trifluoromethylation of caffeine, which was performed on a gram-scale in the absence of any organic solvent to render a single CF_3-derivative [38] (Scheme 3).

2.3. Trifluoromethylation of sp carbon

Direct trifluoromethylation of terminal alkynes was first described using CF_3SiMe_3 and stoichiometric CuI in open air [39]. This procedure was considerably more straightforward than previous approaches for the synthesis of CF_3-substituted alkynes, based on couplings of alkynyl metal reagents. Moreover, a catalytic method was later developed, using conditions analogous to those also applied for the trifluoromethylation of aryl boronic acids [22] (Scheme 4).

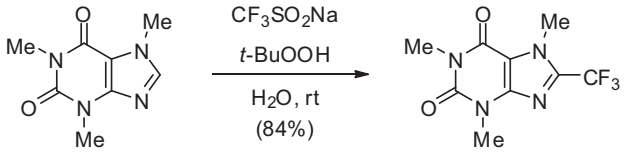
2.4. Trifluoromethylation of sp^2 carbon

In comparison with the trifluoromethylation of aromatic rings, the analogous process on olefinic systems has been much less



Het-H: substituted pyridines, pyrroles, indoles, pyrazines, etc.

Scheme 2. Trifluoromethylation of heterocycles with Langlois' reagent.



Scheme 3. Regioselective trifluoromethylation of caffeine.

studied. Initially, some copper-mediated [16] or catalyzed [23,24] methods for the installation of CF_3 groups into aryl boronic acids were also applied to vinyl boronic acids, albeit leading to mixtures of *E*/*Z* isomers in most cases. It was later found that vinyl trifluoroborate salts lead to the trifluoromethylation products with increased *E*/*Z* selectivity by reaction with Togni's reagent in the presence of catalytic $FeCl_2$ [40] (Scheme 5, path a) or under photoredox catalysis conditions [41].

Trifluoromethyl alkenes have also been accessed from other substituted olefins such as vinyl sulfonates employing CF_3SiMe_3 and a Pd(II) catalyst, although this method was suitable only for cyclohexenyl derivatives [42]. Furthermore, α,β-unsaturated carboxylic acids may experiment a formal decarboxylative trifluoromethylation process with Togni's reagent under copper-catalyzed conditions [43] (Scheme 5, path b) or with Langlois' reagent [44], also with excellent *E*/*Z* selectivity.

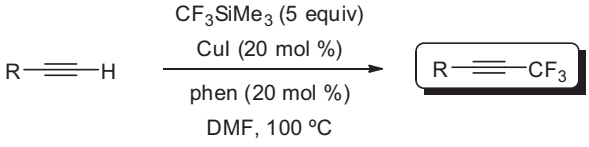
Metal-catalyzed trifluoromethylations of terminal olefins by means of C–H activation are much less common than in the case of aromatic compounds because they are highly substrate-dependent. Thus, in the presence of isomerizable double bonds, these processes usually lead to allylic trifluoromethylation compounds as the major or only products (see below). In this regard, the first successful examples of a vinyl–CF_3 bond formation involved a Cu(I)-catalyzed electrophilic trifluoromethylation with Togni's reagent [45] or a photocatalyzed process with CF_3SO_2Cl [46], but these methods were restricted to enamides as starting substrates. A more general approach was later discovered using a photoredox radical trifluoromethylation with CF_3I, exhibiting a high functional group tolerance which also included isomerizable double bonds [47] (Scheme 5, path c).

Formation of vinyl–CF_3 bonds was also feasible starting from terminal alkynes through a Cu(I)-catalyzed oxytrifluoromethylation reaction. The final compounds incorporated a molecule of the electrophilic Togni's reagent, so the process constitutes a formal addition to the triple bond with excellent regio- and stereoselectivity [48] (Scheme 5, path d).

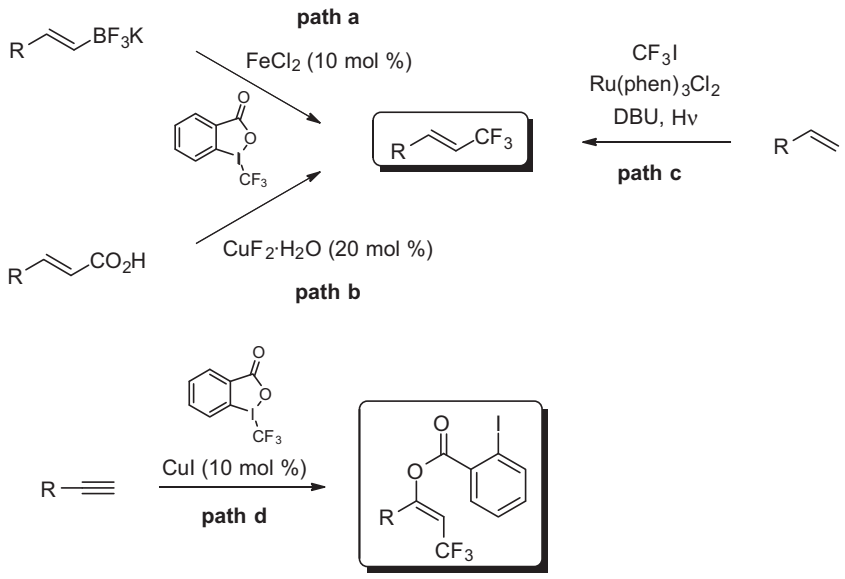
2.5. Trifluoromethylation of sp^3 carbon

By far, formation of C_{sp^3} –CF_3 bonds has been achieved mainly by nucleophilic additions of CF_3 anion equivalents to carbonyl groups [5a]. In the case of chiral or prochiral substrates, an underlying issue is the stereochemical control of the reaction, which can be addressed in a diastereo- or enantioselective fashion, respectively [49].

On the other hand, insertion of trifluoromethyl groups into activated alkyl chains is also a highly pursued approach. A great deal of research has focused on the preparation of α-CF_3 carbonyl



Scheme 4. Catalytic trifluoromethylation of alkynes.



Scheme 5. Selected methods for the synthesis of vinyl–CF_3 compounds.

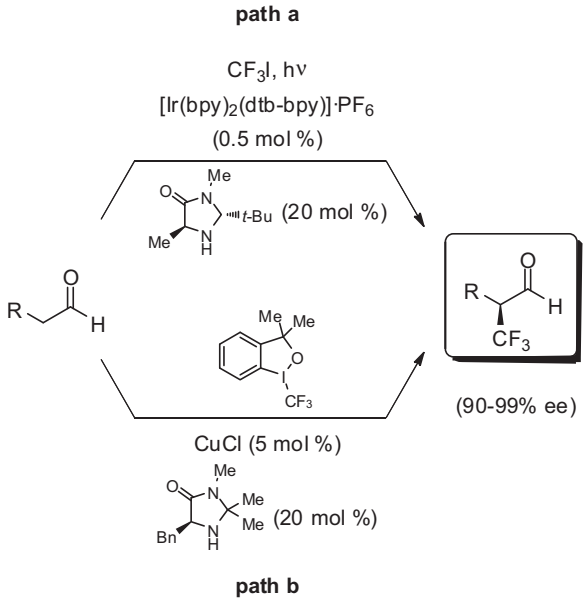
compounds, but, in principle, this cannot be carried out using nucleophilic sources of CF_3, and hence early developments in this regard led to the discovery of widely used electrophilic trifluoromethylation reagents such as Umemoto's [50] or more recently the family of Togni's reagents [51].

An important progress in this area was represented by an enantioselective trifluoromethylation method combining both photo- and organocatalysis. Thus, a radical source of CF_3 (CF_3I) was able to react with aldehydes under visible light, in the presence of a Ru or Ir photocatalyst and a chiral imidazolidinone affording α-CF_3 aldehydes in good enantiomeric excesses, and also exhibiting a high functional group compatibility [52] (Scheme 6, path a). This method was later extended in a non-enantioselective manner to enolsilanes derived from ketones, esters or amides [53]. Furthermore, a complementary protocol consisted in a Cu(I)-catalyzed electrophilic α-trifluoromethylation of aldehydes using Togni's reagent and a similar chiral imidazolidinone, to render α-CF_3 aldehydes in high enantioselectivities as well [54] (Scheme 6, path b). It should also be mentioned that either Umemoto's or Togni's reagents were reported to react with β-ketoesters in an enantioselective manner catalyzed by $Cu(OTf)_2$ and chiral bifunctional ligands [55].

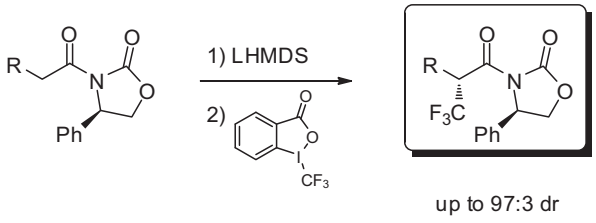
Diastereoselective additions of CF_3 reagents to chiral enolates may also bring on α-trifluoromethylations of carbonyl compounds displaying good stereochemical outcomes [56]. For this purpose, lithium enolates derived from *N*-acyl oxazolidinones (Evans chiral auxiliaries) easily reacted with Togni's reagent to provide the corresponding α-CF_3 products in excellent diastereomeric ratios [57] (Scheme 7). More recently, the parent zirconium enolates were prone to react with CF_3I in a radical process promoted by a ruthenium catalyst [58].

As pointed out above, nucleophilic reagents such as CF_3SiMe_3 may not be used for α-trifluoromethylations of carbonyl compounds. However, a $CuCF_3$ species prepared from fluoroform was suitable for reacting with α-chloro or bromoketones to furnish α-(trifluoromethyl)ketones without affecting the carbonyl group [59]. Similarly, a formal α-trifluoromethylation of esters was accomplished by means of another $CuCF_3$ reagent, this time prepared from CF_3SiMe_3, that served to convert α-diazoesters into α-(trifluoromethyl)esters in a process promoted by water as activating agent [60].

Benzylic trifluoromethylations of suitable substrates have been usually carried out under a variety of conditions using nucleophilic sources of CF_3. However, Cu-mediated electrophilic methods are now available with the aid of trifluoromethylsulfonium salts, in the presence of other sensitive functional groups and without affecting the aromatic ring [61].



Scheme 6. Enantioselective α-trifluoromethylation of aldehydes.



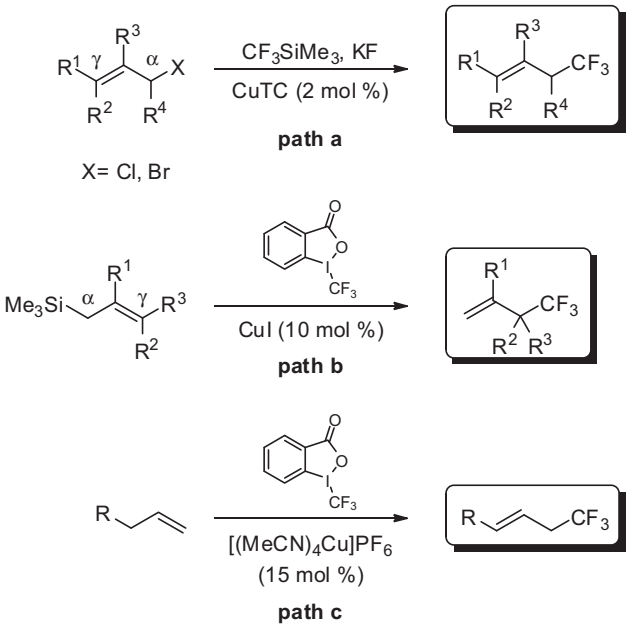
Scheme 7. Diastereoselective α-trifluoromethylation of chiral imides.

In the case of allyl halides, regioselectivity issues could potentially arise, as trifluoromethylation may take place at the α- or γ-positions. A recently described Cu-catalyzed procedure using CF_3SiMe_3 proceeded with complete regiocontrol to afford α-allylic trifluoromethylated products [62] (Scheme 8, path a). The parent allyl silanes can also be transformed into CF_3-allylic compounds, but the regioselectivity observed is the opposite as that of allyl halides, giving rise to γ-trifluoromethylation products by reaction with electrophilic reagents under Cu-catalyzed conditions [63] (Scheme 8, path b). The same process has also been described under photoredox catalysis conditions [64].

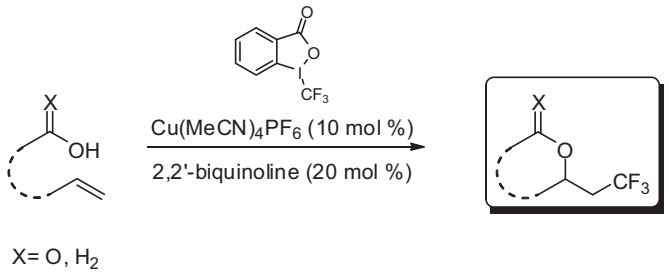
As mentioned above, terminal olefins can be transformed into allylic trifluoromethylated compounds under copper-catalyzed conditions. This process has been described using Togni's reagent [65] as well as Umemoto's reagent [66] (Scheme 8, path c). A related approach used nucleophilic trifluoromethylations with CF_3SiMe_3 and catalytic copper(I)-thiophene-2-carboxylate (CuTC) [67]. Although these methods are limited to monosubstituted terminal olefins, they do not require an activating functional group and in general proceed in good *E*/*Z* selectivity in the isomerized double bond.

Copper-catalyzed oxytrifluoromethylations of olefins allow for the formation of alkyl–CF_3 bonds, in analogous manner as in the process previously mentioned starting from alkynes [48]. 1,3-Dienes also react under similar conditions to afford 1,4-oxytrifluoromethylation products [67]. Photocatalytic methods are also suitable for alkene oxytrifluoromethylations, employing an iridium photocatalyst and Umemoto's reagent in alcohols or water as solvents [68]. In addition, this strategy has been carried out in an intramolecular fashion starting from suitably functionalized olefins, containing carboxyl or hydroxy groups, using Togni's reagent and a Cu(I) catalyst [69] (Scheme 9). A conceptually similar approach allowed for the preparation of β-trifluoromethyl α-aryl ketones from α,α-diaryl allylic alcohols [70].

Similar types of bifunctionalization of double bonds include trifluoromethylaminoxylations [71], aminotrifluoromethylations [72], aryltrifluoromethylations [73], or hydrotrifluoromethylations [74]. The latter case consists in a formal transformation of terminal olefins into CF_3-substituted alkyl chains (Scheme 10).



Scheme 8. Selected methods for the synthesis of allyl–CF_3 compounds.



Scheme 9. Intramolecular oxytrifluoromethylation of olefinic carboxylic acids, alcohols and phenols.

Finally, some other substrates employed for the formation of C_{sp3}–CF_3 bonds include alkyl boronic acids [75], allyl alcohols (resulting from Morita–Baylis–Hillman reaction) [76] or amines [77].

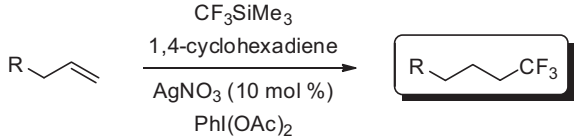
2.6. Trifluoromethylation of sp^3 nitrogen, oxygen and sulfur

Several examples of marketed drugs or compounds in clinical trials contain a trifluoromethyl group linked to an oxygen or sulfur. Although their synthesis is usually carried out from CF_3-containing building blocks, methods for constructing heteroatom–CF_3 bonds are in great demand, and it is logical to assert that most of them are based on the development of electrophilic trifluoromethylation agents.

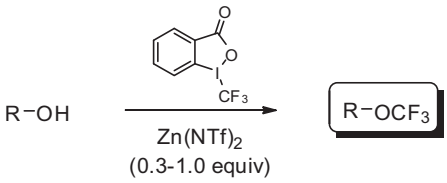
Among this group of compounds, those that contain an N–CF_3 bond are relatively scarce. An early procedure for trifluoromethylation of amines, anilines or pyridines relied on a thermally unstable *O*-(trifluoromethyl)-dibenzofuranium salt [78]. Togni's reagent has been effectively used for constructing N–CF_3 bonds but thus far this procedure was limited to the trifluoromethylation of azoles [79].

Trifluoromethyl ethers are more abundant than the parent nitrogenous compounds, and therefore their syntheses have been further studied [80]. However, current methods for the electrophilic trifluoromethylation of hydroxyl groups use again Umemoto's-type of reagents [78] or Togni's reagent, which proved to be very efficient in its reaction with aliphatic alcohols assisted by a Zn(II) salt [81] (Scheme 11). In contrast, phenols experiment trifluoromethylation predominantly at the aromatic positions [82]. The latter trifluoromethylation reagent also promoted ring-opening of tetrahydrofuran to form oligomeric trifluoromethyl ethers [83].

Finally, trifluoromethyl thioethers have been further studied, but current methodologies have a preference for direct introduction of the SCF_3 group (trifluoromethylthiolation) into appropriate substrates [84]. Nevertheless, Togni's reagent has proved its usefulness in the trifluoromethylation of aromatic and aliphatic thiols [51], including cysteine residues in peptidic molecules [85]. Sulfonic acids have been transformed into trifluoromethyl sulfonates under similar reaction conditions [86].



Scheme 10. Hydrotrifluoromethylation of terminal olefins.



Scheme 11. Trifluoromethylation of alcohols.

3. Trifluoromethyl-containing drugs

It is well known that gradual substitution of fluorine for hydrogen in methyl or phenyl groups leads to rather qualitative differences in chemical reactivity [87]. There are many examples in the literature demonstrating that CF_3- [88] or C_6F_5-containing [89] substrates show dramatically different reactivity and stereochemical outcome as compared to that of fluorine-free molecules. Therefore, the introduction of a CF_3 group into biological molecules, in general, has rather complex metabolic consequences. Furthermore, the methodological choice for introducing trifluoromethyl groups in the desired positions was, until recently, rather limited. As a result, CF_3-containing drugs are substantially rare as compared with mono-fluorinated pharmaceuticals [2].

3.1. Most notable examples of trifluoromethyl-containing marketed drugs

Nevertheless there are quite a few examples of exceptionally successful drugs containing CF_3 groups. According to the recent anthology of pharmaceutical products by US retail sales in 2012, efavirenz **1** (sales rank 14) [90], sitagliptin **2** (17) [91], celecoxib **3** (26) [92], dexlansoprazole **4** (80) [93], cinacalcet **5** (96) [94], dutasteride **6** (127) [95], travoprost **7** (155) [96] and nilotinib **8** (177) [97] are in top 200 (4%) most successful drugs on the market (Fig. 1). Examination of the structures **1**–**8** clearly suggests the overwhelming dominance of the aromatic CF_3-substitution with exception of efavirenz **1** and dexlansoprazole **4**. This trend, most likely, reflects the foregoing state of trifluoromethylation methodology with setting up the aromatic/heteroaromatic CF_3 group being the most advanced. On the other hand, assessment of the drug candidates currently under development by the pharmaceutical industry demonstrates a greater structural diversity providing a formidable incentive for ever accelerated discoveries and innovation in the area of methodology.

Here we profile five promising drug candidates currently in phases II and III of clinical studies. Each selected compound represents a different type of CF_3 group requiring different methods for appropriate trifluoromethylation discussed in Section 2.

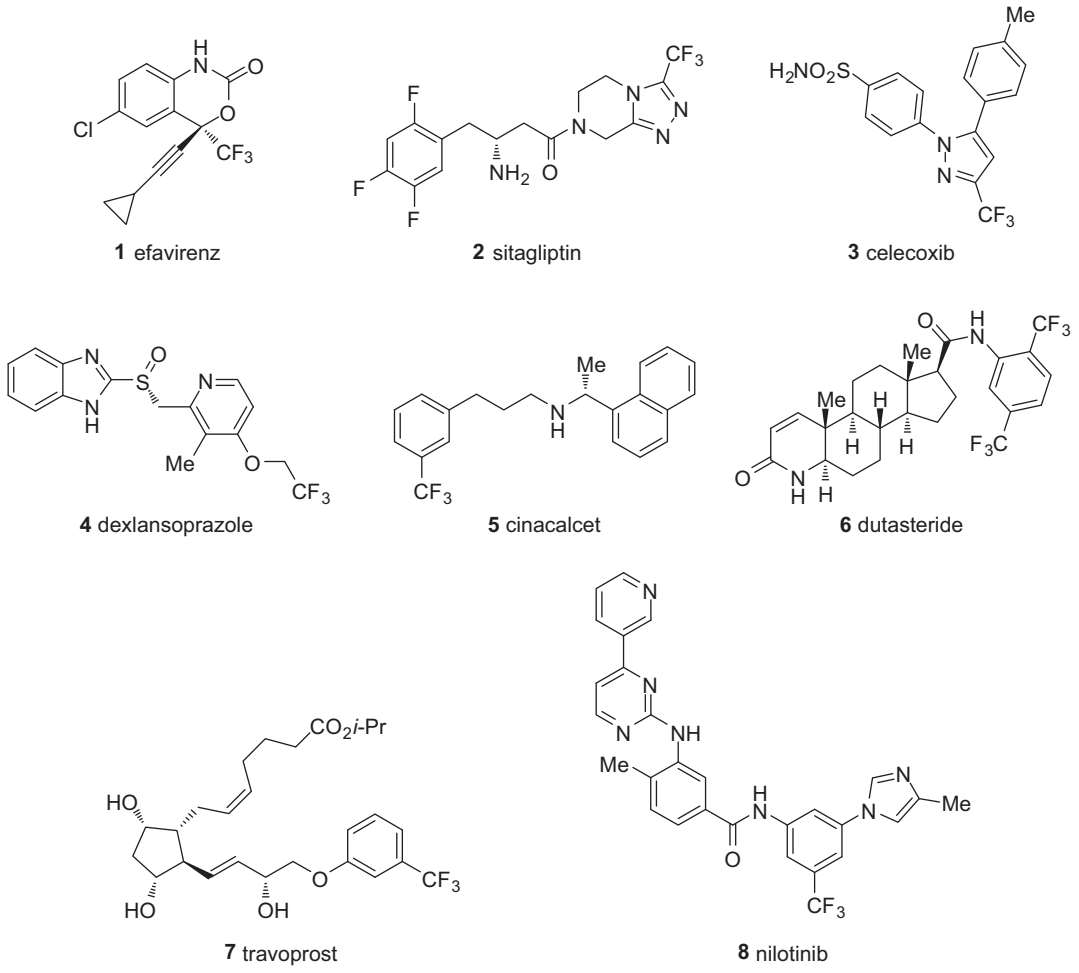


Fig. 1. Structures of CF_3-containing drugs **1-8** currently (2012) among top 200 largest selling pharmaceutical products.

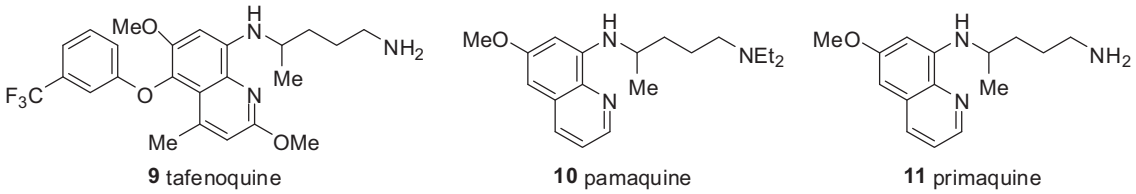


Fig. 2. Structures of tafenoquine, pamaquine and primaquine.

3.2. Selected examples of new trifluoromethyl-containing drugs currently under development by the pharmaceutical industry

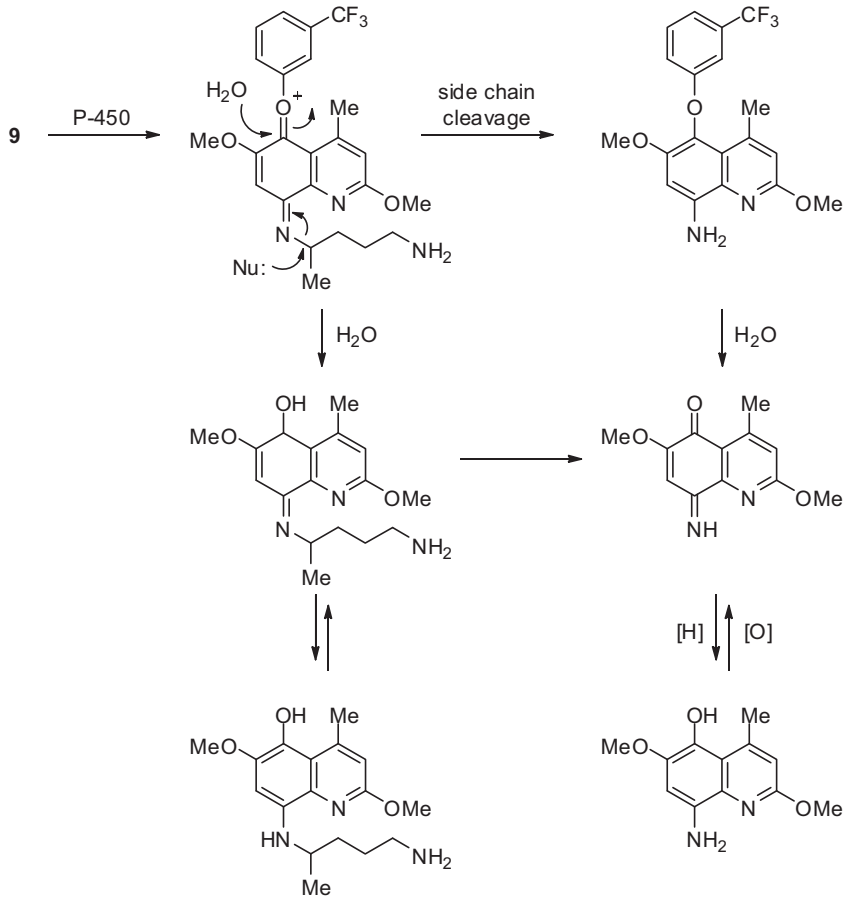
3.2.1. Tafenoquine (phase III clinical trials)

Tafenoquine (**9**), a new 8-aminoquinoline under development by GlaxoSmithKline in collaboration with Medicines for Malaria Venture, is on phase III clinical trials for the treatment of malaria (Fig. 2). The detailed biological action of this drug is still not yet completely understood, but it is believed to be similar to the action of other members of 8-aminoquinoline (8-AQ) antimalarials, such as pamaquine (**10**) and primaquine (**11**) [98].

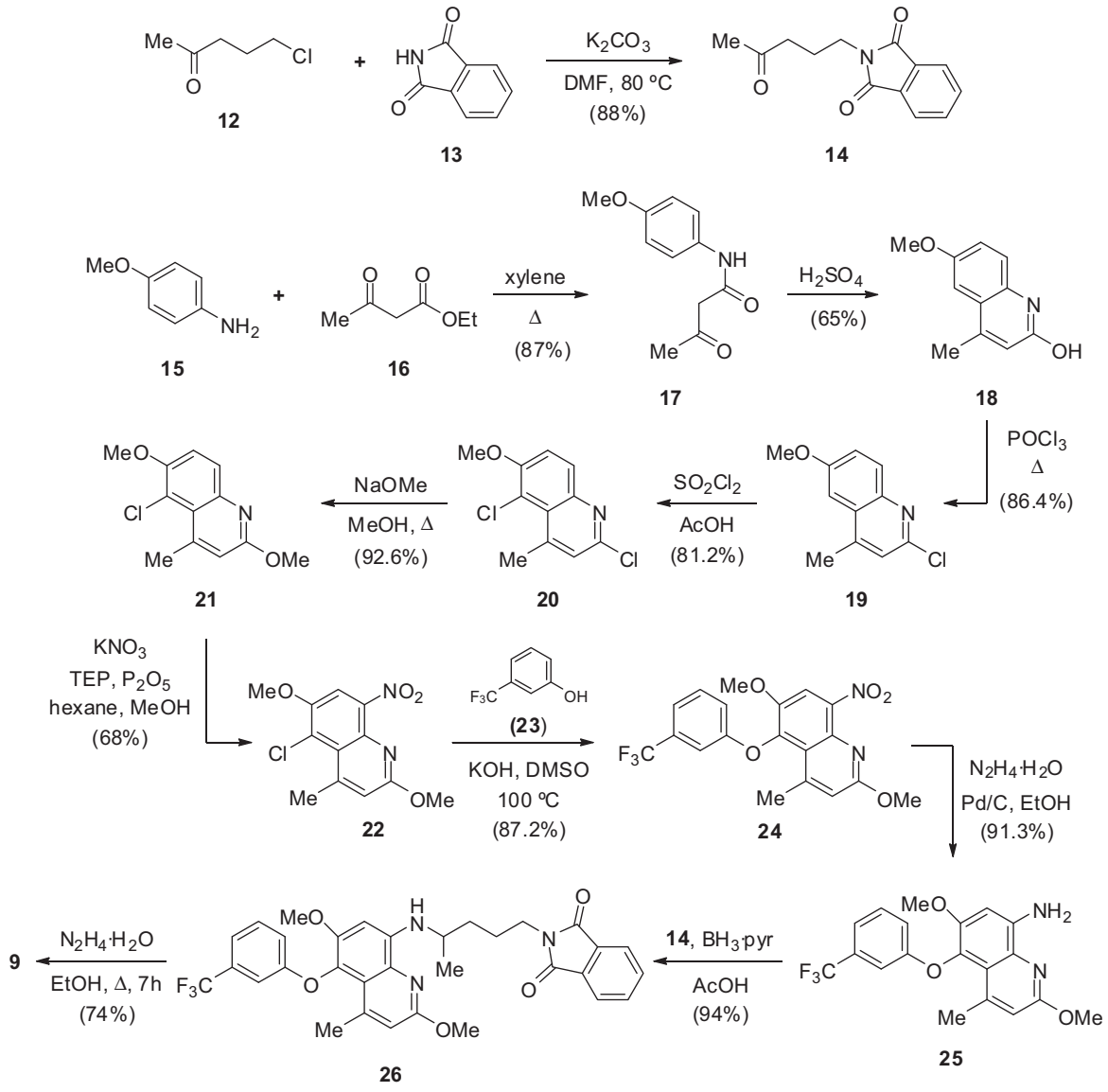
The 8-AQs are the only FDA approved drugs for the treatment of a particular case of relapsing malaria [99]. The general clinical use of this type of drugs is limited by their toxic side effects, specifically, methemoglobinemia and hemolytic anemia, which are apparently caused by the corresponding metabolites of 8-AQ [100].

To reduce the undesired side effects caused by quinoneimine metabolite formation, a great deal of 8-AQs structure modifications have been conducted. Tafenoquine is a 5-phenoxyl derivative of primaquine, which is generally less toxic and more potent than pamaquine. The resistance of the 5-(*m*-(trifluoromethyl)phenyl) group to enzymatic cleavage to generate the phenolic metabolite actually contributes a lot to the reduced toxicity of tafenoquine. In addition, the 3-(trifluoromethyl)phenyloxyl group at the 5-position of tafenoquine may be hydrolyzed to form an 8-iminoquinoline derivative as shown in Scheme 12. Furthermore, the metabolic stability of tafenoquine significantly increases its half-life as compared with that of the parent primaquine.

The synthetic route to tafenoquine developed by GSK is outlined in Scheme 13. *N*-(4-Oxopentyl) phthalimide (**14**) was obtained by alkylation of 5-chloro-2-pentanone (**12**) with phthalimide (**13**). Preparation of fragment **18** was based on the coupling of commercially available *p*-anisidine (**15**) and ethyl acetoacetate (**16**) giving rise to compound **17** which underwent intramolecular ring-closure under acidic conditions. The hydroxyl group in **18** was substituted by a chlorine atom to produce compound **19**, which was further chlorinated with SO_2Cl_2 to furnish intermediate **20** [101]. Next, the chlorine atom of the pyridine ring was replaced by a methoxy group, and the intermediate **21** was further nitrated to



Scheme 12. Proposed metabolic pathway of tafenoquine.



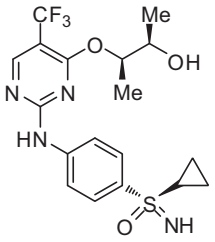
Scheme 13. Synthetic route to tafenoquine.

prepare derivative **22**. The source of a CF_3 group in this synthesis is *m*-CF_3–phenol (**23**), which can be prepared by a variety of methods, including the direct trifluoromethylation reactions of phenol discussed in the Section 2.1 of this review. The activated chlorine atom in **22** can be easily substituted with phenol **23** affording compound **24**. Upon treated with Pd/C and hydrazine hydrate, the nitro group in **24** was transformed into a free amino group. Compounds **14** and **25** thus prepared were next reacted to produce *in situ* the corresponding Schiff base which was further reduced using BH_3·pyridine complex in high yield to give intermediate **26**. Finally, the target molecule of tafenoquine was obtained by the removal of the original phthalimide protecting group [102].

3.2.2. Roniciclib (phase II)

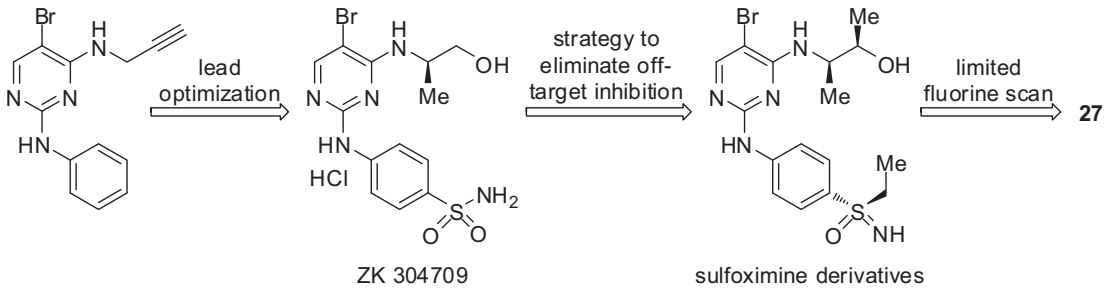
Roniciclib (BAY-1000394, BAY-80-3000) (**27**) is a very potent, nanomolar pan-cyclin-dependent kinase (CDK) inhibitor of great pharmaceutical potential [103] (Fig. 3). This molecule has been developed by Bayer Pharma AG for the oral treatment of multiple cancer-related conditions. The drug inhibits the activity of cell-cycle CDKs (CDK1, CDK2, CDK3 and CDK4) and of transcriptional CDKs (CDK7 and CDK9) [104]. It has very attractive antiproliferative activity against various human cancer cell lines as well as rapid absorption and acceptable oral bioavailability. It is currently in phase II clinical trials in patients with small-cell lung cancer (SCLC).

Roniciclib features an extremely rare chiral sulfoximine group and was developed from a CDK and vascular endothelial growth factor receptor (VEGF-R) inhibitor ZK 304709 [103,105] (Scheme 14). While ZK 304709 had promising activity, its progress was



27 roniciclib

Fig. 3. Structure of roniciclib.



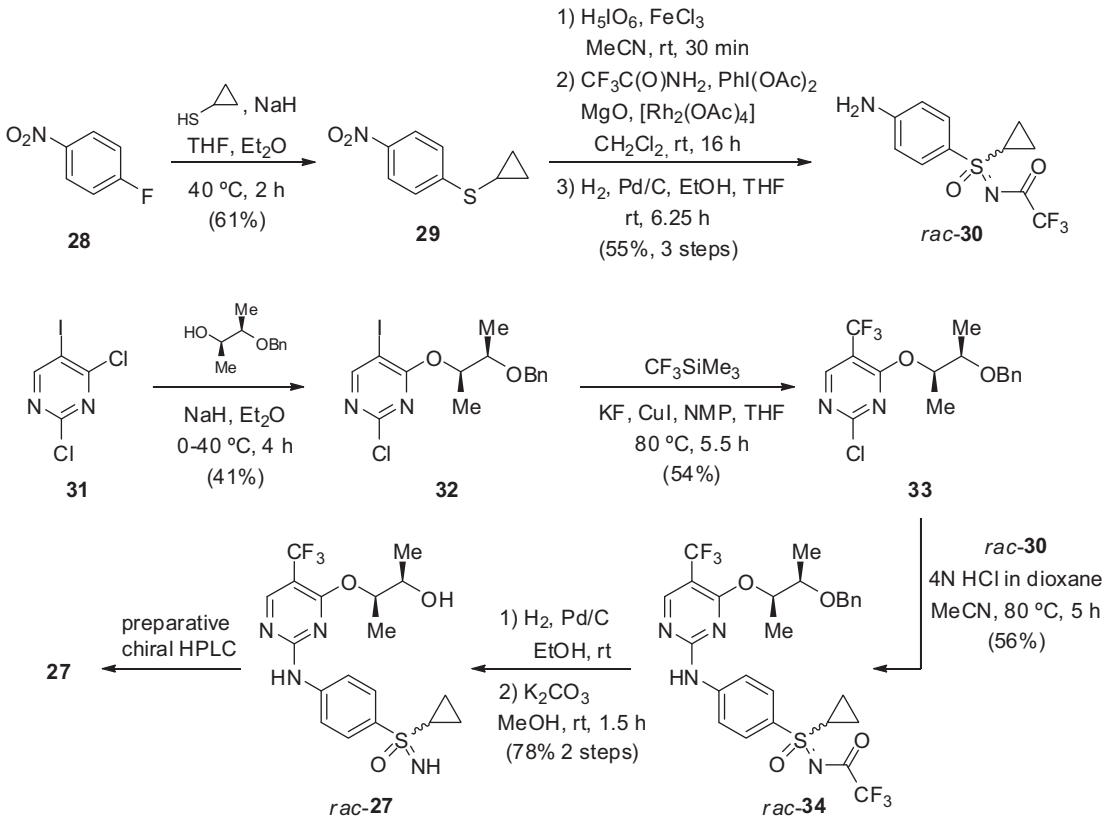
Scheme 14. Discovery of roniciclib.

plagued by off-target inhibition against carbonic anhydrase (CA) and limited solubility in water; consequently it failed the phase I clinical trials. Since the sulfonamide group in ZK 304709 was most likely the reason for the toxicity, this function was replaced with a sulfoximine group, the line that eventually lead to the discovery of roniciclib. As compared to ZK 304709, roniciclib demonstrates less CA-inhibitory activity, enhanced aqueous solubility and quite potent antiproliferative activity. The relevance of the 5-(trifluoromethyl) group in roniciclib was discovered through a fluorine scan and was shown to be essential for overall improved therapeutic properties. It is interesting to note that the 5-(trifluoromethyl) derivatives displayed higher potencies and better antitumor efficacies than the corresponding 5-bromo analogs which are easier and much cheaper to produce.

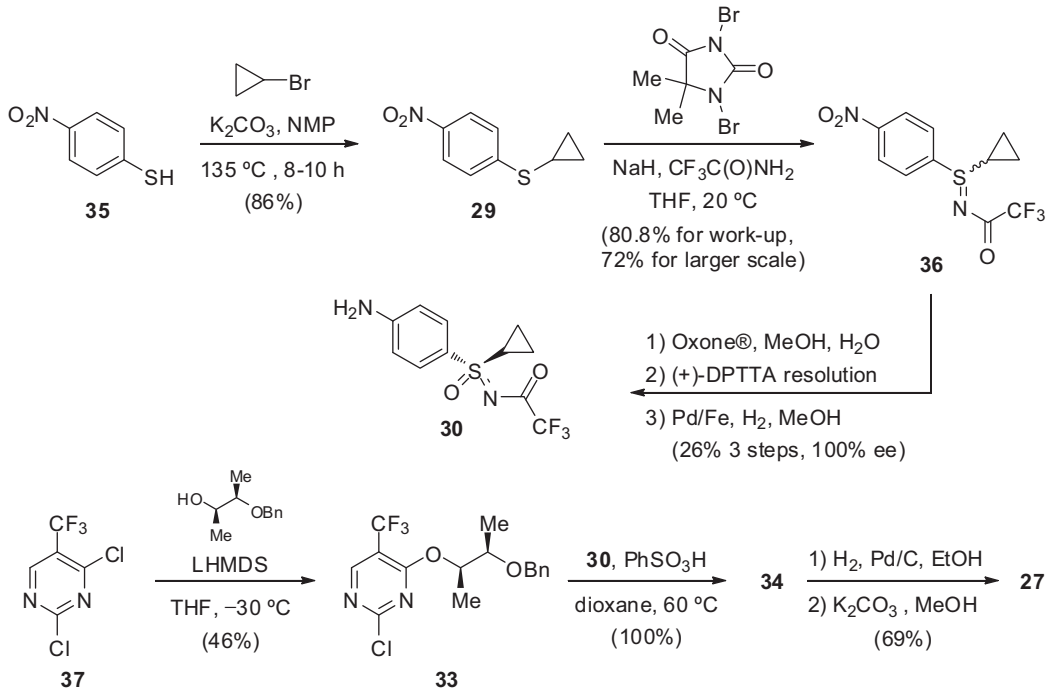
Lucking et al. reported the original convergent synthetic route to roniciclib [103]. In this protocol, 1-fluoro-4-nitrobenzene (**28**) reacted with cyclopropanethiol to afford thioether **29** in 61% yield (Scheme 15). Oxidation of **29** and the following rhodium-catalyzed imination gave rise to the protected sulfoximine, in which the nitro group was then hydrogenated with palladium on charcoal to give aniline derivative **30**. In parallel, commercially available 2,4-dichloro-5-iodopyrimidine (**31**) was functionalized regioselectively at the 4-position to give **32**, which was subsequently converted to **33** by trifluoromethylation. The yield on this step was rather low, only 54%. Then, compounds **30** and **33** were coupled to form the fully protected product **34** in, again, moderate 56% yield. The following high-yield hydrogenation and deprotection afforded racemic roniciclib. Finally, the enantiomerically pure roniciclib was obtained by means of preparative chiral HPLC.

In this approach, the introduction of the 5-(trifluoromethyl) substituent into **32** was carried out with commercial yet quite expensive Ruppert–Prakash reagent. This, as well as the relatively low yield on the trifluoromethylation step rendered this method unattractive.

Recently, a more advanced synthetic procedure for preparation of roniciclib, without recourse to chiral chromatography was published [106]. In this procedure, thioether **29** was synthesized in 86% yield from commercially available 4-nitrobenzenethiol (**35**)



Scheme 15. Original synthetic route to roniciclib.



Scheme 16. Advanced synthetic procedure for preparation of roniciclib.

and cyclopropylbromide (Scheme 16). Oxidative amination of **29** with the oxidizing agent 1,3-dibromo-5,5-dimethylhydantoin led to the trifluoroacetyl-protected sulphilimine **36** in 81% yield. Oxidation of **36** and subsequent racemate resolution of nitrophenyl-sulphoximines was carried out in a one-pot process, followed by reduction of the nitro group in the presence of an iron-doped palladium catalyst to give building block **30**. Compound **33** was obtained from trifluoromethyl pyrimidine **37** in 46% yield. Acid-mediated coupling of building blocks **30** and **33** furnished **34**, which was followed by hydrogenation and deprotection affording the target compound roniciclib.

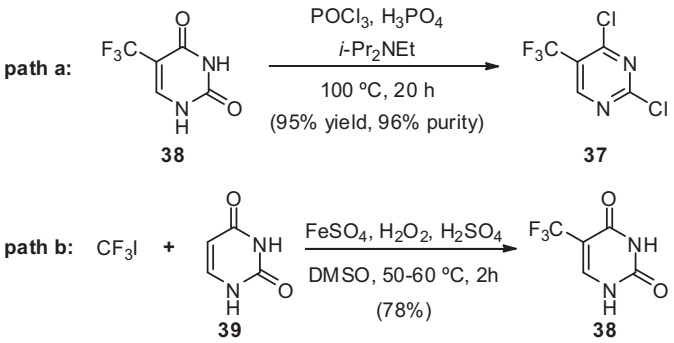
The key fluorine-containing block 2,4-dichloro-5-(trifluoromethyl)pyrimidine (**37**) used in this procedure is commercially available. It can be prepared by chlorination of 5-TFU (5-trifluoromethyluracil) (**38**) with phosphorus oxychloride in 95% yield [107] (Scheme 17, path a). To access the large-scale production of 5-TFU, Uraguchi et al. investigated a novel catalytic system for the convenient one-step trifluoromethylation of uracil (**39**) with CF_3I (78% yield) [108] (Scheme 17, path b). It is worth noting that the trifluoroacetyl group used to protect the nitrogen in the sulfoximine was essential in the synthesis of roniciclib. It allowed avoiding the low-yield sluggish reaction during the corresponding coupling [103].

Most likely, more efficient procedures for preparation of CF_3-containing key building block **37**, using numerous methods listed in Sections 2.1 and 2.2, are being currently developed. It seems that another synthetic challenge is associated with the chiral sulfoximine group. Asymmetric synthesis of chiral sulfoximines is clearly underdeveloped [109] necessitating the resolution procedure step using either HPLC or chiral resolving reagents and recrystallization. In this regard it is interesting to note that the resolution procedure can be significantly aided by yet unconventional approach such as self-disproportionation of enantiomers (SDE) [110]. In particular, it has been established that chiral sulfoxides show remarkably high magnitude of the SDE under the conditions of achiral chromatography, allowing separation of the racemic portion from the excess enantiomer [111]. Accordingly, one might expect that chiral sulfoximines would show similarly high magnitude of the SDE proving for an improved and inexpensive optical purification of partially resolved roniciclib.

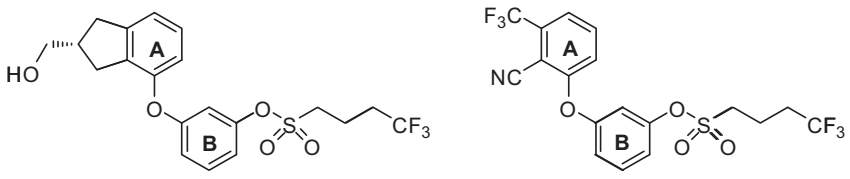
3.2.3. BAY-38-7271 (phase II)

BAY-38-7271 (KN-38-7271) (**40**) is a novel cannabinoid CB1/CB2 receptor agonist which was originally (2005) developed by Bayer for the treatment of traumatic brain injury (TBI) [112] (Fig. 4). Later (November 2007), the therapeutic area of this drug candidate was extended to include stroke and related conditions. In September 2008, it was granted a rare orphan drug status by the EMEA for moderate and severe closed TBI treatment. Now the drug is in the phase II of clinical trials for TBI and the phase I for the stroke related complications.

Being as highly potent and selective full agonist of CB1/CB2 receptor *in vitro* and *in vivo*, BAY-38-7271 demonstrated significant neuroprotective efficacy in various models and had a remarkably wide therapeutic window for the treatment of TBI [112,113]. Structurally, the compound has an unusual fluorination pattern, such as ω-CF_3-containing side chain [114] linked to the diaryl ether core by forming the corresponding sulfonyl ester.



Scheme 17. Synthetic procedure for building block **37**.



40 BAY-38-7271
K_i = 0.46 nM (rCB1)
= 1.85 nM (hCB1)
= 5.96 nM (hCB2)

41 BAY-59-3074
K_i = 55.4 nM (rCB1)
= 48.3 nM (hCB1)
= 45.5 nM (hCB2)

Fig. 4. Structures of BAY-38-7271 and BAY-59-3074 and their therapeutical properties.

Another cannabinoid receptor agonist reported by Bayer, BAY-59-3074 (**41**), sharing a similar structural scaffold, with the only difference in the substitutions on the ring A, exhibited noticeably lower agonist properties and acted as a CB1/CB2 partial agonist with antihyperalgesic and antiallodynic effects [115].

The first synthetic route to BAY-38-7271 disclosed by Bayer started with the reduction of 4-hydroxyindane-2-carboxylic acid ethyl ester (**42**) with $LiAlH_4$ to give hydroxymethyl derivative **43** [116] (Scheme 18). The condensation between **43** and 3-fluoronitrobenzene (**44**) in the presence of K_2CO_3 provided diaryl ether **45** in low yield (32%). The nitro group of **45** was reduced by H_2 over Pd/C to afford aniline **46**, which was transformed into phenol **47** with rather low 38% yield. Compound **47** was coupled with 4,4,4-trifluorobutylsulfonyl chloride (**48**) under basic conditions to give the racemic sulfonate ester *rac*-**40** with 41% yield, which was finally resolved by chiral HPLC to furnish the target (*R*)-enantiomer **40** in 21% yield.

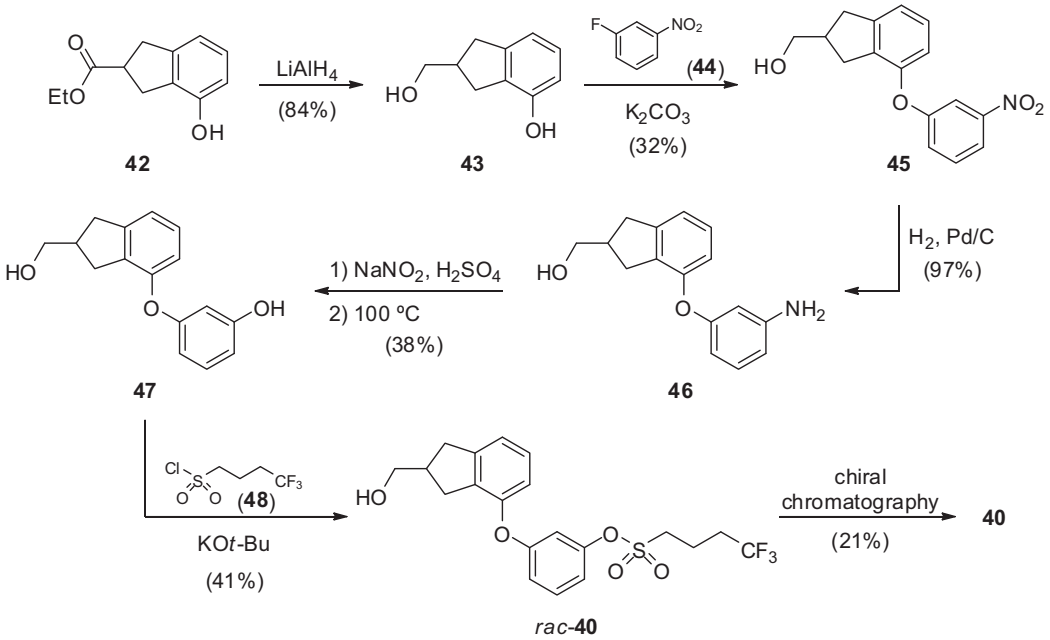
In another, more advanced approach, the diaryl ether **51** was obtained with 68% yield by condensation of 2,3-dimethylphenol (**49**) with 3-bromoanisole (**50**) [117] (Scheme 19). The demethylation of **51** was accomplished with HBr in 83% yield, and the unprotected phenolic OH group was reacted with fluorinated compound **48** in the presence of KO*t*-Bu to afford sulfonate **53** in good yield (95%). Next, NBS bromination and the following cyclization with dimethyl malonate (**55**) furnished indanedicarboxylate **56**, which was hydrolyzed and decarboxylated to give the indane-carboxylic acid **57**. The reduction of the carboxyl group of **57** with $BH_3{\cdot}SMe_2$ led to *rac*-**40** in 72% yield followed by the resolution (HPLC) of enantiomers, as described above.

The fluorine contained building block **48** used in the above syntheses was prepared by a three-step procedure [116,117] (Scheme 20). 4,4,4-Trifluorobutanol (**58**) was treated with methanesulfonyl chloride and then reacted with sodium thiocyanate to provide 4,4,4-trifluorobutyl thiocyanate (**60**), followed by chlorination to give **48** in 89% yield.

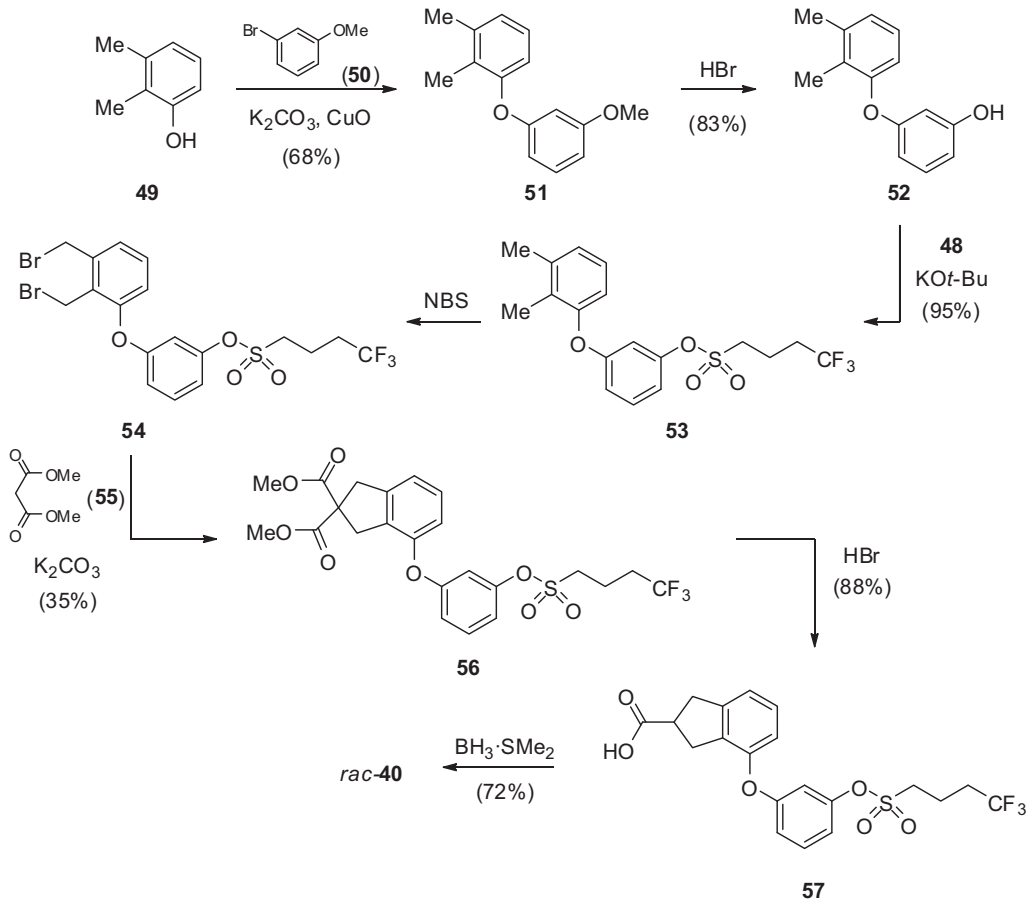
CF_3-butanol (**58**) is commercially available and one of the approaches for its preparation can include the hydrotrifluoromethylation of terminal olefins, as described in Section 2.5 (Scheme 10). Also in this case the problematic preparation of the target enantiomerically pure final product can be helped using SDE [118] via achiral chromatography or sublimation/evaporation, known to be quite efficient for chiral alcohols [119].

3.2.4. Sonidegib (phase III)

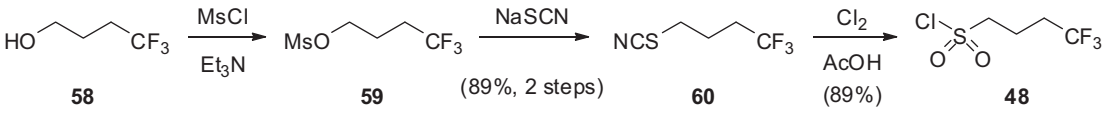
Sonidegib (**61**), also known as NVP-LDE-225 or erismodegib, was developed by Novartis for potential oral treatment of solid tumor and acute leukemia (Fig. 5). Sonidegib is a potent and quite selective (SMO) receptor antagonist and blocks aberrant hedgehog



Scheme 18. Synthetic route to BAY-38-7271.



Scheme 19. Alternative approach for preparing BAY-38-7271.

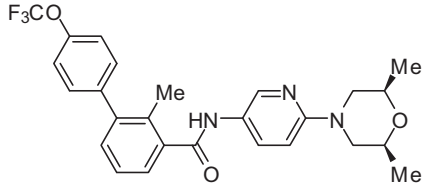


Scheme 20. Preparation of 4,4,4-trifluorobutylsulfonyl chloride (**48**).

(Hh) signaling [120], which is considered as a successful therapeutic strategy against various cancers [121,122].

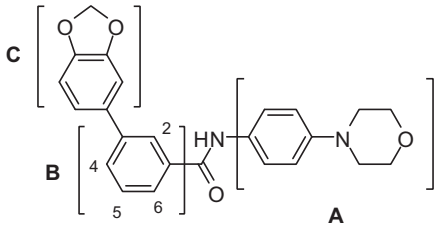
Final structure of sonidegib was derived from a class of biphenyl carboxamides identified as hedgehog signaling inhibitors and optimized via intensive high throughput screening (HTS) [120]. The structure-activity relationships (SAR) study was focused on three key regions in screening of hit compound **62** (Fig. 6). In the region A, the replacement of phenyl with a more electron-deficient pyridine reduced the metabolic toxicity, and the introduction of *cis*-dimethyl groups onto the morpholine ring increased the activity. In the region B, migration of the small hydrophobic methyl group from the 4- to the 2-position remarkably enhanced the potency, and in region C, substituents such as –CN, –OMe, $–CF_3$ and $–OCF_3$ were preferred at the *para*-position. Given its favorable pharmacokinetic properties and antitumor efficacy, in June 2013, sonidegib entered phase III clinical trials for treatment of medulloblastoma related conditions.

Sonidegib was initially prepared in four steps [120]. The *N*-arylation of *cis*-2,6-dimethylmorpholine (**63**) with 2-chloro-5-nitro-pyridine (**64**) afforded **65** (93.2% yield), followed by reduction of the nitro group with H_2 over Pd/C to provide



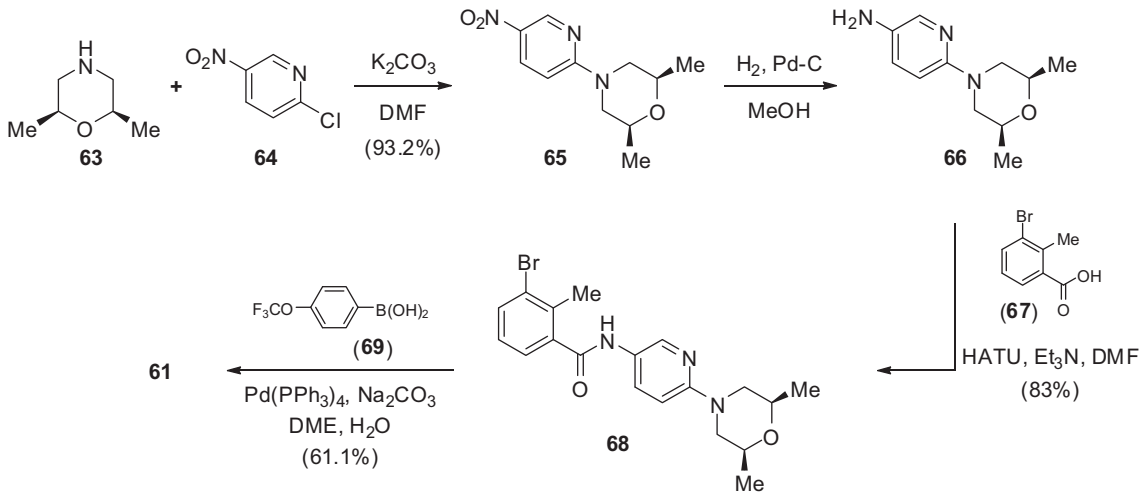
61 sonidegib

Fig. 5. Structure of sonidegib.



62

Fig. 6. Structure of screening hit compound **62**.

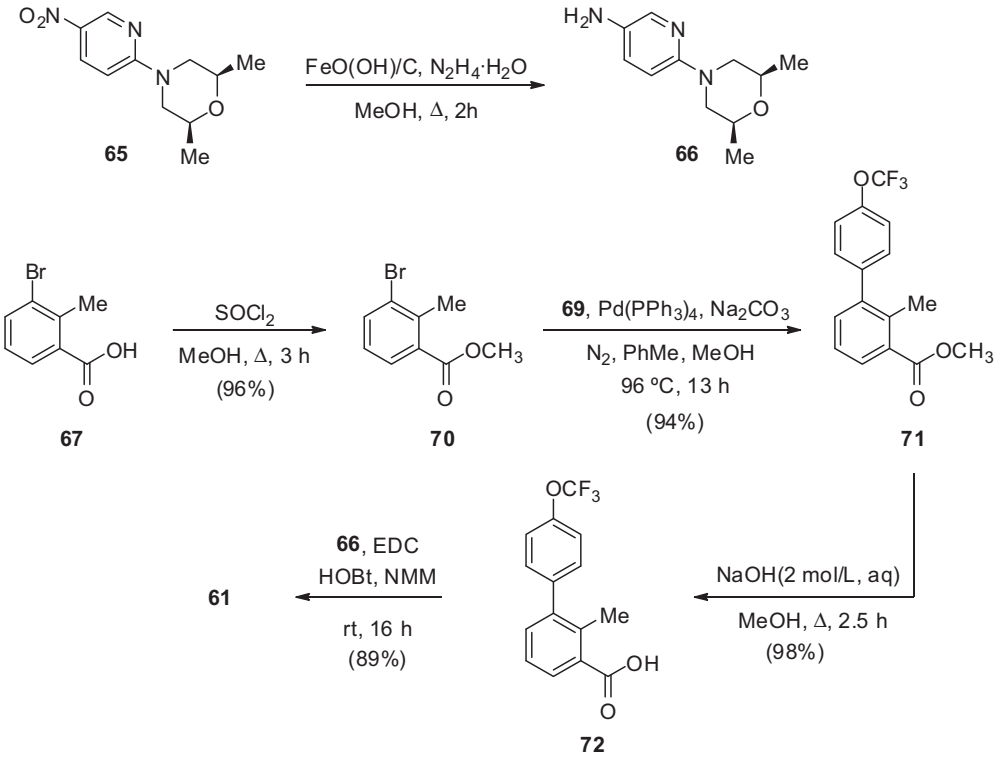


Scheme 21. Initial synthetic route to sonidegib.

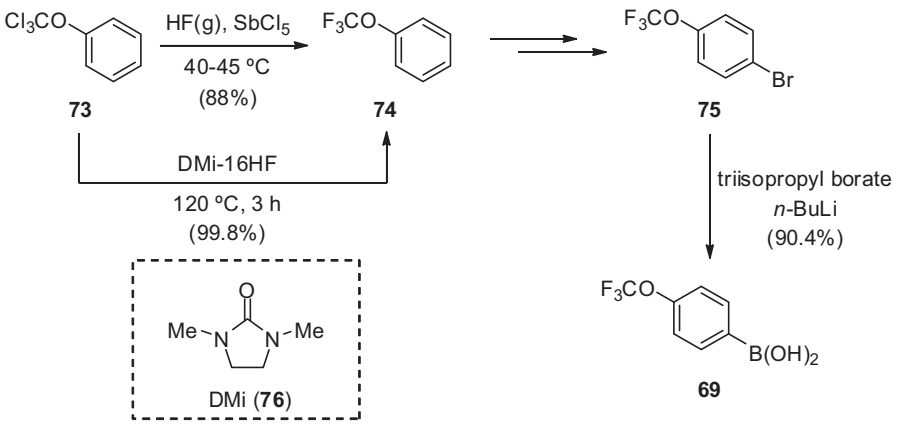
aminopyridine **66** (Scheme 21). Amide bond formation between **66** and 3-bromo-2-methyl benzoic acid (**67**) generated compound **68**, which was next coupled with 4-(trifluoromethoxy)phenylboronic acid (**69**) through a Suzuki coupling reaction to give sonidegib (**61**) in 61.1% yield.

Recently, Hu et al. described a high-yield synthetic procedure which is more suitable for large-scale production of sonidegib [123]. For the reduction of the nitro group in compound **65**, the H_2 and Pd/C system was replaced by hydrazine hydrate and reusable catalyst FeO(OH)/C (Scheme 22). Furthermore, the Suzuki coupling reaction was carried out before the amidation step to overcome the undesirable electronic effects. This modification allowed increasing the yield of the coupling to 94%. Final step in this process was the amide bond formation between **66** and **72** which gave the target sonidegib in 89% yield.

Both routes used commercially available reagent **69** as a CF_3-containing building block, which can be obtained from 1-bromo-4-(trifluoromethoxy)benzene (**75**) by treatment with triisopropyl borate in a conventional manner allowing preparation of compound **69** in good yield [124] (Scheme 23). Numerous methods to synthesize the required CF_3O-benzene **74**, the precursor of **75**, have been reported in the past and reviewed [80]. For industrial scale synthesis, one of the widely used processes is the fluorination of trichloromethoxybenzene (**73**) with gaseous hydrogen fluoride in the presence of antimony pentachloride [125]. Alternatively, using DMi-16HF, the safe and convenient fluorination agent



Scheme 22. Large-scale synthesis of sonidegib.



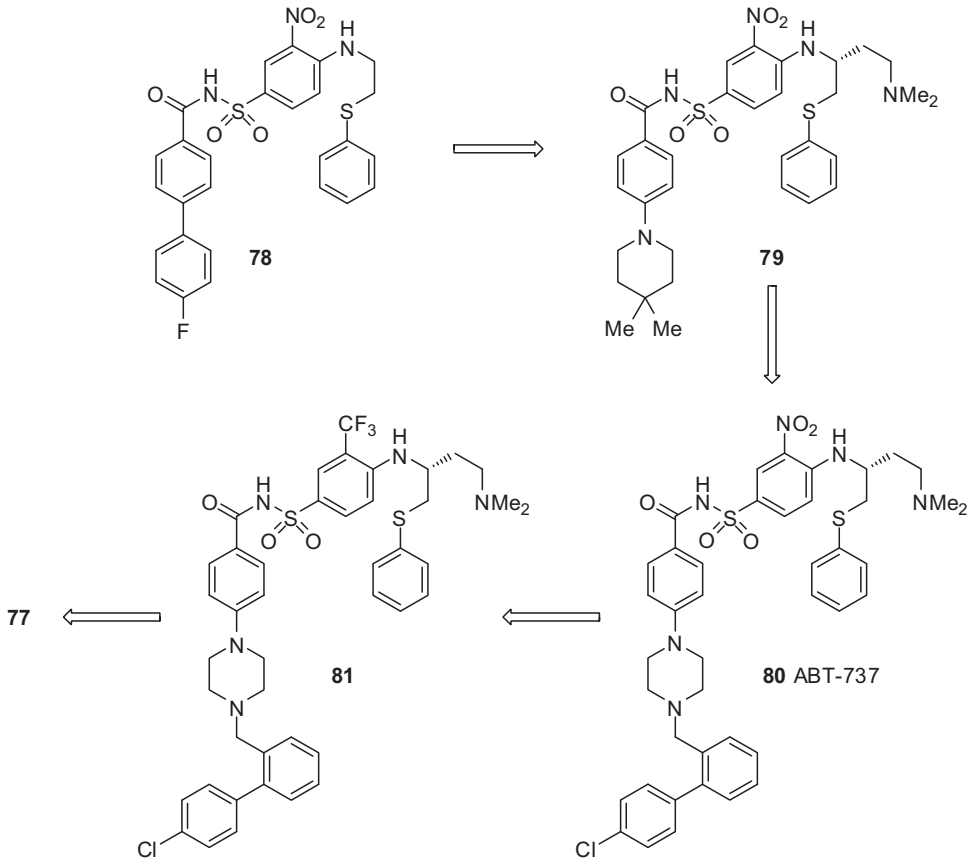
Scheme 23. Preparation process of **69**.

prepared from DMi (**76**) and hydrogen fluoride, the yield of (trifluoromethoxy)benzene **74** approached 99.8% without recourse to special equipment and technique [126]. In this regard, one may agree, that the new methods reviewed in Section 2.6, have some environmental benefits but need to reach a higher level in efficiency and production cost to thump the currently used process presented in Scheme 23.

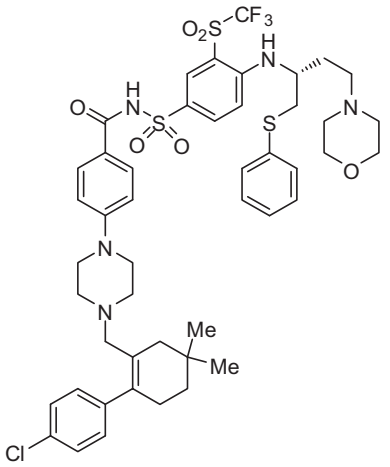
3.2.5. Navitoclax (phase II)

Navitoclax (**77**) (ABT-263; RG-7433) was developed by AbbVie for the potential oral treatment of cancers such as lymphoid malignancies, small-cell lung cancer (SCLC), solid tumors, etc. [127] (Fig. 7). Compound **77** belongs to a type of small-molecule inhibitors of Bcl-2 family proteins (Bcl-2/Bcl-xL/Bcl-$_W$) and elicits complete tumor regressions in SCLC and ALL xenograft models with superior physiochemical and pharmaceutical properties. In April 2013, a phase II clinical trials were initiated in the US in patients with metastatic castrate refractory prostate cancer. The trial is expected to be completed by April 2016 to move to the next clinical trials level.

The general outline of navitoclax **77** development is presented in Scheme 24. The first lead compound **78** was found to bind to a transmembrane protein Bcl-xL (B-cell lymphoma-extra large) with an inhibition constant (K_i) of 36 nM [128]. However, this useful property was significantly diminished in the presence of serum, because of its great affinity for human serum albumin (HAS) domain III [129]. After optimizations of the peripheral positions in **78**, the next lead compound **79** showed higher selectivity for Bcl-xL



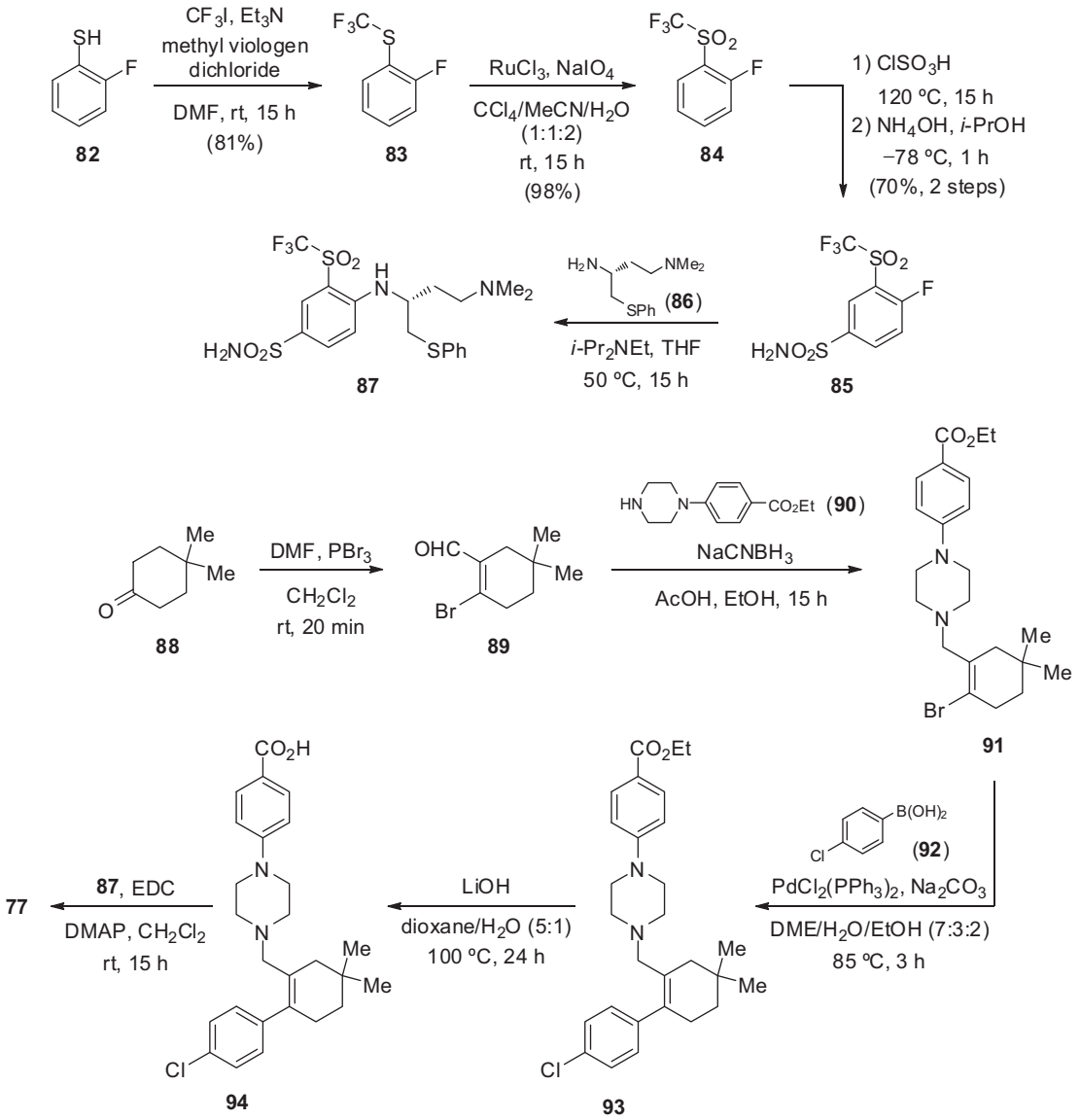
Scheme 24. The R&D process of navitoclax.



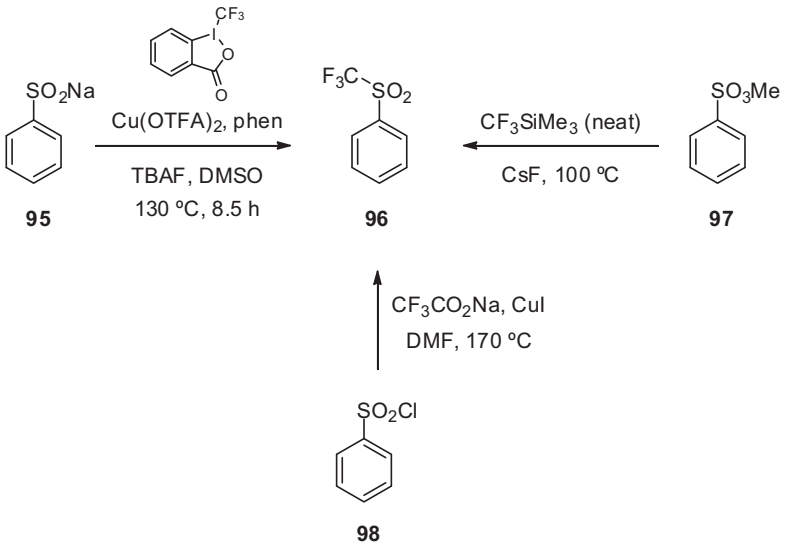
77 navitoclax (ABT-263)

Fig. 7. Structure of navitoclax (ABT-263).

with a K_i of 0.8 nM. In addition, to improve the binding, a lipophilic bi-phenyl group was introduced onto the piperazine, allowing for a deeper access into the well-defined pocket on the protein surface of Bcl-xL/inhibitor complexes. This modification led to the discovery of ABT-737 (**80**) (FL5.12/Bcl-2: EC_{50} = 7.7 nM; FL5.12/Bcl-X_L: EC_{50} = 30 nM; H146/10%HS: EC_{50} = 87 nM) [130]. However, ABT-737 was not orally bioavailable (F = 6%) due to its low aqueous solubility, poor absorption (permeability) and inadequate metabolism [131]. Further research has shown that simply replacing the nitro group in ABT-747 with a trifluoromethyl group (compound **81**) imparted the 16-fold increase in systemic exposure with 24% oral bioavailability. However, compound **81** showed a significant loss of potency (H146/10%HS: EC_{50} = 2.46 uM). The plentiful research data suggested that this loss in potency can be attributed to the less electron-withdrawing property of the CF_3 group as compared with that of the nitro group. This assumption led to an idea to introduce a strongly electron-withdrawing trifluoromethanesulfonyl group which gave the desired biological response. Further optimization included the replacement of one of the phenyls in the bi-phenyl fragment by a gem-dimethylcyclohexene group and the *N*,*N*-di(methyl)amino function by a morpholine ring.



Scheme 25. Synthesis of navitoclax.



Scheme 26. Alternative approaches for preparation of intermediate **96**.

These final steps led to the discovery of navitoclax (**77**) (FL5.12/Bcl-2: EC_{50} = 5.9 nM; FL5.12/Bcl-X_L: EC_{50} = 4.2 nM; H146/10%HS: EC_{50} = 86.7 nM).

The synthesis of navitoclax is shown in Scheme 25 [131]. The key trifluoromethylation step of commercial 2-fluorobenzenethiol **82** was conducted under radical conditions, using inexpensive trifluoromethyl iodide, giving rise to the product **83** in good 81% yield. Intermediate **83** was next oxidized to corresponding sulfone **84** with application of $RuCl_3$ as catalyst and $NaIO_4$ as oxidant. The sulfone **84** was heated with chlorosulfonic acid followed by the treatment with ammonium hydroxide to give sulfonamide **85**. Compound **87** was prepared through nucleophilic aromatic substitution of the fluorine in **85** with the chiral amine **86**. In a parallel line, treatment of cyclic ketone **88** with PBr_3 and DMF led to aldehyde **89**. The reductive amination of **89** and piperazine **90** in the presence of $Na(CN)BH_3$ afforded compound **91**, which was coupled with boronic acid **92** and after that hydrolyzed under basic condition to give benzoic acid **94**. Finally, sulfonamide bond formation, in the presence of EDC and DMAP, between benzoic acid **94** and sulfonamide **87** afforded the targeted product **77**.

It might be of interest to discuss that the trifluoromethylation step could be conducted in many other ways (Scheme 26). One of the approaches is based on an efficient copper-catalyzed protocol for the electrophilic trifluoromethylation of benzenesulfinate **95** with Togni's reagent [132]. The second method involves a CsF-catalyzed, nucleophilic trifluoromethylation of methyl benzenesulfonate **97** with CF_3SiMe_3 [133]. In the third approach, a concise and convenient method for the trifluoromethylation of benzenesulfonyl chloride **98** with commercially available sodium trifluoroacetate was reported by Chang and Cai [134]. In this regard, alternative conditions for the radical trifluoromethylation using CF_3I should be mentioned [135].

4. Conclusions

As one can see from this short review, the current methodological field of trifluoromethylation is not evenly represented form the structural standpoint. Some greater progress achieved in the areas of aromatic and heterocyclic trifluoromethylation corresponds to a greater proportion of CF_3-aromatic/heterocyclic drugs on the market and under development. We trust that the new drug candidates profiled in this review will help the practitioners in this field to pick up the structural trends and focus their innovative activity on the less developed approaches. With the ever increasing understanding and refining the relationships between structural type of fluorination and bioactivity, there will be escalating demand for innovation and discoveries in the fluorine chemistry. Noticeable advances in the drugs' potency and novel therapeutic areas most likely will call for new structural features and types of fluorination. In particular, structural diversity of the CF_3-containing drugs is of great current demand which will continue to fuel truly excited current state of research activity in the area of trifluoromethylation. The noble efforts by fluorine chemists developing trifluoromethylation methods are being continuously rewarded by the development of enhanced drugs that would be helpful to many patients in critical need for new treatments.

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