

ADVANCES IN THE SYNTHESIS AND KINASE INHIBITORY POTENCIES OF NON-FUSED INDAZOLE DERIVATIVES

Francis Giraud, Fabrice Anizon and Pascale Moreau

Clermont Université, Université Blaise Pascal, Institut de Chimie de Clermont-Ferrand,

BP 10448, 63000 Clermont-Ferrand, France.

CNRS, UMR 6296, ICCF, BP 80026, 63171 Aubière, France

(e-mail: pascale.moreau@univ-bpclermont.fr)

Abstract. *The indazole scaffold is frequently found in biologically active compounds. Due to the high potential of this heteroaromatic moiety we report in this review on the recent advances in the synthetic methods used to prepare non-fused indazole derivatives, as well as the kinase inhibitory potencies of non-fused analogues reported in the non-patent literature from 2010 to the end of 2013.*

Contents

1. Introduction
2. Synthetic approaches to indazole scaffold
 - 2.1. Introduction
 - 2.2. [3+2] cycloadditions
 - 2.3. From carbonylated benzenes and their hydrazone/oxime/imine derivatives
 - 2.4. From *ortho*-halobenzonitriles
 - 2.5. From azobenzene derivatives
 - 2.6. From aryltriazenes
 - 2.7. From *ortho*-nitrobenzylamines
 - 2.8. Miscellaneous
3. Kinase inhibitory potencies of various non-fused indazoles
 - 3.1. AGC group (protein kinases A, G and C containing families)
 - 3.2. CAMK group (calcium/calmodulin-dependent protein kinases)
 - 3.3. CMGC group (including CDKs, MAPK, GSK3 and CLK containing families)
 - 3.4. STE group (containing the homologs of yeast Sterile 7, 11 and 20 kinases)
 - 3.5. TK group (tyrosine kinases)
 - 3.6. Other kinases
4. Conclusions
- References

1. Introduction

The indazole moiety is clearly identified as a highly valuable heterocyclic scaffold for the development of new biologically active compounds. More particularly, like many other nitrogen-containing heteroaromatic derivatives, the indazole moiety could be considered as a surrogate of the adenine of ATP, the shared natural substrate of protein kinases and thus, be used for the identification of new ATP-

competitive kinase inhibitors. Protein kinases belong to the transferase group and allow the phosphorylation of the hydroxyl group of serine, threonine or tyrosine residues of protein substrates. To date, the human kinome is composed of 518 protein kinases that are divided in eight main groups according to their structure and functions (AGC, CAMK, CK1, CMGC, STE, TK, TKL and others). Protein kinases, which are involved in many cellular processes, represent interesting targets for the development of new therapies for pathologies such as cancer, diabetes, obesity, neurodegenerative diseases, inflammatory diseases, atherosclerosis and stroke. In 2001, Imatinib/Gleevec[®] was the first protein kinase inhibitor to reach the market and thus constitute the proof of concept that targeting kinases could lead to new cancer therapies. Since this date, numerous research programs have focused on the discovery of kinase inhibitors useful to elaborate new targeted therapies. Numerous indazole derivatives have been described as kinase inhibitors and two of them, showing tyrosine kinase inhibitory potencies, are now on the market: Axitinib for the treatment of advance renal cell carcinoma (RCC) and Pazopanib for RCC and advance soft tissue carcinoma (Figure 1). Thus, as part of our ongoing studies concerning the identification of new heteroaromatic scaffolds as potent kinase inhibitors, we recently developed a research program focused on the synthesis and identification of new indazole derivatives showing Pim kinase inhibitory potencies (Figure 1).¹⁻⁵

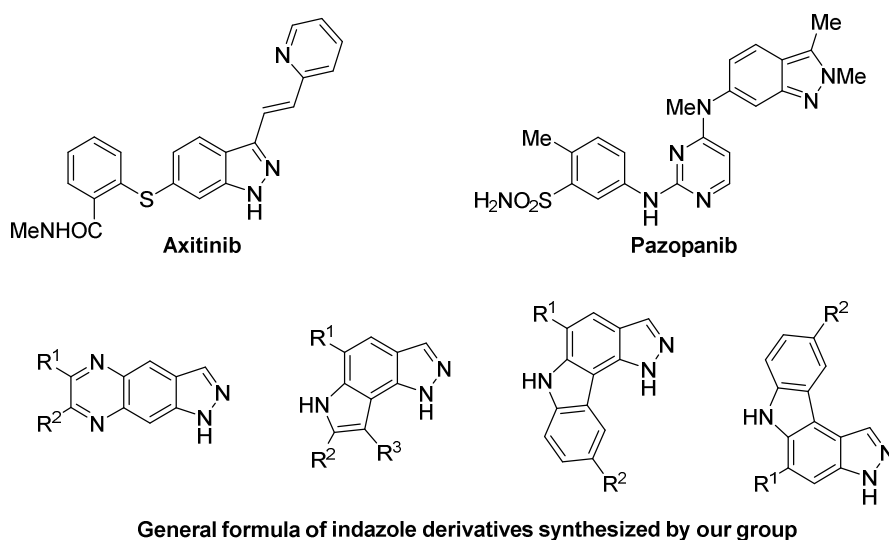


Figure 1. Structure of Axitinib and Pazopanib and various indazole derivatives identified by our group as kinase inhibitors.

Regarding the relevance of indazole derivatives as kinase inhibitors, these compounds could also be considered as useful molecular biological tools to study the cellular implication of identified cellular target and/or to allow the development of new drugs. In the following sections we will describe the recent advances in the synthetic approaches allowing the formation of the indazole ring system, and the structure and kinase inhibitory potencies of recently reported indazole-containing kinase inhibitors.

2. Synthetic approaches to indazole scaffold

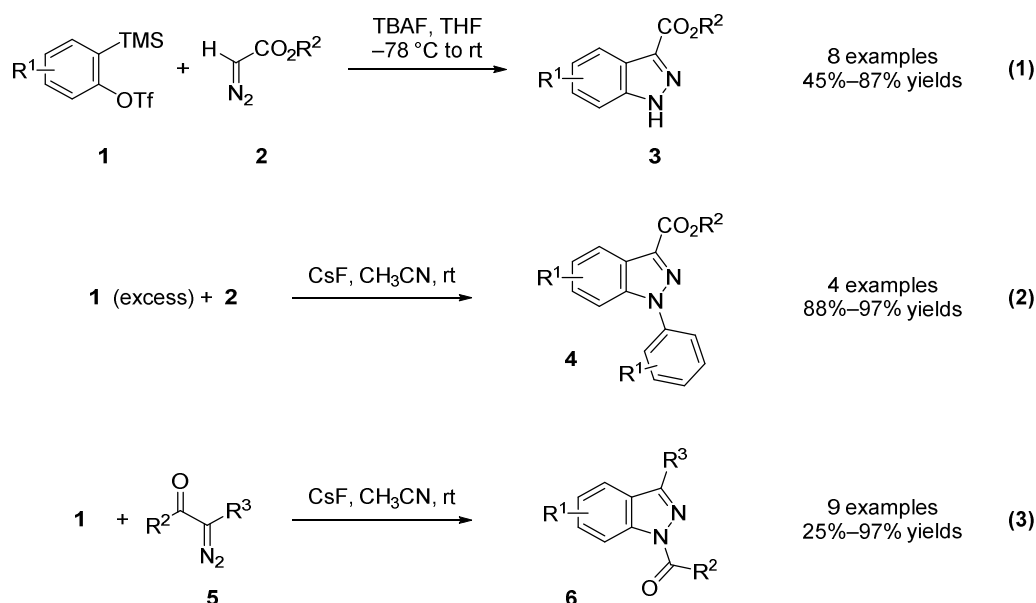
2.1. Introduction

A number of synthetic approaches leading to indazole derivatives have been reported so far and an account of the advances in the chemistry of indazoles was previously published.⁶ Synthetic methods for the

construction of the indazole ring system, mainly developed for 1*H*-indazoles, proved to be useful for the preparation of a number of diversely substituted indazole derivatives, finding applications in domains such as the synthesis of biologically active compounds. However, last years have seen the emergence of new strategies, for the construction of 1*H*-indazoles, as well as for the preparation of 2*H*-indazoles that previously remained limited. These novel synthetic methods provide additional opportunities for the preparation of diversely substituted indazoles at the pyrazole moiety (*i.e.* N1/N2 and C3 positions) or fused benzene ring (*i.e.* C4–C7 positions). The present review reports on the recent advances in the synthesis of non-fused indazole nucleus that have not been reported in the previous account.

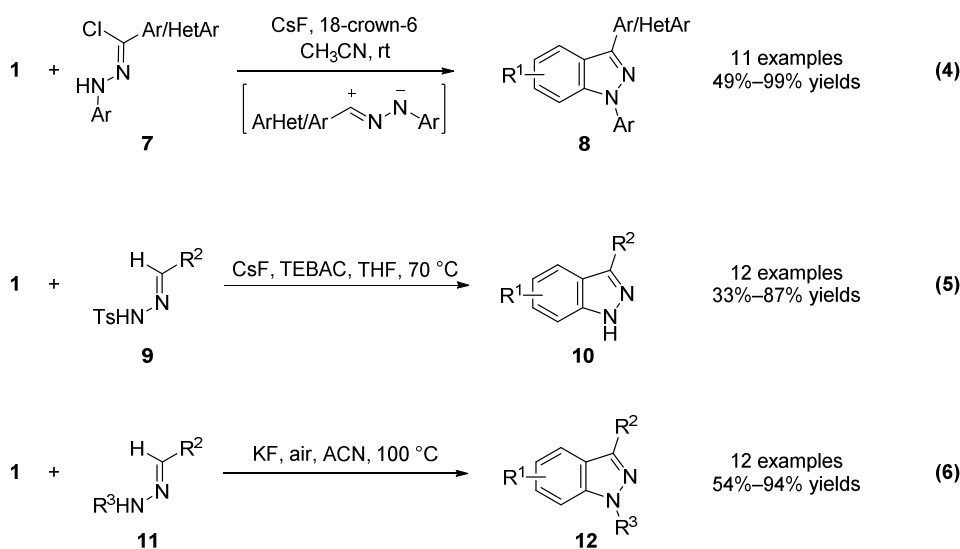
2.2. [3+2] Cycloadditions

Following Yamamoto's work on the 1,3-dipolar cycloaddition of arynes with diazomethane derivatives,⁷ Larock also reported the preparation of 1*H*-indazoles from benzyne under mild reaction conditions (Scheme 1).⁸ When monosubstituted alkyl diazoacetates **2** were studied, indazole N1 atom could be substituted either by a hydrogen atom (**3**, Eq. (1)) or by an aryl group in the presence of an excess of benzyne precursor **1** (**4**, Eq. (2)). Liu showed recently that the regioselectivity of the *N*-arylation reaction with the second benzyne intermediate can be modified in the presence of Ag(I) ions, leading to 2*H*-indazole derivatives.⁹ Larock and co-workers also carried out [3+2] cycloadditions with disubstituted diazo compounds **5** with a carbonyl group attached to the diazo carbon.⁸ The migration of the acyl group leading to 1-acyl-1*H*-indazoles **6** was observed (Eq. (3)). Another recent example of preparation of 1*H*-indazoles from diazo compounds used 1,1-disubstituted-2-diazo-2-(trimethylsilyl)ethanol derivatives, leading to 3-(1-hydroxyalkyl)-1*H*-indazoles.¹⁰ More recently, it was shown that the regioselectivity of the [3+2] cycloaddition between benzyne and diazo compounds can be controlled by the presence at the 3-position of the benzyne intermediates of boryl or silyl substituents.¹¹



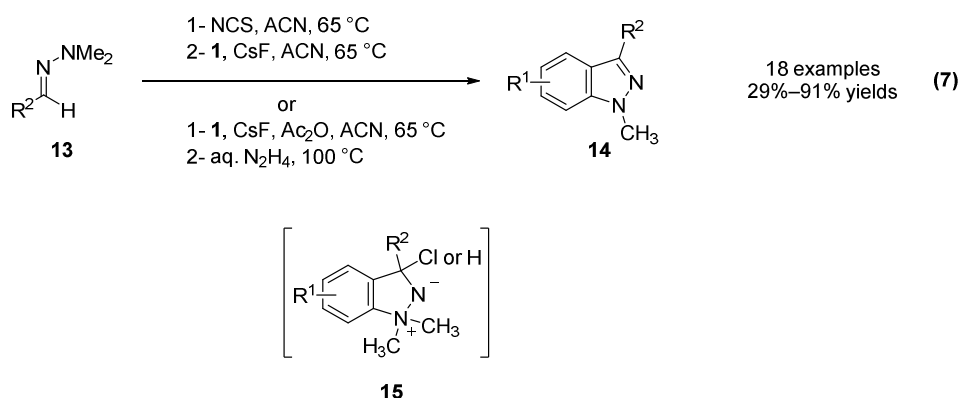
Dipolar cycloaddition between arynes and *in situ* generated nitrile imines from hydrazone chlorides **7** also provided 1*H*-indazoles¹² (Scheme 2, Eq. (4)). An additional approach from hydrazones and benzyne

precursors **1** was recently reported (Eq. (5) and (6)).^{13,14} *N*-Tosylhydrazones **9** in the presence of CsF and phase transfer catalyst TEBAC, yielded 3-substituted 1*H*-indazole **10** (Eq. (5)), whereas hydrazones **11** led to 1,3-disubstituted 1*H*-indazoles (Eq. (6)). Depending on the reaction conditions used, different mechanistic pathways were proposed. The indazole synthesis from **1** and *N*-tosylhydrazones **9** probably involved a diazo intermediate whereas the mechanism leading to **12** remained unclear. The preparation of 1*H*-indazoles from **9** using CsF and TEBAC could also be performed from *o*-trimethylsilylaryl imidazolylsulfonates benzyne precursors.¹⁵



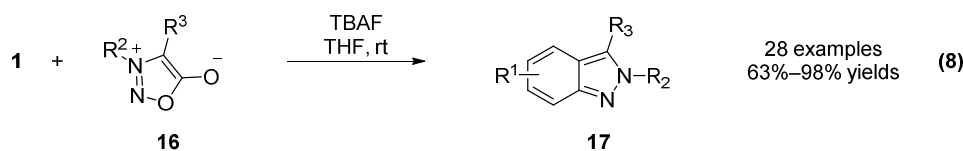
Scheme 2

Larock and co-workers also found that the reaction of 1,1-dialkylhydrazones such as **13** with benzyne afforded 1-alkyl-1*H*-indazoles **14**, employing two different procedures indicated in Scheme 3.^{16,17,18} In both cases the reaction involved the formation of a cyclic intermediate **15**.



Scheme 3

Diversely substituted 2*H*-indazoles **17** can also be synthesized by [3+2] cycloaddition between benzyne and sydnone **16** as 1,3-dipoles and subsequent extrusion of CO₂ (Scheme 4).^{19,20} More recently, thiazolidine-derived sydnone were used in dipolar cycloadditions with benzyne to generate benzodiazafulvenium methides.²¹ These intermediates further reacted in [4+2] cycloaddition with maleimides to give 1,3-disubstituted-1*H*-indazoles or yielded 2,3-disubstituted-2*H*-indazoles after sigmatropic [1,8]H shifts.

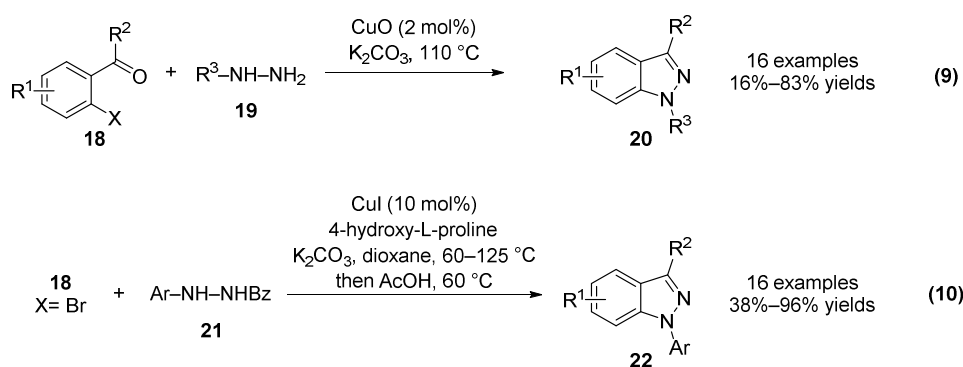


Scheme 4

Finally, the synthesis of 4,7-dihydroxy-1*H*-indazoles has been reported from phenol derivatives and *N*-tosylhydrazones.²² The reaction involved a [3+2] cycloaddition of a benzoquinone intermediate formed in the presence of PIDA with the diazo intermediate derived from the tosylhydrazone in the presence of a base.

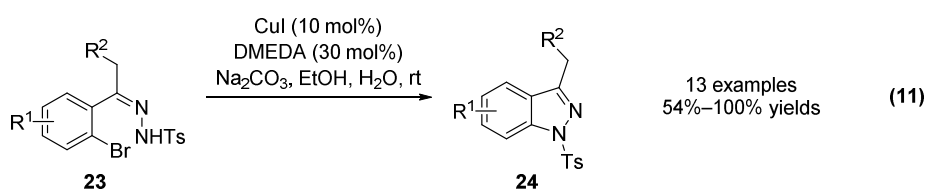
2.3. From carbonylated benzenes and their hydrazone/oxime/imine derivatives

The preparation of indazole from *ortho*-carbonylated aryl halides and hydrazines is a general route that was previously explored. New reaction conditions involving copper-catalyzed *N*-arylation of hydrazines and a following cyclization/condensation have been recently developed. For example, a variety of 1-alkyl- and 1-aryl-1*H*-indazoles **20** were prepared using CuO as a catalyst from ketone or carboxylic acid derivatives **18** and hydrazines **19** (Scheme 5, Eq. (9)).²³ 3-Hydroxy-1*H*-indazoles were obtained when *o*-halobenzoic acids **18** were used in this synthesis. More recently, another one-pot process led to a series of diversely substituted 1-arylidazole products **22** from *o*-carbonylated aryl bromides in the presence of CuI and 4-hydroxy-L-proline as a ligand (Eq. (10)).²⁴ Similar palladium-catalyzed indazole synthesis from *o*-chlorobenzaldehyde has also been developed.²⁵



Scheme 5

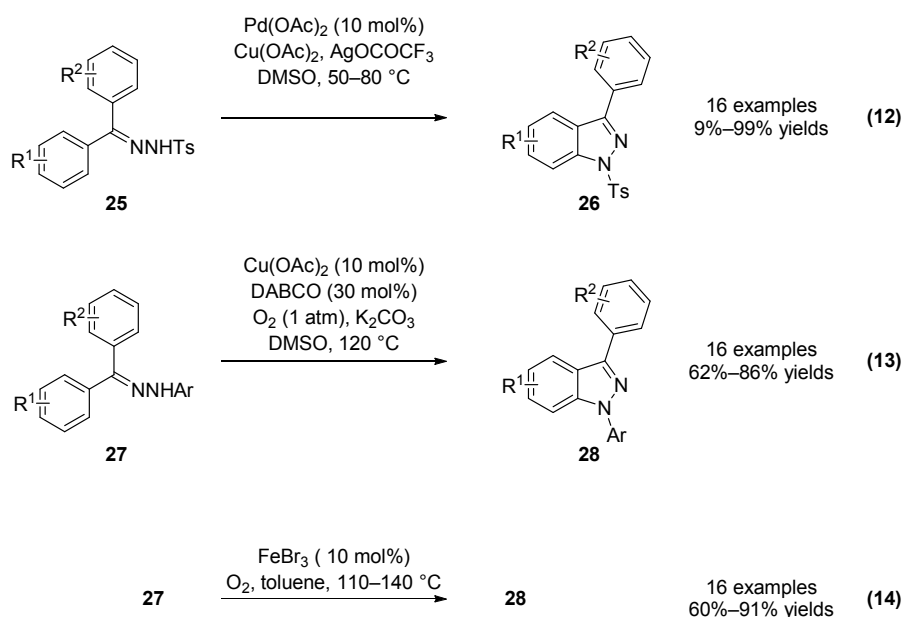
Ortho-carbonylated aryl halides were also used as starting materials to prepare the corresponding hydrazones, which were further used to synthesize indazoles. Following the work performed by Inamoto²⁶ and Venkateswarlu²⁷ under palladium catalysis, copper iodide was used as a catalyst to afford 1-tosyl-1*H*-indazoles **24** from (*Z*)-tosylhydrazones of *o*-bromoacetophenone derivatives. Products **24** were substituted at the 3-position by either methyl²⁸ or aminomethyl²⁹ groups (Scheme 6).



Scheme 6

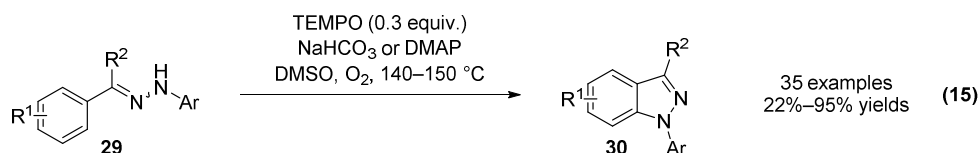
Interestingly, Bolm and co-workers showed that the synthesis of indazoles from *Z*-*o*-bromoacetophenone tosylhydrazones could be carried out under copper-free conditions using DMEDA or *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine and potassium carbonate in toluene at room temperature.³⁰ Other reports described the cyclization of arylhydrazones obtained from *ortho*-carbonylated aryl halides under copper or iron catalysis.^{31,32}

Recent advances have been made in C–H functionalization reactions using various *ortho*-directing groups. More particularly, different synthetic approaches for C–H amination/amidation reactions of benzophenone hydrazones were reported.^{33,34,35} The reactions afforded 3-aryl-1*H*-indazoles and have been performed under Pd-, Cu-, or Fe-catalysis (Scheme 7, Eq. (12), (13), (14)).



Scheme 7

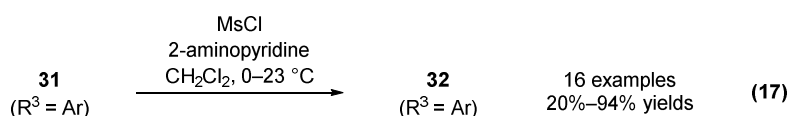
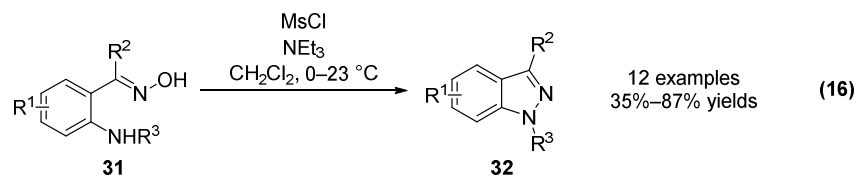
Besides these metal catalyzed C–N bond formation reactions, a transition-metal-free aerobic oxidative C–N coupling was recently reported.³⁶ Thus, diversely substituted 1*H*-indazoles **30** were obtained from phenylhydrazones **29** derived from carbonylated aryl compounds. The proposed mechanism involves the formation of a nitrenium radical intermediate which undergoes intramolecular C–N bond formation (Scheme 8).



Scheme 8

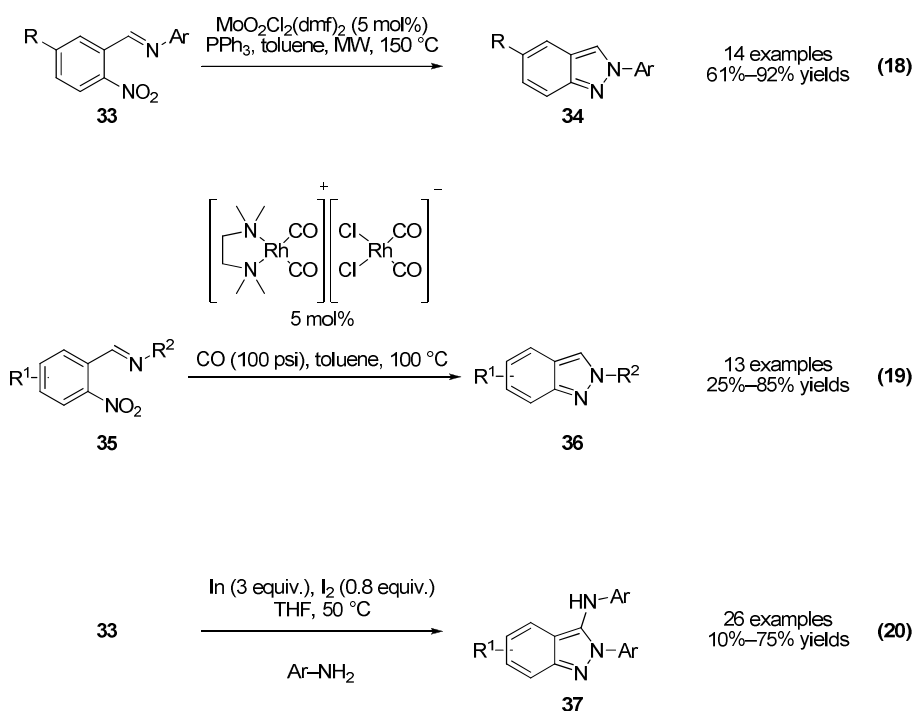
Stambuli and co-workers reported the synthesis of 1*H*-indazoles starting from *o*-aminobenzoximes **31** which were selectively activated by methanesulfonyl chloride in the presence of the amino group (Scheme 9, Eq. (16) and (17)).^{37,38} The synthesis of *N*-aryl-1*H*-indazoles (**32**, $\text{R}^3 = \text{Ar}$, Eq. (17)) was promoted by the use of 2-aminopyridine as a base, whereas triethylamine favored the formation of benzimidazoles.³⁸ A

related indazole synthesis was recently published in which the oxime was activated by the use of triphenylphosphine, I₂ and imidazole.³⁹ No activating agent was required in the case of indazolization involving a *o*-dialkylaminobenzoxime prepared from the corresponding aldehyde and hydroxylamine hydrochloride.⁴⁰



Scheme 9

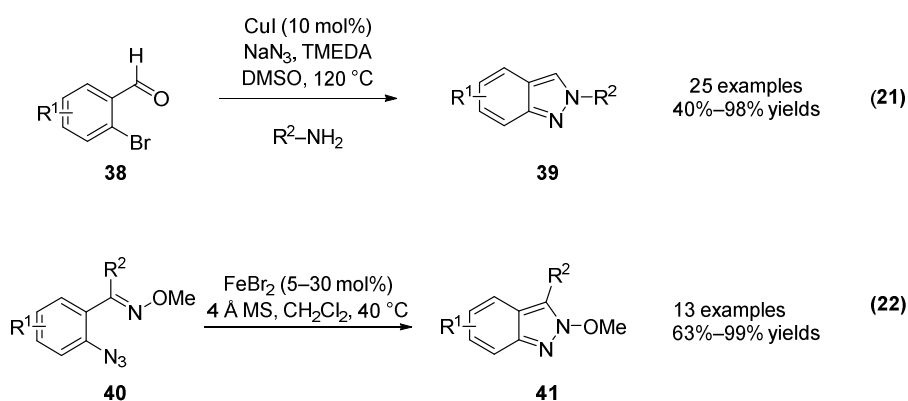
Ortho-nitrobenzaldehyde imine derivatives can undergo reductive heterocyclization to afford 2*H*-indazoles (Scheme 10). For example, a molybdenum-catalyzed preparation of 3-unsubstituted-2-aryl-2*H*-indazoles **34** under microwave irradiation was recently reported (Eq. (18)).⁴¹ Among other recent methods described, a rhodium-catalyzed reductive heterocyclization of imines **35** led to a series of 2*H*-indazoles **36** diversely substituted at the 2-position (Eq. (19))⁴², and the use of indium and iodine in the presence of the parent aniline led to 2-aryl-3-arylamino-2*H*-indazoles **37** (Eq. (20)).⁴³ This indium-mediated reductive reaction was also reported as a one-pot procedure directly starting from benzaldehyde derivatives.⁴³



Scheme 10

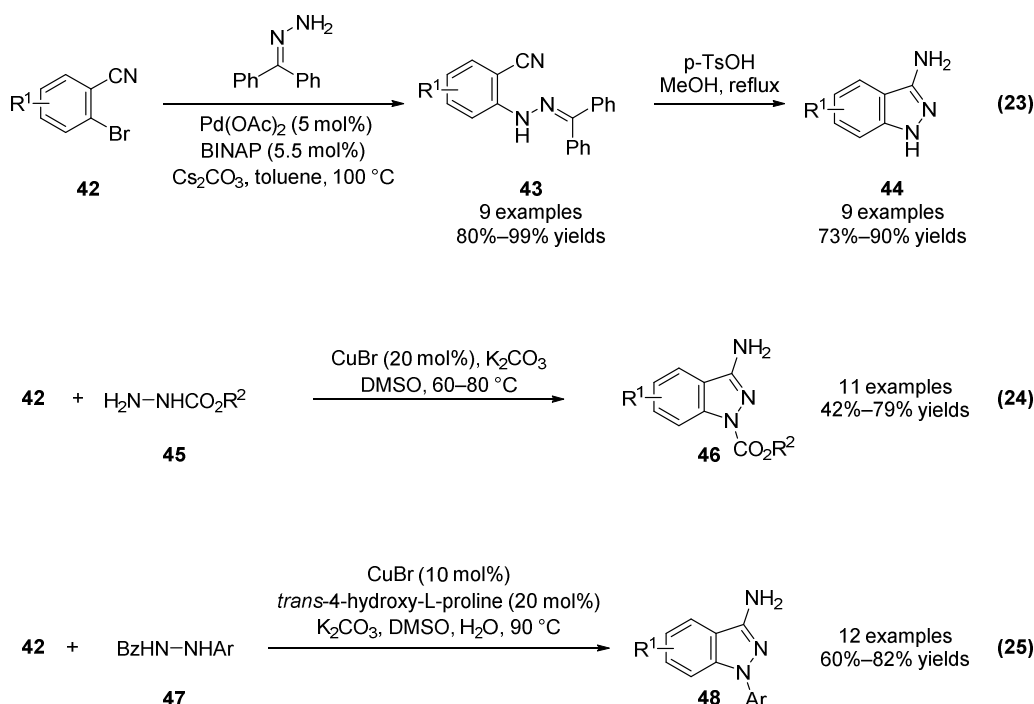
A novel three-components method for the preparation of 2*H*-indazoles has been reported from 2-bromobenzaldehydes **38**, primary amines and sodium azide under copper catalysis (Scheme 11, Eq. (21)).⁴⁴

The proposed mechanism involves the imine formation, copper-catalyzed substitution of the bromine atom by the azido group and indazole formation from the 2-azidobenzylidene amine intermediate with extrusion of N₂. Recently, it was shown that this three-component synthesis could be performed from either 2-bromobenzaldehyde or 2-chlorobenzaldehyde in the presence of copper(I) oxide nanoparticles in polyethylene glycol.⁴⁵ Analogous indazole preparations were also reported by Rao *et al.* from 2-azidobenzaldehydes in the presence of CuI⁴⁶ and by Driver and co-workers from (*E*)-2-azidobenzylidene methoxyamines **40** under FeBr₂ catalysis (Eq. (22)).⁴⁷



2.4. From *ortho*-halobenzonitriles

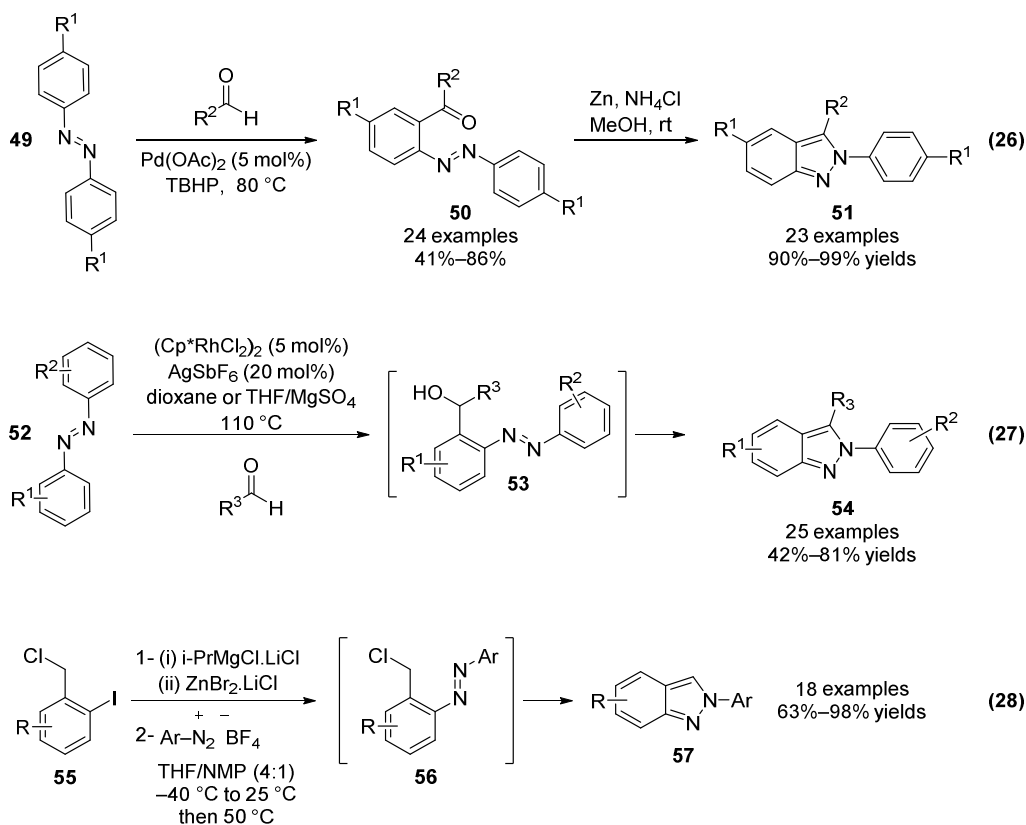
The access to 3-amino-1*H*-indazole derivatives is an important goal due to the potential biological activity of this scaffold. A general route to 3-aminoindazoles involves the reaction between 2-halobenzonitriles and hydrazine *via* nucleophilic aromatic substitution and cyclization. However, many efforts have been devoted to improve the access to 3-aminoindazole derivatives from the same substrates, more particularly by the use of transition metals to catalyze the initial C–N bond formation.



Thus, 3-amino-1*H*-indazole derivatives **44** were obtained *via* a palladium-catalyzed arylation of benzophenone hydrazone with *o*-bromobenzonitriles **42**, and subsequent acidic deprotection/cyclization sequence (Scheme 12, Eq. (23)).⁴⁸ The authors also showed that the selective preparation of 1-alkyl-3-amino-1*H*-indazoles could be performed by the *N*-alkylation of intermediate **43** prior to pyrazole nucleus formation. Using a CuBr-catalyzed coupling/condensation process from **42** and hydrazine derivatives **45** or **47**, Ma and co-workers obtained 3-amino-1*H*-indazole carbamates **46** or N1-aryl analogs **48** (Eq. (24) and (25)).⁴⁹

2.5. From azobenzene derivatives

Azobenzene derivatives are useful for the preparation of 2*H*-indazoles when an electrophilic carbon atom such as a carbonyl group is present at the *ortho*-position. Thus, the preparation of acylated azobenzenes is an important field that was developed recently, using palladium-catalyzed C–H functionalization of azobenzenes.^{50,51,52} Subsequent reduction, using Zn/NH₄Cl^{50,51} or Cu₂Cl₂/NaBH₄⁵², afforded the target 2*H*-indazole ring system. For example, acylated azobenzene derivatives **50**, prepared from **49** and aromatic or aliphatic aldehydes, produced 2-aryl-2*H*-indazoles **51** in the presence of Zn/NH₄Cl in methanol⁵⁰ (Scheme 13, Eq. (26)).

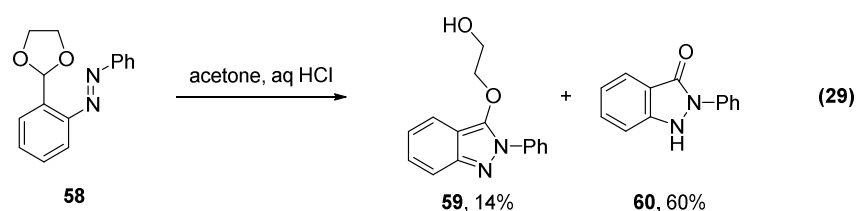


Scheme 13

Another recent example involving azobenzene derivatives was reported by Lavis and Ellman (Eq. (27)).⁵³ The authors described a one-pot preparation of 2*H*-indazoles **54** *via* a rhodium(III)-catalyzed *ortho*-C–H bond addition of azobenzenes **52** to aldehydes. This coupling led to the generation of an alcohol intermediate **53** which produced 2*H*-indazoles after intramolecular nucleophilic substitution and

aromatization. Indazoles **54** substituted at the 2-position by a 4-hydroxy-3,5-dimethylphenyl group were subjected to an oxidative cleavage in the presence of ceric ammonium nitrate to provide the corresponding *1H*-indazoles. Another preparation of 2-aryl-*2H*-indazoles *via* azobenzene intermediates was also reported by Knochel and co-workers (Eq. (28)).⁵⁴ 2-Chloromethylaryl zinc reagents were prepared from compounds **55** and added to phenyldiazonium salts. The proposed mechanism involves the formation of an azobenzene intermediate **56**, bearing a chloromethyl group at the *ortho*-position, that cyclizes by intramolecular nucleophilic substitution at the benzylic carbon atom to give *2H*-indazoles **57**.

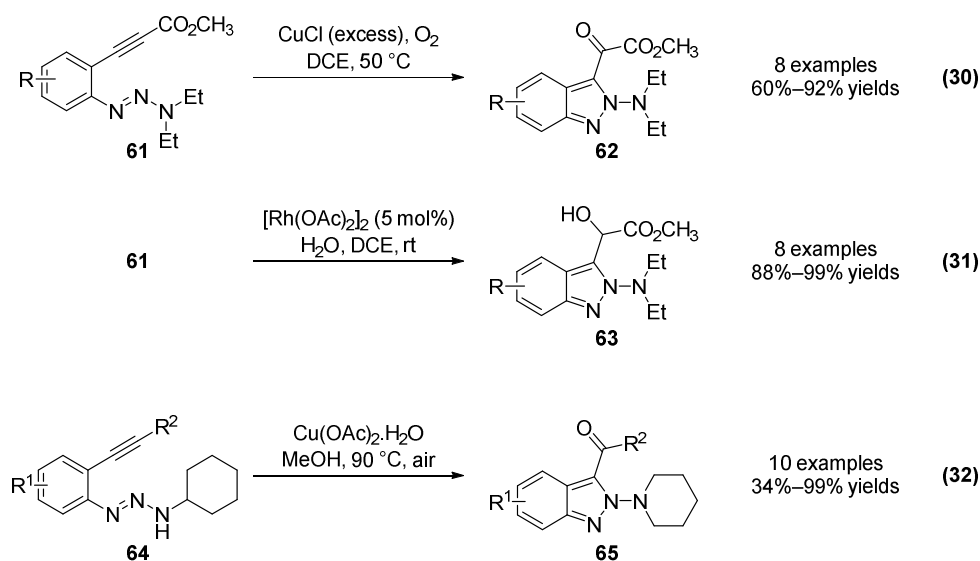
Finally, it has also been shown that the carbonyl electrophile generated under acidic conditions from the ethyleneglycol acetal **58** can be attacked by the azo group to afford *2H*-indazole **59** and 2-phenyl-1,2-dihydroindazol-3-one **60** (Scheme 14).⁵⁵



Scheme 14

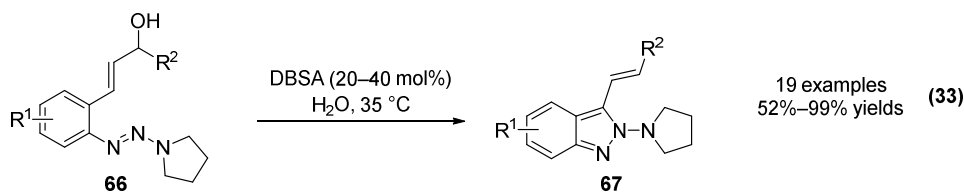
2.6. From aryltriazenes

The cyclization of *o*-alkynylphenyltriazenes is another access to *2H*-indazoles that was previously reported.⁶ An extension of the work performed by Haley and co-workers involved the cyclization of *o*-alkynylphenyltriazenes **61**.⁵⁶ Cu(I) or Rh(II) mediated cyclization and trapping of the carbene intermediate in different conditions yielded various *2H*-indazoles **62** and **63** (Scheme 15, Eq. (30) and (31)). Recently, Yu and Huang described the preparation from *o*-alkynylphenyltriazenes of a series of 3-acyl-2-(piperidin-1-yl)-*2H*-indazoles **65** under Cu(II) catalysis (Eq. (32)), whereas indoles were obtained by the use of silver acetate.⁵⁷ The authors suggested that this Cu(II)-mediated indazolization would not occur *via* a carbene intermediate. 3-Benzoyl-*1H*-indazole was also obtained after oxidative cleavage of the piperidinyl group of compound **65** ($R^1 = H$, $R^2 = Ph$) using ceric ammonium nitrate.



Scheme 15

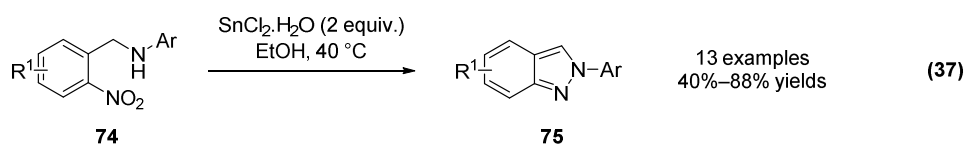
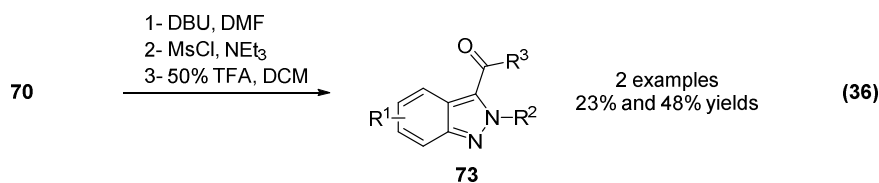
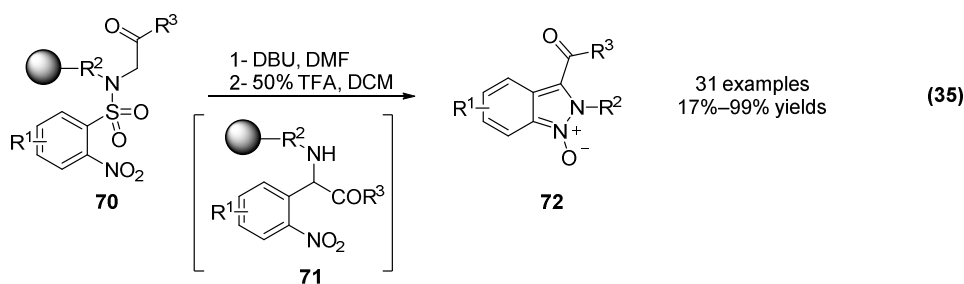
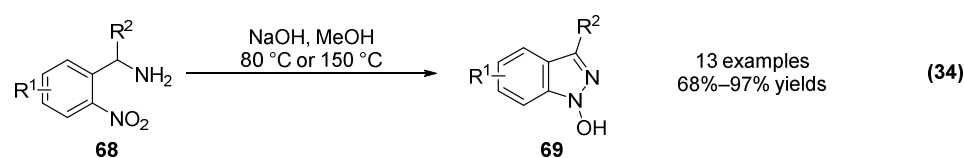
Triazenylphenyl allylic alcohols **66** were also reported as starting materials for the preparation of 3-alkenyl-2*H*-indazoles **67** (Scheme 16).⁵⁸ The reaction was performed in the presence of dodecyl benzenesulfonic acid (DBSA). This work was extended by the removal of the pyrrolidine protecting group using Zn/AcOH to afford the corresponding 3-alkenyl-1*H*-indazoles.



Scheme 16

2.7. From *ortho*-nitrobenzylamines

The cyclization of 2-nitrobenzylamines is another route to substituted 2*H*-indazoles that has been described. As previously reported by Kurth and co-workers, treatment of secondary 2-nitrobenzylamines in alcoholic potassium hydroxide solution led to 3-alkoxy-2*H*-indazoles.^{59,60} It was next shown that this method could serve for the preparation of indazol-3-ones.^{61,62,63} It was also reported that the use of DBU in anhydrous THF led to some 3-amino-2*H*-indazoles.⁶⁴

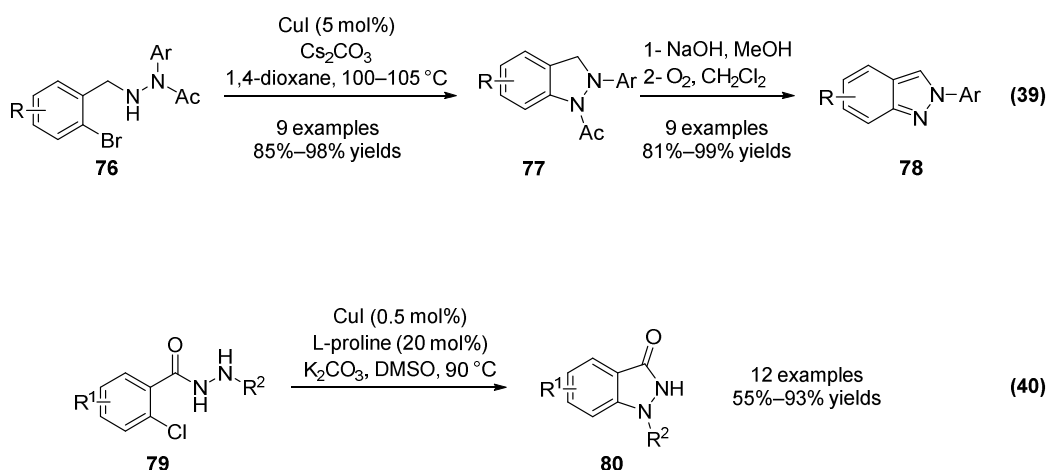


Scheme 17

Other authors showed that primary 2-nitrobenzylamines **68** could also cyclize in methanolic sodium hydroxide solution to afford 1-hydroxyindazoles **69** (Scheme 17, Eq. (34)).⁶⁵ Another method involved the preparation of 3-acyl-2-alkyl-2*H*-indazol-1-oxides **72** and 2*H*-indazoles **73** on solid phase from 2-nitrobenzenesulfonamide derivatives **70** (Eq. (35) and (36)).⁶⁶ This procedure involved the formation of a 2-nitrobenzylamine intermediate **71**. The use of reductive conditions from 2-nitrobenzylamine derivatives was also reported to produce 2*H*-indazole derivatives. Thus, stannous chloride or low-valence titanium reagent in the presence of triethylamine led to 2-aryl-2*H*-indazoles (Eq. (37), (38)).^{67,68} Similar conditions using low-valence titanium reagent from *o*-nitrobenzanilide produced 2-arylindazol-3-ones.⁶⁹

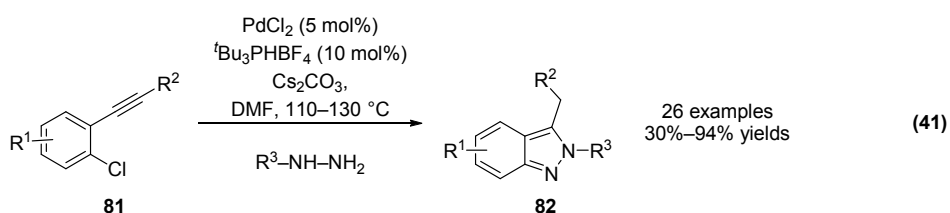
2.8. Miscellaneous

N'-(*o*-bromobenzyl)acetylhydrazines were also used for the preparation of 2*H*-indazoles *via* a Cu(I) catalyzed amidation (Scheme 18 Eq. (39)),⁷⁰ leading to a dihydroindazole product **77**. 2-Aryl-2*H*-indazoles **78** were obtained after acetyl cleavage and aromatization. Copper(II)-catalysis was also recently used for the cyclization of *ortho*-halobenzhydrazides such as **79** to yield 1-substituted indazol-3-ones **80** (Eq. (40)).^{71,72} A series of 1,2-disubstituted indazol-3-ones was also prepared under copper or palladium catalysis from the same type of substrate obtained by an Ugi reaction.⁷³



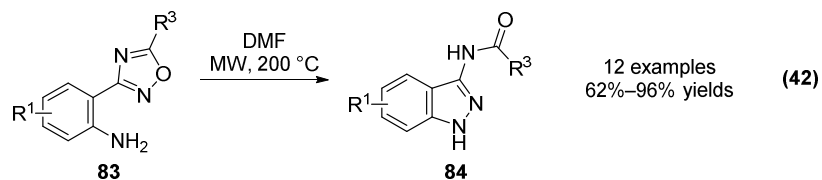
Scheme 18

Hydrazines are an important source of nitrogen atoms for the formation of 1*H*-indazoles. Isomeric 2*H*-indazoles were also prepared using hydrazines as the nitrogen source, from 2-chlorophenylacetylenes **81** under palladium catalysis (Scheme 19).⁷⁴ The reaction proceeds *via* a domino sequence involving a regioselective coupling of the hydrazine to the 2-chloroacetylene, hydroamination and isomerization to 2*H*-indazole **82**.



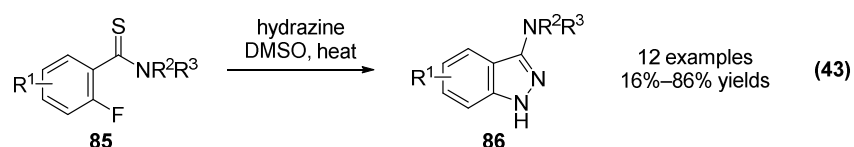
Scheme 19

Recently, Ott *et al.* revisited the preparation of 3-acylaminoindazoles *via* an oxadiazole intermediate (Scheme 20).⁷⁵ A range of products were prepared without substitution at the N1 position. An extension of this methodology directly produced the target compounds from 2-amino-*N*-hydroxybenzamidines and ethyl esters under microwave irradiation.



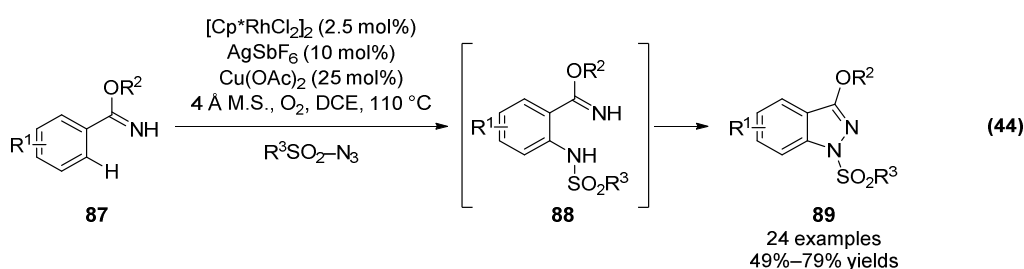
Scheme 20

Another strategy leading to 3-aminoindazoles **86** has been developed in the absence of metal catalysis from hydrazine *o*-fluoroarylthioamide derivatives **85** that were prepared from the corresponding *o*-fluorobenzoic acids (Scheme 21).⁷⁶



Scheme 21

As indicated above, hydrazones have been used as directing groups for C–H amination/amidation reactions (Schemes 7 and 8). Similarly, alkyl benzenecarboximidates **87** have also been used as directing groups for the Rh(III)-catalyzed C–H activation/amidation using arylsulfonylazides (Scheme 22).⁷⁷ The generated 2-(arylsulfonylamino)benzenecarboximidate intermediate **88** could subsequently afford 3-alkoxy-1*H*-indazole **89** by N–N bond formation under Cu(II) catalysis.



Scheme 22

Besides the methods mentioned above for the preparation of diversely substituted 1*H*- or 2*H*-indazoles, some authors reported the formation of indazoles through various pathways. For example, 2*H*-indazoles were obtained *via* Masamune-Bergman cycloaromatization from 3,4-dialkynylpyrazoles.⁷⁸ 1*H*-Indazole was obtained in 82% yield from 2-aminobenzylamine under oxidative conditions by using H₂O₂/Na₂WO₄.⁷⁹ Others reported the construction of the indazole moiety through photochemical transformation of 1,2-dimethyl-2-(2-nitrophenyl)-2,3-dihydro-1*H*-perimidinone⁸⁰, pyrolysis of 2-aryl-1,2,3,4-tetrazoles⁸¹ or tetrazolo[1,5-*a*]quinazolinone⁸², or rearrangement of aryliminodiaziridines.^{83,84}

3. Kinase inhibitory potencies of various non-fused indazoles

Indazole derivatives have been described as inhibitors of nearly all groups of protein kinases. Most of them interact within the ATP-binding pocket with the indazole moiety being involved in the molecular interactions with the targeted kinase. One of the most difficult challenges to address in the development of kinase inhibitors is the selectivity in regards to the entire kinome, especially for ATP-competitive ones. However, as it will be developed in the following paragraphs, various indazole-containing compounds, identified either by rational approaches or high throughput screenings, showed interesting selectivity profiles. Due to the high number of articles in this field of interest, this review is limited to non-fused indazole derivatives reported in the non-patent literature, published from 2010 to 2013.

3.1. Inhibitors of the AGC group

Several groups have recently reported their effort to identify new potent and selective inhibitors of AKT (PKB), a serine/threonine kinase that is involved in a major cellular signaling pathway: PI3K/AKT (Figure 2).

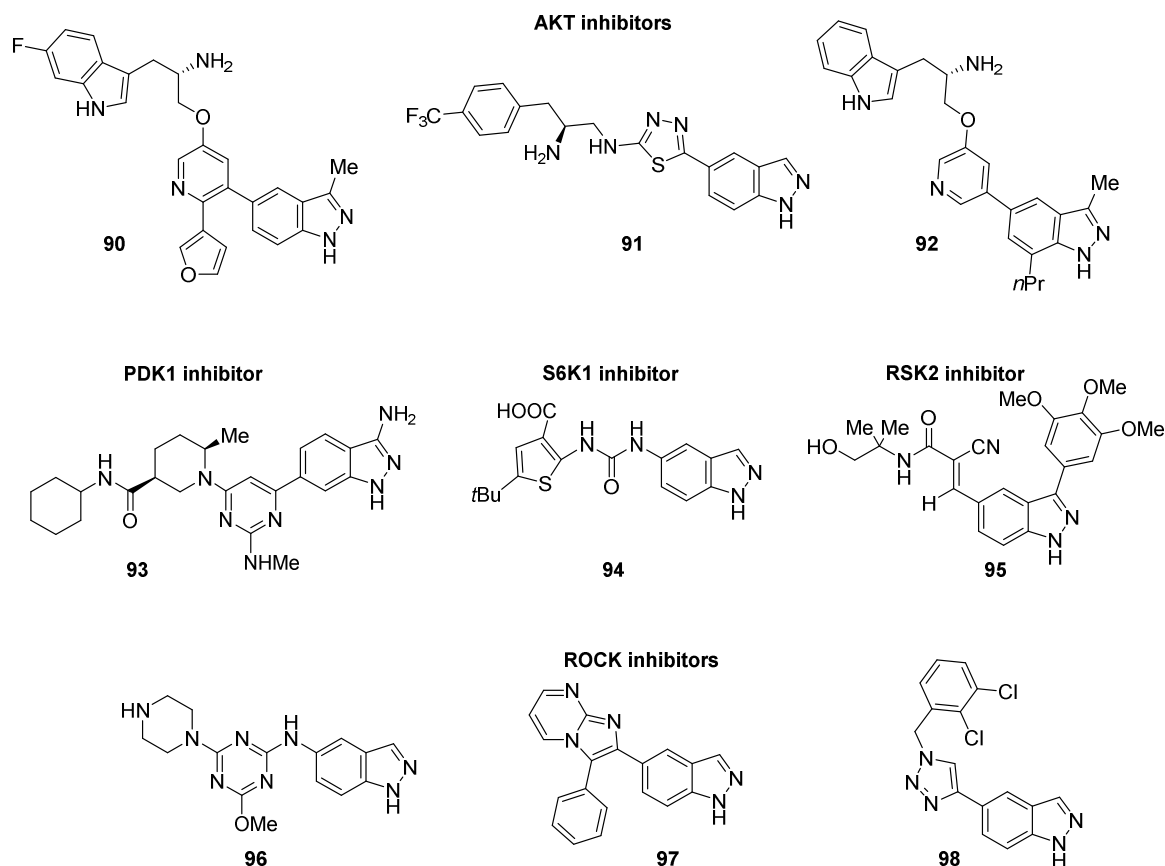


Figure 2. Structures of indazoles showing interesting inhibitory potencies toward protein kinases belonging to the AGC group.

Based on the differences observed in the amino acid sequence around the gatekeeper residue between two members of the AGC group, AKT and ROCK1, AKT selective inhibitors have been designed by GlaxoSmithKline researchers.⁸⁵ The most active compound of the series (**90**, Figure 2) demonstrated an excellent activity toward AKT1 with an IC_{50} value of 0.0008 μ M and an improved selectivity in regards to ROCK1. Compound **91**, described by Amgen group was also identified as an AKT1 inhibitor with a

moderate selectivity showing an IC_{50} value of 6 nM, 108 nM and 24 nM toward AKT1, PKA and CDK2, respectively.⁸⁶ Compound **92** (PrIDZ) coming from a chemical genetic approach exploring the conserved gatekeeper residue across the kinome showed an excellent selectivity when tested toward 191 human wild type kinases and disease mutants with IC_{50} values in the nM range for targeted AKT variants.⁸⁷

Phosphoinositide-dependent protein kinase-1 (PDK1) is an AGC member also involved in a cellular pathway (PI3K/AKT/mTOR) that is frequently deregulated in human cancer. Thus, numerous projects are devoted to the identification of PDK1 inhibitors. An aminoindazole derivative, compound **93** (GSK2334470, Figure 2), was reported as a potent and selective PDK1 inhibitor showing an IC_{50} value of 15 nM. The analysis of the X-ray co-crystal structure of **93** with PDK1 demonstrated that the aminoindazole moiety is directly involved in the binding interactions within the ATP-binding site.^{88,89}

Due to the relevance of the RHO/ROCK pathway as cellular target for various diseases (*e.g.* cardiovascular, cancer, diabetes, nervous system disorders...), an increasing effort was devoted to the identification of ROCK inhibitors. Some of them showing an indazole moiety were already reviewed in a recent paper⁹⁰ and are not mentioned here. Compound **96** (DW1865, Figure 2) discovered by a rational strategy is a selective ROCK inhibitor with IC_{50} of 0.02 μ M and 0.10 μ M toward ROCK2 and ROCK1, respectively. Molecular modeling experiments showed that the indazole moiety participates in the interaction within ROCK ATP-binding site.⁹¹ Abbott laboratories also reported ROCK inhibitors. Compounds **97** and **98** (Figure 2) can exemplify these series obtained by [2+3] cycloaddition reactions in a parallel synthesis approach. These compounds were multi-kinase inhibitors with 0.006 μ M and 0.015 μ M K_i values toward ROCK2, respectively, and also inhibited GSK3 β (**97** and **98**) and Aurora 2 (**98**).^{92,93}

S6K1 (p70 S6 kinase-1) is also an interesting target due to its importance in obesity. Pfizer researchers have reported an indazole derivative (**94**, Figure 2) as a potent and selective S6K1 inhibitor (IC_{50} = 52 nM) showing reliable physicochemical properties. In the plausible pharmacophore model described, the indazole moiety was found to be involved in H-bonds formation with S6K1 hinge region.⁹⁴

To finish this part relative to the inhibition of the AGC kinases group, a new approach of fragment-based ligand design targeting the development of a reversible covalent inhibitor was applied to the MSK/RSK kinase family. Compound **95** (Figure 2) was designed to allow the formation of a covalent bond with a RSK2 non-catalytic cysteine residue by 1,4-addition of the thiol group to the cyanoacrylamide part of the inhibitor.⁹⁵ The indazole moiety was involved in the hydrogen bonding of **95** and RSK2. Compound **95** found to be a reversible covalent inhibitor of RSK2 exhibited a high ligand efficiency (IC_{50} < 2.5 nM) and a good selectivity toward a panel of 26 kinases.

3.2. Inhibitors of the CAMK group

CAMK group also contains kinases that constitute interesting cellular targets to identify new drugs for various pathologies. For example, due to the relevance of targeting serine/threonine Pim kinases in cancer, that unlike others are constitutively active,⁹⁶ several groups reported indazole derivatives as PIM inhibitors. Compound **99** (Figure 3) is a potent and selective inhibitor of Pim kinases (IC_{50} PIM-1 = 3 nM, PIM-2 = 1160 nM, PIM-3 = 13 nM) which was identified after a rational optimization strategy from an indolic analogue.⁹⁷ Like previously mentioned for other kinase inhibitors containing an indazole ring system, this part of **99** is involved in the hydrogen-bonding with the targeted kinase ATP-binding site. Due to the

potential interest of **99**, particularly toward PIM-1, a ^{11}C -methoxy radiolabelled analogue was synthesized and described as a new positron emission tomography (PET) probe for Pim-1 kinase imaging.⁹⁸

MK2, a serine/threonine kinase, is required for tumor necrosis factor- α production and thus is an interesting target for rheumatoid arthritis and related autoimmune diseases. The structure-based optimization of 2,4-diaminopyrimidines allowed the identification of compound **100** (Figure 3) as a potent MK2 inhibitor with an IC_{50} value of 19 nM. However, only a moderate selectivity was observed when **100** was evaluated toward a panel of 79 kinases.⁹⁹ Finally, for this kinase group, Merck research laboratories showed that compound **101**, identified from an automated ligand identification system (ALIS), is a potent inhibitor of CHK1 ($\text{IC}_{50} = 3$ nM) with a good selectivity for CHK1 over CDK2. Nevertheless, the replacement of the indazole moiety by a methoxyoxindole part led to a compound with a better selectivity profile.¹⁰⁰

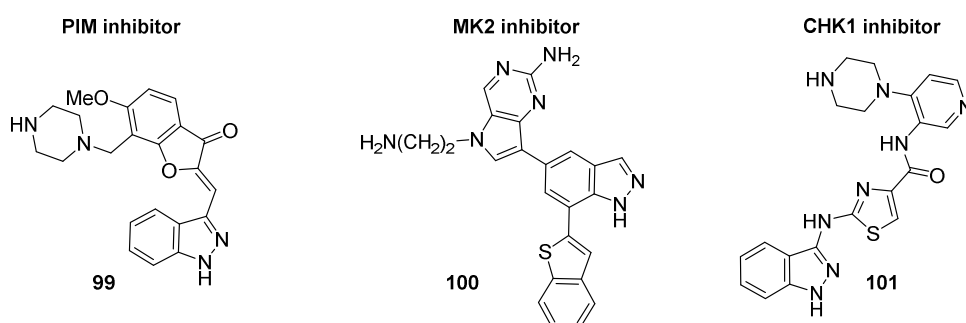


Figure 3. Structures of indazoles showing interesting inhibitory potencies toward protein kinases belonging to the CAMK group.

3.3. Inhibitors of the CMGC group

A number of indazole derivatives have been reported as inhibitors of c-Jun N-terminal kinases (JNKs), CMGC group members that are implicated in various pathologies such as central nervous system, cardiovascular, metabolic and inflammatory disorders. In a review describing small molecules that inhibit JNK, compound **102**, with an IC_{50} value of 3 nM, was introduced as a selective JNK3 inhibitor compared to JNK1 and p38 α (Figure 4).¹⁰¹ A potent and selective JNK dual inhibitor was designed using a NMR fragment-based drug discovery and structure-based design approach combination. Bidentate derivative **103** (Figure 4) potently inhibited both JNK kinase activity ($\text{IC}_{50} = 18$ nM) and JNK substrate binding ($\text{IC}_{50} = 46$ nM). Moreover, compound **103** also inhibited JNK in various cell-based experiments and *in vivo*.¹⁰² Another successful example of bidentate dual inhibitor design strategy allowed the identification of **104** (Figure 4) as a non peptidic inhibitor of JNK3/LRRK2 with IC_{50} values of 12 nM and 99 nM, respectively, that targets ATP and protein interaction sites.¹⁰³ Altogether, these results demonstrated that the development of dual-kinase inhibitors targeting both ATP and substrate specific binding regions could lead to improved potency and selectivity. Thus, this rational approach will certainly find broad applications in the future. Roche Palo Alto laboratories also used a structure guided design approach to identify compound **105** (Figure 4) as a potent JNK1 and JNK2 inhibitor with IC_{50} values of 6 nM and 17 nM, respectively.¹⁰⁴ However, **105** was not retained as the lead compound of the series due to lower physicochemical and pharmacokinetic properties when compared to its indolic analogue. Lastly, indazole **106** (Figure 4) was identified as a JNK3 inhibitor ($\text{IC}_{50} = 40$ nM) after optimization of a pyrazole derivative discovered by high throughput screening.¹⁰⁵

CDKs are members of GMGC group that are involved in the regulation of cell cycle and transcription. A program aiming at identifying novel CDK inhibitor classes led to compound **107** (Figure 4) showing sub-micromolar K_i values: 0.053 μM and 0.017 μM toward CDK1/CyclinB and CDK9/CyclinT1, respectively. Moreover, compound **107** reduced the level of Mcl-1 anti-apoptotic protein, activated caspases 3/7 and induced cancer cell apoptosis.¹⁰⁶

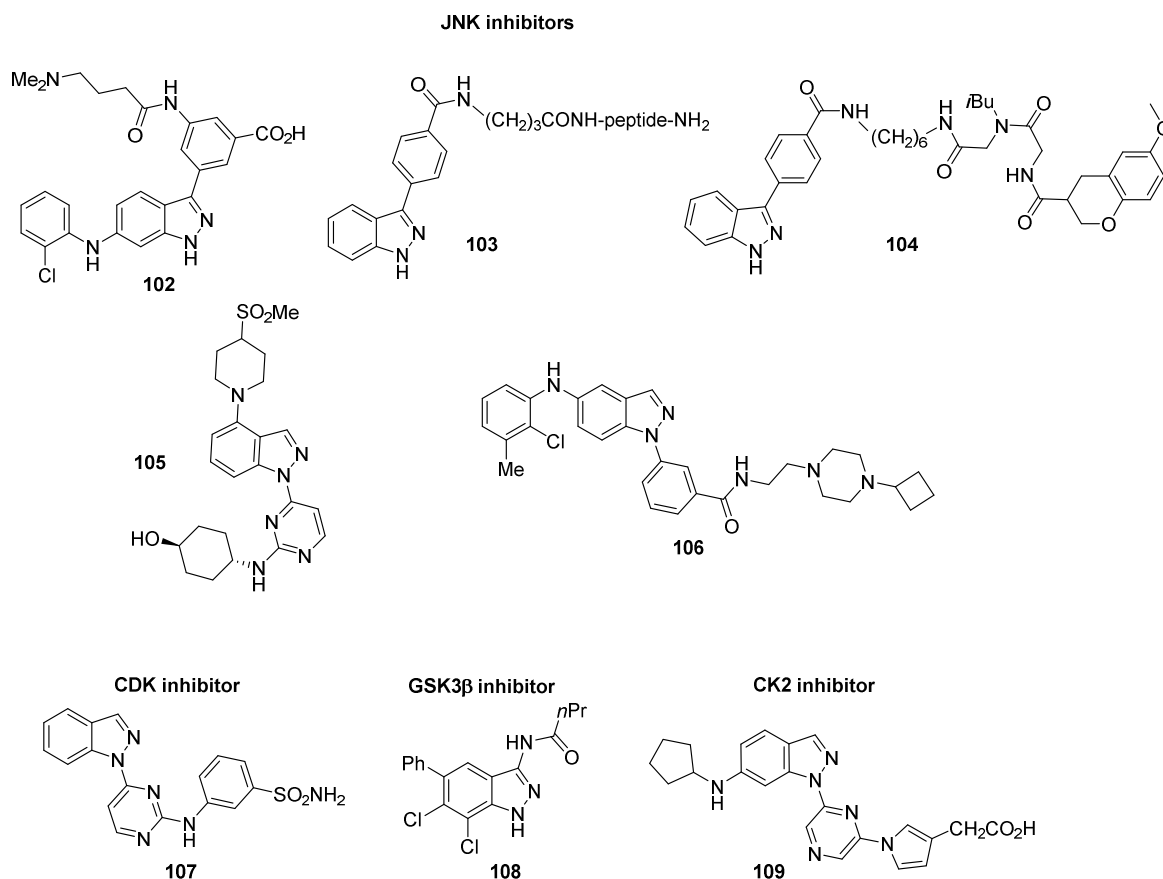


Figure 4. Structures of indazoles showing interesting inhibitory potencies toward protein kinases belonging to the CMGC group.

As tau hyperphosphorylation has been identified as a major hallmark in Alzheimer's disease and glycogen synthase 3 β (GSK3 β) is an enzyme that phosphorylates tau, the inhibition of GSK3 β appeared as an interesting target to discover new therapies for this neurodegenerative disease. Thus, Sanofi-Aventis group identified indazole **108** (IC_{50} = 12 nM) as a potent and selective inhibitor of GSK3 β after optimization of a compound coming from high throughput screening approach (Figure 4). Indazole moiety is directly involved in the hydrogen bonding of **108** 7-fluoro analogue and GSK3 β hinge region.¹⁰⁷

To end up with this group of kinases, deregulation of CK2 has been associated with cancer, inflammatory disorders, pain and viral infections indicating a wide domain of application for CK2 inhibitors. Therefore, Toray industries reported indazole derivative **109** (Figure 4) as a potent CK2 inhibitor with an IC_{50} value of 9.3 nM.¹⁰⁸

3.4. Inhibitors of the STE group

The Ras/Raf/MEK/ERK (MAPK) signaling pathway is involved in the regulation of cell survival, growth, differentiation and proliferation. Mutation of B-Raf (B-Raf^{V600E}) has been reported as an important

feature in the development of cancer. Thus, the identification of B-Raf mutant inhibitors received considerable attention. Indazolylpyrazolopyrimidine **110** (Figure 5) was identified as a potent B-Raf inhibitor ($IC_{50} = 0.16$ nM) with *in vivo* activity against tumor driven by B-Raf mutation. Again, molecular modeling experiments showed that the indazole moiety is highly involved in the hydrogen bonding within B-Raf ATP-binding pocket.¹⁰⁹ Another B-Raf inhibitor, **111** ($IC_{50} = 4.2$ nM, Figure 5), was identified by optimization of compounds in which indanone-oxime moieties were replaced by more metabolically stable groups like indazole.¹¹⁰ Compound **112** (G-894, Figure 5) was identified as a novel allosteric mitogen-activated protein kinase (MEK) inhibitor ($IC_{50} = 13$ nM) using a computer-aided drug design approach. This compound is non-ATP competitive with its indazole ring system establishing a bidentate interaction with MEK1 Ser212 residue. Moreover, **112** is orally active *in vivo* in tumor xenograft models.¹¹¹

Tpl2 kinase is another STE member that has become an interesting target for the treatment of rheumatoid arthritis. A high throughput screening identified indazole **113** as a potent Tpl2 inhibitor ($IC_{50} = 0.047$ μ M) with good cellular potency. Molecular modeling studies indicated that the indazole ring system is hydrogen-bonded with the hinge region of Tpl2.¹¹²

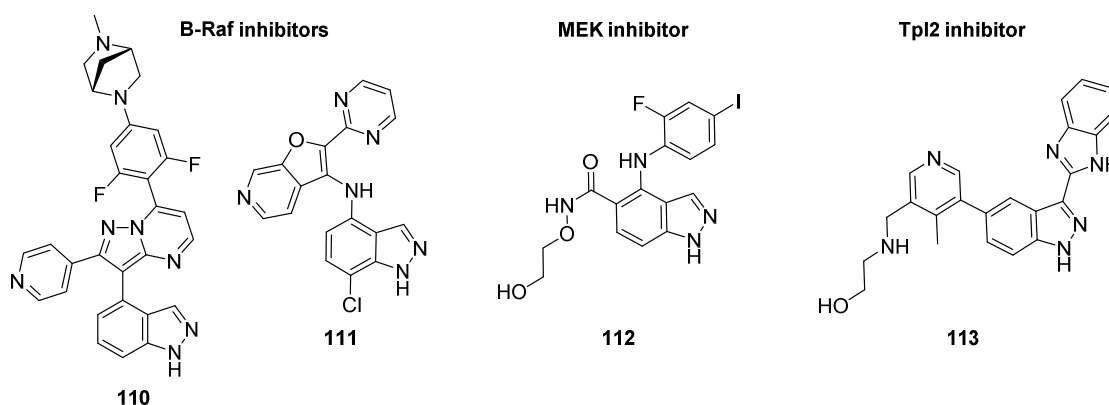


Figure 5. Structures of indazoles showing interesting inhibitory potencies toward protein kinases belonging to the STE group.

3.5. Inhibitors of the TK group

Tyrosine kinases are divided into two categories: the receptor tyrosine kinases (RTKs) that contain a transmembrane domain and the non-receptor tyrosine kinases. A number of indazoles have been identified as potent inhibitors of various RTKs. Members of the RTK family (*e.g.* VEGFR, PDGFR, EphB4 receptors) are involved in angiogenesis and thus are interesting targets to reduce cancer growth and metastasis. Compound **114** (ABT-869, Figure 6) is a multitarget RTK inhibitor (IC_{50} KDR = 4 nM, PDGFR β = 2 nM, FLT3 = 4 nM, CSF-1R = 7 nM) that reduce tumor vascularization in preclinical models.¹¹³ The use of a *de novo* structure-based identification process allowed the identification of compound **115** (JK-P5, Figure 6) as the best *in vitro* multi-tyrosine kinase inhibitor of the JK-P series (IC_{50} VEGFR2 = 7.28 μ M, FGFR1 = 11.4 μ M, FGFR3 = 3.21 μ M). However, due to reduced cellular activities, when compared with a pyrazole analogue, **115** was not deeply studied.¹¹⁴ The *in silico* virtual screening of a library of 90 [1-(substituted)-1*H*-[1,2,3]-triazol-4-yl]-methyl-3-[3'-(chloromethyl)phenyl]ureas led to compound **116** (VH02, Figure 6) as the most promising VEGFR2 inhibitor of the series ($IC_{50} = 0.56$ μ M) showing antiangiogenic effect in cellular assays. The proposed binding mode showed the formation of two hydrogen bonds between **116**

indazole moiety and VEGFR2 active site.¹¹⁵ AstraZeneca group characterized compound **117** (Figure 6) as a potent EphB4 inhibitor ($IC_{50} = 0.0013 \mu\text{M}$) with good cellular activity and pharmacokinetics. Thus **117** could represent an interesting molecular tool to further study the scope of EphB4 inhibitors *in vivo*.¹¹⁶

The resistances coming from frequent mutations observed in cancer cells are one of the main limitations for the use of kinase inhibitor in clinics. Thus, the development of inhibitors that are designed to avoid interaction with the residues that are known to be commonly mutated (*e.g.* the gatekeeper residue) could be of high interest. Consequently, a structure-based drug design approach was used to prepare aminoindazole derivatives **118** and **119** (Figure 6) that were found to highly inhibit FLT3 and PDGFR α -T674M mutant (**118**, EC_{50} FLT3 = 0.005 μM , PDGFR α -T674M = 0.017 μM ; **119**, EC_{50} FLT3 = 0.002 μM , PDGFR α -T674M = 0.001 μM).¹¹⁷

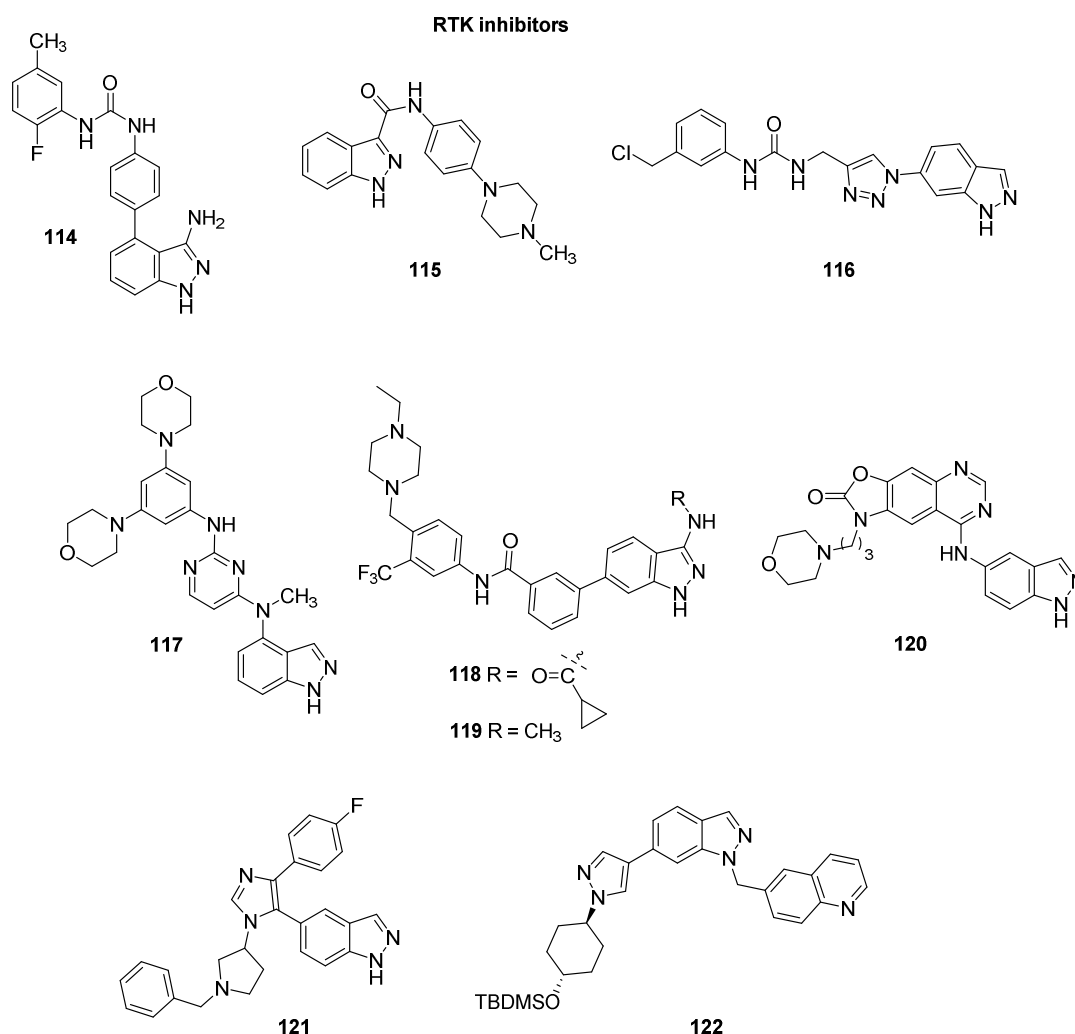


Figure 6. Structures of indazoles showing interesting inhibitory potencies toward protein kinases belonging to the TK group (RTK).

EGFR are other growth factor receptors that are depicted as relevant cellular targets for cancer therapies. Several protein kinase inhibitors containing a quinazoline scaffold have already reached the market (*e.g.* Gefitinib, Erlotinib, Lapatinib). Thus, new quinazoline derivatives were synthesized to identify new EGFR inhibitors which could overcome the resistance to approved drugs that appeared recently. In this series, compound **120** (Figure 6) was the most potent one with an indazole moiety ($IC_{50} = 0.12 \mu\text{M}$).¹¹⁸

Compound **121** (Figure 6), obtained from a parallel synthesis program aiming at the identification of 5-diversely substituted indazoles with kinase inhibitory potency was found to be a potent and selective EGFR inhibitor ($K_i = 0.008 \mu\text{M}$).⁹² Last compound of this section, focused on RTK inhibitors containing an indazole ring, is **122** that is active toward c-Met with an IC_{50} value of $0.17 \mu\text{M}$.¹¹⁹

As mentioned above, the second category of TK includes non-receptor tyrosine kinases. Some of them, like Janus protein tyrosine kinase family (JAK) that are involved in JAK/STAT signaling pathway or Spleen tyrosine kinase (SYK) are valuable targets for the treatment of inflammatory, myeloproliferative and autoimmune diseases. Using a structure-based drug design strategy, Abbott laboratories described 3-aminoindazoles **123** and **124** (Figure 7) as low nanomolar ATP-competitive inhibitors of JAK family (TYK2, JAK1, JAK2, JAK3). Moreover, X-ray crystal structure of both compounds in complex with Tyk2 demonstrated that indazole moiety is directly involved in the binding of **123** and **124** within TYK2 ATP-binding site.¹²⁰ Once more using a structure-based design approach, compound **125**, whose carboxamido-substituted indazole moiety is supposed to be involved in the binding with the hinge region, was identified as a potent JAK kinase inhibitor with JAK1 selectivity over other JAK isozymes, particularly over JAK2.¹²¹

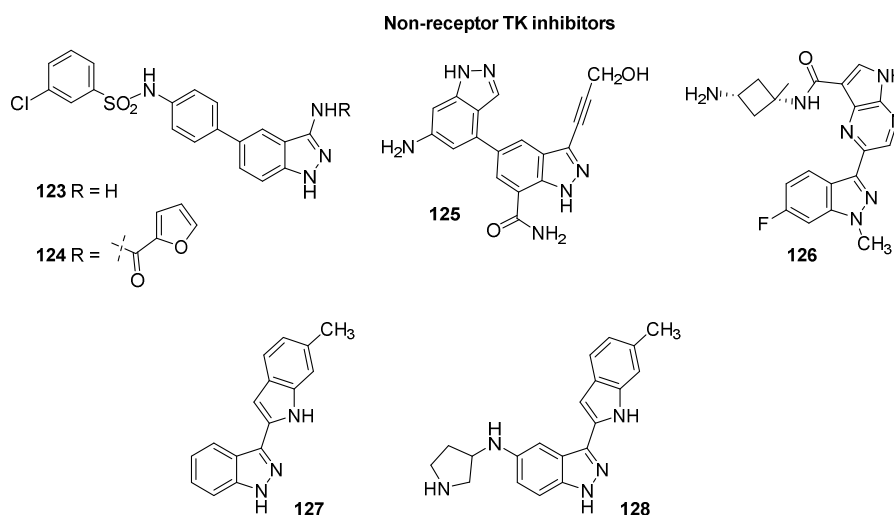


Figure 7. Structures of indazoles showing interesting inhibitory potencies toward protein kinases belonging to the non-receptor tyrosine kinase group.

Starting from pyrrolopyrazine scaffolds previously identified as SYK/JAK kinase inhibitors, after rational design based on X-ray crystal structure analysis, compound **126** (Figure 7), a potent and selective SYK inhibitor was obtained ($\text{IC}_{50} = 4 \text{ nM}$).¹²²

Finally, another non-receptor TK member, Interleukin-2 inducible T cell kinase (ITK) has been found to be inhibited by indazole containing compounds. ITK is considered as an interesting therapeutic target for T cell-mediated diseases. Thus, Herdemann and co-workers described 3-substituted indazole derivatives (*e.g.* compounds **127** and **128**) with sub-micromolar potencies toward ITK. Moreover, in the putative binding model proposed and based on molecular modeling studies, indazole moieties are supposed to be directly hydrogen-bonded within ITK hinge region.^{123,124}

3.6. Inhibitors of other kinases

This section is devoted to the kinases (protein kinase, hexose kinase, lipid kinase) that are either classified as atypical, other or non-classified. Phosphatidylinositol 3-kinase (PI3K) is involved in the

PI3K/AKT/mTOR signaling pathway that regulates various cellular functions such as survival, proliferation, cell motility and invasion. Uncontrolled activity of PI3K isoforms has been reported in various pathologies including cancer, autoimmune and cardiovascular diseases. Thus, the development of PI3K inhibitors is of high interest. Compound **129** (Figure 8) was identified as a multi-kinase inhibitor targeting PI3K/AKT/mTOR pathway with an IC_{50} of 0.36 μM toward PI3K α . The results obtained by molecular modeling indicated that the indazole ring system participated in the hydrogen bonding interactions within PI3K α ATP-binding site. Moreover **129** showed a good selectivity profile when tested against a panel of 314 kinases.¹²⁵ Another PI3K inhibitor, **130** (Figure 8, IC_{50} = 0.44 μM), was discovered using a rational design approach undertaken to optimize a potent pyridofuropyrimidine PI3K inhibitor that had low water solubility and was too rapidly cleared from plasma.¹²⁶ Structure-based optimization of a hit compound identified by high throughput screening led to **131** (Figure 8) which exhibited a better bioavailability than the parent compound and an IC_{50} value of 0.0068 μM toward PI3K α .

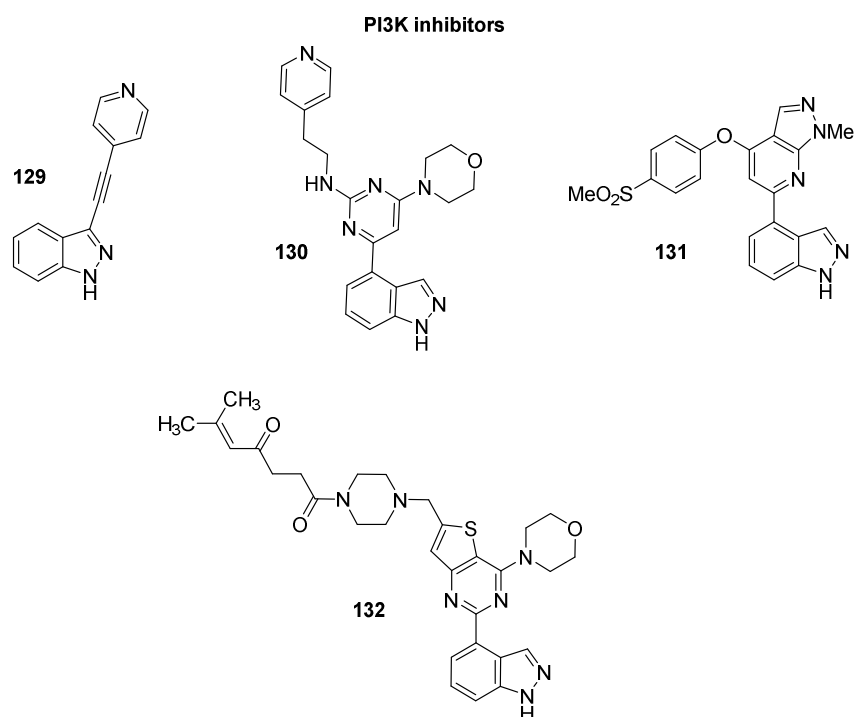


Figure 8. Structures of indazoles showing interesting inhibitory potencies toward PI3K.

Once again, the indazole part of **131** participated in the binding with the biological target.¹²⁷ Finally, compound **132** (Figure 8) was designed as an isoform-selective targeted covalent PI3K α inhibitor. This compound covalently binds a cysteine residue that is only present in α isoform and specifically inhibits signaling in PI3K α -dependent cancer cell lines (EC_{50} < 100 nM). Therefore, **132** is an interesting molecular tool to further study PI3K α cellular implications.¹²⁸

Ketohexokinase (KHK) is involved in the regulation of dietary sugar metabolism and thus, represents an interesting target to treat obesity and diabetes. Another rational approach using fragment-based drug design successfully conducted to **133** (IC_{50} = 330 nM, Figure 9) as a KHK inhibitor showing interesting selectivity and pharmacokinetic profiles.¹²⁹

Aurora kinase family is involved in cellular mitosis regulation. Moreover, Aurora A and B have been found over-expressed in many tumor types. Therefore, the inhibition of these kinases is interesting to

develop new antitumor therapies. However, Aurora B has been described as a more valuable target for cancer therapy. Thus, an optimization strategy was applied to an indazole scaffold with the aim to identify potent and selective Aurora B inhibitors. The most selective of the series was compound **134** (IC_{50} Aurora A = 1.9 μ M, Aurora B = 0.099 μ M, Figure 9) showing an almost 20-fold selectivity for Aurora B in comparison to Aurora A. Molecular modeling studies indicated that the indazole moiety is part of the hydrogen bonding interactions of **134** within Aurora B ATP-binding site.¹³⁰

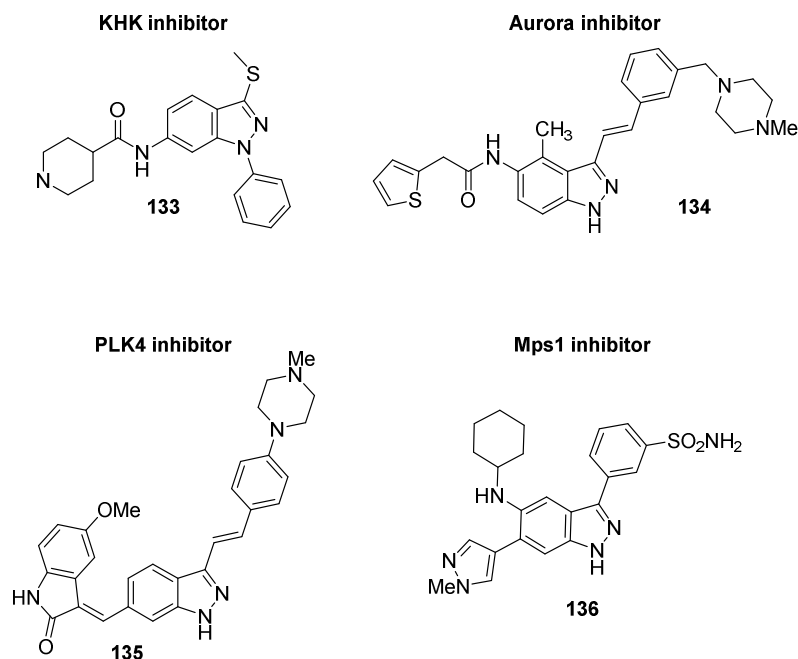


Figure 9. Structures of indazoles showing interesting inhibitory potencies toward other protein kinases.

Serine/threonine Polo-like kinases (PLK) are important regulators of the mitotic progression. PLK4, the most distinct and less studied member of the family, recently emerged as an attractive target for cancer therapies. Compound **135** (CFI-400437, Figure 9) was identified as a potent and fairly selective PLK4 inhibitor by rational optimization of a phenolic analog identified from a virtual screening strategy. Moreover, when tested in a breast cancer cell mouse xenograft model, the optimized compound exhibited *in vivo* efficacy illustrating the relevance of PLK4 inhibitors in this field.¹³¹

Monopolar spindle 1 (Mps1), also called TKK, is a dual kinase that phosphorylate both tyrosine and serine/threonine residues. Due to its essential role in centrosome duplication, mitotic checkpoint signaling and maintenance of chromosomal instability, Mps1 is a promising target for cancer therapeutics. A rational design optimization process based on a pan-kinase inhibitor showing an anthrapyrazolone scaffold allowed the identification of **136** (IC_{50} = 10.4 nM, Figure 9), a potent and selective Mps1 inhibitor with improved cellular potencies when compared with previous lead compound.¹³²

4. Conclusions

Various heteroaromatic derivatives containing indazole scaffolds were identified as kinase inhibitors using both rational and large screening approaches. In most cases, the indazole moiety is strongly implicated in the hydrogen bonding interactions within the targeted protein kinase. Some of them represent druggable

kinase inhibitors with good pharmacokinetic profiles and therefore are useful molecular tools to further study the cellular implications of the inhibited kinase and/or offer new perspective for therapies. Therefore, in recent years, much effort have been devoted to the development of novel synthetic approaches to diversely substituted 1*H*- or 2*H*-indazoles. Thus, a diversity of indazole syntheses has now been reported, offering new opportunities to the preparation of novel biologically active indazole derivatives.

In conclusion, the increasing number of papers that reported new indazole derivatives as kinase inhibitors demonstrated that this research field of great interest is still in full expansion, as attested for example by a recent article describing the preparation of new derivatives of Pazopanib in order to reduce the side-effects observed in clinics.¹³³ As recently mentioned, the next challenges to get over in the discovery of new generation kinase inhibitors are the decrease of side effects, the overcoming of drug resistance and the development of kinase inhibitors useful in other diseases than cancer. Different ways are under consideration to solve these issues such as the improvement of kinase inhibitor selectivity, the development of irreversible inhibitors, the targeting of mutant kinases rather than wild type ones and the enlargement of the panel of kinases for which inhibitors are described (*e.g.* lipid kinases).^{134,135} Due to their great potential, indazole derivatives will certainly have an important role to play in the further developments coming in the field of kinase inhibitor discovery.

References

- Gavara, L.; Saugues, E.; Alves, G.; Debiton, E.; Anizon, F.; Moreau, P. *Eur. J. Med. Chem.* **2010**, *45*, 5520.
- Gavara, L.; Anizon, F.; Moreau, P. *Tetrahedron* **2011**, *67*, 7330.
- Gavara, L.; Saugues, E.; Anizon, F.; Moreau, P. *Tetrahedron* **2011**, *67*, 1633.
- Gavara, L.; Suchaud, V.; Nauton, L.; Théry, V.; Anizon, F.; Moreau, P. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2298.
- Suchaud, V.; Gavara, L.; Saugues, E.; Nauton, L.; Théry, V.; Anizon, F.; Moreau, P. *Bioorg. Med. Chem.* **2013**, *21*, 4102.
- Schmidt, A.; Beutler, A.; Snovydyovych, B. *Eur. J. Org. Chem.* **2008**, 4073.
- Jin, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3323.
- Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219.
- Wang, C.-D.; Liu, R.-S. *Org. Biomol. Chem.* **2012**, *10*, 8948.
- Hari, Y.; Sone, R.; Aoyama, T. *Org. Biomol. Chem.* **2009**, *7*, 2804.
- Ikawa, T.; Takagi, A.; Goto, M.; Aoyama, Y.; Ishikawa, Y.; Itoh, Y.; Fujii, S.; Tokiwa, H.; Akai, S. *J. Org. Chem.* **2013**, *78*, 2965.
- Spiteri, C.; Keeling S.; Moses, J. E. *Org. Lett.* **2010**, *12*, 3368.
- Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. *Org. Lett.* **2011**, *13*, 3340.
- Li, P.; Wu, C.; Zhao, J.; Rogness, D. C.; Shi, F. *J. Org. Chem.* **2012**, *77*, 3149.
- Kovács, S.; Csincsi, Á. I.; Nagy, T. Z.; Boros, S.; Timári, G.; Novák, Z. *Org. Lett.* **2012**, *14*, 2022.
- Markina, N. A.; Dubrovskiy, A. V.; Larock, R. C. *Org. Biomol. Chem.* **2012**, *10*, 2409.
- Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2011**, *13*, 4136.
- Dubrovskiy, A. V.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 11232.
- Wu, C.; Fang, Y.; Larock R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2234.
- Fang, Y.; Wu, C.; Larock, R. C.; Shi, F. *J. Org. Chem.* **2011**, *76*, 8840.

21. Soares, M. I. L.; Nunes, C. M.; Gomes, C. S. B.; Pinho e Melo, T. M. V. D. *J. Org. Chem.* **2013**, *78*, 628.
22. Hou, Y.; Lu, S.; Liu, G. *J. Org. Chem.* **2013**, *78*, 8386.
23. Viña, D.; del Olmo, E.; López-Pérez, J. L.; San Feliciano, A. *Org. Lett.* **2007**, *9*, 525.
24. Xiong, X.; Jiang, Y.; Ma, D. *Org. Lett.* **2012**, *14*, 2552.
25. Lundgren, R. J.; Stradiotto, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8686.
26. Inamoto, K.; Katsuno, M.; Yoshino, T.; Arai, Y.; Hiroya, K.; Sakamoto, T. *Tetrahedron* **2007**, *63*, 2695.
27. Suryakiran, N.; Prabhakar, P.; Venkateswarlu, Y. *Chem. Lett.* **2007**, *36*, 1370.
28. Kylmälä, T.; Udd, S.; Tois, J.; Franzén, R. *Tetrahedron Lett.* **2010**, *51*, 3613.
29. Kylmälä, T.; Hämäläinen, A.; Kuuloja, N.; Tois, J.; Franzén, R. *Tetrahedron* **2010**, *66*, 8854.
30. Thomé, I.; Besson, C.; Kleine, T.; Bolm, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 7509.
31. Liu, R.; Zhu, Y.; Qin, L.; Ji, S. *Synth. Commun.* **2008**, *38*, 249.
32. Duncan, N. C.; Garner, C. M. *Tetrahedron Lett.* **2011**, *52*, 5214.
33. Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya K. *Org. Lett.* **2007**, *9*, 2931.
34. Li, X.; He, L.; Chen, H.; Wu, W.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 3636.
35. Zhang, T.; Bao, W. *J. Org. Chem.* **2013**, *78*, 1317.
36. Hu, J.; Xu, H.; Nie, P.; Xie, X.; Nie, Z.; Rao, Y. *Chem. Eur. J.* **2014**, *20*, 3932.
37. Counciller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, *10*, 1021.
38. Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 4576.
39. Paul, S.; Panda, S.; Manna, D. *Tetrahedron Lett.* **2014**, *55*, 2480.
40. Sather, A. C.; Berryman, O. B.; Rebek, J., Jr. *Org. Lett.* **2012**, *14*, 1600.
41. Moustafa, A. H.; Malakar, C. C.; Aljaar, N.; Merisor, E.; Conrad, J.; Beifuss, U. *Synlett* **2013**, 1573.
42. Okuro, K.; Gurnham, J.; Alper, H. *Tetrahedron Lett.* **2012**, *53*, 620.
43. Ahn, G. H.; Lee, J. J.; Jun, Y. M.; Lee, B. M.; Kim, B. H. *Org. Biomol. Chem.* **2007**, *5*, 2472.
44. Kumar, M. R.; Park, A.; Park, N.; Lee, S. *Org. Lett.* **2011**, *13*, 3542.
45. Sharghi, H.; Aberi, M. *Synlett* **2014**, 1111.
46. Hu, J.; Cheng, Y.; Yang, Y.; Rao, Y. *Chem. Commun.* **2011**, *47*, 10133.
47. Stokes, B. J.; Vogel, C. V.; Urnezis, L. K.; Pan, M.; Driver, T. G. *Org. Lett.* **2010**, *12*, 2884.
48. Lefebvre, V.; Cailly, T.; Fabis, F.; Rault, S. *J. Org. Chem.* **2010**, *75*, 2730.
49. Xu, L.; Peng, Y.; Pan, Q.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2013**, *78*, 3400.
50. Li, H.; Li, P.; Wang, L. *Org. Lett.* **2013**, *15*, 620.
51. Xiong, F.; Qian, C.; Lin, D.; Zeng, W.; Lu, X. *Org. Lett.* **2013**, *15*, 5444.
52. Li, H.; Li, P.; Tan, H.; Wang, L. *Chem. Eur. J.* **2013**, *19*, 14432.
53. Lian, Y.; Bergman, R. G.; Lavis, L. D.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 7122.
54. Haag, B.; Peng, Z.; Knochel, P. *Org. Lett.* **2009**, *11*, 4270.
55. Peters, M. V.; Stoll, R. S.; Goddard, R.; Buth, G.; Hecht, S. *J. Org. Chem.* **2006**, *71*, 7840.
56. McClintock, S. P.; Forster, N.; Herges, R.; Haley, M. M. *J. Org. Chem.* **2009**, *74*, 6631.
57. Fang, Y.; Wang, C.; Su, S.; Yu, H.; Huang, Y. *Org. Biomol. Chem.* **2014**, *12*, 1061.
58. Yang, W.; Yang, Z.; Xu, L.; Zhang, L.; Xu, X.; Miao, M.; Ren, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 14135.
59. Mills, A. D.; Nazer, M. Z.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2006**, *71*, 2687.
60. Mills, A. D.; Maloney, P.; Hassanein, E.; Haddadin, M. J.; Kurth, M. J. *J. Comb. Chem.* **2007**, *9*, 171
61. Oakdale, J. S.; Solano, D. M.; Fettinger, J. C.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2009**, *11*, 2760.
62. Donald, M. B.; Conrad, W. E.; Oakdale, J. S.; Butler, J. D.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2010**, *12*, 2524.

63. Conrad, W. E.; Fukazawa, R.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2011**, *13*, 3138.
64. Avila, B.; El-Dakdouki, M. H.; Nazer, M. Z.; Harrison, J. G.; Tantillo, D. J.; Haddadin, M. J.; Kurth, M. J. *Tetrahedron Lett.* **2012**, *53*, 6475.
65. Lehmann, F.; Koolmeister, T.; Odell, L. R.; Scobie, M. *Org. Lett.* **2009**, *11*, 5078.
66. Bouillon, I.; Zajíček, J.; Pudělová, N.; Krchňák, V. *J. Org. Chem.* **2008**, *73*, 9027.
67. Shi, D.-Q.; Dou, G.-L.; Ni, S.-N.; Shi, J.-W.; Li, X.-Y.; Wang, X.-S.; Wu, H.; Ji, S.-J. *Synlett* **2007**, 2509.
68. Sun, F.; Feng, X.; Zhao, X.; Huang, Z.-B.; Shi, D.-Q. *Tetrahedron* **2012**, *68*, 3851.
69. Dou, G.; Shi, D. *J. Comb. Chem.* **2009**, *11* 1073.
70. Liu, R.; Zhu, Y.-M.; Qin, L.-N.; Ji, S.-J.; Katayama, H. *Heterocycles* **2007**, *71*, 1755.
71. Tanimori, S.; Ozaki, Y.; Iesaki, Y.; Kirihata, M. *Synlett* **2008**, 1973.
72. Tanimori, S.; Kobayashi, Y.; Iesaki, Y.; Ozaki, Y.; Kirihata, M. *Org. Biomol. Chem.* **2012**, *10*, 1381.
73. Welsch, S. J.; Kalinski, C.; Umkehrer, M.; Ross, G.; Kolb, J.; Burdack, C.; Wessjohann, L. A. *Tetrahedron Lett.* **2012**, *53*, 2298.
74. Halland, N.; Nazaré, M.; R'kyek, O.; Alonso, J.; Urmann, M.; Lindenschmidt, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 6879.
75. Ott, G. R.; Anzalone, A. V. *Synlett* **2011**, 3018.
76. Burke, M. J.; Trantow, B. M. *Tetrahedron Lett.* **2008**, *49*, 4579.
77. Yu, D.-G.; Suri, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 8802.
78. Ichikawa, H.; Ohfuné, H.; Usami, Y. *Heterocycles* **2010**, *81*, 1651.
79. Coşkun, N.; Çetin, M. *Tetrahedron* **2007**, *63*, 2966.
80. Chen, W.-Z.; Wei, H.-Y.; Yang, D.-Y. *Tetrahedron* **2013**, *69*, 2775.
81. Lucero, P. L.; Peláez, W. J.; Riedl, Z.; Hajós, G.; Moyano, E. L.; Yranzo, G. I. *Tetrahedron* **2012**, *68*, 1299.
82. Kvaskoff, D.; Bednarek, P.; George, L.; Waich, K.; Wentrup, C. *J. Org. Chem.* **2006**, *71*, 4049.
83. Quast, H.; Ross, K.-H.; Philipp, G.; Hagedorn, M.; Hahn, H.; Banert, K. *Eur. J. Org. Chem.* **2009**, 3940.
84. Quast, H.; Ross, K.-H.; Philipp, G. *Eur. J. Org. Chem.* **2010**, 2212.
85. Lin, H.; Yamashita, D. S.; Zeng, J.; Xie, R.; Wang, W.; Nidarmarthy, S.; Luengo, J. I.; Rhodes, N.; Knick, V. B.; Choudhry, A. E.; Lai, Z.; Minthorn, E. A.; Strum, S. L.; Wood, E. R.; Elkins, P. A.; Concha, N. O.; Heering, D. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 673.
86. Zeng, Q.; Bourbeau, M. P.; Wohlhieter, G. E.; Yao, G.; Monenschein, H.; Rider, J. T.; Lee, M. R.; Zhang, S.; Lofgren, J.; Freeman, D.; Li, C.; Tominey, E.; Huang, X.; Hoffman, D.; Yamane, H.; Tasker, A. S.; Dominguez, C.; Viswanadhan, V. N.; Hungate, R.; Zhang, X. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1652.
87. Okuzumi, T.; Ducker, G. S.; Zhang, C.; Aizenstein, B.; Hoffman, R.; Shokat, K. M. *Mol. BioSyst.* **2010**, *6*, 1389.
88. Medina, J. R.; Becker, C. J.; Blackledge, C. W.; Duquenne, C.; Feng, Y.; Grant, S. W.; Heering, D.; Li, W. H.; Miller, W. H.; Romeril, S. P.; Scherzer, D.; Shu, A.; Bobko, M. A.; Chadderton, A. R.; Dumble, M.; Gardiner, C. M.; Gilbert, S.; Liu, Q.; Rabindran, S. K.; Sudakin, V.; Xiang, H.; Brady, P. G.; Campobasso, N.; Ward, P.; Axten, J. M. *J. Med. Chem.* **2011**, *54*, 1871.
89. Najafov, A.; Sommer, E. M.; Axten, J. M.; DeYoung, M. P.; Alessi, D. R. *Biochem. J.* **2011**, *433*, 357.
90. Guan, R.; Xu, X.; Chen, M.; Hu, H.; Ge, H.; Wen, S.; Zhou, S.; Pi, R. *Eur. J. Med. Chem.* **2013**, *70*, 613.
91. Oh, K.-S.; Oh, B. K.; Park, C. H.; Seo, H. W.; Kang, N. S.; Lee, J. H.; Lee, J. S.; Lee, B. H. *Eur. J. Pharmacol.* **2013**, *702*, 218.

92. Akritopoulou-Zanze, I.; Wakefield, B. D.; Gasiiecki, A.; Kalvin, D.; Johnson, E. F.; Kovar, P.; Djuric, S. W. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1480.
93. Akritopoulou-Zanze, I.; Wakefield, B. D.; Gasiiecki, A.; Kalvin, D.; Johnson, E. F.; Kovar, P.; Djuric, S. W. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1476.
94. Ye, P.; Kuhn, C.; Juan, M.; Sharma, R.; Connolly, B.; Alton, G.; Liu, H.; Stanton, R.; Kablaoui, N. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 849.
95. Miller, R. M.; Paavilainen, V. O.; Krishnan, S.; Serafimova, I. M.; Taunton, J. *J. Am. Chem. Soc.* **2013**, *135*, 5298.
96. Anizon, F.; Shtil, A. A.; Danilenko, V. N.; Moreau, P. *Curr. Med. Chem.* **2010**, *17*, 4114.
97. Nakano, H.; Saito, N.; Parker, L.; Tada, Y.; Abe, M.; Tsuganezawa, K.; Yokoyama, S.; Tanaka, A.; Kojima, H.; Okabe, T.; Nagano, T. *J. Med. Chem.* **2012**, *55*, 5151.
98. Gao, M.; Wang, M.; Miller, K. D.; Zheng, Q.-H. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4342.
99. Harris, C. M.; Ericsson, A. M.; Argiriadi, M. A.; Barberis, C.; Borhani, D. W.; Burchat, A.; Calderwood, D. J.; Cunha, G. A.; Dixon, R. W.; Frank, K. E.; Johnson, E. F.; Kamens, J.; Kwak, S.; Li, B.; Mullen, K. D.; Perron, D. C.; Wang, L.; Wishart, N.; Wu, X.; Zhang, X.; Zmetra, T. R.; Talanian, R. V. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 334.
100. Huang, X.; Cheng, C. C.; Fischmann, T. O.; Duca, J. S.; Richards, M.; Tadikonda, P. K.; Reddy, P. A.; Zhao, L.; Siddiqui, M. A.; Parry, D.; Davis, N.; Seghezzi, W.; Wiswell, D.; Shipps Jr. G. W. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2590.
101. Siddiqui, M. A.; Reddy, P. A. *J. Med. Chem.* **2010**, *53*, 3005.
102. Stebbins, J. L.; De, S. K.; Pavlickova, P.; Chen, V.; Machleidt, T.; Chen, L.-H.; Kuntzen, C.; Kitada, S.; Karin, M.; Pellechia, M. *J. Med. Chem.* **2011**, *54*, 6206.
103. Feng, Y.; Chambers, J. W.; Iqbal, S.; Koenig, M.; Park, H.; Cherry, L.; Hernandez, P.; Figuera-Losada, M.; LoGrasso, P. V. *ACS Chem. Biol.* **2013**, *8*, 1747.
104. Gong, L.; Han, X.; Silva, T.; Tan, Y.-C.; Goyal, B.; Tivitmahaisoon, P.; Trejo, A.; Palmer, W.; Hogg, H.; Jahagir, A.; Alam, M.; Wagner, P.; Stein, K.; Filonova, L.; Loe, B.; Makra, F.; Rotstein, D.; Rapatova, L.; Dunn, J.; Zuo, F.; Dal Porto, J.; Wong, B.; Jin, S.; Chang, A.; Tran, P.; Hsieh, G.; Niu, L.; Shao, A.; Reuter, D.; Hermann, J.; Kuglstatter, A.; Goldstein, D. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3565.
105. Jiang, R.; Frackowiak, B.; Shin, Y.; Song, X.; Chen, W.; Lin, L.; Cameron, M. D.; Duckett, D. R.; Kamenecka, T. M. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2683.
106. Lukasik, P. M.; Elabar, S.; Lam, F.; Shao, H.; Liu, X.; Abbas, A. Y.; Wang, S. *Eur. J. Med. Chem.* **2012**, *57*, 311.
107. Lesuisse, D.; Dutruc-Rosset, G.; Tiraboschi, G.; Dreyer, M. K.; Maignan, S.; Chevalier, A.; Halley, F.; Bertrand, P.; Burgevin, M.-C.; Quarteronet, D.; Rooney, T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1985.
108. Fuchi, N.; Iura, Y.; Kaneko, H.; Nitta, A.; Suyama, K.; Ueda, H.; Yamaguchi, S.; Nishimura, K.; Fujii, S.; Sekiya, Y.; Yamada, M.; Takahashi, T. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4358.
109. Wang, X.; Berger, D. M.; Salaski, E. J.; Torres, N.; Dutia, M.; Hanna, C.; Hu, Y.; Levin, J. I.; Powell, D.; Wojciechowicz, D.; Collins, K.; Frommer, E.; Lucas, J. *J. Med. Chem.* **2010**, *53*, 7874.
110. Ren, L.; Wenglowky, S.; Miknis, G.; Rast, B.; Buckmelter, A. J.; Ely, R. J.; Schlachter, S.; Laird, E. R.; Randolph, N.; Callejo, M.; Martinson, M.; Galbraith, S.; Brandhuber, B. J.; Vigers, G.; Morales, T.; Voegtli, W. C.; Lyssikatos, J. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1243.
111. Heald, R. A.; Jackson, P.; Savy, P.; Jones, M.; Gancia, E.; Burton, B.; Newman, R.; Boggs, J.; Chan, E.; Chan, J.; Choo, E.; Merchant, M.; Rudewicz, P.; Ultsch, M.; Wiesmann, C.; Yue, Q.; Belvin, M.; Price, S. *J. Med. Chem.* **2012**, *55*, 4594.

112. Hu, Y.; Cole, D.; Denny, R. A.; Anderson, D. R.; Ipek, M.; Ni, Y.; Wang, X.; Thaisrivongs, S.; Chamberlain, T.; Hall, J. P.; Liu, J.; Luong, M.; Lin, L.-L.; Telliez, J.-B.; Gopalsamy, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4758.
113. Jiang, F.; Albert, D. H.; Luo, Y.; Tapang, P.; Zhang, K.; Davidsen, S. K.; Fox, G. B.; Lesniewski, R.; McKeegan, E. M. *J. Pharmacol. Exp. Ther.* **2011**, *338*, 134, and references cited therein.
114. Kankanala, J.; Latham, A. M.; Johnson, A. P.; Homer-Vanniasinkam, S.; Fishwick, C. W. G.; Ponnambalam, S. *Brit. J. Pharmacol.* **2012**, *166*, 737.
115. Sanphanya, K.; Wattanapitayakul, S. K.; Phowichit, S.; Fokin, V. V.; Vajragupta, O. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2962.
116. Bardelle, C.; Barlaam, B.; Brooks, N.; Coleman, T.; Cross, D.; Ducray, R.; Green, I.; Lambert-van der Brempt, C.; Olivier, A.; Read, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6242.
117. Deng, X.; Zhou, W.; Weisberg, E.; Wang, J.; Zhang, J.; Sasaki, T.; Nelson, E.; Griffin, J. D.; Jänne, P. A.; Gray, N. S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4579.
118. Lin, J.; Shen, W.; Xue, J.; Sun, J.; Zhang, X.; Zhang, C. *Eur. J. Med. Chem.* **2012**, *55*, 39.
119. Ye, L.; Ou, X.; Tian, Y.; Yu, B.; Luo, Y.; Feng, B.; Lin, H.; Zhang, J.; Wu, S. *Eur. J. Med. Chem.* **2013**, *65*, 112.
120. Argiriadi, M. A.; Goedken, E. R.; Banach, D.; Borhani, D. W.; Burchat, A.; Dixon, R. W.; Marcotte, D.; Overmeyer, G.; Pivorunas, V.; Sadhukhan, R.; Sousa, S.; St John Moore, N.; Tomlinson, M.; Voss, J.; Wang, L.; Wishart, N.; Woller, K.; Talanian, R. V. *BMC Struct. Biol.* **2012**, *12*, 22.
121. Kim, M. K.; Shin, H.; Cho, S. Y.; Chong, Y. *Bioorg. Med. Chem.* **2014**, *22*, 1156.
122. Padilla, F.; Bhagirath, N.; Chen, S.; Chiao, E.; Goldstein, D. M.; Hermann, J. C.; Hsu, J.; Kennedy-Smith, J. J.; Kuglstatter, A.; Liao, C.; Liu, W.; Lowrie Jr.; L. E.; Luk, K. C.; Lynch, S. M.; Menke, J.; Niu, L.; Owens, T. D.; O-Yang, C.; Railkar, A.; Schoenfeld, R. C.; Slade, M.; Steiner, S.; Tan, Y.-C.; Villaseñor, A. G.; Wang, C.; Wanner, J.; Xie, W.; Xu, D.; Zhang, X.; Zhou, M.; Lucas, M. C. *J. Med. Chem.* **2013**, *56*, 1677.
123. Herdemann, M.; Heit, I.; Bosch, F.-U.; Quintini, G.; Scheipers, C.; Weber, A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6998.
124. Herdemann, M.; Weber, A.; Jonveaux, J.; Schwoebel, F.; Stoeck, M.; Heit, I. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1852.
125. Barile, E.; De, S. K.; Carlson, C. B.; Chen, V.; Knutzen, C.; Riel-Mehan, M.; Yang, L.; Dahl, R.; Chiang, G.; Pellecchia, M. *J. Med. Chem.* **2010**, *53*, 8368.
126. Large, J. M.; Torr, J. E.; Raynaud, F. I.; Clarke, P. A.; Hayes, A.; di Stefano, F.; Urban, F.; Shuttleworth, S. J.; Saghir, N.; Sheldrake, P.; Workman, P.; McDonald, E. *Bioorg. Med. Chem.* **2011**, *19*, 836.
127. Staben, S. T.; Heffron, T. P.; Sutherlin, D. P.; Bhat, S. R.; Castanedo, G. M.; Chuckowree, I. S.; Dotson, J.; Folkes, A. J.; Friedman, L. S.; Lee, L.; Lesnick, J.; Lewis, C.; Murray, J. M.; Nonomiya, J.; Olivero, A. G.; Plise, E.; Pang, J.; Prior, W. W.; Salphati, L.; Rouge, L.; Sampath, D.; Tsui, V.; Wan, N. C.; Wang, S.; Weismann, C.; Wu, P.; Zhu, B.-Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6048.
128. Nacht, M.; Qiao, L.; Sheets, M. P.; St. Martin, T.; Labenski, M.; Mazdiyasi, H.; Karp, R.; Zhu, Z.; Chaturvedi, P.; Bhavsar, D.; Niu, D.; Westlin, W.; Petter, R. C.; Medikonda, A. P.; Singh, J. *J. Med. Chem.* **2013**, *56*, 712.
129. Giggs, A. C.; Abad, M. C.; Zhang, X.; Tounge, B. A.; Lewandowski, F. A.; Struble, G. T.; Sun, W.; Sui, Z.; Kuo, L. C. *J. Med. Chem.* **2010**, *53*, 7979.
130. Blanchard, S.; William, A. D.; Lee, A. C.-H.; Poulsen, A.; Teo, E. L.; Deng, W.; Tu, N.; Tan, E.; Goh, K. L.; Ong, W. C.; Ng, C. P.; Goh, K. C.; Bonday, Z.; Sun, E. T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2443.

131. Laufer, R.; Forrest, B.; Li, S.-W.; Liu, Y.; Sampson, P.; Edwards, L.; Lang, Y.; Awrey, D. E.; Mao, G.; Plotnikova, O.; Leung, G.; Hodgson, R.; Beletskaya, I.; Mason, J. M.; Luo, X.; Wei, X.; Yao, Y.; Feher, M.; Ban, F.; Kiarash, R.; Green, E.; Mak, T. W.; Pan, G.; Pauls, H. W. *J. Med. Chem.* **2013**, *56*, 6069.
132. Kusakabe, K.-I.; Ide, N.; Daigo, Y.; Tachibana, Y.; Itoh, T.; Yamamoto, T.; Hashizume, H.; Hato, Y.; Higashino, K.; Okano, Y.; Sato, Y.; Inoue, M.; Iguchi, M.; Kanazawa, T.; Ishioka, Y.; Dohi, K.; Kido, Y.; Sakamoto, S.; Yasuo, K.; Maeda, M.; Higaki, M.; Ueda, K.; Yoshizawa, H.; Baba, Y.; Shiota, T.; Murai, H.; Nakamura, Y. *J. Med. Chem.* **2013**, *56*, 4343.
133. Qi, H.; Chen, L.; Liu, B.; Wang, X.; Long, L.; Liu, D. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1108.
134. Laufer, S.; Bajorath, J. *J. Med. Chem.* **2014**, *57*, 2167.
135. Botta, M. *ACS Med. Chem. Lett.* **2014**, *5*, 270.