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Invited review

Imidazothiazole and related heterocyclic systems. Synthesis, chemical and biological properties

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Biological activities

ABSTRACT

Fused heterobicyclic systems have gained much importance in the field of medicinal chemistry because of their broad spectrum of physiological activities. Among the heterocyclic rings containing bridgehead nitrogen atom, imidazothiazoles derivatives are especially attractive because of their different biological activities.

Since many imidazothiazoles derivatives are effective for treating several diseases, is interesting to analyze the behavior of some isosteric related heterocycles, such as pirrolothiazoles, imidazothiadiazoles and imidazotriazoles. In this context, this review summarizes the current knowledge about the syntheses and biological behavior of these families of heterocycles. Traditional synthetic methodologies as well as alternative synthetic procedures are described. Among these last methodologies, the use of multicomponent reaction, novel and efficient coupling reagents, and environmental friendly strategies, like microwave assistance and solvent-free condition in ionic liquids are also summarized. This review includes the biological assessments, docking research and studies of mechanism of action performed in order to obtain the compounds leading to the development of new drugs.

1. Introduction

Heterocyclic compounds play a vital role in the metabolism of all living cells; most of them are five and six member heterocyclic compounds having at least one heteroatom in their nucleus and, in many cases, are fused with other heterocyclic ring. Fused heterocyclic systems have great interest in the field of medicinal chemistry because of their broad spectrum of physiological activities, such as anticancer, anti-inflammatory, antioxidant, antiviral and antimicrobial activities [1–3]. As an example, the work of Emini and col. [4] reported the effects of fused heterocycles on antiviral activity and pharmacokinetic properties of a series of 1,3,4-trisubstituted pyrrolidine C–C chemokine receptor antagonists.

Among fused five-membered heterocyclic rings containing bridgehead nitrogen atom, the levamisole (Fig. 1) is the most popular commercial derivative. This compound, apart from its anthelmintic properties, belongs to a general class of agents called biologic response modifiers, has immune-modulating and immuno-stimulating properties and it is also used in cancer adjuvant therapy. It helps to restore the function of certain cells of the body's defense system when they have been impaired. It is currently indicated in combination with 5-fluorouracil (5-FU) as adjuvant treatment after surgical resection of stage TNM 3 or Duke's C colon cancer over duration of one year postoperatively, and is also combined with radiation therapy for Duke's stage B2 and TNM stage 4 cancers [5].

The biological significance of levamisole aroused the interest of many researchers in studying structurally related aromatic heterocycles such as imidazothiazoles (Fig. 1). Although some compounds with this heterocyclic present in their structures showed anthelmintic properties but less than the levamisole [6], other derivatives showed a broad spectrum of biological activities, like as antipsychotic [7], antimicrobial [8], antifungal [9] and antitumor activities [10–13].

The proven effectiveness of imidazothiazoles for the treatment of several diseases attracted the scientific community towards the study of isosteric related fused heterocyclic systems, such as pyrrolothiazoles, imidazotriazoles and imidazothiadiazoles.

In this context, the pyrrolothiazole is an isostere of the imidazothiazole system, where the nitrogen atom of imidazolic ring was

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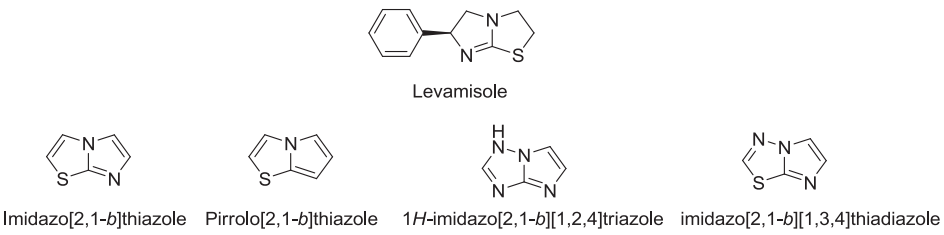


Fig. 1. Structure of levamisole, imidazothiazole and related fused heterocycles.

replaced by CH group (Fig. 1). The pyrrolothiazole derivatives show different applications, such as hepatoprotective [14], anticonvulsant [15], antidiabetic [16] between other activities [17].

On the other hand, imidazotriazole derivatives (Fig. 1), in which the thiazole ring present in the imidazothiazole is changed by other biologically attractive heterocycle, the triazole ring, showed antibacterial activity [18].

In addition, the imidazo[2,1-*b*][1,3,4]thiadiazole (Fig. 1) is other attractive fused heterocyclic nuclei discovered in the early 1950's and since then have been extensively studied. This heterocyclic system is an isostere of imidazothiazole in which the 3-CH group of thiazole ring is substituted by 3-*N*.atom. As in the case of imidazothiazole compounds, a variety of biological activities for a large number of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives has been reported, such as antibacterial, anticancer, anthelmintic, antifungal, anticonvulsant, anti-inflammatory, analgesic, antipyretic, local anesthetic, cardiotonic, diuretic, leishmanicidal and herbicidal activities [19,20].

The vast number of bioactive compounds containing some of these fused heterocycles and the large amount of papers and reviews recently reported show the interest of scientific community in this field.

On the other hand, the broad spectrum of biological activities (i.e. antitumoral, antiviral) has stimulated the study of new synthetic approaches giving special attention in the key reactions involved in the mechanisms proposed.

In this review we summarized the novel and efficient synthetic developments to prepare imidazothiazole derivatives and their isosteric heterocyclic ring: pyrrolothiazole, imidazotriazole and imidazothiadiazole.

Also, we present their biological activities, the mechanism of action, the docking studies and we show the differences biological behavior between the isosteric heterocyclic systems including their toxicity. The perspectives of these heterocyclic derivatives to be used for clinical applications are also discussed.

2. Imidazo[1,2-*b*]thiazole

A traditional methodology to obtain imidazothiazoles involves the reaction of α–substituted ketones with sulfur heterocycles (Scheme 1) [21].

There are also reports of this kind of sulfur heterocyclic systems reacting with acyl chlorides, esters or even carboxylic acids substituted on α-position with a halogen atom to yield imidazo[1,2-*b*]thiazoles [22,23]. For example, treating phenacyl bromide derivatives (**1a**–**c**) with thiourea, 2-amino-4-arylthiazoles (**2a**–**c**) were obtained. Reaction of these sulfur heterocycles with chloroacetic acid led to the obtention of 3-arylimidazo[2,1-*b*]thiazol-6(5*H*)-one (**3a**–**c**) in 72–82% yield, as it shown in Scheme 2 [23,24].

Many researchers have employed the synthetic strategies described above to obtain a variety of imidazothiazole derivatives which show a broad spectrum of therapeutic properties. Recently, Andreani et al. reported the synthesis and anticancer properties of imidazo[2,1-*b*]thiazolic ring with polyphenol groups as substituents [25]. Compounds **4** and **5** (Fig. 2) showed inhibition of the transcription factor NFκB (nuclear factor kappa beta, involved in the cancer development and progression) with IC_{50} of 0.36 ± 0.42 μM and 0.53 ± 0.4 μM respectively, using tosyl phenylalanyl chloromethyl ketone; IC_{50} 3.8 ± 1.1 μM and BAY-11(IC_{50} 2.0 ± 0.54 μM) as positive controls. The antioxidant activity of compound **5** is similar to that of quercetin, a powerful natural antioxidant. Both compounds **4** and **5** also enhanced the activity of NAD (P) Quinone reductase 1 (QR1), a cytoprotective enzyme, which protects against carcinogenesis by detoxifying and eliminating carcinogens (4′-bromoflavone are using as a positive control) [26].

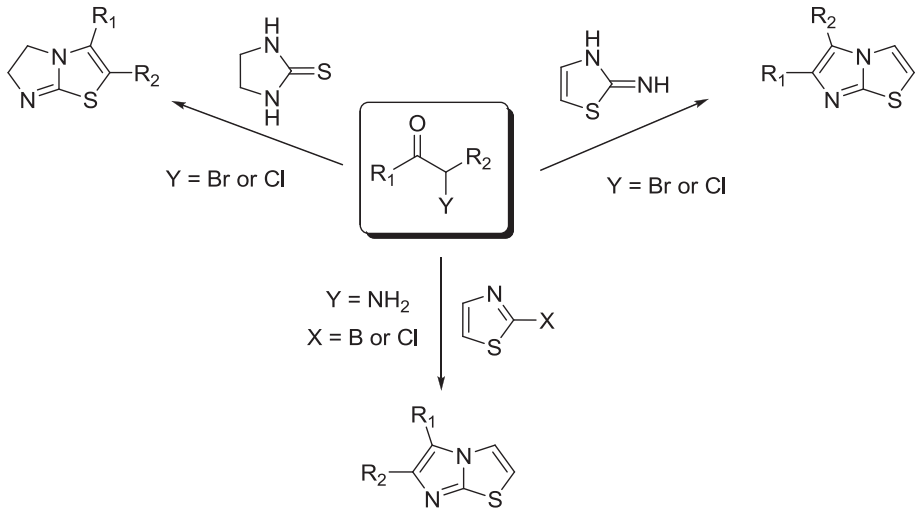
Among the broad spectrum of imidazothiazoles possessing antitumoral activity [10–13,27–33], those bearing a pyrazole ring were thoroughly studied [34–39]. In this context, Ali et al. [40] reported the synthesis of a series of imidazothiazole pyrazole derivatives obtained by refluxing different 3-aryl-6-hydrazinylimidazo[2,1-*b*]thiazoles with diethyl malonate, ethyl acetoacetate or acetylacetone in glacial acetic acid. Compounds bearing pyrazolidine-3,5-dione (**6a**–**c**), 3-methyl-1*H*-pyrazol-5(4*H*)-one (**7a**–**c**) or 3,5-dimethyl-1*H*-pyrazoles (**8a**–**c**) as substituent showed to be promising leads for further development of anticancer drugs (Fig. 3).

On the other hand, Andreani et al. reported the synthesis of imidazo[2,1-*b*]thiazole guanylhydrazone derivatives endowed with antitumor and cardiotonic activity [33]. These products were obtained by coupling an imidazothiazol appropriately substituted with and hydrazine hydrate (Scheme 3).

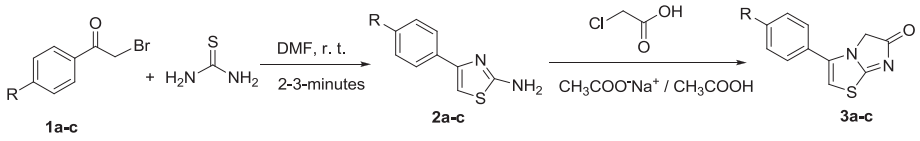
The authors pointed that a 3- or 4-nitrophenyl group (Fig. 4) is a suitable pharmacophoric group in the imidazothiazole guanylhidrazones series, giving rise to three potent antitumoral agents (**9**–**11**). Between them, the pharmacological profile of compound **11** was more promising since in six cellular lines (leukemia, non-small cell lung cancer, colon, melanoma, ovarian and breast cancer) it was possible to note a significant difference between cytostatic and cytotoxic doses. Even though the mechanism of action was not determined, an interesting concomitant cardiotonic effect was found in two of the studied compounds (**9** and **11**). These "bivalent functions" could help to prevent antitumor induced apoptosis of cardiac myocytes.

In a more recently work, Andreani et al. [11] tested, as cytotoxic agents and as RSK2 inhibitors, a new series of imidazo[2,1-*b*]thiazole guanylhydrazones. Particularly, the analogues of compound **9**, such as 2-F, 2-Br and 2-Cl-7-(4-nitrophenyl)-imidazo[2,1-*b*]thiazole guanylhydrazones showed high degree of selectivity for inhibition of RSK2 kinase compared to a spectrum of other related kinases. These results turn the members of this family of compounds into promising leads for the development of novel drugs intervening in the growth and metastasis of tumor cells.

Besides, pyrimidinyl substituted imidazo[2,1-*b*]thiazole derivatives were reported as Rapidly Accelerated Fibrosarcoma (RAF) kinases inhibitors [41]. This class of inhibitors has good impact



Scheme 1. Traditional methodologies to obtain imidazothiazoles from sulfur heterocycles.



a: R= H; b: R= Cl; c: R= CH_3

Scheme 2. Synthesis of 3-arylimidazo[2,1-*b*]thiazol-6(5*H*)-one.

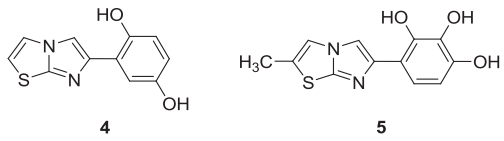
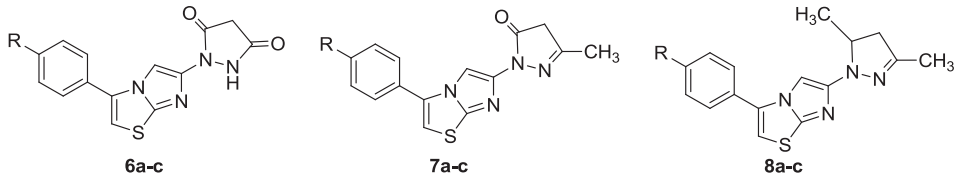


Fig. 2. Imidazothiazoles endowed with polyfenolic structures.

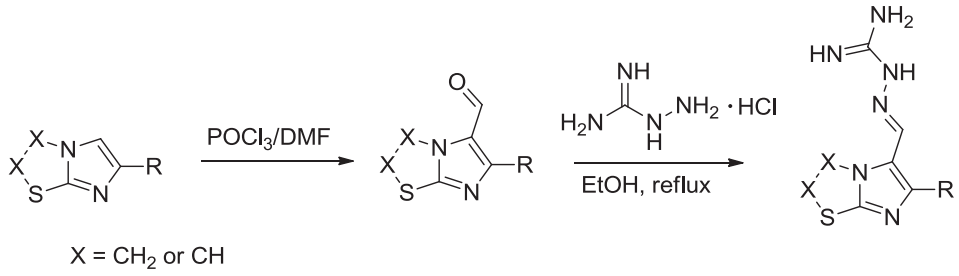
against different cancer types including melanoma. Compounds **12** and **13** showed in Fig. 5 were more selective for melanoma cell lines than for other cancer types. The IC_{50} of these compounds was in sub-micromolar scale over six melanoma cell lines (MALME-3M, M14, MDA-MB-435, SK-MEL-28, UACC-257, UACC-62) [41].

The targets compounds were successfully synthesized from 2-aminothiazoles as is shown in Scheme 4. The precursor 2-aminothiazole was refluxing with α-bromo-3-



a R=H; b: R=Cl; c: R=CH_3

Fig. 3. Imidazothiazole pyrazole derivates synthesized by Ali.



Scheme 3. Synthesis of imidazo[2,1-*b*]thiazole guanylhydrazones.

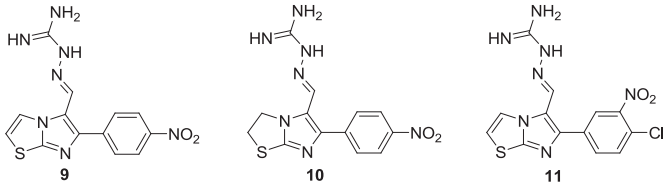


Fig. 4. Imidazo[2,1-*b*]thiazole guanylhydrazones.

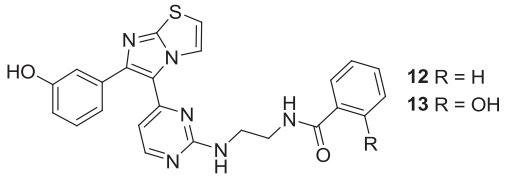


Fig. 5. Structure of pyrimidinyl substituted imidazo[2,1-*b*]thiazoles.

methoxyacetophenone obtaining the cyclic 6-(3-methoxyphenyl) imidazo[2,1-b]thiazole. Heating this last compound with 4-iodo-2-(methylthio)pyrimidine in presence of palladium acetate, cesium carbonate, and triphenylphosphine afforded the corresponding methylthiopyrimidinyl derivative.

The oxidation of the sulfide moiety using oxone gave the corresponding sulfonyl compound derivative, the key intermediate compound. The side chain was introduced refluxing this sulfonyl compound with the corresponding amine derivative in presence of diisopropylethylamine (DIPEA). Finally, the demethylation of the methoxy group was carried out in presence of boron tribromide yielding the corresponding hydroxyl target compounds.

As another example of imidazothiazoles biologically active, we could mentioned the 2,5-disubstituted imidazothiazole derivatives SRT1460, SRT1720, and SRT2183 (Fig. 6), which result to be the first synthetic Sirtuin 1 activating compounds (STACs) [42]. Sirtuin 1 (SIRT1) is an enzyme that removes the acetyl groups of the proteins involved in cellular regulation. It was demonstrated that transgenic mice overexpressing SIRT1 are leaner than their control littermates, displaying a significantly improved metabolic profile.

A wide variety of age related diseases in animal models including cancer, Alzheimer's disease, and type 2 diabetes are related to upregulation of SIRT1. Several studies have demonstrated a protective role for SIRT1 in reducing tumor number and growth in colon cancer, prostate cancer, and DNA damage induced thymic lymphomas [43].

Although it is generally accepted that STACs increase SIRT1 activity *in vivo*, two opposing mechanism models were proposed to account that activity: (i) direct allosteric activation of Sir2/SIRT1; and (ii) indirect activation resulting from off-target effects. Hubbard et al., have proposed an assisted-allosteric activation (AAA) mechanism in which STACs bind to a substrate-induced exposited on SIRT1 and in turn stabilize substrate binding and subsequent deacetylation [44,45] (Fig. 7).

Although the resveratrol (3,5,4′-trihydroxystilbene) is the most potent of the natural activators of SIRT1, the synthetic imidazothiazoles SIRT1 activating showed a similar response to the resveratrol but at a much lower concentration.

The potency of the drugs were evaluated by determining the concentration of compound required to increase enzyme activity by 50% ($EC_{1.5}$) and the maximum percentage of activation achieved at the highest doses of compound tested. While resveratrol present an $EC_{1.5}$ = 46.2 μM and maximum activation = 201%, the imidazothiazole SRT1460, SRT2183 and SRT1720 showed values of $EC_{1.5}$ = 2.9 μM, 0.36 μM and 0.16 μM, and maximum activation = 447%, 296% and 781%, respectively.

The first synthetic pathway to obtain the SIRT1 inhibitors was described by Vu et al. [46]. The imidazo[1,2-*b*]thiazoles ethyl esters were obtained in good yield (79%) from a mixture of 2-aminothiazole-4-carboxylate or 2-aminothiazole-5-carboxylate and 2-bromo-1-(2-nitrophenyl)ethanone in methyl ethyl ketone under reflux conditions for 18 h (Scheme 5) [47]. The following steps involved the reduction of the ester group to the corresponding alcohol and its conversion into the corresponding mesilate derivative. The subsequent displacement of this last group with a variety of amines gave the corresponding tertiary amines. Finally, the reduction of the nitro group and its reaction with a variety of acid chlorides gave the analogues shown in Scheme 5.

Besides, the authors proposed an alternative synthetic pathway to obtained imidazothiazole derivative **15** (Scheme 6). In this case, the aminothiazole derivative was synthesized using a palladium coupling reaction between the bromide and the boronic acid. After reaction of aminothiazole with ethyl bromopyruvate, an imidazothiazole derivative **14** was obtained. Standard reduction of the nitro group with sodium hydrosulfide hydrate followed by amide coupling and ester hydrolysis afforded the final product **15,** which was unable to activate SIRT1.

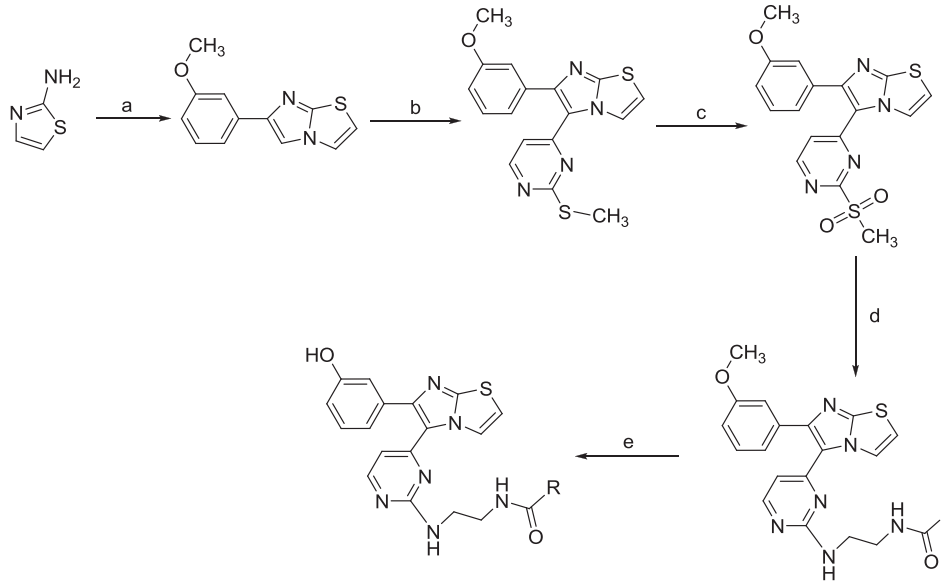
Substituted imidazothiazoles have also been proved to be useful for the treatment of some heart diseases. The 1,4-dihydropyridines (1,4-DHPs), such as Nifedipine (Fig. 8), are a L-type calcium channel (LTCCs) blockers. This kind of drugs has a critical role in the treatment of different cardiovascular pathologies [48]. Unfortunately, it is well known that high doses of these drugs cause also a variety of brain pathologies, but it is not clear if these effects are mediated by LTCCs o by other blocking agents, because there is not a selective LTCC modulator for the brain. Indeed, Nifedipine binds both $Ca_v1.2$ (widely expressed in cardiovascular systems and in neurones) and Ca_v 1.3 (predominantly expressed in neurons) with high affinity.

The replacement of the phenyl group on C-4 position of the niferipine (using as the reference drug) by an imidazo[2,1-*b*]thiazole group [49] confers to the dihydropyridine scaffold a high selectivity toward the nonvascular tissue without inotropic and/or chronotropic effects on cardiovascular tissues. The selectivity and potency of drugs were correlated with the substituents and their positions on the heterocyclic system (SAR). Thus, the presence of a methyl group in R_1 and a chlorine or 6-nitro-2,5-dimethoxyphenyl in R_2 position led to the compounds with the best inotropic potency (Fig. 8); the best chronotropic potency was found when R_1 was H and R_2 was 3,5-dimethoxyphenyl. However, the best inotropic selectivity was observed when R_2 was 4-nitro-2,5-dimethoxyphenyl and R_1 was CH_3, while the best chronotropic potency was found when R_1 was H and R_2 was 3-methoxyphenyl.

Locatelli et al. [50], synthesized a small library of compounds to study the influence of chemical modifications of the imidazo[2,1-*b*] thiazole-1,4-DHPs on the peripheral and central activity and/or on the selectivity of calcium channel. The authors took into account the inotropic or chronotropic effects caused by substituents of the heterocyclic ring [49].

Syntheses were accomplished by one pot condensation of the appropriate β-ketoester, methylacetoacetate or ethylacetoacetate with and aldehyde (Hantzsch reaction) (Scheme 7).

The imidazo[2,1-*b*]thiazole-1,4-DHPs were subjected to functional assays and bindings studies. Most of the derivatives showed interesting activity profile exhibiting both negative inotropic and chronotropic properties. Besides, all the compounds had no effect on vascular muscle while all of them were able to inhibit K^+ induced contraction on guinea pig nonvascular smooth muscle. To further investigate this selectivity, computational studies were also carried out. For these studies, only compounds able to inhibit K^+ induced contraction with strong selectivity have been chosen



Scheme 4. Reagents and conditions: a) α-bromo-3-methoxyacetophenone, ethanol, reflux-16 h; b) 4-iodo-2-(methylthio)pyrimidine, $Pd(OAc)_2$, $CsCO_3$, PPh_3, DMF, 80 °C, 12 h; c) oxone, metanol, water, rt, 16 h; d) $H_2NCH_2CH_2NHCOR$, DIPEA, DMSO, 80 °C, 8 h; e) BBr_3, CH_2Cl_2, −78 °C, 30 min then rt, 1 h.

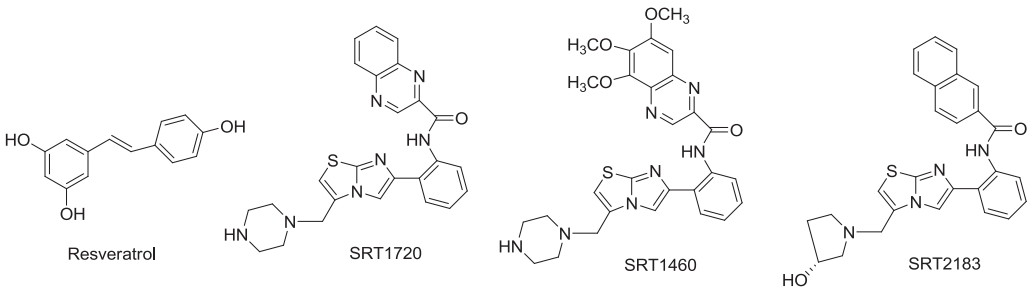


Fig. 6. Sirtuin 1 activanting structures.

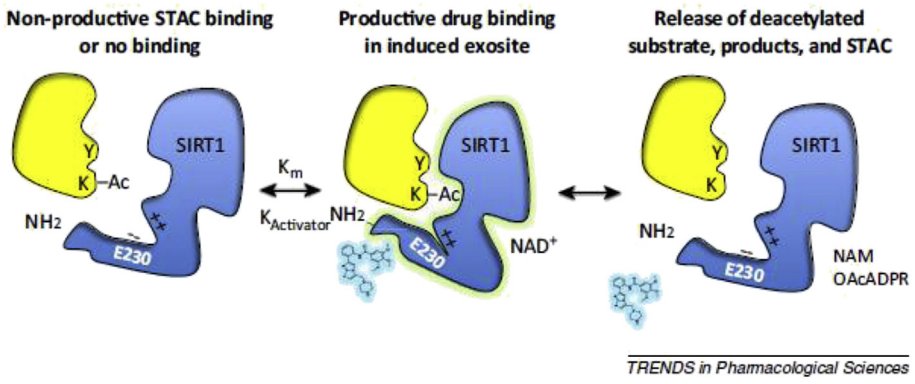


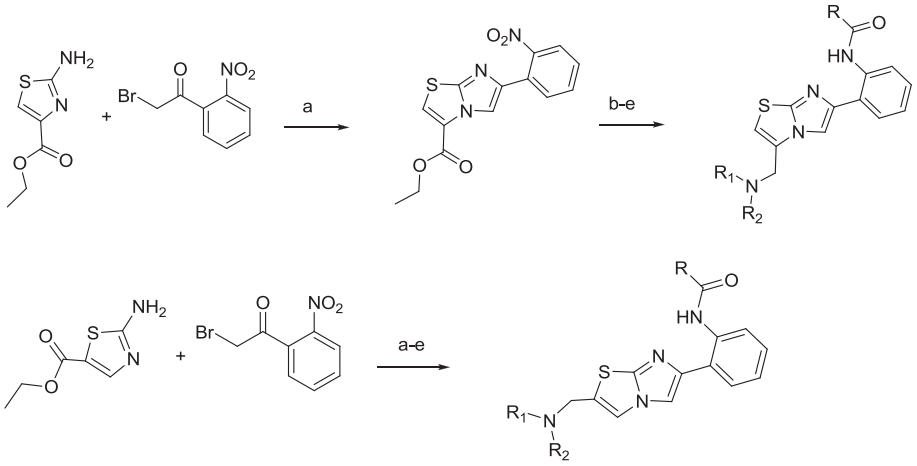
Fig. 7. Proposed mechanism for allosteric SIRT1 activation by sirtuin activating compounds (STACs). Reprint from Trends Pharmacol. Sci., Vol. 35, P. Hubbard, D. A. Sinclair, Small molecule SIRT1 activators for the treatment of aging and age-related diseases, 146–154, Copyright© 2014, with permission from Elsevier Ltd.[45].

(Fig. 9). Docking results could not explain this selectivity since they revealed that compounds were able to share the same binding pose (Fig. 10) within the LTCC, regardless the considered isoform ($Ca_v1.2$ and $Ca_v1.3$). These results were reasonable giving the high sequence identity of two binding sites, but it leaves the explanation of the selectivity of these compounds unresolved.

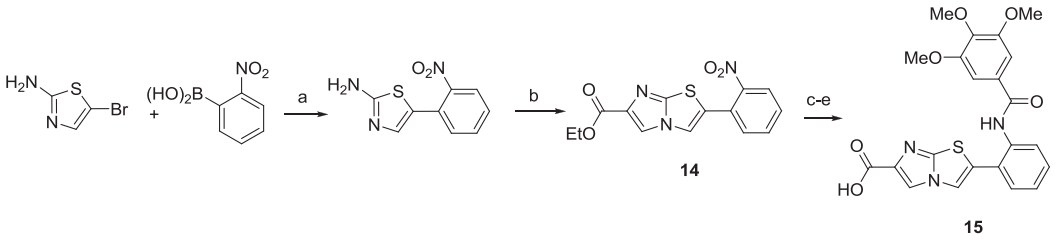
However, since $Ca_v1.2$ and $Ca_v1.3$ channels have diverse and essential functions the development of an isoform-selective activator or blocker could be therapeutically valuable in a wide range of diseases.

The imidazothiazoles described above were in all cases obtained by traditionally methodologies using sulfur heterocycles as raw materials and the availability of these sulfur heterocycles restricts the type of substitution of the final products.

The interest in this heterocyclic family led to many scientists to work in the development of novel synthetic pathways. In this sense,



Scheme 5. Reagents and conditions: (a) methyl ethyl ketone, reflux; (b) LiOH, isobutyl chloroformate, DIEA, THF, $NaBH_4$; (c) MsCl, Et_3N; NHR_1R_2, DIEA; (d) NaHS, MeOH, H_2O, reflux; (e) RCOCl, pyridine, microwave, 140 °C × 10 min; for NR_1R_2) Boc-piperazine, 25% TFA in CH_2Cl_2.



Scheme 6. . Reagents and conditions: (a) toluene, EtOH, H_2O, [1,1′-bis(diphenylphosphino) ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (1:1), Na_2CO_3, 90 °C; (b) ethyl bromopyruvate, methyl ethyl ketone, reflux; (c) sodium hydrosulfide hydrate, MeOH, H_2O, reflux; (d) 3,4,5-trimethoxybenzoyl chloride, pyridine, microwave, 160 °C × 10 min; (e) THF, H_2O, NaOH.

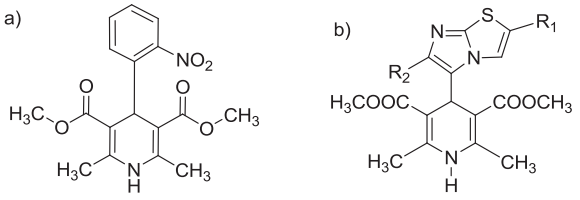
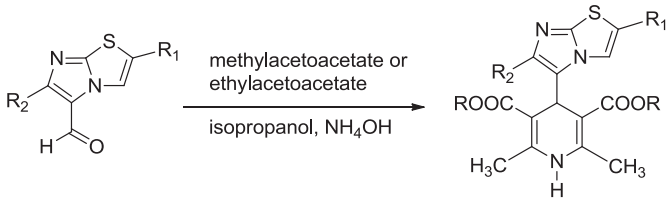


Fig. 8. Structure of a) nifedipine and b) the new imidazo[2,1-*b*]thiazole derivatives.



16 R: methyl; R_1: methyl; R_2: 4-nitro-2,5-dimethoxyphenyl
17 R: methyl; R_1: methyl; R_2: Cl
18 R: methyl; R_1: H; R_2: 2-(trifluormethoxy)phenyl

Scheme 7. Synthesis of the three most active imidazo[2,1-*b*]thiazole-1,4-DHPs.

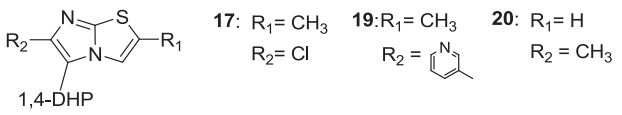


Fig. 9. Structure of the imidazo[2,1-*b*]thiazole-1,4-DHPs derivatives.

a coupling reaction to obtain 6-substituted imidazothiazoles was reported by Kamali et al. [51]. The authors have developed a successful coupling of a thiazolium alkyne using palladium/cupper as catalyst (Sonogashira coupling) in presence of sodium lauryl sulfate as the surfactant and cesium carbonate as the base, in a water medium. A plausible mechanism for the formation of 6-substituted imidazo[2,1-*b*]thiazoles at 60 °C is showed in Scheme 8.

Treatment of 2-aminothiazole with propargyl bromide in refluxing acetonitrile afforded 2-amino-3-(2-propynyl)thiazolium bromide in good yield. Reactions of this compound with aryl iodides (ArI) and cesium carbonate in water in the presence of bis(-triphenylphosphine)palladium(II) chloride, copper iodide, and sodium lauryl sulfate at 60 °C, allows obtaining 6-substituted imidazo[2,1-*b*]thiazoles in moderate to high yields.

Mechanistically, the synthesis of 6-substituted imidazo [2,1-b] thiazoles involves as a first step, the formation of ArPdI through oxidative addition of Pd (0) to ArI [36] and the subsequent transmetallation ArPdI with Cu salt, to produce the alkynyl palladium intermediate. Extrusion of Pd (0) leads to obtain the alkyne. A subsequent isomerization to allene intermediate and sequential attack of the amino group gives the cyclized product, 6-substituted imidazo [2,1-b] thiazoles (Scheme 8).

Barradas et al. obtained substituted imidazo[2,1-*b*]thiazoles by convergent synthetic pathways (Scheme 9) [52,53].

It is important to note the versatility of this synthetic strategy due to both the *N,N*-dimethyl-*N*′-(thiazol-2-yl)amidine and α-bomoketone can be obtained from carbohydrate derivatives, leading to compounds with different substitution pattern. In Scheme 10 is shown the mechanism involving in the key reaction of the synthesis.

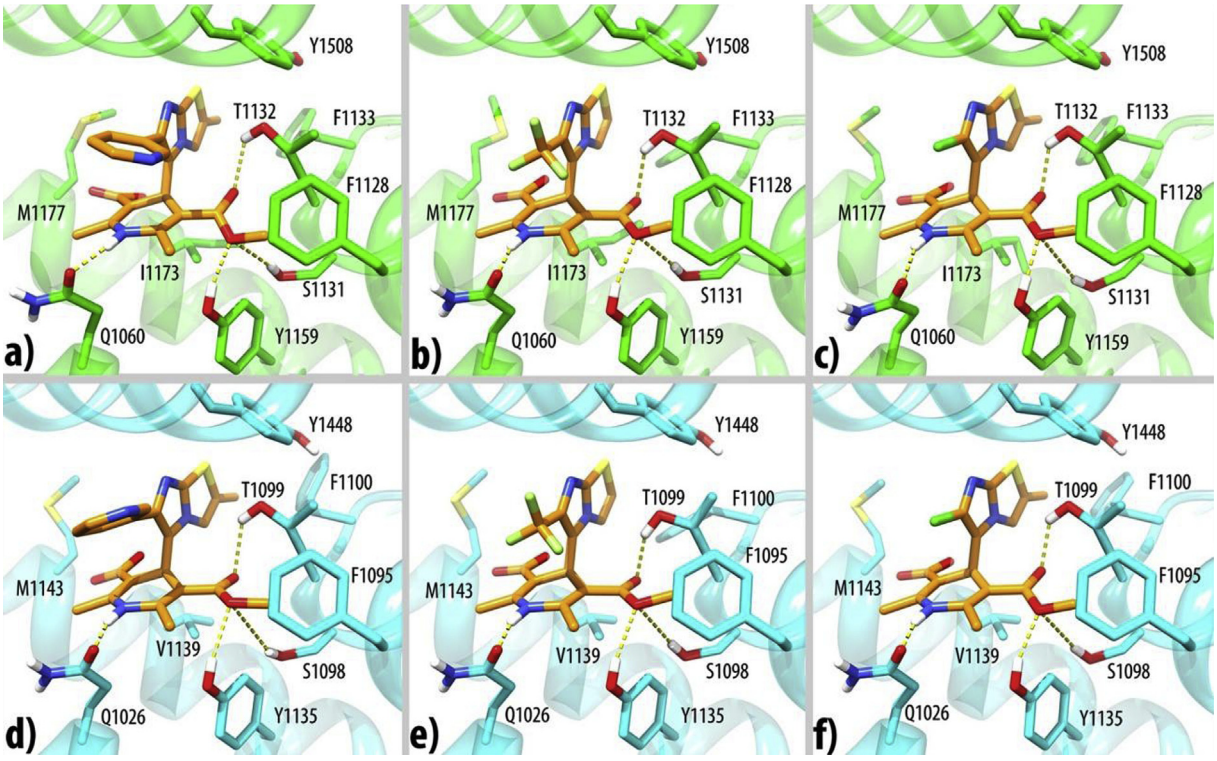


Fig. 10. Docked structures of **19** (a,d), **20** (b,e), and **17** (c,f) in the three-dimensional structure of $Ca_v1.2$ (a–c) and $Ca_v1.3$ (d–f) LTCC. DHPs are displayed as orange sticks, and key interacting residues are shown in green ($Ca_v1.2$) and cyan ($Ca_v1.3$). Hydrogen bonds as represented with dashed yellow lines. Reprinted with permission from A. Locatelli, S. Cosconati, M. Micucci, A. Leoni, L. Marinelli, A. Bedini, P. Ioan, S.M. Spampinato, E. Novellino, A. Chiarini, R. Budriesi, Ligand based approach to L-type calcium channel by imidazo [2.1*b*]thiazole-1,4-dihydropyridines: from heart activity to brain affinity, J. Med. Chem. 56 (2013) 3866–3877, Copyright © 2013, American Chemical Society [50].

The cyclization step was performed in two different conditions by using thermal or microwave heating. Comparing the results of both methodologies, the authors found that the microwave assistance is an improved alternative to obtain this family of heterocyclic compounds. Compounds were evaluated as antiviral agents against Junin virus (JUNV) (etiological agent of hemorrhagic fever). The most active compounds (**22** and **23**), showed a level of antiviral activity against JUNV in monkey Vero cells better than the ribavirin (reference substance). Then, they proved to be promising lead compounds for further analysis and characterization to establish their therapeutic potential against hemorrhagic fever viruses.

More recently, Babu and col [54]. describes a novel and efficient synthesis of new diversely functionalized fused imidazole analogues. Babu employed simple solvent-free and catalyst-free conditions in ionic liquid. The short reaction time, good isolated yields, and the environmentally benign reaction media are the more significant features of this protocol, which provides direct access for regioselective synthesis of fused imidazo-heterocycles.

3. Pyrrolo[2,1-b]thiazole

Pyrrolo[2,1-*b*]thiazoles possess the same hydrocarbon skeleton than the imidazothiazoles with the isosteric replacement of nitrogen for a carbon atom at position seven of the heterocyclic ring. Tverdokhlebov [17] reported a review where summarized the advances of the synthetic methodologies, properties and utilities of pyrrolothiazoles and related compounds. This work involved the scientific researches in this field between 1940 and 2005 years.

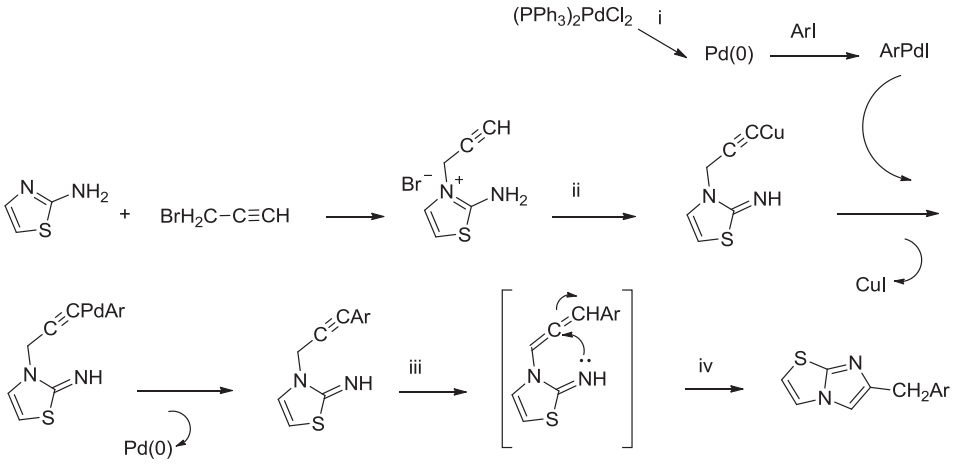
Among this family, the benzo[d]pyrrolo[2,1-*b*]thiazole nuclei have been proved to possess antitumor properties. In this context, a series of novel 2,3-bis(hydroxymethyl)benzo[d]- pyrrolo[2,1-*b*] thiazoles and their bis(alkylcarbamate) derivatives were synthesized starting from benzothiazole. Acyl or aryl chloride was added to a solution of benzothiazole in methylene chloride, then a catalytic amount of aluminum chloride and trimethylsilyl cyanide was incorporate to obtain compound 30. This last compound was treated with tetrafluoroboric acid in ether, and directly further reacted with dimethyl acetylenedicarboxylate (DMAD) to yield the diester **31** in low yields.

The diester was reduced to the corresponding bis-alcohol derivative **32** using $LiAlH_4$ in a mixture of ether/CH_2Cl_2. Treatment of **32** with ethyl or isopropyl isocyanate in the presence of triethylamine afforded the desired bis(ethylcarbamate) or bis(isopropylcarbamate) derivatives (**33** or **34**, respectively) in good yield. It is important to note that all reactions were performed with different derivatives given **30**–**34a**–**j** compounds [55] (Scheme 11).

The anti-proliferative activity of these agents against human leukemia and various solid tumor cell growths was studied *in vitro*. The structure–activity relationship studies revealed that the bis(alkylcarbamates) derivatives are generally more cytotoxic than the corresponding bis(hydroxymethyl) congeners in inhibiting human lymphoblastic leukemia CCRF-CEM and various human solid tumor cell growth in culture. These agents have no cross-resistance to taxol or vinblastine (antitumor agents that have significant activity in several human malignancies).

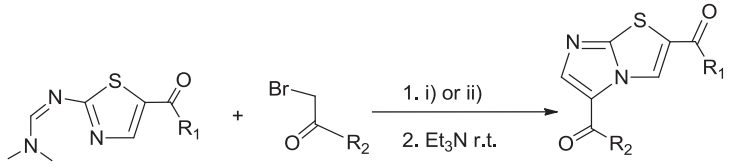
Studies on the therapeutic effect against human breast carcinoma MX-1 xenograft showed that complete tumor remission (CR) were achieved by treating with C1-4′-F- or C1-4′-Cl-Ph-bis(*i*-propylcarbamate) derivatives (**34b** and **34c**, respectively) and more than 99% tumor suppression by the corresponding bis(ethylcarbamates) **33b** and **33c** at the maximal tolerated dose. Alkaline agarose gel shifting assay revealed that the newly synthesized compounds are able to induce DNA interstrand cross-linking [55].

Soares et al. synthesized a series of chiral 1*H*,3*H*-pyrrolo[1,2-*c*] thiazoles with the aim to find the best compound with anti-breast cancer properties. In a first work [56] these authors found that



Ar: 2-NO_2-C_6H_4; 4-NO_2-C_6H_4; 2-CH_3-4-NO_2-C_6H_3; 2-Cl-4-NO_2-C_6H_3; 4-Cl-2-NO_2-C_6H_3; 4-Cl-3-NO_2-C_6H_3;

Scheme 8. (i) Reduction of Pd(II) to Pd(0) with alkyne and Cs_2CO_3; (ii) CuI, Cs_2CO_3; (iii) isomerization to an allene with CuI, Cs_2CO_3; (iv) intermolecular nucleophilic attack.



Reagents : i) Thermal condition: dioxane (anh.) reflux,16 h
ii) Microwave condition: THF (anh.) 300W, 105°C, 90 -150 m

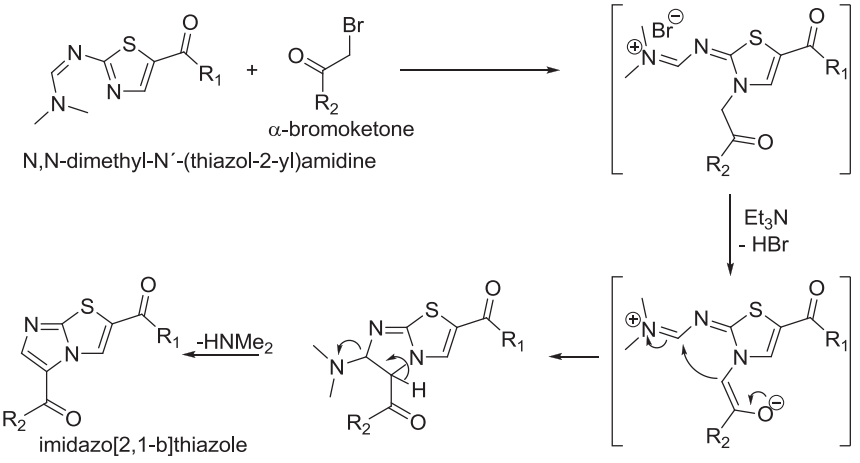
21 R_1 = -phenyl
22 R_1 = -p-bomophenyl
23 R_1 = -p-chlorophenyl
24 R_1 = -p-chlorophenyl

R_2 =

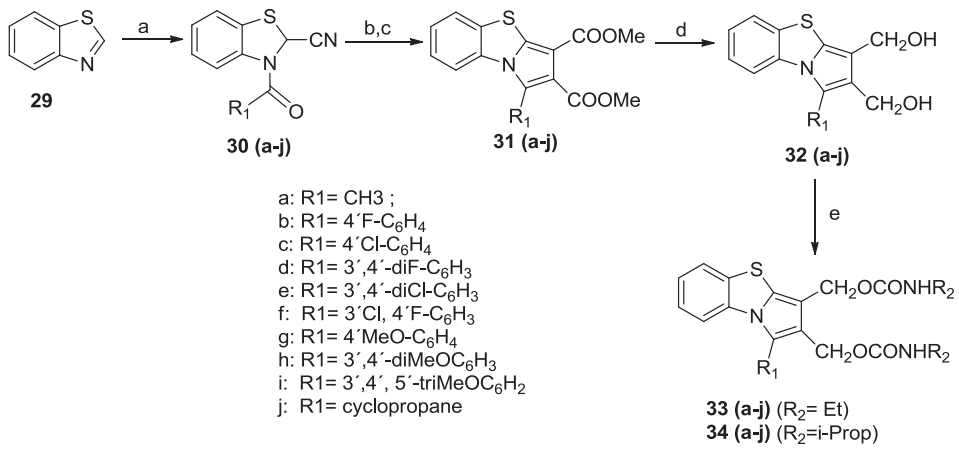
25 R_2 = -phenyl
26 R_2 = -p-bomophenyl
27 R_2 = -p-chlorophenyl
28 R_2= -p-chlorophenyl

R_1=

Scheme 9. Convergent synthetic pathway to obtain imidazothiazoles.



Scheme 10. Synthetic mechanism proposed to obtained imidazo[2,1-*b*]thiazoles from *N,N*-dimethyl-*N′*-(thiazol-2-yl)amidine and α-bromoketone.



Scheme 11. Reagents and conditions: a) acyl or aryl chloride/$AlCl_3$/trimethylsilyl cyanide/CH_2Cl_2,rt; b) tetrafluoroboric acid in ether; c) DMAD/DMF, rt; d) $LiAlH_4$/CH_2Cl_2/ether 0 °C; e) R_2NCO/TEA.

compound **35** had a very high performance against breast cancer cell lines MCF7 (IC_{50} 1.0 μM) (Fig. 11). In a later article [57] structural changes on this lead compound were performed in order to propose a possible structure–activity relationship.

The results of the activity *in vitro* allowed the authors draw conclusions regarding structure–activity relationships. Thus, they were able to demonstrate that the presence of a phenyl group at C-3 and a methyl group at C-5 in the 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole moiety is crucial to the cytotoxic activity against MCF7 breast cancer cell line. To probe whether the absolute configuration of the lead compound (**35**), a chiral compound with R configuration, might affect the anticancer activity, its enantiomer (compound **42**) was prepared and the activity against MCF7 cells was evaluated, resulting to be the most active compound, with IC_{50} value of 0.3 μM.

Recently, Barradas et al. [58] synthesized two series of pyrrolo [2,1-*b*]thiazoles substituted with a *p*-halophenyl and 1,2-*O*-isopropylidene-3-*O*-methyl carbohydrate group at C-2 and C-5 position (Fig. 12).

The synthetic pathway is shown in the Scheme 12. The first step involves the reaction of the thiazadiene (**43**) with α-haloketones allows obtaining the thiazole intermediates. A second reaction with other α-haloketone in presence of a base yielded the 2,5-disubstituted-pyrrolo[2,1-*b*]thiazoles. In this synthetic pathway, one of the α-haloketone used was 6-bromo-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylohexofuranos-5-ulose or 6-bromo-6-deoxy-1,2-*O*-isopropylidene-3-*O*-p-methoxybenzyl-α-D-xylo-hexofuranos-5-ulose, while the other α-haloketone was a *p*-halophenyl group.

These series of pyrrolo[2,1-*b*]thiazole derivatives were evaluated against JUNV. Unfortunately, eventhough most of the compounds were active inhibitors of JUNV in Vero cells, they were also

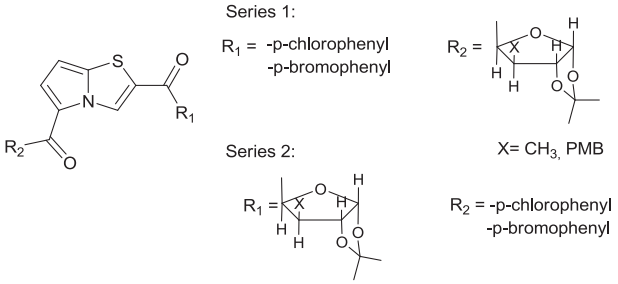


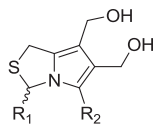
Fig. 12. Pyrrolo[2,1-*b*]thiazoles substituted at positions 2 and 5.

cytotoxic at low concentrations (see Table 1).

Comparison of these results with those obtained by analyzing the antiviral activity of imidazothiazoles with equal substitution pattern [53], shows that the isosteric replacement of the nitrogen at position 7 of the heterocyclic ring by a methine group, lead to the loss of selectivity of these compounds.

4. Imidazotriazoles

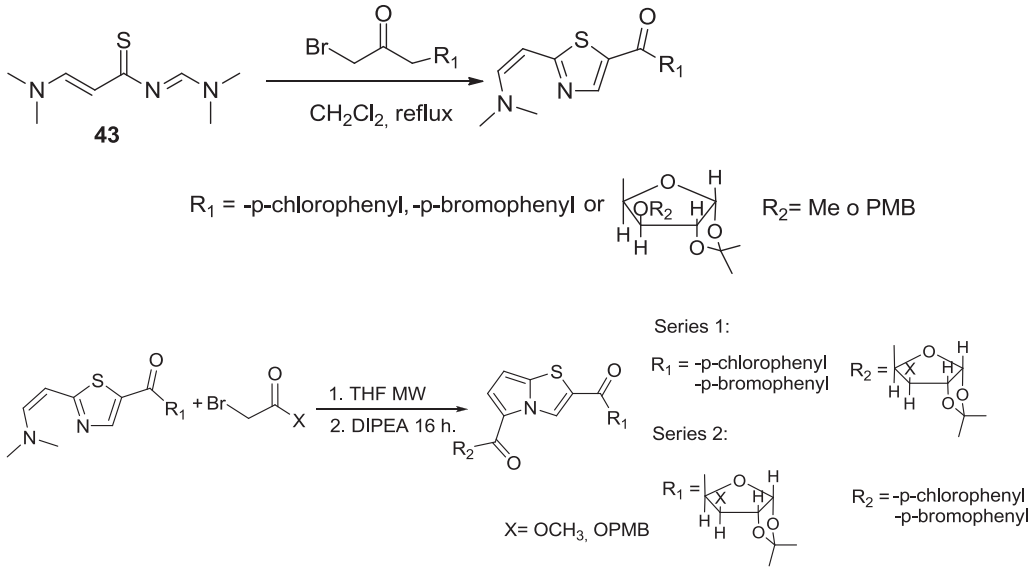
There are many reports of [1,2,4]-triazoles possessing pharmacological activities and, as examples, we could mention: alprazolam (tranquilizer) [59], estazolam (hypnotic, sedative, and tranquilizer), rilmazafon (hypnotic, anxiolytic), benatradin (diuretic), trapidil (hypotensive), trazodon (antidepressant, anxiolytic), etoperidone (antidepressant), nefazodone (antidepressant, 5-HT2 A-antagonist), anastrozole, letrozole, vorozole (antineoplastics, nonsteroidal competitive aromatase inhibitors), ribavirin (antiviral), fluconazole,



	35	36	37	38	39	40	41	42
R_1	(*R*)-Ph	H	(*R*)-3,4,5-$(MeO)_3C_6H_2$	(*R*)-Ph	(*R*)-pyridyl	(*R*)-Ph	(*R*)-Ph	(*S*)-Ph
R_2	Me	Me	Me	H	H	Ph	4-FC_6H_4	Me
IC_{50}*	0.6	21.5	59.9	ND	30.6	70.2	26.4	0.30

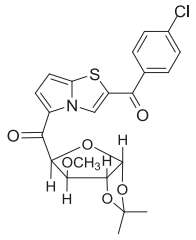
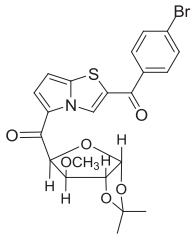
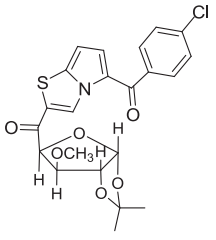
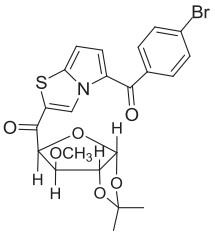
* Concentration (μM) needed to inhibit cell proliferation by 50% as determined from dosee-response curves by exponential decay fitting (r2 > 0.9).

Fig. 11. Structures of chiral 6,7-bis(hydroxymethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles and cytotoxicity of compounds 35–42 against MCF7 breast cancer cell lines. Cells were incubated during 96 h with a DMSO solution and then cell proliferation was evaluated by MTT test.



Scheme 12. Synthetic pathway to obtain pyrrolo[2,1-*b*]thiazoles substituted at positions 2 and 5.

Table 1
Cytotoxicity and antiviral activity of pyrrolo[2,1-b]thiazoles.

Compound				
Cytotoxicity MNCC (mM)[a]	12.5	12.5	>50	>50
Antiviral activity[b]	97.8	98.1	75.0	Inactive

[a] Maximum noncytotoxic concentration (MNCC): maximum compound concentration at which there were no morphological differences when compared with control cells after 48 h incubation.
[b] Antiviral activity was determined as % inhibition in virus yield after 48 h of infection in cells infected with JUNV in the presence of 10 mM of each compound in comparison with cells infected without compound treatment.

itraconazole, terconazole (antifungal) [60–62]. The broad spectrum of biological activity of this family of compounds has stimulated the synthesis of imidazotriazoles to further investigate their therapeutic properties.

Traditional methodologies for the preparation of imidazotriazoles include the use of either imidazole [63] or 1,2,4- triazole derivatives [64] as the starting materials.

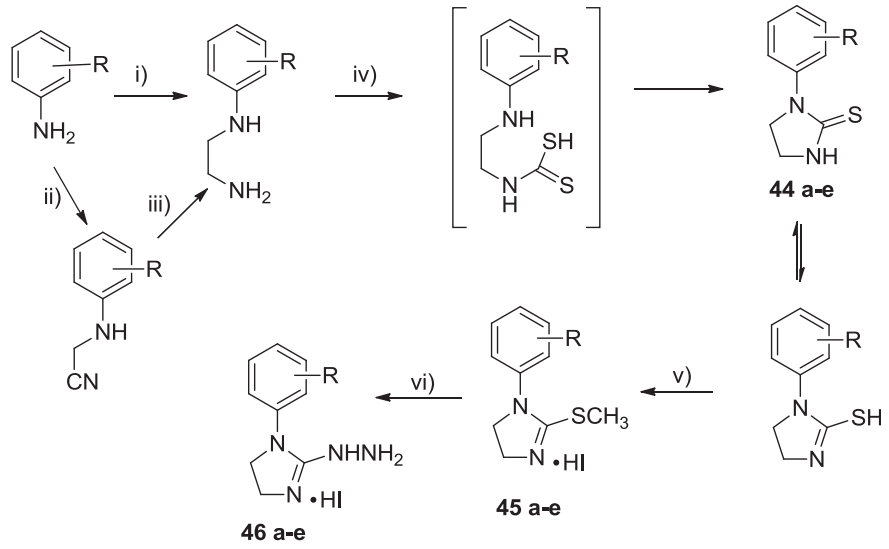
Sztanke et al. synthesized these bridgehead nitrogen-heterocyclic systems by fusion of the 4,5-dihydroimidazole and [1,2,4]triazole nuclei [18,60]. In the first step, commercially available anilines were converted into the corresponding *N*-arylethylenediamines. Their further condensation with carbon disulfide in a xylene medium led to the formation of dithiocarbaminic acid derivatives, which were cyclized in boiling solvent to the 1-arylimidazolidine-2-thiones (compounds **44a**–**e**) with concomitant liberation of a hydrogen sulfide molecule. Alkylation of these compounds with methyl iodide afforded the 1-aryl-2-methylthioimidazolines (**45a**–**e**) in 75–85 % yields. These last compounds were refluxed with hydrazine hydrate to obtain 1-aryl-2-hydrazinoimidazolines in good yields (**46a**–**e**) (Scheme 13).

Cyclocondensation of 1-aryl-2-hydrazinoimidazolines with triethyl orthoformate or derivatives of fenoxyacetic acid in refluxing DMF afforded the corresponding 3-unsubstituted (**49 a,c-e**) or 3-phenoxymethyl (**50**–**58**) 7-aryl-5*H*-6,7-dihydroimidazo [2,1-*c*][1,2,4]triazoles respectively.

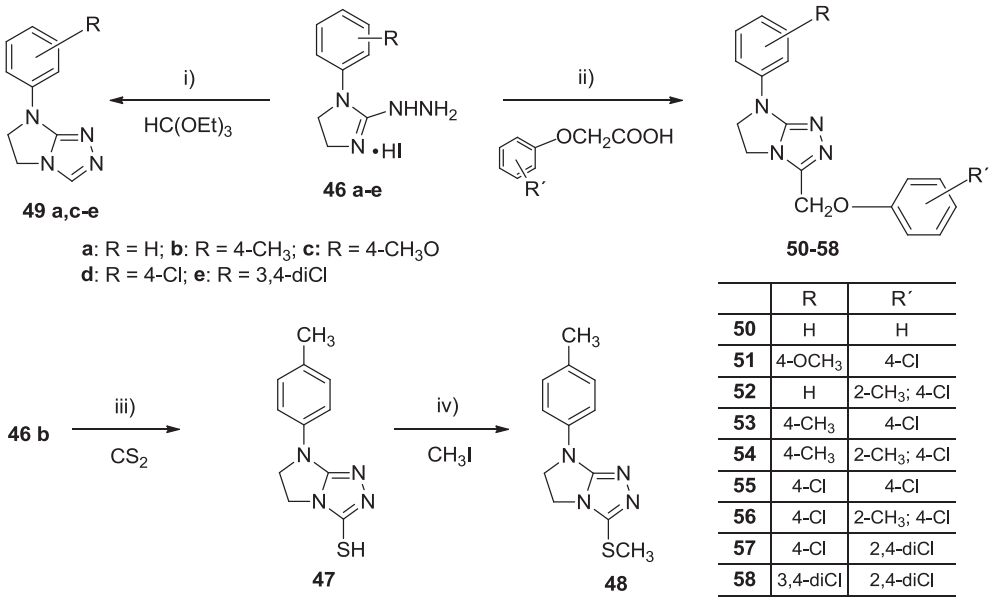
On the other hand, boiling compound **46 b** with carbon disulfide in aqueous potassium hydroxide, the 7-aryl-5H-6,7-dihydroimidazo[2,1-c][1,2,4]triazol-3-thiol (**47**) was obtained. Finally, the 7-(4-methylphenyl)-3-methylthio-5H-6,7-dihydroimidazo[2,1-*c*][1,2,4]triazole (**48**) was obtained in good yield (78%) from **47** by alkylation with methyl iodide (Scheme 14).

Compound **48** was strongly active against *Staphylococcus aureus* ATCC 25923, with a MIC (Minimal Inhibitory Concentration) value of 31.7 μM, showing superior antibacterial activity to ampicillin (standard drug) [18].

Besides, some of the synthesized compounds (**52** and **57**) were evaluated against different human tumor cell lines derived from various human cancer types (colon, breast, uterus), such as LS180 (ECACC 87021202, human Caucasian colon adenocarcinoma cells), SiHa (ECACC 85060701, uterus cancer cells), T47D (ECACC 85102201, human breast carcinoma cells) showing antiproliferative and apoptotic properties. Compound **57** was found to be the most active against the LS180 cell line, reaching comparative growth inhibition values (48 and 54%) for each tested concentration:



Scheme 13. Reactives and conditions: i) aziridine, $AlCl_3$, dry toluene; ii) HCHO, $Na_2S_2O_5$, NaCN, water, reflux; iii) H_2, Ni/Ra, metanol/NH_3, 100 °C; iv) CS, xilene, rt, 20 min, reflux, 7 h; v) CH_3I/MeOH, rt, 48 h, reflux, 6 h; vi) hydrazine hydrate-MeOH, reflux, 24 h.



	R	R´
50	H	H
51	4-OCH_3	4-Cl
52	H	2-CH_3; 4-Cl
53	4-CH_3	4-Cl
54	4-CH_3	2-CH_3; 4-Cl
55	4-Cl	4-Cl
56	4-Cl	2-CH_3; 4-Cl
57	4-Cl	2,4-diCl
58	3,4-diCl	2,4-diCl

Scheme 14. Reactives and conditions: i) DMF, reflux, 6 h; ii) DMF, reflux, 6 h, NaOH 6%; iii) MeOH, NaOH-water, rt, 30 min, reflux, 14 h; iv) abs EtOH, rt, 24 h, reflux, 5 h, Na_2CO_3.

25.3 μM and 126.7 μM, respectively. Moreover, it's distinctly marked lower cytotoxicity towards normal cell lines, especially towards human skin fibroblasts. These results suggest that compound **57** could be further investigated as a potential anticancer agent.

Moreover, compound **52** was efficient for DNA strand breakage of cancer cell lines such as the cytotoxic antibiotic – bleomycin, concluding that this compound may be promising for the development of novel agents that induce the DNA strand breakage.

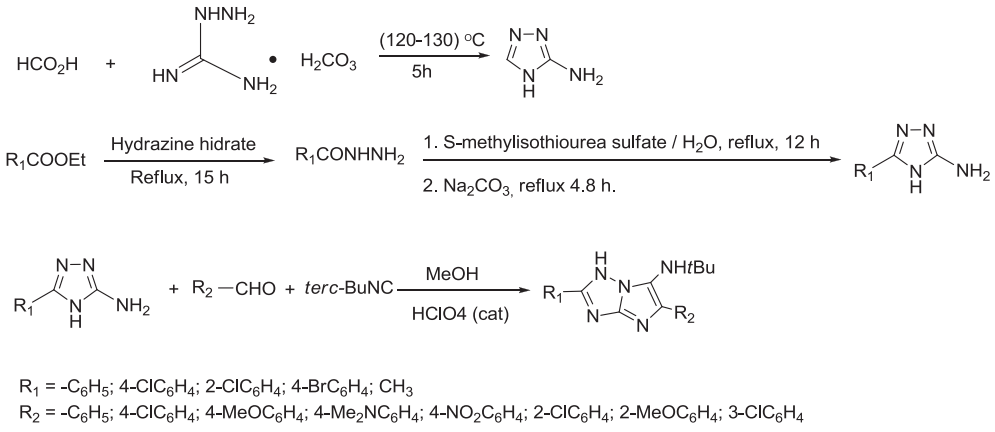
On the other hand, it is well known that multicomponent reactions (MCR) have been steadily gaining importance in synthetic organic chemistry. In that context, Yan Huang et al., reported a MCR synthetic strategy to obtain imidazo[1,2-*b*]-1,2,4-triazoles with yields between 28% and 77% (Scheme 15) [65].

While this work is interesting from the viewpoint of the synthetic route used, however, in this particular case, the products showed no significant biological activity.

Even though there are results suggest that the fusion of the dihydromidazole and 1,2,4-triazole nuclei might lead to bioactive molecules, it is noteworthy that this type fused heterocyclic has so far been poorly explored yet.

5. Imidazo[1,2-*b*]thiadiazoles

Imidazo[2,1-*b*][1,3,4]thiadiazoles are fused heterocycles structurally closely related to imidazo[2,1-*b*]thiazoles and are also being deeply explored. Although the structural differences between both heterocycles are minimal, their properties are often markedly



Scheme 15. Multicomponent synthetic strategy to obtain imidazotriazoles.

different. Recently, synthetic studies as well as their biological properties were summarized first by Khazi et al. [20] and later by Bhongade et al. [19], in a work especially focused in the biological activities of this family of compounds. Anticancer, antitubercular, antibacterial, antifungal, anticonvulsant, analgesic, cardiotonic, antisecretory, anti-inflammatory, diuretic and herbicidal activities of substituted imidazo[2,1-*b*][1,3,4]thiadiazole were reported here.

Just like imidazo[2,1-*b*]thiazoles, traditional synthetic strategies to obtain imidazo[2,1-*b*][1,3,4]thiadiazoles involve the reaction between a 2-amino-[1,3,4]thiadiazole derivatives and an appropriate α-haloketone [66–71]. The substituted 2-amino[1,3,4]thiadiazole derivatives needed for the synthesis must be obtained by condensation between an aryl chloride [72], and an arylcarboxylic acid [73–75] or an aryl carboxaldehyde [76–78] with thiosemicarbazide under strongly acidic conditions such as H_2SO_4, $POCl_3$, and $FeCl_3$ as reagents. Consequently, imidazo[2,1-*b*][1,3,4] thiadiazole with an acid-sensitive substituent in R_2 position (Scheme 16) cannot be obtained by this methodology.

In order to introduce a wide range of functional groups, Copin et al. [79], synthesized a series of 2,6-disubstituted imidazo[2,1-*b*] [1,3,4]thiadiazoles **64** from 2-bromo-6-disubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles **63** using Suzuki–Miyaura cross-coupling protocol (Scheme 16).

Highest yields were obtained when a mixture of the bromide derivative **63**, K_2CO_3, boronic acid, Xantphos and $Pd(OAc)_2$ in a degassed 1,4-dioxane medium, was heating under microwave irradiation (30 min at 150 °C).

Recently, Zarganes-Tzitzikas et al. [80] described a new one-pot synthetic method for the construction of this heterocyclic nucleus using imidazole-2-thiones, isocyanides, and azodicarboxylates (DEAD) as a basic catalyst (Scheme 17). When the reaction mixture was stirring at room temperature, the imidazo[2,1-*b*][1,3,4]thiadiazoles were isolated as the only reaction product in good yields.

As mentioned above imidazo[2,1-*b*][1,3,4]thiadiazole derivatives have shown a wide range of biological activities. Moderate antitubercular activity of these heterocyclic derivatives against *Mycobacterium tuberculosis* H37Rv (MTB) was reported [19]. Alegaon et al. [81] described the synthesis of 5-{[2-(trifluoromethyl)-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazol-5-yl]methylene} thiazolidine-2,4-dione (**68a**–**g**), 5-{[2-(trifluoromethyl)-6-arylimidazo [2,1-*b*][1,3,4]-thiadiazol-5-yl]methylene}-2-thioxothiazolidin-4-one (**70a**–**g**) and 2-[(5Z)-5-{[2-(trifluoromethyl)-6-arylimidazo [2,1-*b*][1,3,4]-thiadiazol-5-yl]methylene}-4-oxo-2-thioxo thiazolidin-3-yl]acetic acid (**69a**–**g**) and their antitubercular activity were evaluated (Scheme 18). Syntheses of the compounds were carried out by microwave irradiation and conventional heating techniques. Reactions under microwave irradiation were completed within 10–15 min whereas similar reactions under conventional heating (oil bath) at reflux gave poor yields after 15 h of reaction.

Promising antitubercular activity profile against *M. tuberculosis* H37Rv (MTB) was found in five compounds (**69 b-f**) of the different series synthesized, which resulted active with a minimum inhibitory concentration of 1.56–3.12 μg/ml. The compound **69f** was the most active against MTB at a Minimum Inhibitory Concentration (MIC) 1.56 μg/ml comparable to that of isoniazid (Fig. 13), suggesting that imidazo[2,1-*b*][1,3,4]thiadiazole carrying rhodanine-3-acetic acid as substituent can be potential antitubercular agents.

Antitubercular and antibacterial activity of other series of 2,5,6-trisubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles (Fig. 14) was also evaluated by Joshi et al. [82].

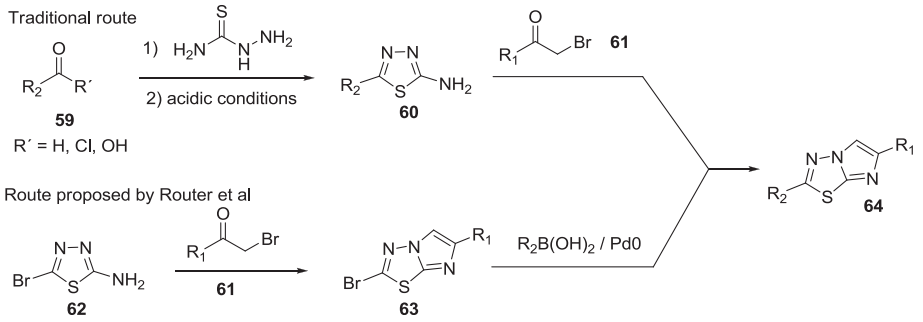
The antitubercular activity against MTB was, like the previous example, considerably affected by substitutents at five position on the imidazo[2,1-*b*][1,3,4]thiadiazole nucleus.

Compound having formyl group at five position (**71**), showed activity at MIC value of 1.6 μg/ml, but compounds **72** and **73** having a thiazolidinone and guanylhydrazone groups respectively at this position (Fig. 14), showed highest antitubercular activity at a MIC of 0.8 μg/ml.

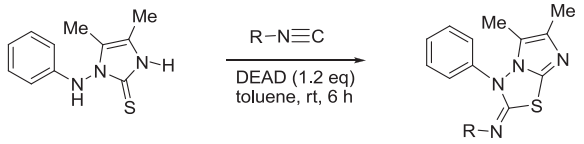
These two last compounds also showed an antibacterial activity against Gram-negative bacterias as *Vibrio cholera* and *Escherichia coli*, comparable with Norfloxacillin (1 μg/ml). However, these compounds showed only moderate activity against Gram positive bacterias (*S. aureus* and *Bacillus subtilis*).

The antibacterial activity was also determined in 2-biphenyl-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazole derivatives (Fig. 15) [83]. In this case, all the compounds studied exhibited good activity against both, Gram-positive bacterias (*B. subtilis*) and Gram-negative bacterias (*E. coli* and *Pseudomonas aeruginosa*).

Moreover, the antibacterial and the antifungal activities of a sequence of 2-(4-substituted-phenyl)-6-(4-substituted-aryl)-imidazo[2,1-*b*][1,3,4]thiadiazole were tested [84]. These new derivatives were synthesized under microwave activation from 2-amino-5-substituted-1,3,4-thiadiazoles and the appropriate α-bromoketones in dimethylformamide. All the compounds were obtained in good yield and the time was drastically reduced compared with the conventional thermal-assisted synthesis (4–7 min against 8–10 h under ethanol reflux). Among the synthesized derivatives, compound **74** showed antibacterial activity against Klebsiella at 5 μg/ml and the zone of inhibition was 14 mm (on comparing to standard ciprofloxacin 28 mm at 10 μg/ml) while compound **75** showed good antifungal activity comparable to that of standard fluconazole ((Fig. 16)).

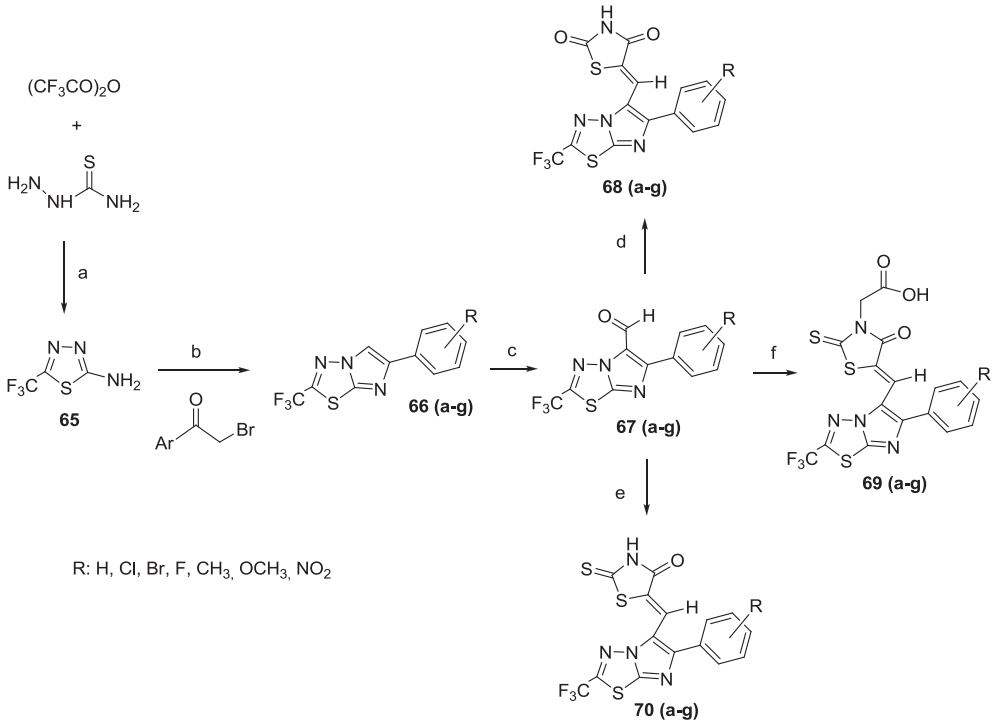


Scheme 16. Synthetic pathways to obtain 2-amino[1,3,4]thiadiazoles.



Scheme 17. One Pot synthesis of imidazothiadazoles from imidazole-2-thiones.

Firstly, Noolvi et al. [85] reported the synthesis and anticancer properties (screened *in vitro* over a 60 cell line panel by the National Cancer Institute-USA (NCI)) of a new series of 2,6-disubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles. Two of the analyzed compounds: 4-(2-(4-methoxyphenyl)imidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)benzene-1,3-diol (**76**) and 3-(2-(4-methoxyphenyl)imidazo



Scheme 18. Reagents and conditions: (a) -5-0 °C, 2 h (81%); b) MW (600 W) 10–15 min (65–71 %); c) Vilsmeiere Haack reagent, 8 h (50–66 %); d) thiazolidine,2,4-dione, MW (600 W) 12 min (60–74 %); e) rhodanine, MW (600 W) 12 min (69–75 %); f) rhodanine, acetic acid, MW (600 W) 12 min (68–76 %).

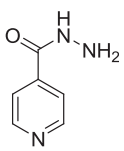


Fig. 13. Structure of isoniazid.

The potential anticancer activity of an important number of imidazo[2,1-*b*][1,3,4]-thiadiazoles derivatives, was also investigated.

[2,1-*b*][1,3,4]thiadiazol-6-yl)aniline (**77**) were more selective for Breast Cancer cell lines than other cancer types (Fig. 17). However, the last compound demonstrated the most marked effects on Non Small Cell Lung Cancer HOP-92 cell line (GI_{50}: 0.114 μM) and Renal Cancer CAKI-1 cell line (GI_{50}: 0.743 μM).

More recently, Kamal *el al.* [86] reported the synthesis of a series of new imidazo[2,1-*b*][1,3,4]thiadiazole-linked oxindoles (Fig. 18). The effectiveness of these compounds as anticancer drugs as well as their cell cycle effects and their capacity to inhibit tubulin polymerization was investigated. The synthesis were carried out by a single-step Knoevenagel reaction between the corresponding

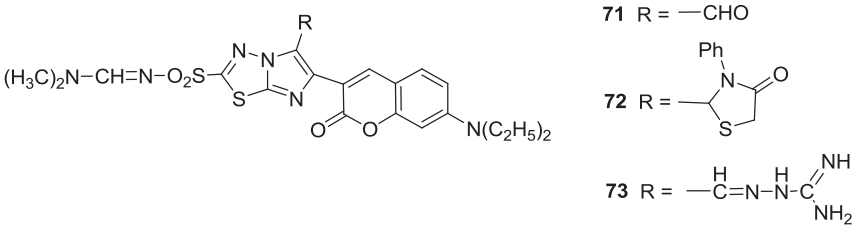
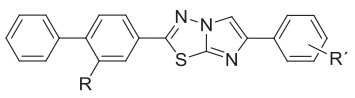


Fig. 14. . 2,5,6-trisubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles.



R = H or F
R' = a: H; b: 4-Cl; c: 4-F; d: 2,4-diCl; e: 4-NH_2; f: 2,4-diOH; g: 4-Br; h: 2-OH

Fig. 15. Biphenyl imidazo[2,1-*b*][1,3,4]-thiadiazoles.

linked globular polypeptides called α- and β-tubulin, which polymerize to form microtubules. In the last years there has been considerable interest in the development of small molecules that affect tubulin polymerization and dynamics of the microtubules as new drugs in the treatment of cancer.

Compound **78**, which potently inhibited cell growth, also significantly decreased tubulin assembly, with an IC_{50} value of 0.15 μm. Compound **82** was only slightly less potent, with IC_{50}

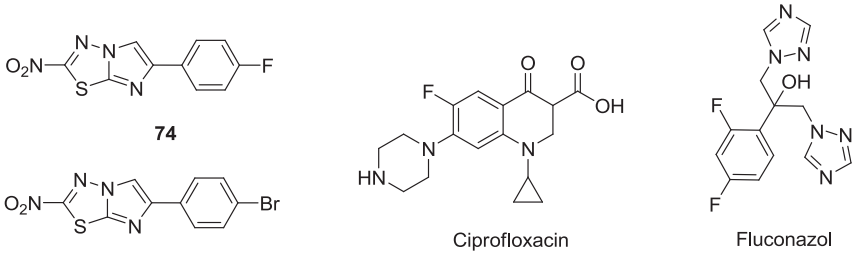


Fig. 16. Structures of imidazothiadiazoles **74**, **75**, ciprofloxacin and fluconazol.

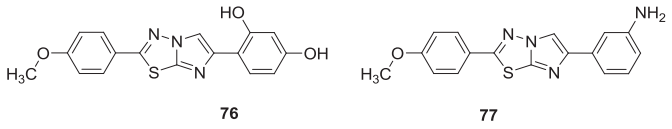


Fig. 17. Chemical structure of some substituted imidazothiadiazoles.

imidazo[2,1-*b*]-[1,3,4]thiadiazole-5-carbaldehydes derivatives and various substituted oxindoles in ethanol/piperidine. These compounds were evaluated against A549, HeLa, MCF-7, and HCT116 human cancer cell lines.

Compounds **78**–**87** showed considerable cytotoxicity, with IC_{50} values ranging from 1.1 to 8.9 μm against the four human cancer cell lines above mentioned.

Methylated derivatives (**78**–**82**) and compounds without ring D substituent (**83**–**87**) showed the strongest activity in the series. To further determine their potency in other cell types, compounds **78**, **82**, **86** and **92** were evaluated in the sixty-cell-line panel of the US National Cancer Institute (NCI). Compounds **82** and **92** were selected for the five-dose assay. These compounds displayed significant cytotoxicity in most of the NCI panel cell lines, with GI_{50} values ranging from 0.30 to 5.8 μm. Particularly, compound **82** showed promising cytotoxicity, with GI_{50} values of 0.30 and 0.42 μm against OVCAR-4 (ovarian cancer) and HOP-92 (lung cancer) cell lines.

The authors also studied whether the anti-proliferative properties of **78** and **82** were due to inhibition of tubulin polymerization. Tubulin is a heterodimer of two closely related and tightly

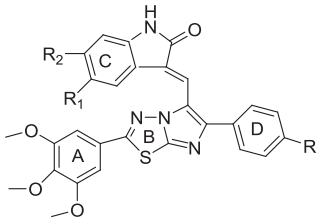
values of 1.23 μm.

In order to determine whether these active compounds exert their cytotoxicity and capacity to block tubulin polymerization by binding to tubulin at the same binding site of the colchicine, a potent microtubule polymerization blocker, molecular docking studies were performed (Fig. 19). Docking analyses showed a hydrogen bonding between the 3,4,5-trimethoxyphenyl ring and αGln11 and βAsn258, hydrogen bonding interactions of *p*-tolyl groups with αSer178, hydrogen bonding interactions between ring C and βThr353, βCys241, and αAsn101. Moreover, the imidazo[2,1-*b*]-thiadiazoles rings (ring B) of compounds **78** and **82** are involved in hydrophobic interactions with aThr179.

The results of these studies suggest that both compounds occupy the same binding site of α/β-tubulin of the colchicines and therefore these new compounds proved to be an appropriate template for the design of a new class of inhibitors of tubulin polymerization for cancer treatment.

A novel series of 2,5,6-trisubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles were rationally designed as antihyperlipidemic drugs through the Hologram Quantitative Structure Activity Relationship (QSAR) [87]. Antihyperlipidemic agents promote reduction of lipid levels in the blood. The studies, based upon QSAR model proposed by Kathia M. Honorio et al. [88] suggested that the 1,3-benzodioxol fragment is strongly related to the biological activity. This information, combined with the interesting biological properties of the imidazo[2,1-*b*][1,3,4]thiadiazole rings, has prompted to the authors to synthesize 2,5,6-trisubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles containing 1,3-benzodioxol moiety as novel Farnesoid-X-Receptor (FXR) ligands.

78: R= CH_3 ; R_1= F; R_2= H
79: R= CH_3 ; R_1= OCH_3; R_2= H
80: R= CH_3 ; R_1= Cl; R_2= H
81: R= CH_3 ; R_1= H; R_2= Cl
82: R= CH_3 ; R_1= H; R_2= H
83: R= H ; R_1= H; R_2= H
84: R= H ; R_1= OCH_3; R_2= H
85: R= H ; R_1= Cl; R_2= H
86: R= H ; R_1= H; R_2= Cl
87: R= H ; R_1= F; R_2= H
88: R= OCH_3 ; R_1= H; R_2= H
89: R= OCH_3 ; R_1= OCH_3; R_2= H



90: R= OCH_3 ; R_1= Cl; R_2= H
91: R= OCH_3 ; R_1= H; R_2= Cl
92: R= OCH_3 ; R_1= F; R_2= H
93: R= OCH_3 ; R_1= NO_2; R_2= H
94: R= Cl ; R_1= H; R_2= H
95: R= Cl ; R_1= OCH_3; R_2= H
96: R= Cl ; R_1= Cl; R_2= H
97: R= Cl ; R_1= H; R_2= Cl
98: R= Cl; R_1= F; R_2= H
99: R= Cl ; R_1= NO_2; R_2= H
100: R= F ; R_1=Cl R_2= H
101: R= F ; R_1= OCH_3; R_2= H
102: R= F ; R_1= F; R_2= H
103: R= F ; R_1=H; R_2= Cl

Fig. 18. Biphenyl imidazo[2,1-*b*]-thiadiazoles linked oxindoles.

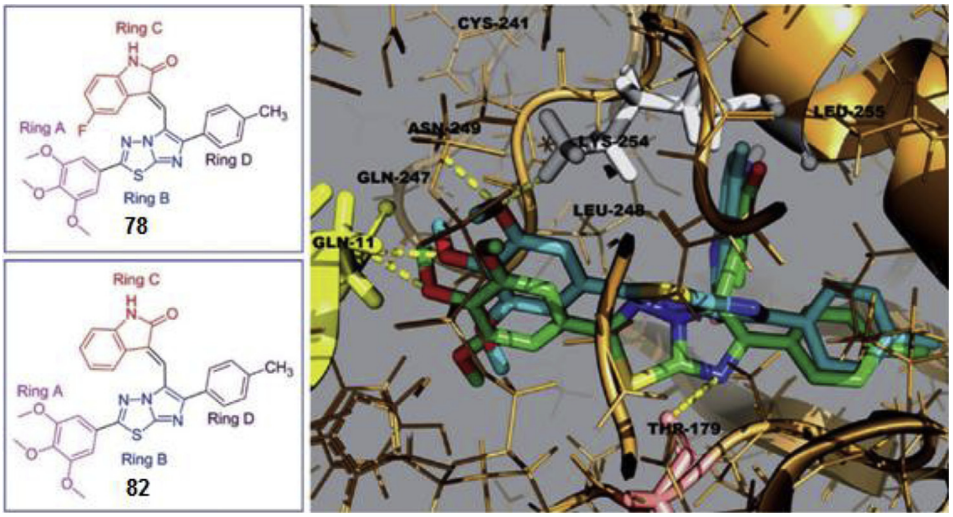


Fig. 19. Superposition of the docked conformations of **106** (green sticks) and **102** (blue sticks) over the X-ray crystal structure of the colchicine binding site of tubulin (PDB ID: 3E22). Reprint from *ChemMedChem*, Vol. 9, A. Kamal, M.P.N. Rao, P. Das, P. Swapna, S. Polepalli, V.D. Nimbarte, K. Mullagiri, J. Kovvuri, N. Jain, Synthesis and biological evaluation of imidazo [2,1-*b*][1,3,4]thiadiazole-linked oxindoles as potent tubulin polymerization inhibitors, 1463–1475, © 2014, with permission from WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[86]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

These compound were obtained by condensation of the 5-(benzo[*d*][1,3]dioxol-5-yl)-[1,3,4]thiadiazol-2-amine [89] with the respective bromoacetyl compound (traditional synthesis pathway) in dimethylformamide, yielding imidazo-thiadiazoles in good yields [88]. Vilsmeier–Hack reaction of these imidazo-thiadiazoles in DMF and $POCl_3$ provided the respective 5-formyl derivatives [90]. When the aldehyde functional group was treated with amines gave the corresponding imine derivatives. Several of synthesized derivatives showed *in vitro* antihyperlipidemic activity compared to the standard drug Fenofibrate (Fig. 20).

The two more potent compounds were modeled by positioning them in the co-crystallized ligand Fexaramine binding site and the entire complex was then subjected to alternate cycles of minimization and dynamics (Fig. 21).

These docking studies have revealed that the compounds shows H-bonding with HIE-298 amino acid backbone via *N*-6 of imidazo [2,1-*b*][1,3,4]thiadiazoles. It is also important the presence of oxygen in the form of sulfonamide, carboxylic acid, amide and nitro group linked to the imidazo[2,1-*b*][1,3,4]thiadiazoles moiety because a new H-bonding interaction with backbone of HIE-298 and SER-336, could be observed. These interactions underscore the importance of both nitrogen and oxygen as hydrogen bond acceptor for binding and the subsequent agonistic capacity.

The increasing number of publications involving imidazo[2,1-*b*][1,3,4]thiadiazoles derivatives in the last years, demonstrates the interest of researchers in this class of heterocycles. That interest is justified if we consider the existence of versatile synthetic strategies and evidence of their variety in terms of the treatment of numerous pathologies.

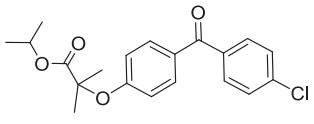


Fig. 20. Structure of Fenofibrate.

6. Conclusions

This review summarizes the synthetic strategies to obtain the imidazotiazole and related fused heterocyclic derivatives as well as their biological studies.

Even though traditional synthetic route remains the most widely used, other synthetic approaches have begun to be applied lately. Thus, microwave irradiation has been employed successfully to obtain the imidazothiazole and imidazothiadiazole derivatives, in good yields and in much shorter reaction time. Multicomponent

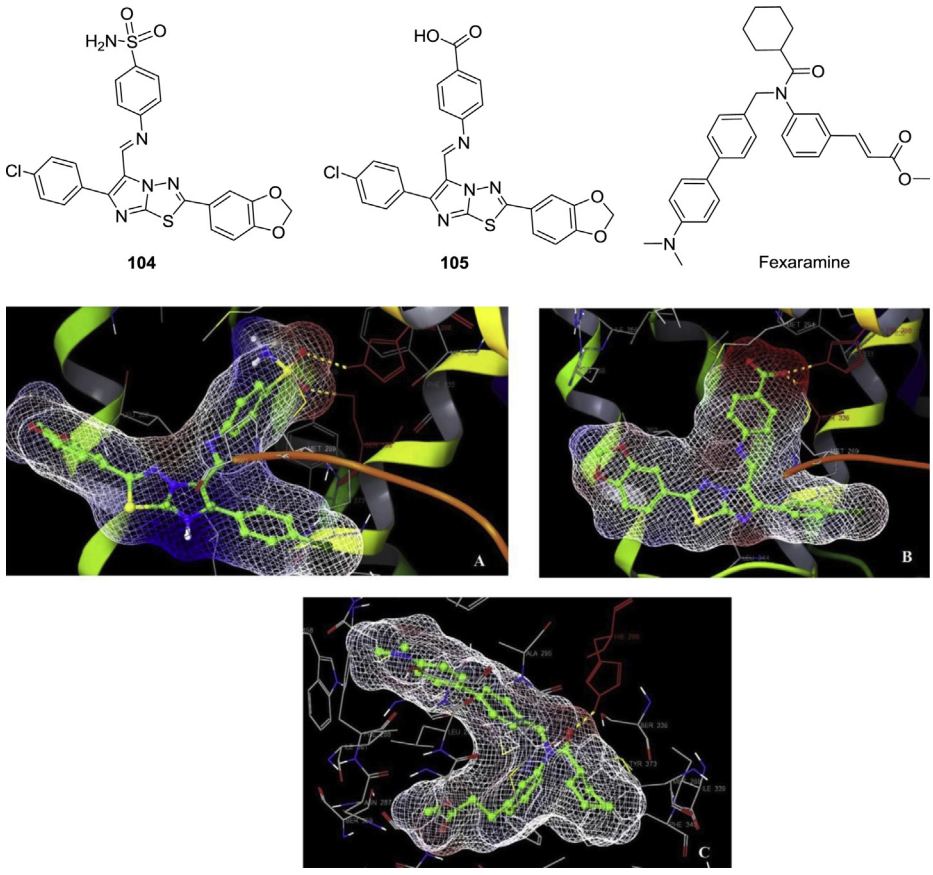


Fig. 21. Binding mode of **104**, **105** and co-crystallized ligand Fexaramine in the FXR binding pocket (PDB: 1OSH). Compound **104** shows H-bond interaction between oxygen of sulfonamide group and compound **105** shows H-bond interaction between oxygen of carboxyl group with Histidine-298 and Serine-336 amino acid backbone of FXR (A and B). Similarly co-crystallized ligand Fexaramine shows H-bond interaction between oxygen of carboxamide group with Histedine-298 backbone of FXR (C). Reproduced from H.M. Patel, M.N. Noolvi, A. Goyal, B.S. Thippeswamy, 2,5,6-Trisubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles: Search for antihyperlipidemic agents, Eur. J. Med. Chem. 2013, 65, 119–133, Copyright © 2013, with permission from Elsevier Masson SAS. All rights reserved.[87].

reaction was applied to the synthesis of tri-substituted imidazo[1,2-*b*]-1,2,4-triazoles while an ionic liquid was used to obtain imidazo [1,2-*b*]thiazole derivatives. In addition, imidazothiazoles with a substitution pattern which could not be achieved by the traditional route could be prepared using palladium coupling reactions.

Among these fused rings, imidazothiazoles and imidazothiadiazoles were the most widely studied but, lately, imidazothiadiazoles have gain the interest of the researchers as is evidenced by the increase in the number of publications. The proven efficiency of imidazothiazole and imidazothiadiazole derivatives for the treatment of several diseases, turn them in to promising leaders for further studies. Besides, computational or docking studies have been realized in order to understand the mechanism of action and the molecular requirements of this class of compounds.

Despite other systems such as imidazotriazoles and pirrolotriazoles, have promising perspectives have not been studied enough until now.

Publications in this field are continuously increasing and therefore new therapeutic applications involving members of this family of heterocycles could be discovered in the near future.

Acknowledgments

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