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1,2,4-TRIAZOLES: SYNTHETIC APPROACHES AND PHARMACOLOGICAL IMPORTANCE. (REVIEW)

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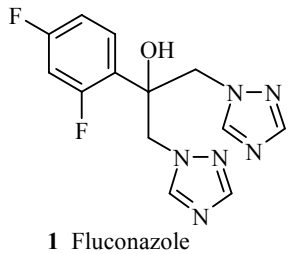
The synthetic routes of 1,2,4-triazole compounds as well as their pharmacological properties have been described. The review focuses intensively on two methods: cycloaddition reaction in the syntheses of various 1,5-dialky-1H-1,2,4-triazole derivatives from the reactive cumulenes with the nitrile precursors as well as the microwave irradiation method.

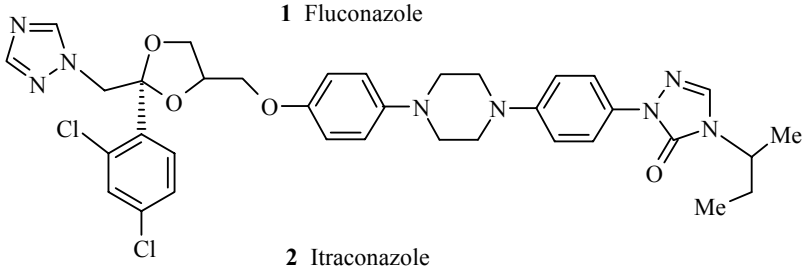
Keywords: 1,2,4-triazoles, pharmacological properties, synthetic routes.

1. PHARMACOLOGICAL PROPETIES

The 1H-1,2,4-triazole compounds are considered interesting heterocycles since they possess important pharmacological activities such as antifungal and antiviral activities. Examples of antifungal drugs [1, 2] are fluconazole **1** [3, 4], itraconazole **2** [5], ravuconazole **3** [6], voriconazole **4** [7-9], ICI 153066 **5** [10], and posaconazole **6** [11]. The action of these compounds is based on the inhibition of biosynthesis of ergosterol, the major steroid in fungal membranes, by blocking 14-α-demethylation, which occurs with accumulation of 14-α-methyl-steroids and disruption of the fungal membranes [12-14]. Fluconazole **1** causes second bronchial arch anomalies in mice [15].



1 Fluconazole



2 Itraconazole

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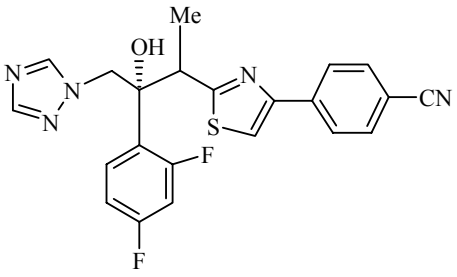
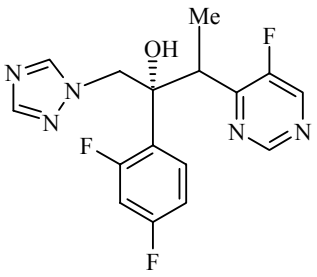
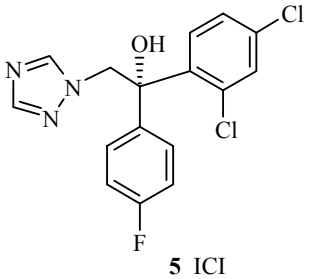


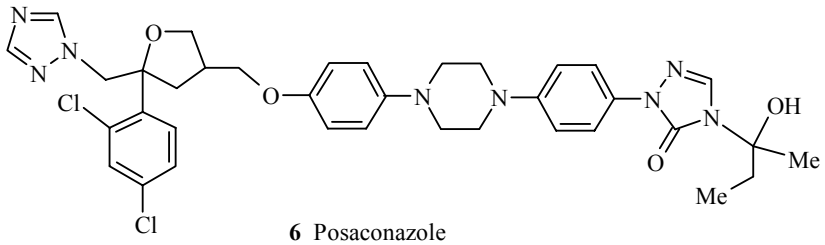
3 Ravuconazole



4 Voriconazole

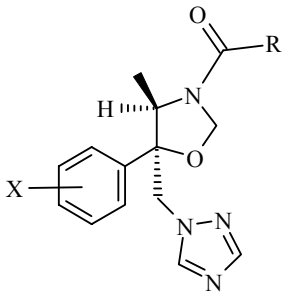


5 ICI



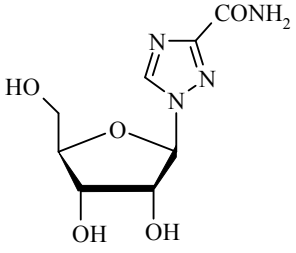
6 Posaconazole

Some 3-amino-1H-1,2,4-triazoles have been used as herbicides and defoliants; meanwhile they were described as catalase inhibitors [16] and blockers for certain ethanol-induced behavior effects [17]. It has been reported that only certain enantiomers of triazoles containing oxazolidine rings (e.g., **7**, 4(*R*), 5(*R*)) are active against *Candida albicans* infections in mice [18].

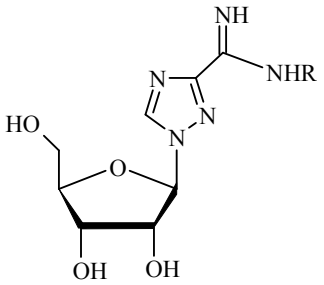


7

Ribose N-glycoside **8** [19-23] is a broad spectrum antiviral agent containing the 3-aminocarbonyl-triazole moiety. It is active against both RNA and DNA viruses and is used in an aerosol for lower respiratory tract viral disease as well as in the treatment of influenza, Lassa fever, and Hantaan virus [24, 25]. Amidine and guanidine derivatives **9** (R = H·HCl, Me, CN) exhibiting a broad spectrum of antiviral activity [26] have been prepared.

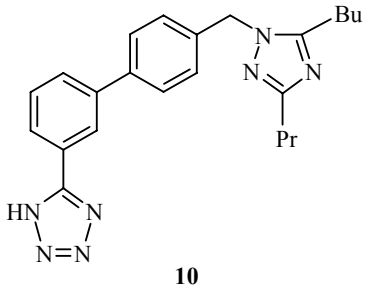


8 Ribavirin



9

Some triazole derivatives are considered as angiotensin II receptor antagonists [27-31]. These compounds, such as **10** and **11**, are used to increase the blood pressure. Furthermore, various 1,2,4-triazole derivatives have been reported as fungicidal [32], insecticidal [33], antimicrobial [34, 35], and antiastmatic [36] agents, anticonvulsants [37], antidepressants [38], and plant growth regulators [39]. In addition, it was reported that compounds having triazole moieties, such as vorozole **12**, letrozole **13**, and anastrozole **14**, appeared to be very effective aromatase inhibitors, which in turn prevented breast cancer [40-42]. It is known that 1,2,4-triazole moieties interact strongly with heme iron, and aromatic substituents on the triazoles are very effective for interacting with the active site of aromatase [43]. Other laboratories reported the same biological activity of the triazole family [44-46].



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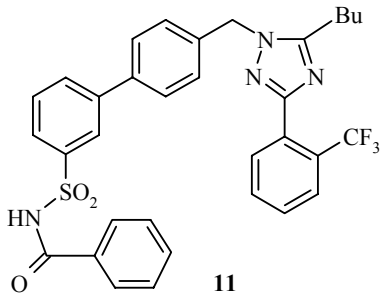

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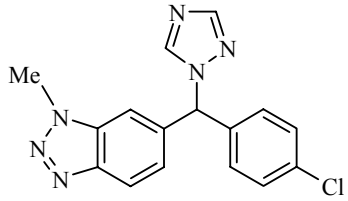
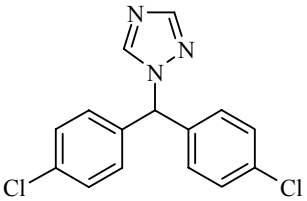
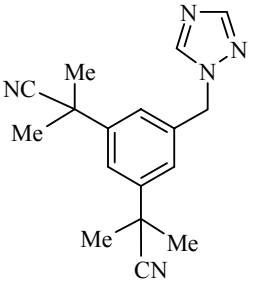


12 Vorozole

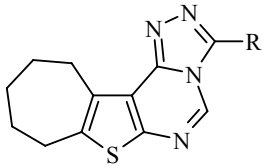


13 Letrozole



14 Anastrozole

The derivatives of *s*-triazolo[1,5-*c*]pyrimidines are important as potential therapeutic agents [47, 48]; some 3-amino-1,2,4-triazole (ATZ), 3-mercapto-1,2,4-triazole (MTZ), and 3-nitro-1,2,4-triazole (NTZ) derivatives showed antithyroid activity [49]. In recent work [50] thienopyrimido-1,2,4-triazoles **15** have been synthesized as pharmacologically interesting compounds. Some acyclic 1,2,4-triazole C-nucleosides [51] lacked antiviral properties against *herpes simplex* virus 1 and 2 (HSV-1 and -2) along with other viruses.



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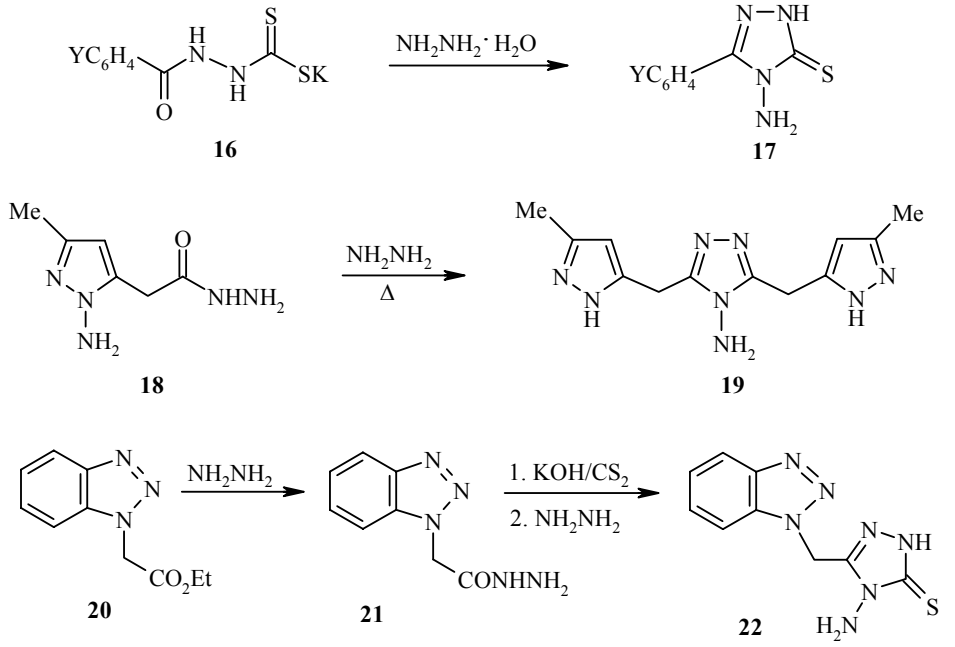
2. SYNTHESIS OF 1H-1,2,4-TRIAZOLE COMPOUNDS

There are five methods to buildup the 1,2,4-triazole ring.

2.1. Methods employing hydrazine derivatives

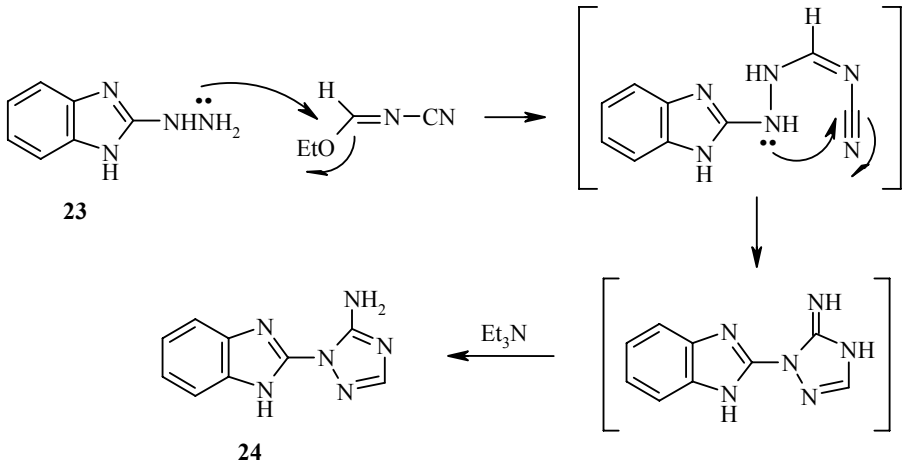
The reaction of hydrazine or substituted hydrazines with suitable electrophiles is the most common method for the preparation of the triazoles. Examples where hydrazines provide the triazole ring [52-54] are described in Scheme 1.

Scheme 1



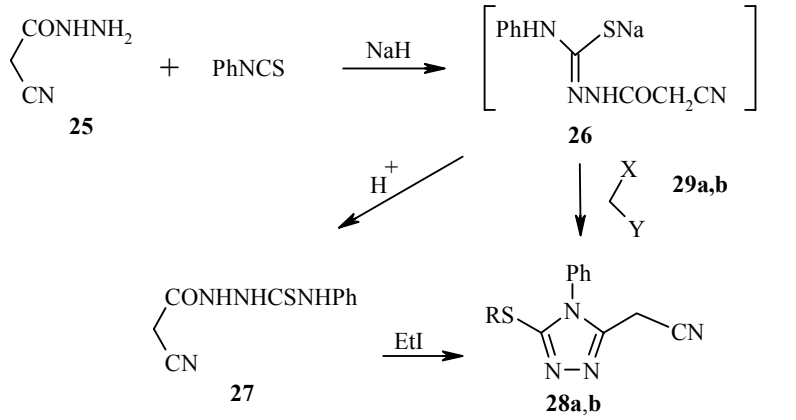
Another example of such type of reaction is the interaction of ethyl N-cyanoformimidate with the hydrazine derivative **23** in triethylamine to give the corresponding 5-aminotriazole **24** [55, 56] (Scheme 2).

Scheme 2



3-Alkylthio-1,2,4-triazole derivatives **28a**,**b** are produced [57] by the reaction of phenyl isothiocyanate with 2-cyanoacetohydrazide (**25**) *via* intermediate **26** and cyclization of **27**. The structures of **28a**,**b** were proved by an independent synthesis involving the treatment of **26** with **29a**,**b** to yield **28a**,**b** (Scheme 3).

Scheme 3

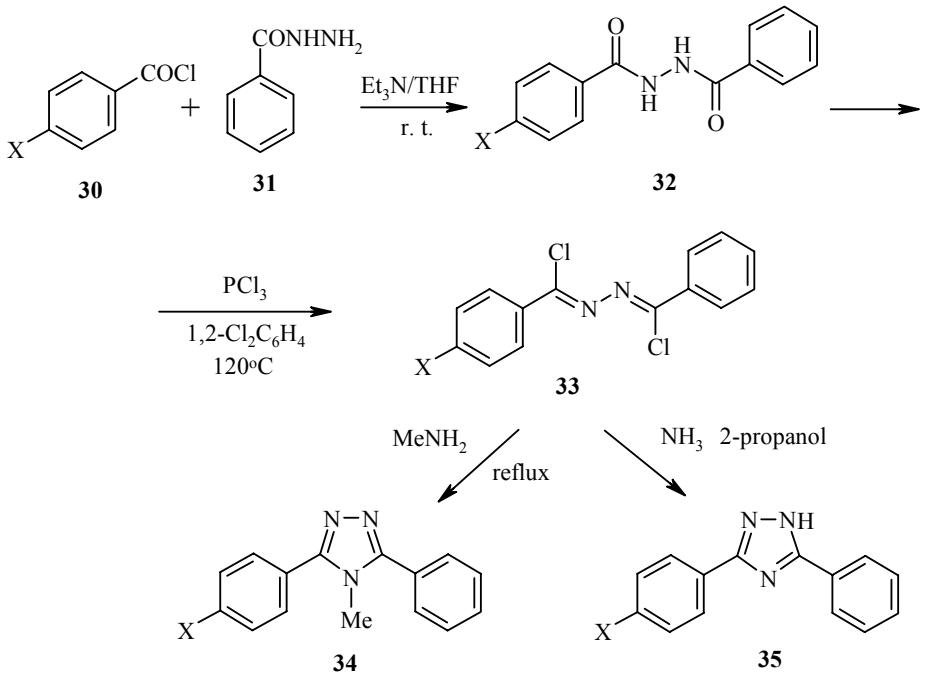


28 a R = Et, **b** R = CH_2CO_2Et; **29** **a** X = Me, Y = I, **b** X = CO_2Et, Y = Br

Dimova *et al*. [58] recently synthesized a series of 4-substituted 5-aryl-1,2,4-triazoles by cyclization of the corresponding substituted thiosemicarbazides.

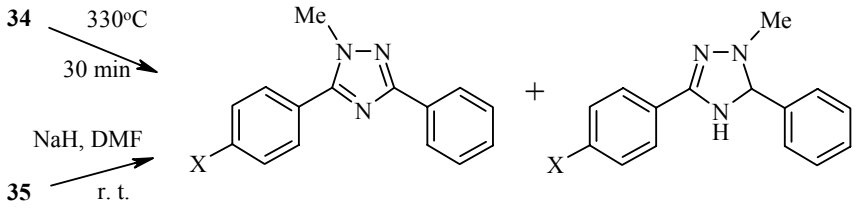
Carlsen *et al.* [59] have prepared triazoles **34** and **35** from earlier described unsymmetrical bis(*p*-alkylaminobenzylidene)hydrazines **32** [60] using a modified procedure outlined in Scheme 4.

Scheme 4



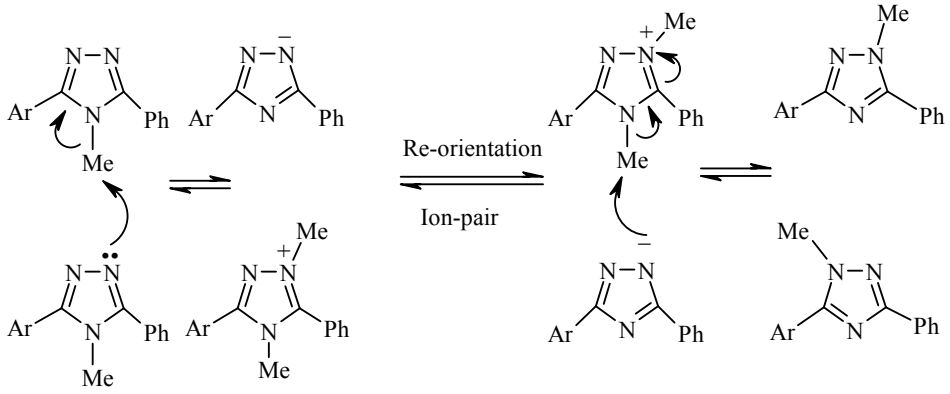
A series of neat unsymmetrically substituted 3,5-diaryl-4-methyl-4H-1,2,4-triazoles **34** were next thermolyzed at 330°C for 30 min to investigate the regioselectivity as a function of the electronic conditions induced by the *para*-substituents in one of the phenyl rings. These results were also compared with those obtained upon alkylation of the corresponding unsymmetrical 3,5-diaryl-1H-1,2,4-triazoles **35** with MeI. The general reactions are shown in Scheme 5.

Scheme 5



The rearrangement of 3,5-diaryl-4-methyl-4H-1,2,4-triazoles to the corresponding 3,5-diaryl-1-methyl-1H-1,2,4-triazoles exhibited a regioselectivity comparable to that for alkylation of 3,5-diaryl-1H-1,2,4-triazoles, providing further support to the previously proposed mechanism for the rearrangement [61], which would involve consecutive nucleophilic displacement steps (Scheme 6).

Scheme 6

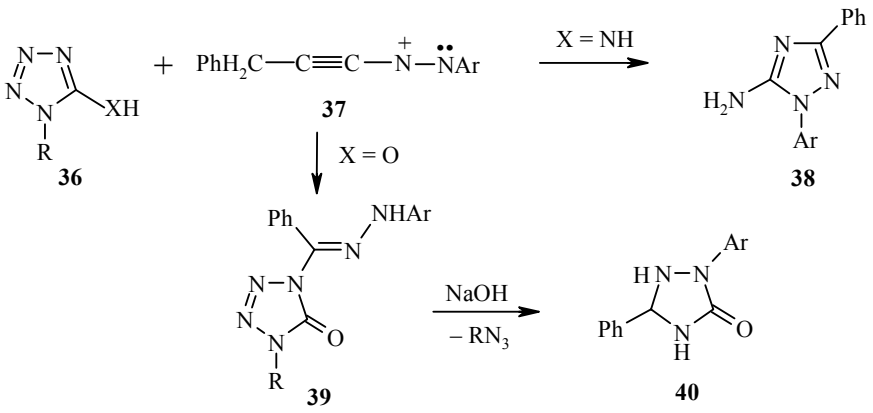


Nair *et al*. [62] recently reported an extensive review on the synthesis of 1,2,4-triazoles and thiazoles from thiosemicarbazide and its derivatives.

2.2. Methods employing nitrile imines and triazines

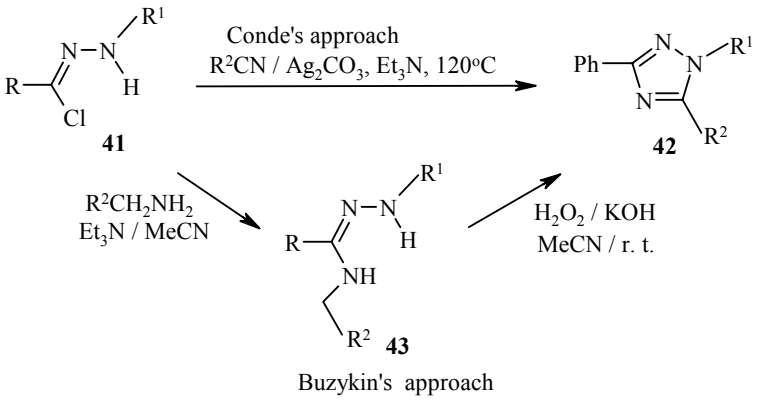
1,3-Dipolar cycloaddition has been extensively used for the synthesis of triazoles. An example of this method is the reaction of nitrile imine **37** with the tetrazole (**36**, X = NH) to give triazole **38**. Reaction of **37** with the tetrazole (**36**, X = O) gave **39**, which on treatment with a base afforded triazolinone **40** [63] (Scheme 7).

Scheme 7



An improved synthesis of 1,3,5-trisubstituted 1,2,4-triazoles **42** has been reported [64] *via* 1,3-dipolar cycloaddition of nitrile imine, generated *in situ* from **41** in the presence of Ag_2CO_3 and Et_3N. In an alternative two-step approach, Buzykin *et al*. [65] first prepared intermediate **43** from the reaction of **41** with a primary amine and Et_3N, which was then treated with a solution of 30% H_2O_2 / aqueous KOH to yield **42** (Scheme 8).

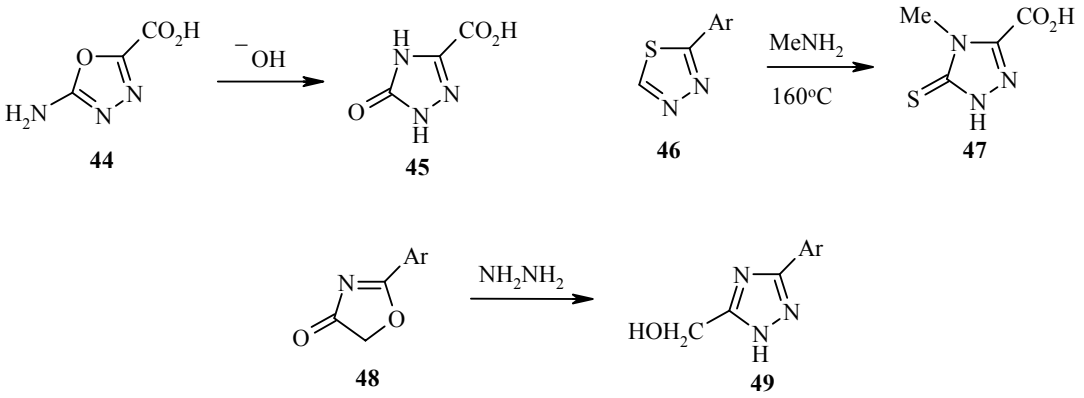
Scheme 8



2.3. Synthesis of triazoles by transformation of other heterocyclic systems

The conversion of a non-triazole ring system into a triazole usually included the substitution of nitrogen for another heteroatom in a five-membered ring. The process usually involved nucleophilic ring opening of the heterocycle followed by ring closure and loss of the other atom. Little new material in this area has appeared after it was reviewed by Polya [66] in 1984, and only a few typical examples [67-69] are illustrated in Scheme 9.

Scheme 9

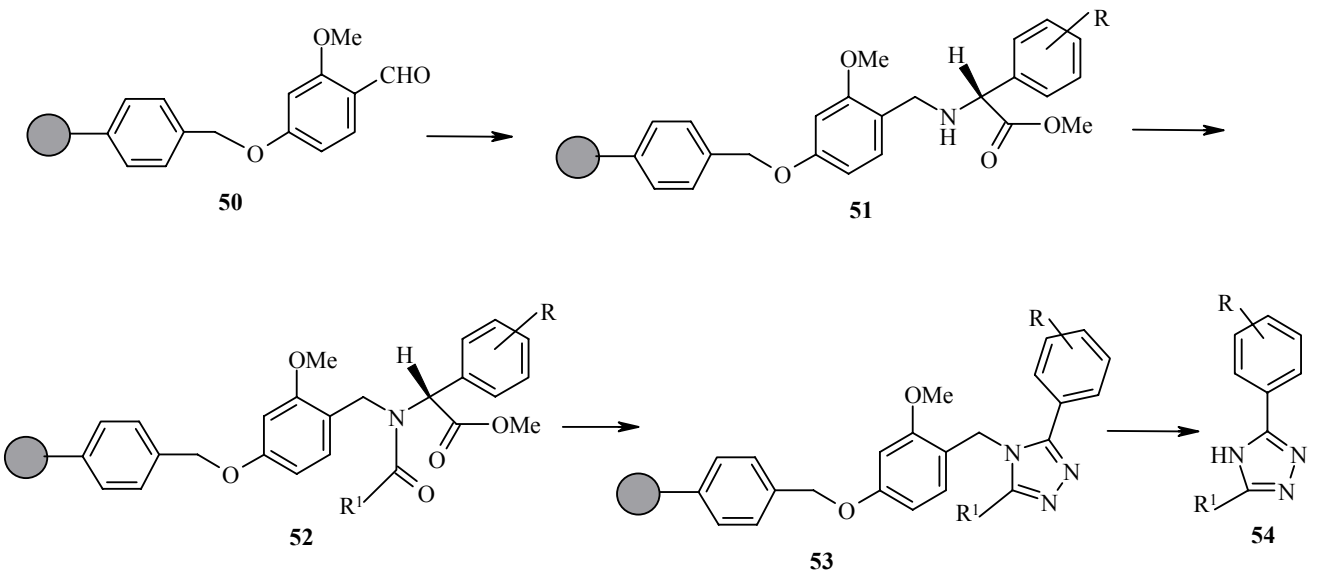


There are, so far, only a few published studies about the solid-phase synthesis of substituted 1,2,4-triazoles. Katritzky reported the synthesis of tri-substituted 1,2,4-triazoles on a solid support based on the condensation reaction between an acyl hydrazide and substituted amidines [70]. The yields were 37-90% and the purities depended on the substituents of the triazole core.

This procedure enables the alkylation of the 1-position, giving the trisubstituted 1,2,4-triazoles, but suffers from the nontraceless nature of the reaction sequence. Hence, the synthesized 1,2,4-triazoles contain the 4-hydroxyphenyl linker of the starting Wang resin. 3,4,5-Trisubstituted 1,2,4-triazoles were also prepared on solid supports [71].

A traceless synthesis of 3,5-disubstituted 1,2,4-triazoles has been developed on polymeric supports [72], using immobilized mesoionic 1,3-oxazolium 5-oxides (münchnones) as key intermediates in the 1,3-dipolar cycloaddition reaction, as shown in Scheme 10.

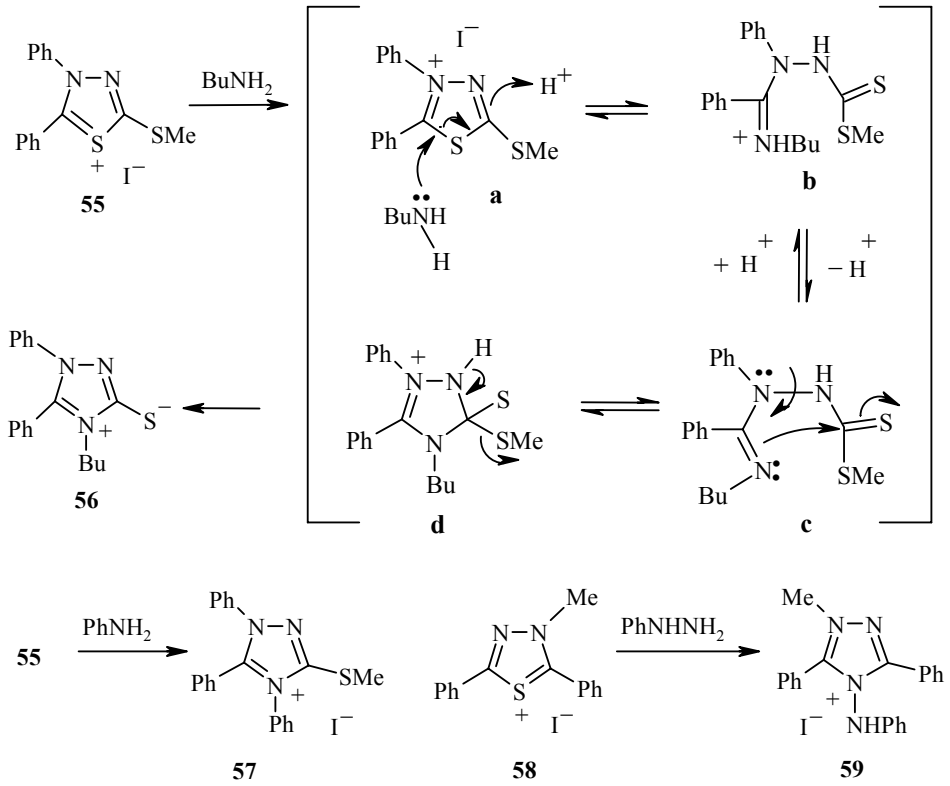
Scheme 10



2.4. Synthesis of particular classes of compounds and critical comparison of methods

Triazolium salts **56** and **57** can be prepared [73] from methylthiadiazolium salt **55** by treatment with butylamine and aniline, respectively. The proposed mechanism of transformation of mesoionic 1,3,4-thiadiazole **55** to mesoionic 1,2,4-triazole **56** by the action of primary amine is explained in terms of the intermediate **a** ring opening by butylamine to give the iminium salt **b**, which is subsequently deprotonated to the intermediate **c**, and by delocalization of the unpaired electrons of the nitrogen, allowing the butyliminium group to attack the C=S bond to give the protonated cyclic **d**, followed by lose of the proton and SMe group to give **56**. Thiadiazolium salt **58** reacts similarly with phenyl hydrazine [74] to give the triazolium salt **59**, as shown in Scheme 11.

Scheme 11



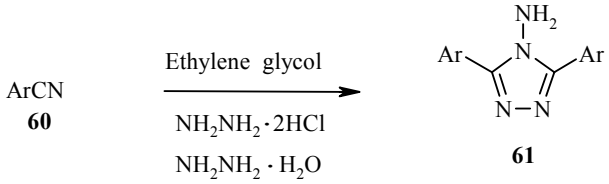
2.5. Synthesis of 1,2,4-triazoles under microwave irradiation

Microwave irradiation has become a widely used method to synthesize many useful organic chemicals rapidly, with good yields and high selectivity [75-89]. A great many relevant works suggest only a thermal nature of the microwave action, which means that microwaves are considered to be a method to heat chemical reagents rapidly and without any overheating. Some other works describe specific nonthermal effects, and these effects are likely to exist. Sometimes the effects are thought to be only specific forms of heat effects, but not always.

Kappe *et al.* [90-92] have used this method extensively for the synthesis of their organic molecules; meanwhile Molteni and Ellis [93] reviewed the work carried out since 1994 in the field of microwave-assisted synthesis of heterocyclic compounds and reactions in which a heteroatom is directly participating in the bond forming process that gives rise to a heterocyclic core.

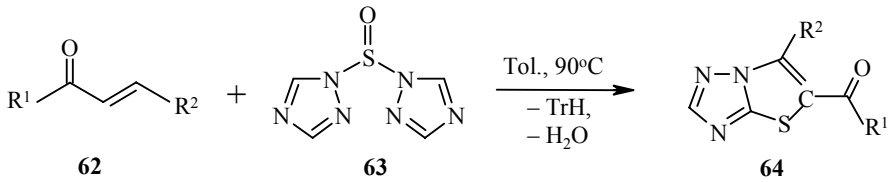
By applying the microwave irradiation method, several 1,2,4-triazole derivatives were recently reported. Bentiss *et al.* [94] have synthesized 3,5-disubstituted 4-amino-1,2,4-triazoles **61** from the reaction of aromatic nitriles **60** with $NH_2NH_2{\cdot}2HCl$ in the presence of $NH_2NH_2{\cdot}2H_2O$ excess in ethylene glycol under microwave irradiation (Scheme 12).

Scheme 12

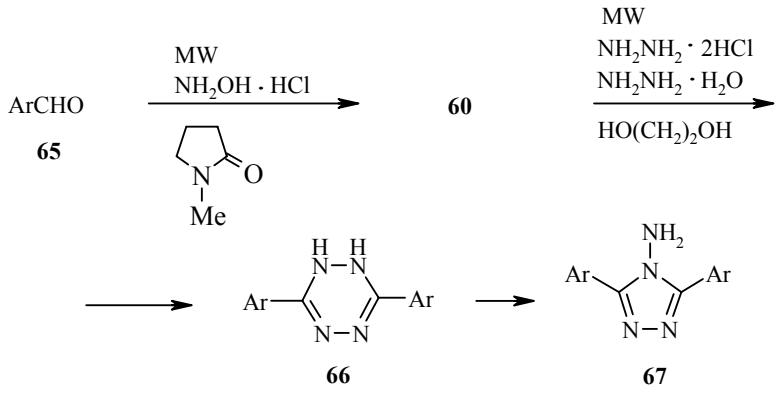


A novel one-step synthesis of thiazolo[3,2-*b*]-1,2,4-triazoles **64** was reported from the reaction of chalcones **62** with bis(1,2,4-triazolyl)sulfoxide **63** [95] (Scheme 13). Symmetrical 3,5-substituted 4-amino-1,2,4-triazoles **67** are quickly prepared from aromatic aldehydes **65** *via* nitriles **60** by two-step reactions without any separation under microwave irradiation for each several minutes [96] (Scheme 14).

Scheme 13

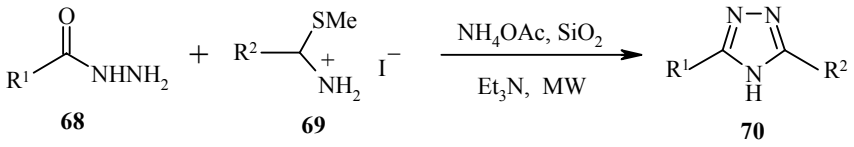


Scheme 14



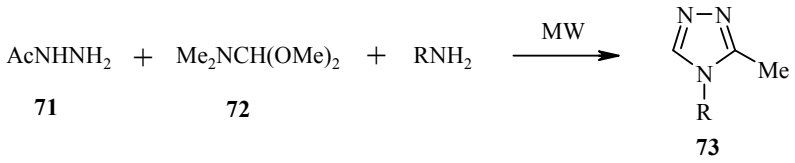
Condensation of acid hydrazide **68** with S-methylisothioamide hydroiodide **69** and ammonium acetate on the surface of silica gel under microwave irradiation afforded 1,2,4-triazoles **70** [97] (Scheme 15).

Scheme 15



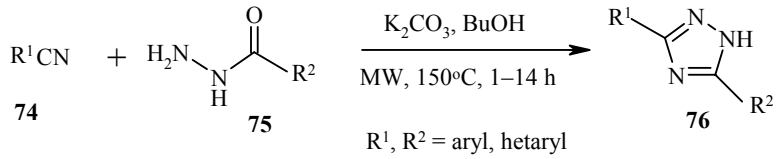
An efficient microwave-assisted one-pot and three-component synthesis of substituted 1,2,4-triazoles **73** has been achieved utilizing substituted primary amines [98] (Scheme 16).

Scheme 16

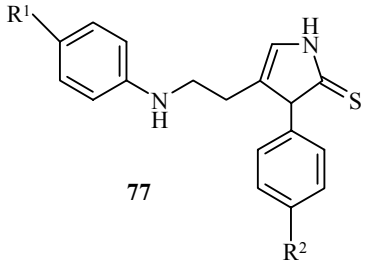


A recent publication by Yeung *et al.* [99] described a convenient and efficient one-step, base-catalyzed synthesis of 3,5-disubstituted 1,2,4-triazoles **76** by the condensation of nitriles **74** and hydrazides **75** under microwave irradiation (Scheme 17). Under the reaction conditions, a diverse range of functionality and heterocycles are tolerated. The reactivity of the nitrile partner is relatively insensitive to electronic effects.

Scheme 17



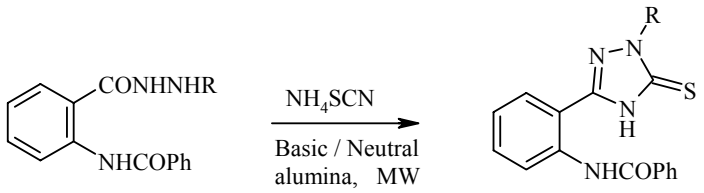
A new protocol for Biginelli reaction microwave irradiation in the synthesis of some 1,2,4-triazoles **77** as a potential antifungal agents against *Candida albicans* and *Aspergillus niger* has been reported recently [100].



R1 = H, OMe, Br, Cl; R2 = H, Me, Br, Cl

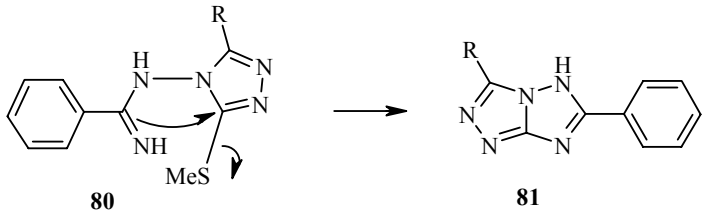
Kidwai *et al.* [101] have synthesized new antifungal azoles including 1,2,4-triazole derivatives from substituted hydrazide 7**8** using various solid supports under microwave irradiation, as shown in Scheme 18.

Scheme 18



A simple and fast synthesis of 6-aryl-3-substituted 5H-[1,2,4]-triazolo-[4,3-*b*][1,2,4]triazoles **81** in high yields has been developed by microwave assisted heterocyclization of N-(3-methylthio-5-substituted 4H-1,2,4-triazol-4-yl)benzenecarboximidates **80** [102] (Scheme 19).

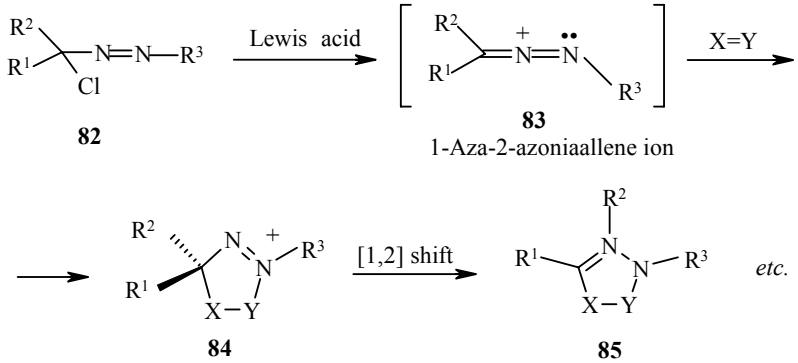
Scheme 19



2.6. Dipolar cycloaddition of 1-aza-2-azoniaallene salts with nitriles

Recently, Jochims *et al*. [103] described a synthesis of a new class of carbenium ions, heterocumulenic cations, namely, 1-aza-2-azoniaallene cations **83**, which was prepared from (*E*)-1-(2-chloroalkan-2-yl)-2-alkyldiazenes **82** and a Lewis acid, such as $SbCl_5$. Although the positive charge of **83** is stabilized by the adjacent atom, the salts are short lived, making their separation impossible. However, the heterocumulenes salts **83** were found to undergo cycloadition to the multiple bonds of alkenes, alkynes, isocyanates, carbodiimides, and nitriles to furnish pyrazolium ions **84**, which in most cases undergo a spontaneous successive transformation [103-109] to afford different heterocycles, including 1,2,4-triazole derivatives **85**, as shown in Scheme 20.

Scheme 20

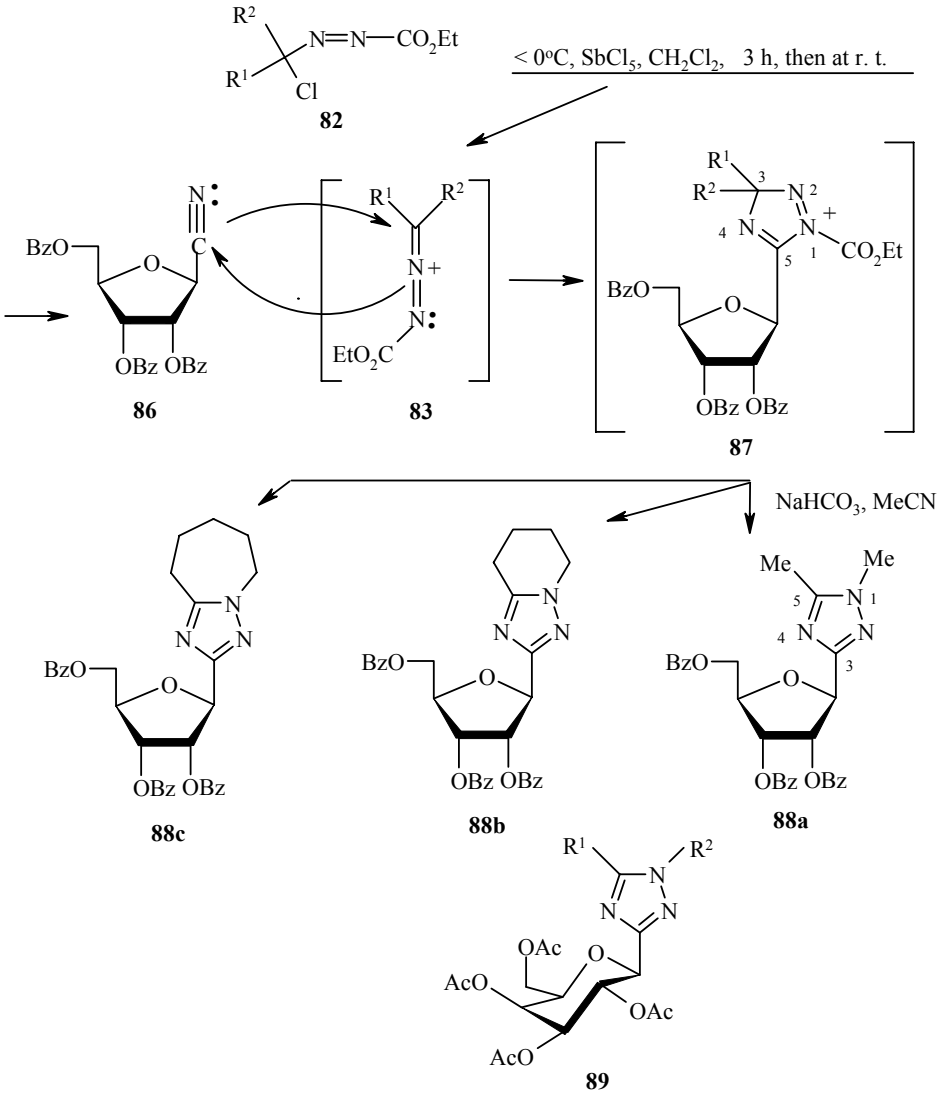


X = Y = nitrile, alkene, isocyanate, carbodiimide

The mechanism for the formation of the triazole derivatives **85** is explained in terms of the characteristic features of cations **83**, which favored the rearrangements in most reactions [110]. Most important are Wagner–Meerwein rearrangements, which are defined as migration of a C-atom to a vicinal electron-deficient carbon atom, the carbonium center [111]. An example is the well-known pinacol/pinacolone rearrangement. Equally important are [1,2] shifts of a hydrogen atom (often referred to as hydride shifts). Transformation **84** → **85** resembles Wagner–Meerwein rearrangements. However, in most of these cases the migration takes place to an electron-deficient nitrogen atom. A ring expansion using this reaction has been described [112].

Al-Masoudi *et al*. [113] have used the cycloaddition of cations **83** with sugar nitriles as a novel method to prepare the C-nucleosides, since a few 1,2,4-triazole C-ribonucleosides were prepared [114-119]. Thus, cycloaddition of the peracylated β-D-ribofuranosyl nitrile **86** [120] with **83a-c**, formed from (chloroalkyl)azo compounds **82** in the presence of $SbCl_5$, afforded iminium salts **87a-c**. These salts were directly subjected to hydrolysis with aqueous sodium bicarbonate to give, after loss of the CO_2Et group, 1,2,4-triazole nucleosides of peracylated β-D-ribofuranoside **88a-c**. Similarly, the β-D-galactopyranosyl-1,2,4-triazole nucleosides **89** were prepared [113] (Scheme 21).

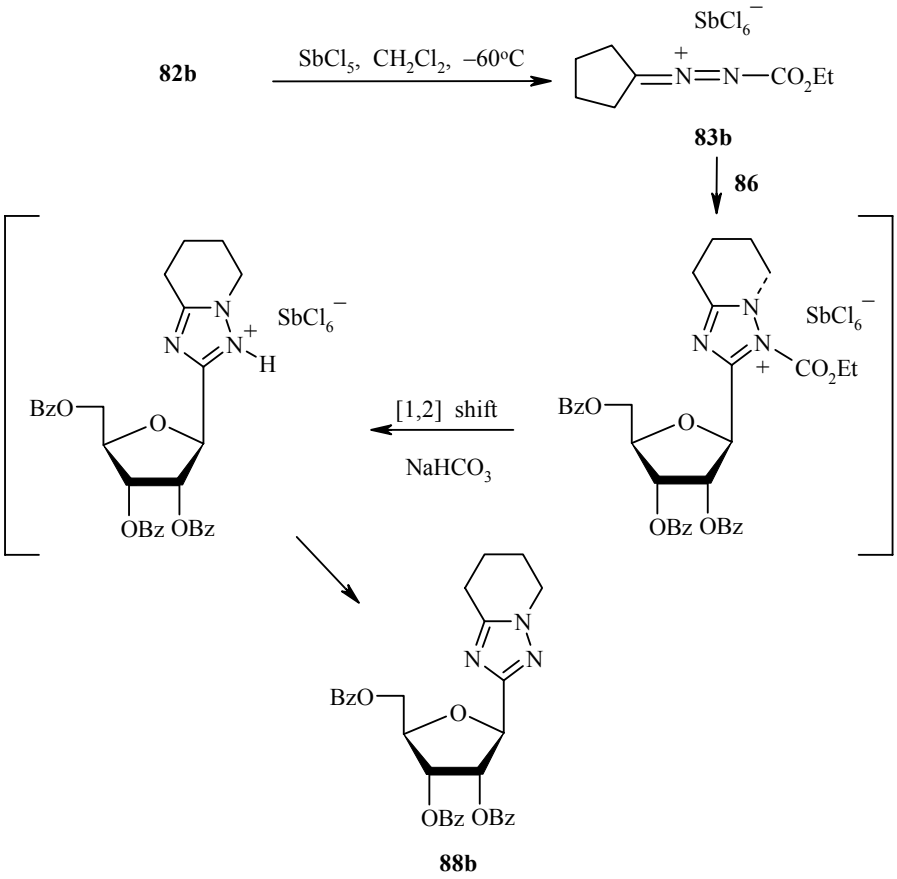
Scheme 21



a $R^1 = R^2 = Me$, **b** $R^1 + R^2 = (CH_2)_4$, **c** $R^1 + R^2 = (CH_2)_5$; **a-c** $R^3 = CO_3Et$

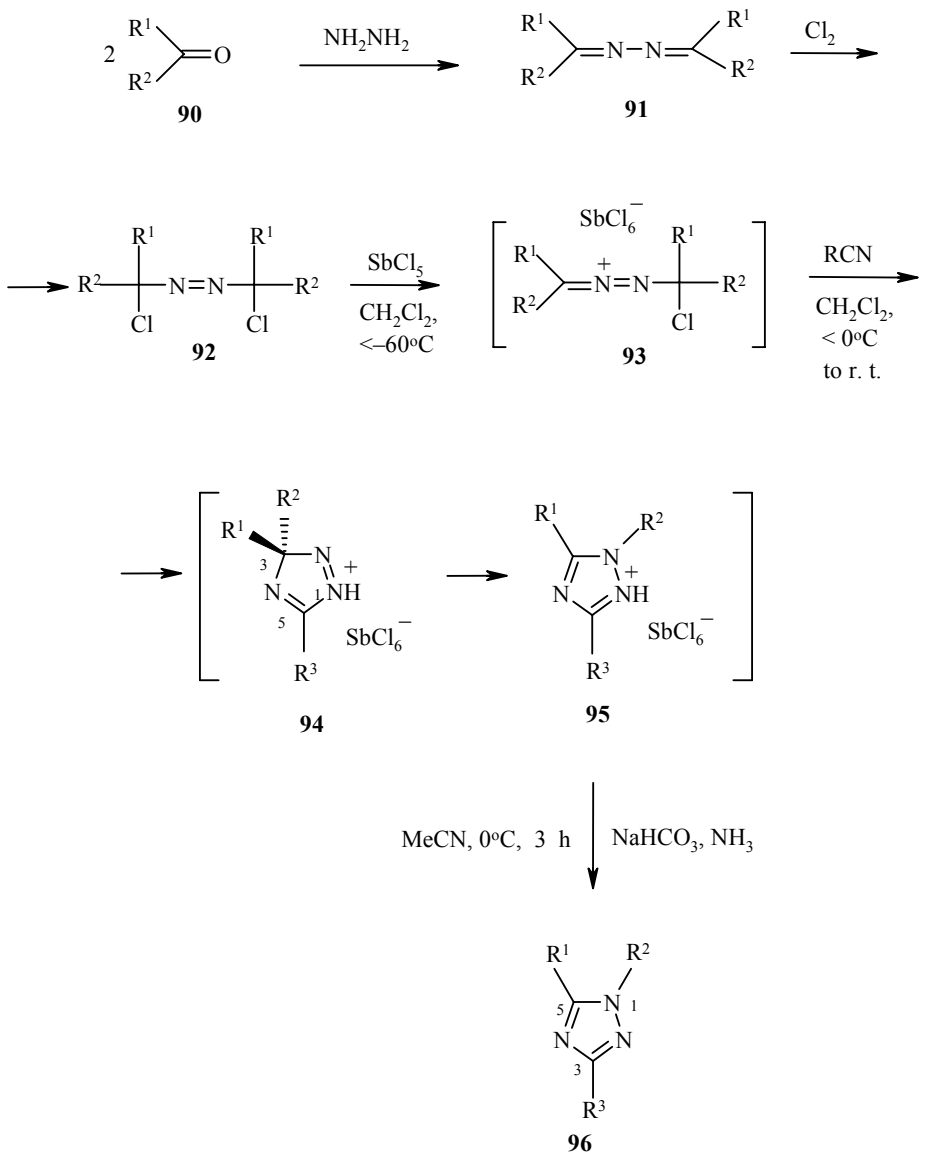
The formation of the triazolopyridine **88b** can be explained in terms of the ring expansion of intermediate **83b**, formed from 1-chloro-1-cyclopentylazocarboxylate **82b** in the presence of $SbCl_5$, during cycloaddition with nitrile **86** followed by the [1,2] shift, as shown in Scheme 22. Similarly, triazoloazepine derivative **88c** is prepared from intermediate **83c** formed from 1-chloro-1-cyclohexylazocarboxylate **82c** (Scheme 21).

Scheme 22



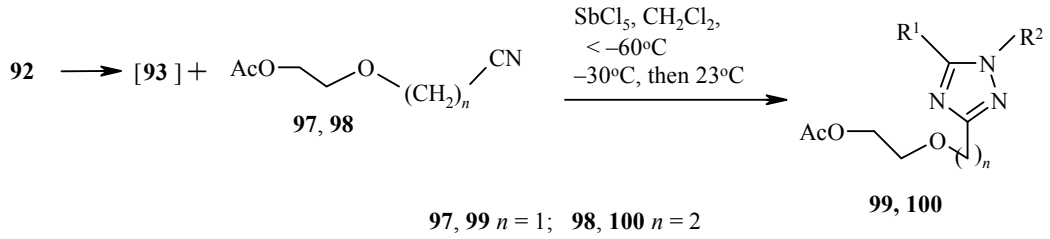
α,α'-Dichloroazoalkanes **92** were prepared by chlorination of ketazines **91** [121-130], which were obtained by reaction of 2 eq. of ketone **90** with 1 eq. of hydrazine [131-136]. The azo compounds **92** have been converted at low temperature (~ -60°C) to the reactive intermediates (chloroalkyl)azohexachloroantimonates **93** in the presence of $SbCl_5$. During the addition of the nitrile compounds at ~ -30°C the color changed from orange to brown, indicating that **93** undergoes cycloaddition with the nitrile compounds to give inseparable 5-alkyl-3H-1,2,4-triazolium hexachloroantimonates **94**. When the temperature is raised to ~ 0°C, **94** furnishes the protonated triazoles **95** by [1,2]-migration [103, 106] of the alkyl group R^2 of **94** from C-3 to N-2 associated with elimination of the ($CClR^1R^2$) group from N-1. Hydrolysis of **95** *in situ* with sodium hydrogen carbonate and ammonia solution afforded the 1,2,4-triazole derivatives **96** (Scheme 23).

Scheme 23



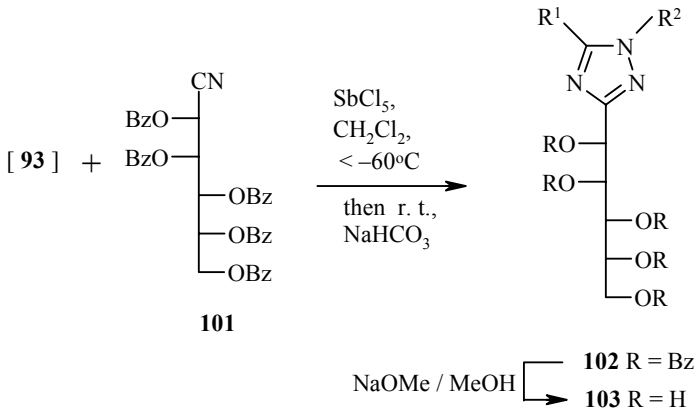
Several potentially bioactive 1,2,4-triazole compounds have been synthesized by Al-Masoudi *et al.* applying the above 1,3-cycloaddition method from different nitriles with the 1-(chloroalkyl)azo salts **93** in the presence of $SbCl_5$ as a Lewis acid [137-140]. Examples of these triazoles are **88** [138], which were prepared previously from chlorocarbazate **82**, whereas the potentially interesting acyclic C-nucleosides **99** and homo-C-analogues **100** [139] were synthesized from the cycloaddition of the reactive intermediates **93** with the 2-acetoxyethoxyalkyl cyanides **97** [140] and **98** [139], respectively (Scheme 24). The formation of these nucleosides proceeds by a similar mechanistic pathway, described for the formation of **88a-c**. The free acyclic nucleosides of these derivatives showed potential activity as herbicides, fungicides, and insecticides.

Scheme 24



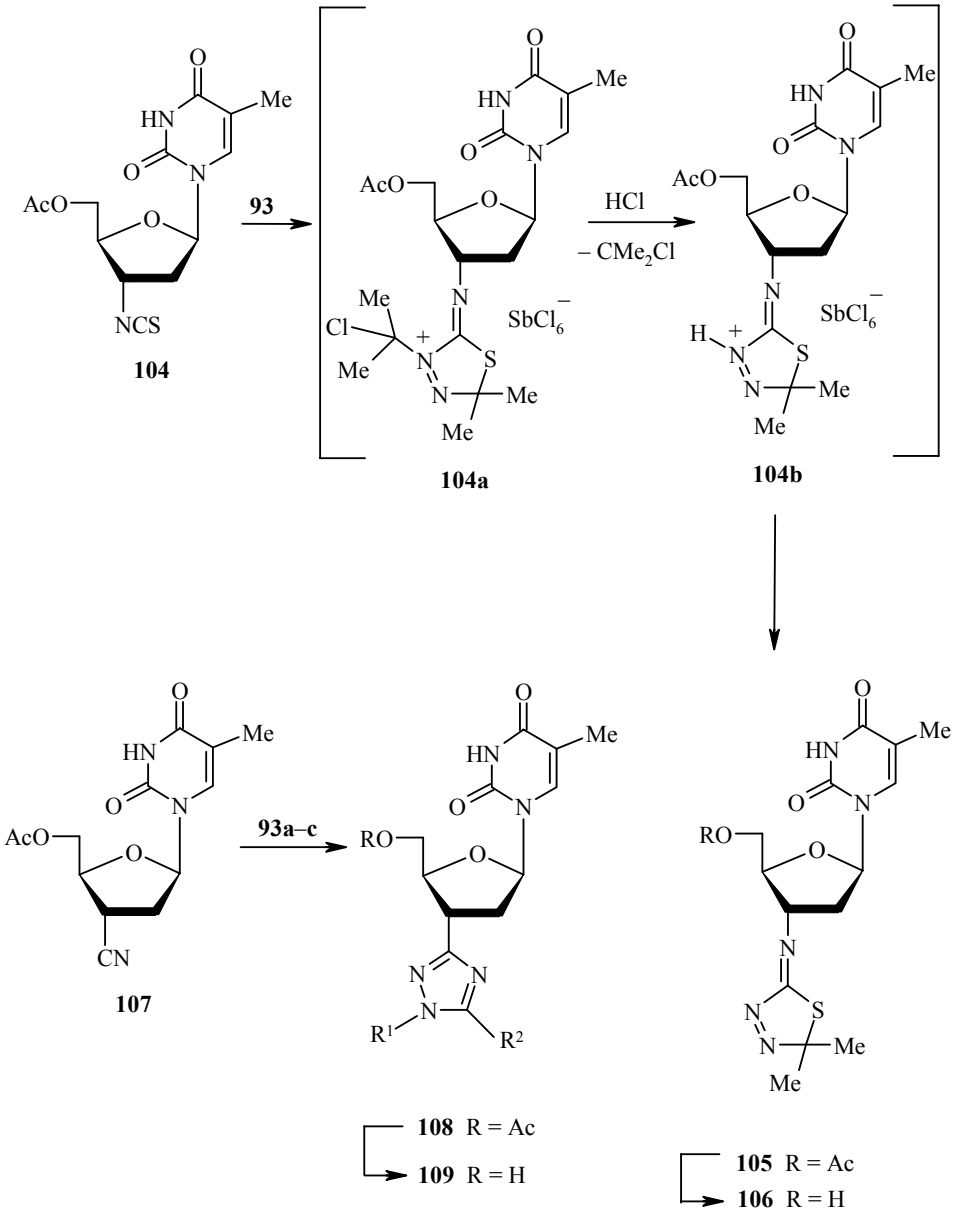
Since some successful attempts in the synthesis of several 1H-1,2,4-triazole derivatives have been made, the chemistry of their nucleosides has been explored, such as the synthesis of acyclic nucleosides [141], 1,3-dialkyl-(D-mannopentitol-1-yl)-1H-triazole nucleosides, **102**, derived from 1-(chloroalkyl)-1-aza-2-azoniaallene salts **93** and the penta-O-benzoyl-D-mannonic acid **101** [142]. Deblocking of **102** with NaOMe in MeOH at room temperature proceeded smoothly to give the free nucleosides **103**; their structures were confirmed by 2D-NMR spectroscopy (Scheme 25).

Scheme 25



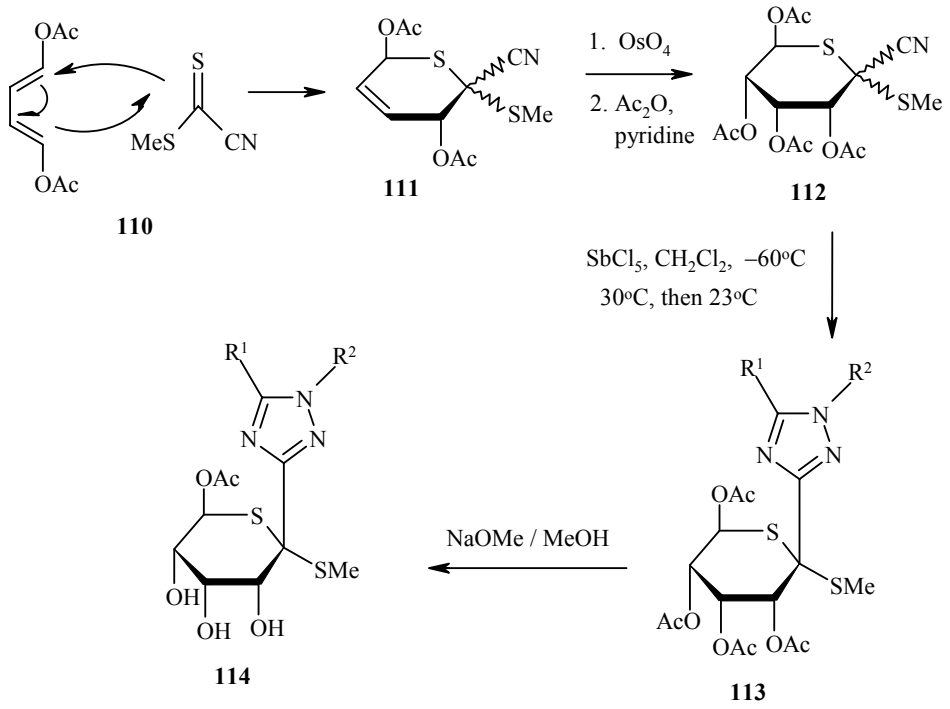
A new 5'-acetyl-3'-(1,3,4-thiadiazolimino)thymidine, **105**, was prepared [143] *via* spontaneous rearrangements by cycloaddition of 5'-acetyl-3'-isothiocyanatothymidine **104** [144, 145] with the reactive cumulene **93a**. Although the *concerted* cycloaddition to isothiocyanates is known to occur both on the C=S and the C=N bond in a competitive manner [146], the cycloaddition in such reaction occurred *via* the C=S and not the N=C bond. The isothiocyanate group of compound **104** reacts as an S-nucleophile, resulting, *via* the intermediates **104a** and **104b**, in 2,5-dihydro-1,3,4-thiadiazole **105**, and not as an N-nucleophile. These findings are consistent with the results obtained by Jochims *et al.* [147, 148]. Similarly, 3'-cyano analogue **107** was reacted with the reactive cumulenes **93** to furnish 3'-(1,2,4-triazolo)thymidines **108**, which both gave the free nucleosides **106** and **109**, respectively, on deblocking with NaOMe in MeOH, as shown in Scheme 26.

Scheme 26



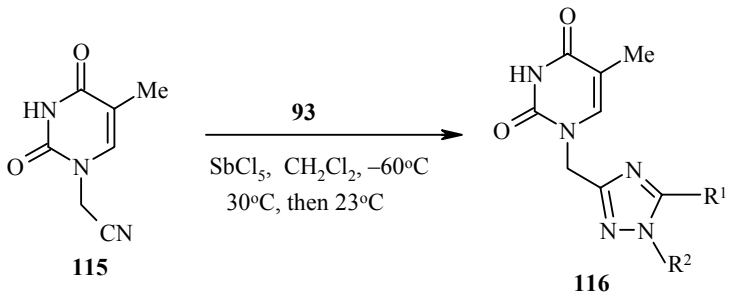
Recently, 1,2,4-triazole nucleosides **113** bearing an unusual thiosugar have been synthesized [149] from cycloaddition of the 1,5-dithio-1-thiomethyl-*arabino*pentulopyranose **112** with the cumulenes **93**. Deblocking of **113** with NaOMe in MeOH afforded free thionucleosides **114**, as shown in Scheme 27.

Scheme 27



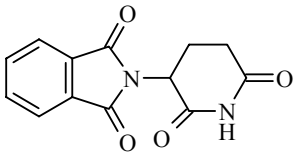
Extensive work has demonstrated the feasibility of using synthetic nucleoside and non-nucleoside analogues as anticancer and antiviral chemotherapeutic agents, and some of them are anti-HIV drugs, with 1-substituted pyrimidines being among the most widely studied [150]. Based on these biological data, the 1-[(1,5-dialkyl-1H-1,2,4-triazol-3-yl)methylthymines **116** [151] have been prepared from cycloaddition of the 1-cyanothymine **115** [152] with the reactive cumulenes **93**, as potential anti-HIV agents since some acyclic 1,2,4-triazole C-nucleosides [153] showed remarkable antiviral properties against HSV-1 and -2 along with other viruses (Scheme 28).

Scheme 28

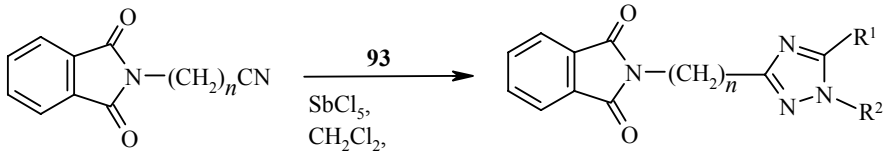


Tumor necrosis factor alpha (TNF-α) is an important cytokine secreted by activated monocytes/macrophages and possesses favorable biological activities, including direct tumor toxicities [154, 155]. Phthalimide derivative, Thalidomide® [N-(α)-phthalimidoglutarimide] **117** was selected as a potential inhibitor of TNF-α production [156, 157]. A series of new 1,2,4-triazoloalkylphthalimides **121-123** [158] has been synthesized from cycloaddition of the cyanoalkylphthalimides (alkylmethyl, ethyl, propyl) **118-120**, respectively, with the reactive cumulenes **93**, as promising inhibitors of TNF-α production (Scheme 29).

Scheme 29



117 Thalidomide

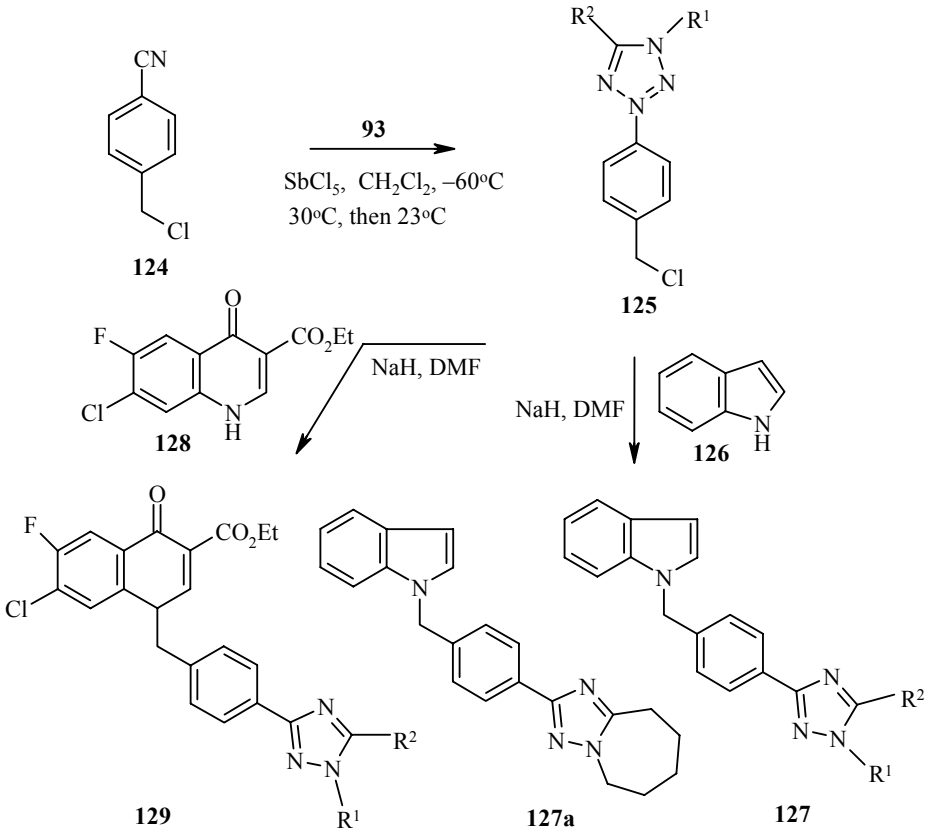


118–**120** **121**–**123**

118, **121** n = 1; **119**, **122** n = 2; **120**, **123** n = 3

The use of synthetic quinolones as antibacterial [159], antiviral [160], or anticancer agents [161], and dehydrogenase inhibitors [162] as well as indole compounds such as the antibiotic rebecamycin as an anticancer agent [163], has stimulated extensive research in the synthesis of this class of compounds. The quinolone and indole moieties bearing substituted 1,2,4-triazoles **127** and **129** have been synthesized [164] from coupling of the 1,2,4-triazolylbenzyl chloride **125** with **126** and **128**, respectively, in the presence of hydride ions, where **125** was prepared from cycloaddition of the reactive intermediates **93** with 4-cyanobenzyl chloride **124**, as shown in Scheme 30. Compound **127a** exhibited a remarkable toxicity against nine tumor cell lines.

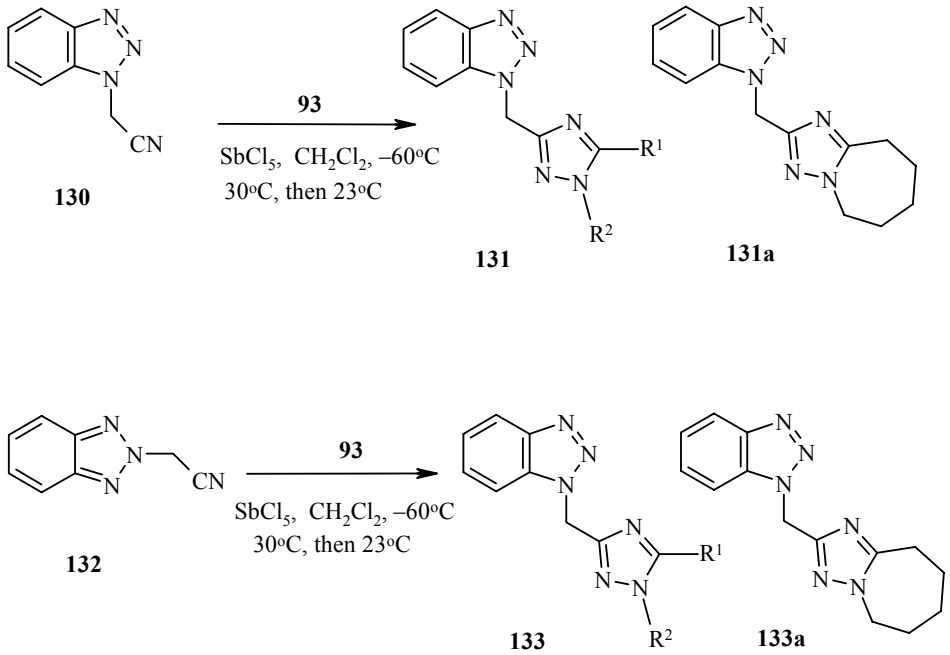
Scheme 30



124 **125** **128** **126** **129** **127a** **127**

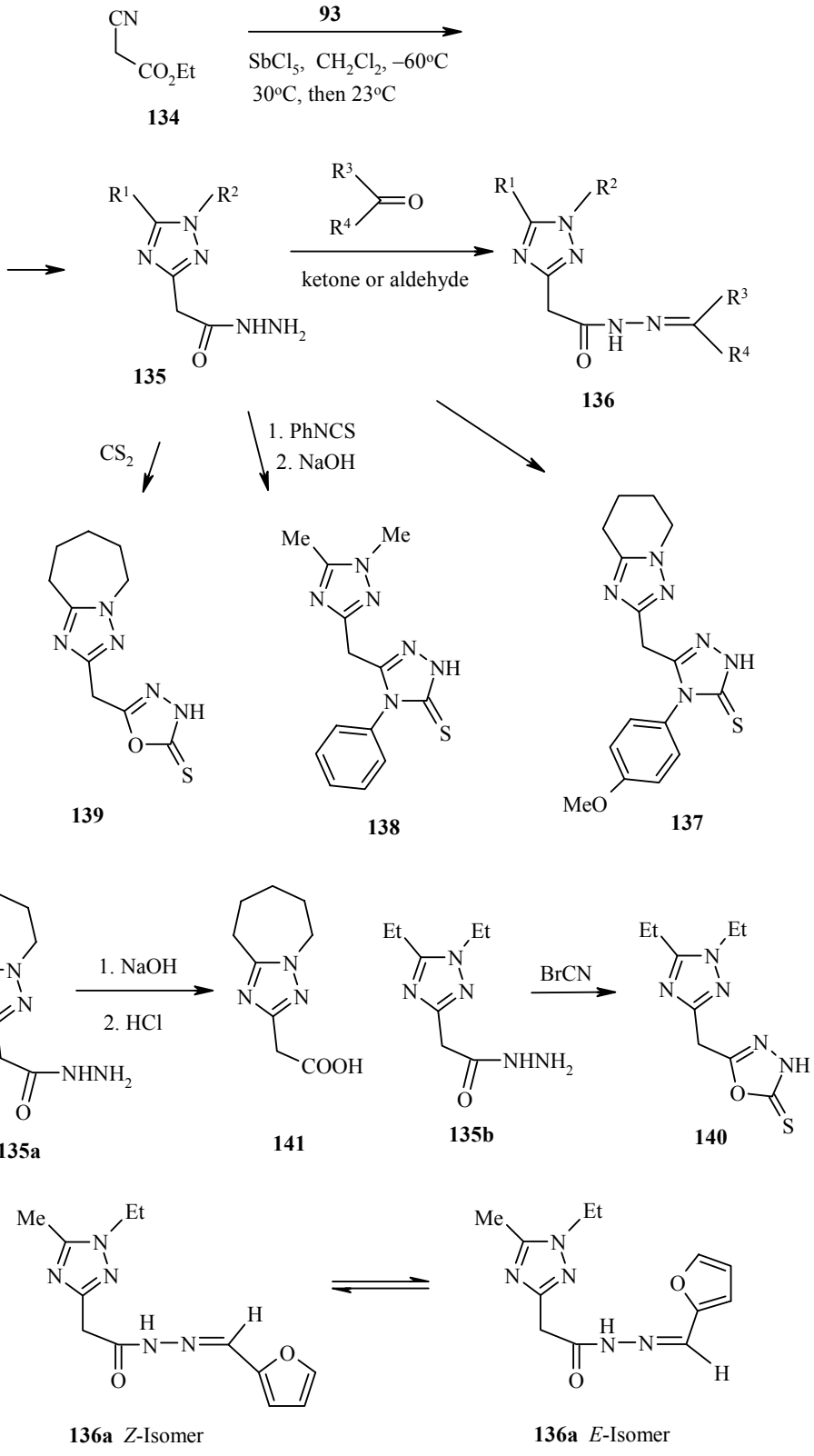
The 1H-benzotriazole compounds possess important pharmacological activities such as anti-inflammatory [165], antiviral [166], antineoplastic [167], and antidepressant [168] effects. With respect to the biological activity of these molecules and the structurally related benzo-fused imidazoles (rifaximin [169] as antineoplastic and anticancer agent), attention was focused on the design of a novel type of trisubstituted 1,2,4-triazoles [170] bearing methyl benzotriazole residues in positions 2 and 3. Thus, cycloaddition of 1-(cyanomethyl)benzotriazole **130** [171] with **93** afforded, after spontaneous rearrangements, the N-1-triazolylmethylbenzotriazoles **131**, where the compound **131a** showed a remarkable potential activity against leukemia. Similarly, the N-2 isomer [172] gave the analogue **133** (Scheme 31), while **133a** showed a high potency against *Mycobacterium tuberculosis* growth inhibitor (99%).

Scheme 31



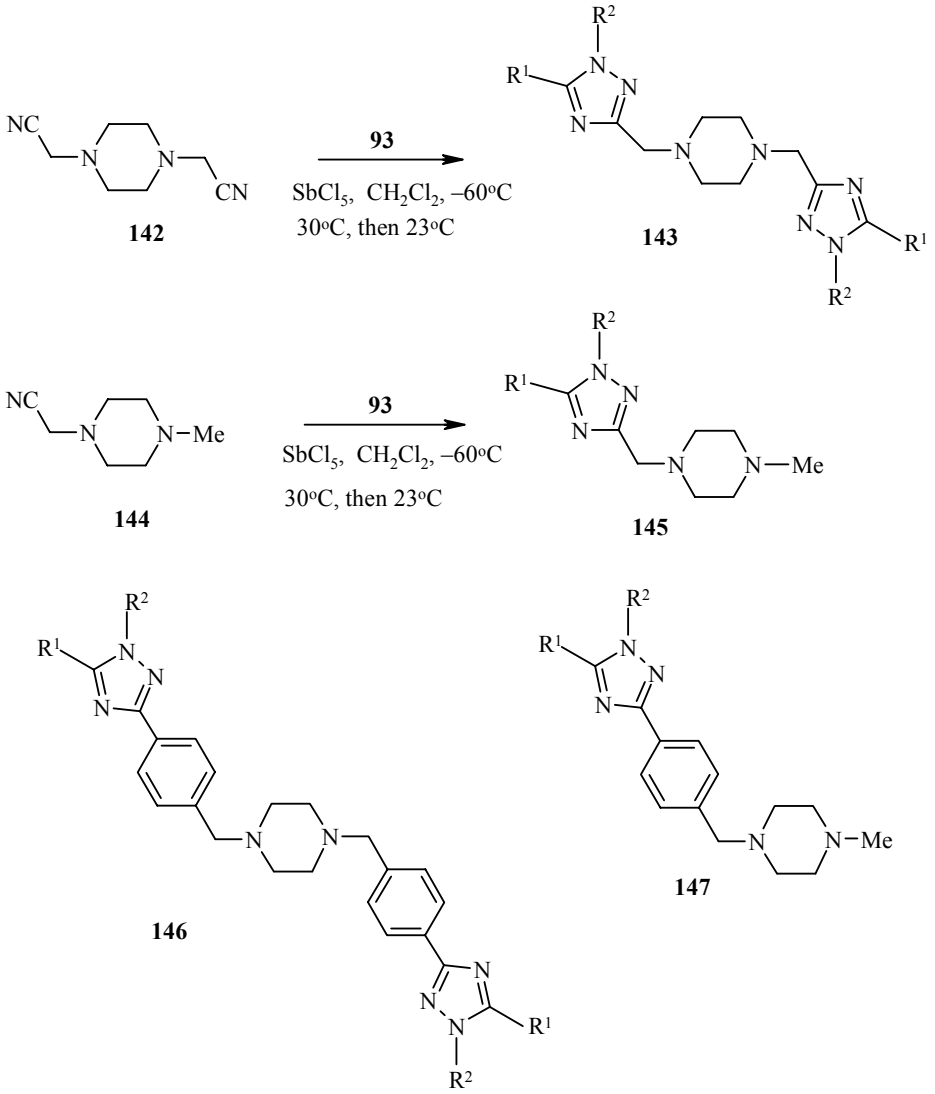
More examples of 1,2,4-triazole derivatives carrying different alkyl groups have been prepared [173] such as 1,5-dialkyl-1,2,4-triazole derivatives of acetic acid alkylidene hydrazides **136** from coupling of the hydrazides **135** with carbonyl compounds. The hydrazides **135** were synthesized from cycloaddition of ethyl cyanoacetate **134** with the intermediates **93**. The key intermediates **135** were used in the synthesis of 5-((5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)methyl)-4-(4-methoxyphenyl)-2H-1,2,4-triazole-3-thione **137**, and 5-((1,5-dimethyl-1H-1,2,4-triazol-3-yl)methyl)-4-phenyl-2H-[1,2,4]triazole-3-thione **138**, by reaction with *p*-methoxyphenyl isothiocyanate and phenyl isothiocyanate respectively, followed by treatment with sodium hydroxide. Treatment of **135** with carbon disulfide in basic medium resulted [174] in the formation of 5-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-*a*]azepin-2-yl)methyl-[1,3,4]oxadiazole-2-thione **139**, while treatment of **135b** with cyanobromide afforded the 5-((1,5-diethyl-1H-1,2,4-triazol-3-yl)methyl)-1,3,4-oxadiazole-2-thione **140**. The alkaline hydrolysis of **135a**, followed by acidification with HCl, furnished the 2-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-*a*]azepin-2-yl)acetic acid **141**. It is noteworthy that compounds **136a** existed as two isomers (*E*/*Z*-isomers) at 30°C, whereas it existed as one isomer at 130°C, as proved by ^{1}H NMR spectroscopy, thus establishing the effect of free rotation around the double bond between 30°C and 130°C (Scheme 32).

Scheme 32


CN
CO2Et
134
93
SbCl5, CH2Cl2, −60°C
30°C, then 23°C
R1
R2
N
N
N
NHNH2
O
135
R3
R4
O
ketone or aldehyde
N
H
136
CS2
1. PhNCS
2. NaOH
Me
NH
S
139
138
MeO
137
1. NaOH
2. HCl
COOH
141
Et
BrCN
135a
135b
140
H
136a Z-Isomer
136a E-Isomer

During the last decade, several piperazine derivatives were synthesized as useful chemotherapeutic agents for various diseases, such as Crivixan® (Indinavir sulphate) [175-177] and delaviridine (Rescriptor) [178], powerful inhibitors for the protease and reverse transcriptase inhibitor of HIV enzymes, respectively. On the basis of the exciting biological results of the piperazine derivatives, several substituted 1,2,4-triazole derivatives carrying piperazine residue, **143** and **145** [179], have been synthesized from cycloaddition of **93** with the 1,4-bis(cyanomethyl)piperazine **142** [180] and 1-cyanomethyl-4-methylpiperazine **144** [181], respectively (Scheme 33).

Scheme 33



Compounds **143** and **145** were screened against breast, lung, and CNS cancers, as well as their DNA affinity assay. More derivatives of 1,2,4-triazoles, such as **146** and **147** [181], have been synthesized from the precursor **125**, which was prepared previously in our laboratory [163].

REFERENCES

1. M. Yagisawa, *Jpn. J. Med. Mycol.*, **45**, 77 (2004).
2. E. M. Johnson, A. Szekely, and D. W. Warnock, *Antimicrob. Agents Chemother.*, **43**, 1260 (1999).
3. Y. Tsukuda, M. Shiratori, H. Watanabe, H. Ontsuka, K. Hattori, M. Shirai, and N. Shimma, *Bioorg. Med. Chem. Lett.*, **8**, 1819 (1998).
4. A. Narayanan, D. R. Chapman. S. P. Upadhyaya, and L. Bauer, *J. Heterocycl. Chem.*, **30**, 1405 (1993).
5. E. M. D. J. Krakovsky and M. J. Rybak, *Pharmacotherapy*, **10**, 146 (1990).
6. J. Roberts, K. Schock, S. Marino, and V. T. Andriole, *Antimicrob. Agents Chemother.*, **44**, 3381 (2000).
7. H. Sanati, P. Belanger, R. Fratti, and M. Ghannoum, *Antimicrob. Agents Chemother.*, **41**, 2492 (1997).
8. K. Richardson, A. S. Bell, R. P. Dickinson, S. Naryanaswami, and S. J. Hay, *Abstr. 35th Intersci. Conf. Antimicrob. Agents Chemother.*, 1995, F69, p. 125.
9. A. Espinel-Ingroff, *J. Clin. Microbiol.*, **36**, 198 (1998).
10. F. T. Boyle, D. J. Gilman, M. B. Gravestock, and J. M. Wardleworth, *Ann. N.Y. Acad. Sci.*, **544**, 86 (1988).
11. M. A. Pfaller, S. Messer, and R. N. Jones, *Antimicrob. Agents Chemother.*, **41**, 1124 (1997).
12. H. V. Bossche, P. Marichal, L. Le Jeune, M. C. Coene, J. Gorrens, and W. Cools, *Antimicrob. Agents Chemother.*, **37**, 2101 (1993).
13. S. Massa, R. Disanto, A. Retico, M. Artico, N. Simmonetti, G. Fabrizi, and D. Lamba, *Eur. J. Med. Chem.*, **27**, 495 (1992).
14. F. Doignon and N. Rozes, *Lett. Appl. Microbiol*., **15**, 172 (1992).
15. G. M. Tiboni, *Res. Commun. Chem. Pathol. Pharmacol.*, **79**, 381 (1993).
16. E. A. Konorev, A. T. Struck, J. E. Baker, S. Ramanujam, J. P. Thomas, R. Radi, and B. Kalyanaraman, *Free Rad. Res. Commun.*, **19**, 397 (1993).
17. A. Aspberg, M. Soderback, and O. Tottmar, *Biochem. Pharmacol.*, **46**, 1873 (1993).
18. T. Konosu, Y. Tajima, T. Miyaoka, and S. Oida, *Tetrahedron Lett.*, **32**, 7545 (1991).
19. J. T. Witkowski, R. K. Robins, R. W. Sidwell, and L. N. Simon, *J. Med. Chem.*, **15**, 1150 (1972).
20. R. W. Sidwell, J. H. Hoffmann, G. P. Khare, L. B. Allene, J. T. Witkowski, and R. K. Robins, *Science*, **177**, 705 (1972).
21. R. A. Smith and W. Kirkpatrick, *Ribavirin. A Broad Spectrum Antiviral Agent*, Acad. Press, New York, 1985, p. 49.
22. R. W. Smith, G. R. Revankar, and R. K. Robins, in *Viral Chemotherapy*; D. Shugar (ed.); Pergamon Press, New York, 1985, vol. 2, p. 13.
23. A. Smith, V. Knight, and J. A. D. Smith, *Clinical Applications of Ribavirin*; Acad. Press, New York, 1984.
24. N. B. Hanna, S. Dimitrijevich, S. B. Larson, R. K. Robins, and G. R. Ravankar, *J. Heterocycl. Chem*., **25**, 1857 (1988).
25. T. C. Jenkins, I. J. Stratford, and M. A. Stephens, *Anticancer Drug Des.*, **4**, 145 (1989).
26. G. D. Kini, R. K. Robins, and T. L. Avery, *J. Med. Chem.*, **32**, 1447 (1989).
27. P. R. Bovy, D. B. Reitz, J. T. Collins, T. S. Chamberlain, G. M. Olins, V. M. Corpus, E. G. McMahon, M. A. Palomo, J. P. Koepke, G. J. Smits, D. E. McGraw, and J. F. Gaw, *J. Med. Chem.*, **36**, 101 (1993).
28. W. T. Ashton, C. L. Cantone, I. L. Chang, S. M. Hutchins, R. A. Strelitz, S. M. MacCoss, R. S. L. Chang, V. I. Lotti, and K. A. Faust, *J. Med. Chem.*, **36**, 591 (1993).
29. H. C. Haung, D. B. Reitz, T. S. Chamberlain, G. M. Olins, V. M. Corpus, E. G. McMahon, M. A. Palomo, J. P. Koepke, and G. J. Smits, *J. Med. Chem.*, **36**, 2172 (1993).
30. W. H. Ashton, L. I. Chang, K. I. Flanagan, S. M. Hutchins, E. M. Naylor, P. K. Charkravarty, A. A. Patchett, W. J. Ggeenlee, and T.-B. Chen, *J. Med. Chem.*, **37**, 2808 (1994).

31. L. I. Chang, W. T. Ashton, A. I. Flanagan, T.-B. Chen, S. S. O'Malley, G. Z. Zingaro, P. K. S. Siegl, S. D. Kivlighn, and V. J. Lotti, *J. Med. Chem.*, **37**, 4464 (1994).
32. G. Heubach, B. Sachse, and H. Buerstell, Ger. Offen Pat. 2826760, *Chem. Abstr.* **92**, 181200 (1980).
33. G. Tanaka, Japan Kokai, 973, 7495 (1974), *Chem. Abstr.*, **82**, 156320 (1975).
34. D. A. Griffin and S. K. Mannion, Eur. Pat. 199474, *Chem. Abstr.*, **106**, 98120 (1987).
35. S. Papakonstantinou-Garoufalias, N. Pouli, P. Marakos, and A. Chytyroglou-Ladas, *Farmaco*., **57**, 973 (2002).
36. Y. Naito, F. Akahoshi, S. Takeda, T. Okada, M. Kajii, H. Nishimura, M. Sugiura, C. Fukaya, and Y. Kagitani, *J. Med. Chem.*, **39**, 3019 (1996).
37. M. I. Husian and M. Amir, *J. Indian Chem. Soc.*, **106**, 317 (1986); *Chem. Abstr.*, **106**, 176272 (1987).
38. S.-H. L. Chiu and S.-E. W. Huskey, *Drug Metab. Dispos.*, **26**, 838 (1998).
39. R. Eliott, R. L. Sunley, and D. A. Griffin; UK Pat. Appl. GB. 175301, *Chem. Abstr.*, **107**, 134310 (1987).
40. P. E. Goss and K. Strasser-Weippl, *Best Pract. Res. Clin. Endocrinol. Metab.*, **18**, 113 (2004).
41. J. R. Santen, *Steroids*, **68**, 559 (2003).
42. M. Clemons, R. E. Coleman, and S. Verma, *Cancer Treat. Rev.*, **30**, 325 (2004).
43. S. Chen, Y. C. Kao, and C. A. Laughton, *J. Steroid Biochem.*, **61**, 107 (1997).
44. I. Chaaban and O. O. Oji, *J. Indian Chem Soc.*, **61**, 523 (1984); *Chem. Abstr.*, **102**, 62157 (1985).
45. A.-M. M. E. Omar, and O. M. AboulWafa, *J. Heterocycl. Chem.*, **21**, 1415 (1984).
46. C. Francois, Fr. Pat. 539127; *Chem. Abstr.*, **102**, 95677 (1985).
47. F. A. Eid, A. H. f. Abd El-Wahab, G. A. M. El-Hag Ali, and M. M. Khafagy, *Acta Pharma*, **54**, 13 (2004).
48. R. B. Shankar and R. G. Pews, *Heterocycles*, **53**, 1151 (2000).
49. M. Takaoka, S. Manabe, T. Yamoto, N. Matsunuma, and H. Masuda, N. Goto, *J. Vet. Med. Sci.*, **56**, 341 (1994).
50. A. B. A. El-Gazzar, M. I. Hegab, S. A. Swelam, and A. S. Aly, *Phosphorus*, *Sulfur*, *Silicon*, **177**, 123 (2002).
51. S. W. Schneller, J. I. May, and E. De Clercq, *Croat. Chem. Acta*, **596**, 307 (1986).
52. S. M. El-Khawass and N. S. Habib, *J. Heterocycl. Chem.*, **26**, 177 (1989).
53. G. Tarrago, C. Marzin, D. Najimi, and V. Pellegrin, *J. Org. Chem.*, **55**, 420 (1990).
54. J. de Mendoza, J. M. Ontoria, M. C. Ortega, and T. Torres, *Synthesis*, 398 (1992).
55. R. Heckendorn and T. Winkler, *Helv. Chim. Acta*, **63**, 1 (1980).
56. J. Sveteik, *Heterocycles*, **20**, 1495 (1983).
57. R. A. Mekheimer and R. M. Shaker, *J. Chem. Res.* (*S*), 76 (1999).
58. K. Colanceska-Ragenovic, V. Dimova, V. Kakurinov, D. G. Molnar, and A. Buzarovska, *Molecules*, **6**, 815 (2001).
59. O. R. Gautun and P. H. J. Carlsen, *Molecules*, **6**, 969 (2001).
60. O. R. Gautun and P. H. J. Carlsen, *Acta Chem. Scand.*, **45**, 609 (1991).
61. O. R. Gautun and P. H. J. Carlsen, *Eur. J. Org. Chem.*, 3749 (2000).
62. S. M. Mustafa, V. A. Nair, J. P. Chittoor, and S. Krishnapillai, *Mini-Reviews in Organic Chemistry*, **1**, 375 (2004).
63. R. N. Butler, E. P. Ni Bhradaigh, and K. J. Fitzgerald, *J. Chem. Res.* (*S*), 306 (1993).
64. K. Paulvannan, T. Chen, and R. Hale, *Tetrahedron*, **56**, 8071 (2000).
65. B. I. Buzykin, and Z. A. Bredikhina, *Synthesis*, 59 (1993).
66. J. B. Polya, *Comp. Heterocycl. Chem.* 1st ed., **5**, 733 (1984).
67. A. Ya. Lazaris, S. M. Shmuilovich, and A. N. Egorochkin, *Chem. Heterocyl. Comp.*, **9**, 1216 (1973). [*Chemistry of Heterocyclic Compounds*, 1345 (1973)].
68. J. Goerdeler and J. Galinke, *Chem. Ber.*, **90**, 202 (1975).

69. E. J. Brown, E. E. Nunn, and J. B. Polya, *J. Chem.*, *Soc.* (*C*), 1515 (1970).
70. A. R. Katritzky, M. Qi, D. Feng, G. Zhang, M. C. Griffith, and K. Watson, *Org*., *Lett.*, **1**, 1189 (1999).
71. D. Boeglin, S. Cantel, A. Heitz, J. Martinez, and J.-A. Fehrentz, *Org*. *Lett.*, **5**, 4465 (2003).
72. S. K. Samanta and J. Yli-Kauhaluoma, *J. Comb. Chem.*, **7**, 142 (2005).
73. P. B. Talukdar, S. K. Sengupta, and A. K. Datta, *Indian J. Chem*., **11**, 753 (1973).
74. O. P. Shvaika and V. I. Formenko, *Zh. Org. Khim.*, **10**, 377 (1974).
75. H. M. Kingston and S. J. Haswell, *Microwave-Enhanced Chemistry Fundamentals, Sample Preparation and Application*, American Chemical Society: Washington, D. C., 1997.
76. A. Loupy, *Microwaves in Organic Synthesis*, Wiley-VCH: Weinheim, 2002.
77. B. L. Heyes, *Microwaves Synthesis*; *Chemistry at the Speed of Light*, CEM Publ: Matthews, NC, 2002.
78. L. Perreaux and A. Loupy, *Tetrahedron*, **57**, 9199 (2001).
79. P. Lidström, J. Tierney, B. Wathey, and J. Westman, *Tetrahedron*, **57**, 9225 (2001).
80. A. Fini and A. Breccia, *Pure Appl. Chem.*, **71**, 573 (1999).
81. R. A. Abramovich, *Org. Prep. Proced. Int.*, **23**, 685 (1991).
82. S. Caddick, *Tetrahedron*, **51**, 10403 (1995).
83. C. R. Strauss and R. W. Trainor, *Aust. J. Chem.*, **48**, 1665 (1995).
84. A. K. Bose, B. K. Banik, N. Lavlinskaia, M. Jayaraman, and M. S. Manhas, *Chemtech*., **27**, 18 (1997).
85. C. R. Strauss, *Aust. J. Chem.*, **52**, 83 (1999).
86. M. Kidwai and R. Kumar, *Gazz. Chim. Ital.*, **127**, 203 (1997).
87. M. Larhed, C. Moberg, and A. Hallberg, *Acc. Chem. Res*., **35**, 717 (2002).
88. M. Nüchter, U. Müller, B. Ondruschka, and W. Lautenschläger, *Chem. Eng. Technol.*, **26**, 1208 (2003).
89. M. Nüchter, B. Ondruschka, W. Bonrath, and A. Gum, *Green Chem.*, **6**, 128 (2004).
90. C. O. Kappe and A. Stadler, *Microwave-Assisted Combinatorial Chemistry*, in *Microwaves in Organic Synthesis*, A. Loupy, (ed.), Wiley-VCH, 2002, p. 405.
91. C. O. Kappe, *Curr. Opin. Chem. Biol.*, **6**, 314 (2002).
92. C. O. Kappe, *Am. Lab*., **33**, 13 (2001).
93. V. Molteni and D. A. Ellis, *Curr. Org. Synth.*, **2**, 333 (2005).
94. F. Bentiss, M. Lagrenee, and D. Barby, *Tetrahedron Lett.*, **41**, 1539 (2000).
95. A. R. Katritzky, A. Pastor, M. Voronkov, and P. Steel, *Org. Lett.*, **2**, 429 (2000).
96. H. Koshima, M. Hamada, M. Tani, S. Iwasaki, and F. Sato, *Heterocycles*, **57**, 2145 (2002).
97. S. Rostamizadeh, H. Tajik, and S. Yazdanfarahi, *Synth. Commun*., **33**, 113 (2003).
98. D. Li, H. Bao, and T. You, *Heterocycles*, **65**, 1957 (2005).
99. K.-S. Yeung, M. E. Farkas, J. F. Kadow, and N. A. Meanwell, *Tetrahedron Lett*., **46**, 3429 (2005).
100. A. Siddiqui, A. Arora, N. Siddiqui, and A. Misra, *Indian J. Chem*., **44B**, 838 (2005).
101. M. Kidwai and R. Mohan, *J. Korean Chem. Soc*., **48**, 177 (2004).
102. M. Rahimizadeh, A. Davoodnia, M. M. Heravi, and M. Bakavoli, *Phosphorus*, *Sulfur*, *Silicon*, **177**, 2923 (2002).
103. Q. Wang, J. C. Jochims, St. Köhlbrandt, L. Dahlenburg, M. Al-Talib, A. Hamed, and A. E.-H. Ismail, *Synthesis*, 710 (1992).
104. Q. Wang, A. Amer, C. Troll, H. Fischer, and J. C. Jochims, *Chem. Ber.*, **126**, 2519 (1993).
105. Q. Wang, A. Amer, S. Mohr, E. Ertel, and J. C. Jochims, *Tetrahedron*, **49**, 9973 (1993).
106. Q. Wang, M. Al-Talib, and J. C. Jochims, *Chem. Ber.*, **127**, 541 (1994).
107. Q. Wang, S. Mohr, and J. C. Jochims, *Chem. Ber.*, **127**, 947 (1994).
108. Y. Guo, Q. Wang, and J. C. Jochims, *Synthesis*, 274 (1996).
109. Y. A. Al-Soud, W. Wirschum, N. A. Hassan, G.-M. Maier, and J. C. Jochims, *Synthesis*, 721 (1998).
110. V. G. Shubin, *Topics in Current Chemistry*, Springer Verlag, Berlin, Vol. 116/117, 1984, p. 267.
111. J. March, *Advanced Organic Chemistry*, 3rd. ed., Wiley Interscience, New York, 1985, p. 949.
112. H. Gstach, P. Seil, J. Schantl, A. Gieren, Th. Hübner, and J. Wu, *Angew. Chem.*, **98**, 1111 (1986).

113. N. A. Al-Masoudi, N. A. Hassan, Y. A. Al-Soud, P. Schmidt, A. E.-D. M. Gaafar, M. Weng, S. Marino, A. Schoch, A. Amer, and J. C. Jochims, *J. Chem. Soc*., *Perkin Trans. 1*, 947 (1998).
114. G. Just and M. Ramjeesingh, *Tetrahedron Lett.*, 985 (1975).
115. T. Huynh-Dinh, J. Igolen, E. Bisagni, J. P. Marquet, and A. Civier, *J. Chem. Soc. Perkin Trans. 1*, 761 (1977).
116. M. S. Poonian and E. F. Nowoswiat, *J. Org. Chem.*, **45**, 203 (1980).
117. N. Katagiri, N. Tabei, S. Atsuumi, T. Haneda, and T. Kato, *Chem. Pharm. Bull*., **33**, 102 (1985).
118. Y. S. Sanghvi, N. B. Hanna, S. B. Larson, J. M. Fujitaka, R. C. Willis, R. A. Smith, R. K. Robins, and G. R. Ravanker, *J. Med. Chem.*, **31**, 330 (1988).
119. G. Y. Shen, R. K. Robins, and G. R. Ravanker, *Nucleosides*, *Nucleotides*, **10**, 1707 (1991).
120. F. G. de las Heras and P. Fernandez-Resa, *J. Chem. Soc. Perkin Trans. 1*, 903 (1982).
121. S. Goldschmidt and B. Acksteiner, *Chem. Ber.*, **91**, 502 (1958).
122. . S. Goldschmidt and B. Acksteiner, *Liebigs Ann. Chem.*, **618**, 173 (1958).
123. E. Benzig, *Chimia* (*Zürich*), **13**, 89 (1050).
124. E. Benzig, *Liebigs Ann. Chem.*, **631**, 1 (1960).
125. E. Benzig, *Liebigs Ann. Chem.*, **631**, 10 (1960).
126. D. S. Malament and J. M. McBride, *J. Am. Chem. Soc*., **92**, 4586 (1970).
127. D. S. Malament and J. M. McBride, *J. Am. Chem. Soc*., **92**, 4593 (1970).
128. P. L. Grizzle, D. W. Miller, and S. E. Scheppele, *J. Org. Chem.*, **40**, 1902 (1975).
129. W. Duismann, H.-D. Beckhaus, and C. Rüchardt, *Liebigs Ann. Chem.*, 1348 (1974).
130. A. F. Hegarty, J. A. Kearney, and F. L. Scott, *Tetrahedron Lett.*, **15**, 2927 (1974).
131. A. F. Hegarty, J. A. Kearney, and F. L. Scott, *J. Org. Chem.*, **40**, 3529 (1975).
132. Th. Curtius and K. Thun, *J. Prakt. Chem.*, **44**, 161 (1891).
133. Th. Curtius and F. Rauterberg, *J. Prakt. Chem.*, **44**, 161 (1891).
134. K. Taipale, *Ber. Dtsch. Chem. Ges.*, **63**, 248 (1930).
135. W. A. Schulze and H. L. Lochte, *J. Am. Chem. Soc*., **48**, 1030 (1926).
136. J. Elguero, R. Jacquier, and C. Marzin, *Bull. Soc. Chim. Fr*., 713 (1963).
137. P. Brun, A. Tenaglia, and B. Waegell, *Tetrahedron*, **41**, 5019 (1985).
138. Y. A. Al-Soud, W. A. Al-Masoudi, R. A. El-Halawa, and N. A. Al-Masoudi, *Nucleosides*, *Nucleotides*, **18**, 1095 (1999).
139. N. A. Al-Masoudi, Y. A. Al-Soud, and A. Geyer, *Tetrahedron*, **55**, 751 (1999).
140. H. Tanaka, T. Miyasaka, R. T. Walker, and E. De Clercq, *Nucleosides*, *Nucleotides*, **11**, 447 (1992).
141. N. A. Al-Masoudi, Y. A. Al-Soud, and I. M. Lagoja, *Carbohydr. Res*., **318**, 67 (1999).
142. E. R. de Labriola and V. Deulofeu, *J. Org. Chem*., **12**, 726 (1947).
143. Y. A. Al-Soud and N. A. Al-Masoudi, *Heteroatom Chem*., **14**, 298 (2003).
144. P. Monila, M. Alajarin, and A. Arques, *Synthesis*, 596 (1982).
145. A. Zehl and D. Cech, *Liebigs Ann. Chem*., 595 (1997).
146. R. N. Butler, D. C. Grogan, P. D. McDonald, and I. A. Bruke, *J. Chem. Soc.*, *Perkin Trans. 1*, 3587 (1997).
147. Y. A. Al-Soud, W. Wirschum, N. A. Hassan, G.-M. Maier, and J. C. Jochims, *Synthesis*, 721 (1998), references therein.
148. A.-R. B. A. El-Gazzar, K. Scholten, Y. Guo, K. Weissenbach, M. G. Hitzler, G. Roth, H. Fischer, and J. C. Jochims, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999 (1999).
149. N. A. Al-Masoudi and Y. A. Al-Soud, *J. Carbohydr. Chem*., **23**, 111 (2004).
150. C. Perigaud, G. Gosselin, and J.-L. Imbach, *Nucleosides*, *Nucleotides*, **11**, 903 (1992), references therein.
151. Y. A. Al-Soud and N. A. Al-Masoudi, *Arch. Pharm. Med. Chem*., **4**, 143 (1999).
152. J. Spychala, *Synth. Commun.*, **27**, 3431 (1997).

153. E. A. Carswell, I. J. Old, R. I. Green, N. Foire, and B. Williamson, *Proc. Natl. Acad. Sci. USA*, **72**, 3666 (1975).
154. R. J. Debs, H. J. Fuchs, R. Philip, E. N. Brunette, N. Duzgunes, J. E. Shellito, and D. Liggitt, *J. Patton, Cancer Res.*, **50**, 175 (1990).
155. S. Makonkawkeyoon, R. N. R. Limson-Pombre, A. I. Moreira, V. Schauf, and G. Kaplan, *Proc. Natl. Acad. Sci. USA*, **90**, 5974 (1993).
156. E. P. Sampio, E. N. Sarno, R. Gallily, Z. A. Cohn, and G. Kaplan, *J. Exp. Med*., **173**, 699 (1991).
157. Y. A. Al-Soud and N. A. Al-Masoudi, *Pharmazie*, **5**, 372 (2001).
158. J. T. Smith and C. S. Lewis, *The Quinolines*, V. T. Andriole (ed.), Acad. Press, London, 1988, ch. 2.
159. M. Nasr, J. C. Darch, S. H. Smith, C. Shipman, and J. H. Burckhalter, *J. Med. Chem.*, **31**, 1347 (1988).
160. H. I. El-Subbagh, A. H. Abadi, I. E. Al-Khawad, and K. A. Rashood, *Arch. Pharm. Pharm. Med. Chem*., **19**, 332 (1999).
161. B. R. Baker and R. R. Bramhall, *J. Med. Chem.*, **15**, 230 (1972).
162. J. A. Bush, B. H. Long, J. J. Catino, W. T. Brandner, and K. Tomita, *J. Antibiotics*, **40**, 668 (1987).
163. Y. A. Al-Soud, R. F. Halah, and N. A. Al-Masoudi, *Org. Prep. Proc. Intern*. (*OPPI*), **34**, 658 (2002).
164. A. Boido, I. Vazzana, and F. Sparatore, *Studi Sassar Sez. 2*, **57**, 787 (1979), *Chem. Abstr*., **93**, 23930 (1980).
165. D. Neikova, D. Simov, G. Galunska, E. Velichkova, A. Gulubov, and A. Karparov, *Arzeim. Forsch.*, **31**, 747 (1981).
166. V. Mues, W. Brandes, and V. Paul; Germ. Offen. Pat. 105433, *Chem. Abstr*., **98**, 16701p (1983).
167. F. Savelli, G. Cordella, and F. Sparatore, *Studi Sassar Sez. 2*, **60**, 345 (1982); *Chem. Abstr.*, **101**, 90839 (1984).
168. F. Collino and S. Volpe, *Boll. Chem. Farm.* (*Ital*.), **121**, 221 1982.
169. Y. A. Al-Soud, N. A. Al-Masoudi, A. El-Rahman, and S. Ferwanah, *Bioorg. Med. Chem.*, **11**, 1701 (2003).
170. P. Sanna, A. Carta, and M. E. R. Nikookar, *Eur. J. Med. Chem.*, **35**, 535 (2000).
171. A. R. Katritzky, S. A. Belyakov, A. E. Sorochinsky, S. A. Henderson, A. Scott, and J. Chen, *J.Org. Chem*., **62**, 6210 (1997).
172. Y. A. Al-Soud, M. N. Al-Dweri, and N. A. Al-Masoudi, *Farmaco*, **59**, 775 (2004).
173. J. R. Reid and N. D. Heindel, *J. Heterocycl. Chem.*, **13**, 925 (1976).
174. J. P. Vacca, B. D. Dorsey, W. A. Schleif, R. B. Levin, S. L. McDaniel, P. L. Darke, J. Zugay, J. C. Quintero, O. M. Blahy, E. Roth, V. V. Sardana, A. J. Schlabach, P. I. Graham, J. H. Condra, L. Gotlieb, M. K. Holloway, J. Lin, I.-W. Chen, K. Vastag, D. Ostovic, P. S. Anderson, E. A. Emini, and J. R. Huff, *Proc. Natl Acad. Sci. USA*, **91**, 4096 (1994).
175. B. D. Dorsey, R. B. Levin, S. L. McDaniel, J. P. Vacca, J. P. Guare, and P. L. Darke, *J. Med. Chem.*, **37**, 3443 (1994).
176. D. L. Romero, R. A. Morge, M. J. Genin, C. Biles, M. Busso, L. Resnick, I.-W. Althaus, F. Reusser, R. C. Thomas, and W. G. Trapley, *J. Med. Chem*., **36**, 1505 (1993).
177. D. L. Romero, R. A. Morge, C. Biles, T. N. Berrios-Pina, P. D. May, J. R. Palmer, P. D. Johnson, H. W. Smith, M. Busso, C.-K. Tan, R. L. Voorman, F. Reusser, I. W. Althaus, K. M. Downey, A. G. So, L. Resnick, W. G. Tarlpey, and P. A. Aristoff, *J. Med. Chem*., **37**, 999 (1994).
178. Y. A. Al-Soud and N. A. Al-Masoudi, *Farmaco*, **59**, 41 (2004).
179. D. E. Adelson and C. B. Polland, *J. Am. Chem. Soc*., **57**, 1280 (1935).
180. D. E. Luten, *J. Org. Chem*., **3**, 588 (1937).
181. Y. A. Al-Soud, M. N. A. Qalalweh, H. H. Al-Sa'doni, and N. A. Al-Masoudi, *Heteroatom Chem*., **16**, 28 (2005)