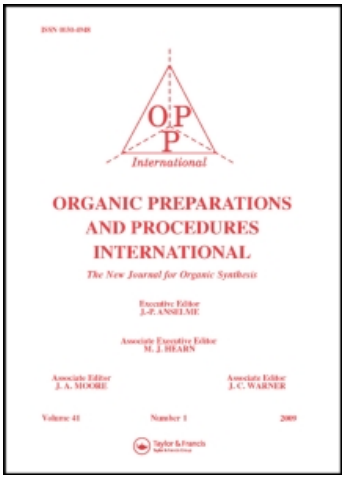


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

RECENT DEVELOPMENTS IN TETRAZOLE CHEMISTRY. A REVIEW

Steven J. Wittenberger[a]
[a] Process Chemistry, Department 45L/AP 10 Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL

To cite this Article Wittenberger, Steven J.(1994) 'RECENT DEVELOPMENTS IN TETRAZOLE CHEMISTRY. A REVIEW', Organic Preparations and Procedures International, 26: 5, 499 — 531
To link to this Article: DOI: 10.1080/00304949409458050
URL: http://dx.doi.org/10.1080/00304949409458050

ORGANIC PREPARATIONS AND PROCEDURES INT., 26 (5), 499-531 (1994)

RECENT DEVELOPMENTS IN TETRAZOLE CHEMISTRY. A REVIEW

Steven J. Wittenberger

Process Chemistry, Department 45L / AP10
Pharmaceutical Products Division, Abbott Laboratories
One Abbott Park Road, Abbott Park, IL 60064-3500

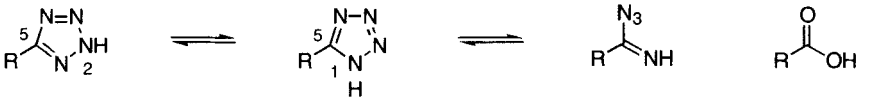
RECENT DEVELOPMENTS IN TETRAZOLE CHEMISTRY. A REVIEW

Steven J. Wittenberger

Process Chemistry, Department 45L / AP10
Pharmaceutical Products Division, Abbott Laboratories
One Abbott Park Road, Abbott Park, IL 60064-3500

INTRODUCTION

This article is intended to survey recent progress in the synthesis and reactions of tetrazoles whose discovery dates back to over a century ago.[1] There have been several comprehensive reviews of tetrazole chemistry,[2,3,4] the most recent being that of Butler.[5] Specific aspects of the chemistry of tetrazoles have been covered in shorter reviews: the chemistry of 2-substituted tetrazoles,[6] the azidoazomethine-tetrazole isomerization,[7] solvent effects on tetrazole synthesis by 1,3-cycloaddition of azides,[8] complexes of tetrazoles,[9] alkylation reactions,[10] and tetrazole synthesis from aminoguanidines.[11]

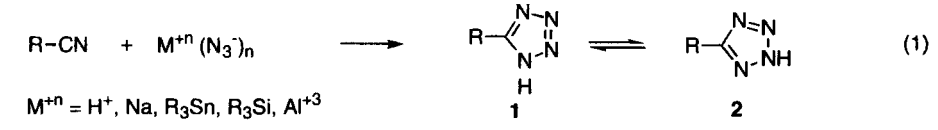


Many tetrazole derivatives possess biological activity. The tetrazole functional group acts as a metabolically stable isostere for the carboxylic acid[12] and this has been a primary driving force for continual research in the area. Most recently, because of the intense effort to discover and develop nonpeptidic inhibitors of the vasoactive octapeptide angiotensin II, there has been renewed interest in the preparation of tetrazoles (a key subunit in many of the most active compounds). The present survey reviews the literature from the early 1980's through early 1994. New methods of synthesis, unusual reactivities, novel applications, and the medicinal chemistry of tetrazoles will be highlighted.

I. SYNTHESIS

1. 5-Substituted 1*H*-Tetrazoles

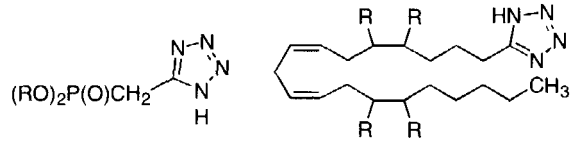
The nature and substitution pattern of the tetrazole product often determines which synthetic route is best for its preparation. For the most part, recent literature reports have been extensions or improvements of existing methodology. The most convenient preparation of 5-substituted-1*H*-tetrazoles is the reaction of nitriles with azide ion (Eq. 1).



(1)

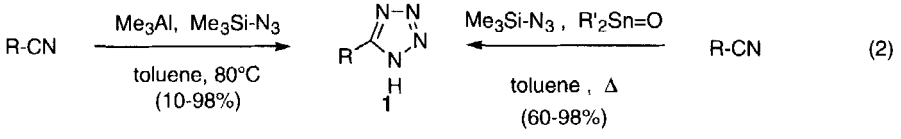
Generally, a mixture of nitrile, sodium azide, and a proton source (to generate hydrazoic acid *in situ*) is heated in a suitable solvent (e. g., dimethylformamide) at relatively high temperature to produce, in

most cases, good yields of tetrazole products.[13] Aluminum triazide,[14] formed *in situ* from aluminum trichloride and sodium azide, was used to prepare 5-(phosphonomethyl)-1*H*-tetrazole **3**[15] and the 1*H*-tetrazol-5-yl analogues of arachidonic **4** and linoleic acids **5** in moderate yields (Fig. 1).[16] A drawback to this reagent is that upon hydrolytic work-up, two moles of hydrazoic acid are generated per mole of product. Huff and Staszak demonstrated that tetrazoles **1** were obtained by treatment of aliphatic or aromatic nitriles with "equimolar" trimethylaluminum and trimethylsilylazide.[17] Typically, 1.5 mole equivalent of each reagent was used to afford good to excellent yields of tetrazoles (Eq. 2). Highly hindered nitriles (R = *t*-Bu, Ph_2MeC-) resulted in low conversion and diminished yields It is likely that the trimethylaluminum acts as a Lewis acid in this reaction, activating the nitrile towards azide addition. However, caution must be exercised during the quenching of the reaction which can be exothermic with vigorous gas evolution. As an alternative to trialkyltin azide,[18] a reagent typically prepared *in situ* from a trialkyltin chloride (volatile and toxic) and sodium azide, Wittenberger and Donner reported that trimethylsilyl azide in the presence of dialkyltin oxide, reacts efficiently with nitriles to produce 5-substituted-1*H*-tetrazoles **1** (Eq. 2).[19] The reactive intermediate was suggested to be a dialkyl (O-trimethylsilyl)-azidostannylhydrin **6**.

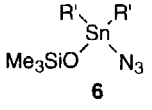


3 **4** R = *Z*-alkene
5 R = H

Fig. 1

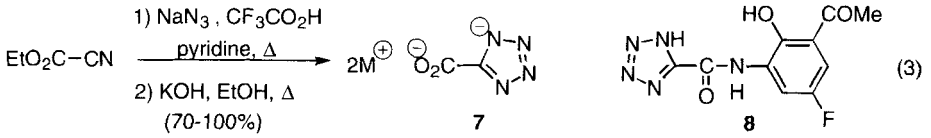


(2)

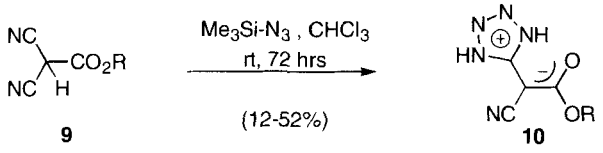


6

A high yielding preparation of the di(alkali metal) salt of 1*H*-tetrazole-5-carboxylic acid **7** by reaction of an alkali metal azide with an alkyl cyanoformate (Eq. 3) was disclosed by Griffiths *et al.*[20] These compounds were shown to be valuable intermediates in the preparation of 1*H*-tetrazole-5-carboxanilides **8**, which are claimed to be useful in the treatment of allergic conditions. 2-(1*H*-Tetrazol-5-yl)-2-cyanoacetate betaines **10** were prepared from the corresponding dicyanoacetates **9** and trimethylsilyl azide in chloroform at ambient temperature (Eq. 4).[21]



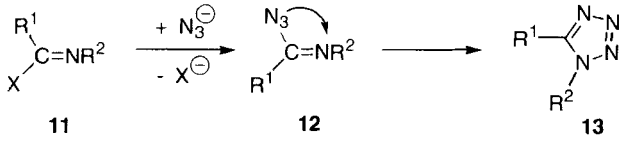
(3)



(4)

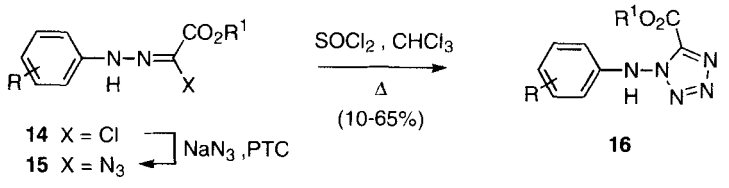
2. 1,5-Disubstituted Tetrazoles

Of the many routes to 1,5-disubstituted tetrazoles **13**, most culminate in the 1,5-electrocyclization of an imino azide **12** (-C(N_3)=N-) species.[4] A widely used and convenient approach to imino azide intermediates entails displacement of an imidoyl halide **11** by azide ion (Eq. 5).[5] Imidoyl chlorides are readily obtained by the reaction of amides with phosphorus pentachloride or thionyl chloride.



(5)

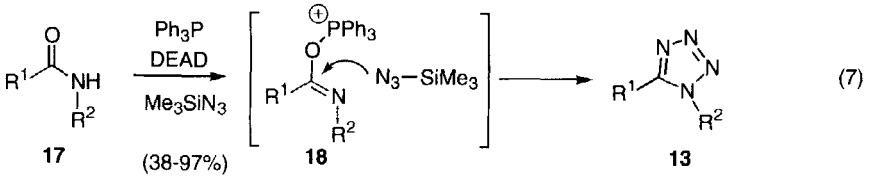
Garanti *et al.* recently reported a related example where hydrazonyl chlorides **14** were converted to the corresponding azidohydrazones **15** with sodium azide under phase-transfer conditions (Eq. 6).[22]



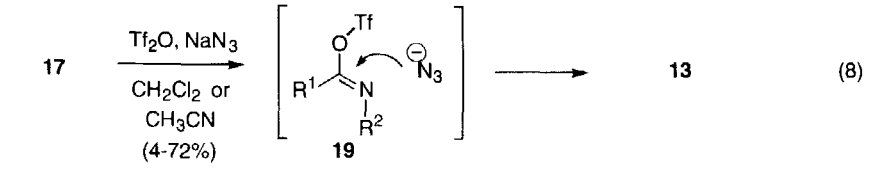
(6)

Compounds **15** were unexpectedly reluctant to undergo cyclization to the 1-arylamino-5-carboalkoxytetrazoles **16**. Addition of various Lewis acids, in order to polarize the system, effected the electrocyclic closure. The best results were obtained with two molar equivalents of thionyl chloride.

Similar approaches have been published that use heteroatoms other than halides as the leaving group. Duncia *et al.* described the reaction of an oxyphosphonium salt **18** (prepared under Mitsunobu conditions from the corresponding amide **17**) with trimethylsilyl azide leading to the 1,5-disubstituted tetrazole **13** (Eq. 7).[23] In the case of an *N*-(2-cyanoethyl)-substituted amides, the 1-(*N*-(2-cyanoethyl))-5-substituted tetrazole products (**13**, R^2 = CH_2CH_2CN) could be readily *N*-dealkylated by aqueous base treatment to give the 5-monosubstituted tetrazoles **1**. This method should prove to be especially useful for applications when an *N*-protected tetrazole is required. Preservation of chirality in the synthesis of a tetrazole analogue of an α-amino acid (phenylalanine) was demonstrated.

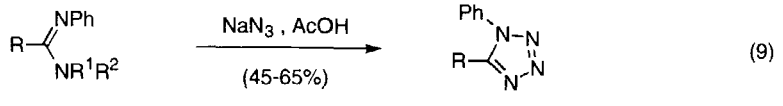


(7)

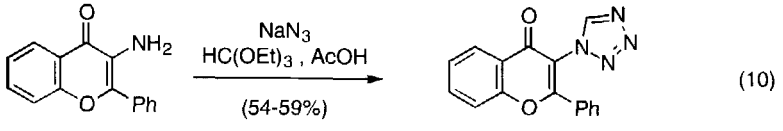


(8)

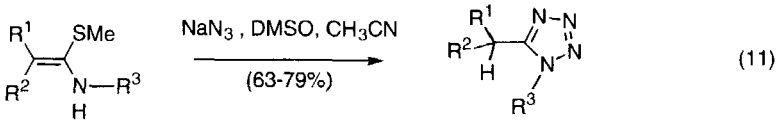
Treatment of imidoyl triflates **19**, generated *in situ* from amides and trifluoromethanesulfonic anhydride, with sodium azide provided 1,5-disubstituted tetrazoles (Eq. 8).[24]



(9)

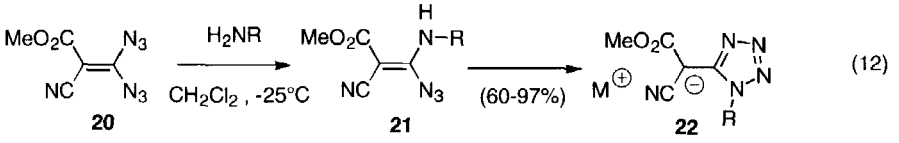


(10)



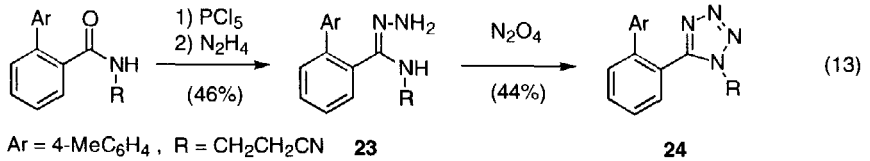
(11)

Examples of nitrogen,[25] oxygen,[26] and sulfur[27] displacements have also appeared (Eqs. 9-11). In a series of papers, Saalfrank and coworkers have described addition-elimination reactions of nitrogen nucleophiles to 3,3-diazido-2-cyanoacrylates **20** to give, initially, vinyl azides **21** which undergo 1,5-electrocyclization under basic conditions to yield dihydrotetrazolylidene cyanoacetates **22** in good to excellent yield (Eq. 12).[28]



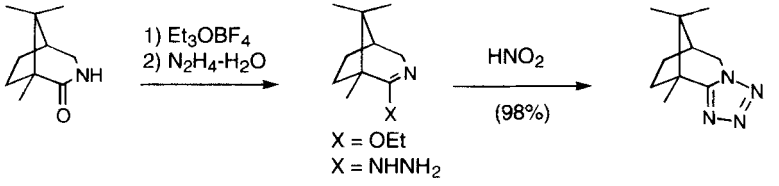
(12)

Imidoyl azides can also be prepared by diazotization of substituted hydrazines (and amidrazones) which can be prepared by the hydrazinolysis of imidoyl derivatives bearing leaving groups

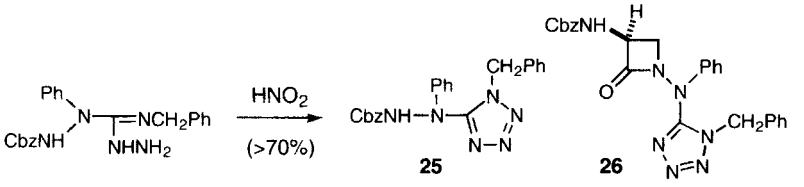


(13)

(Eq. 13). Duncia *et al.* utilized dinitrogen tetroxide as the nitrosating agent in the conversion of amidrazone **23** into tetrazole **24**.[23] Examples from Sakakibara[29] and Lambert[30] are more classical, though the latter used tetrazole **25** for the preparation of some novel 5-aminotetrazole containing β-lactam derivatives **26** (Eqs. 14 and 15).

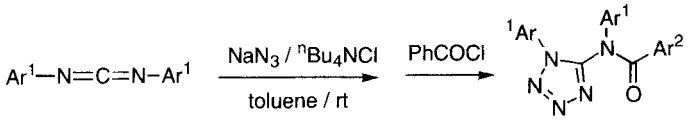


(14)



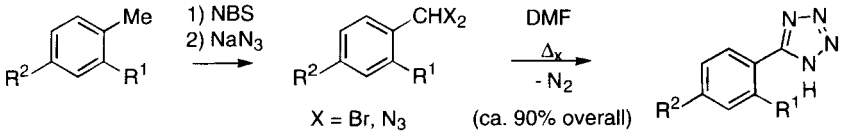
(15)

1-Substituted-5-aminotetrazoles are readily prepared by addition of azide to carbodiimides.[5] This reaction has recently been exploited to prepare several tetrazoles bearing sugar substituents[31,32] as well as a one pot preparation of 1-aryl-5-(*N*-aryl-*N*-benzamido)tetrazoles **27** under solid-liquid phase-transfer catalyzed reaction conditions (Eq. 16).[33]

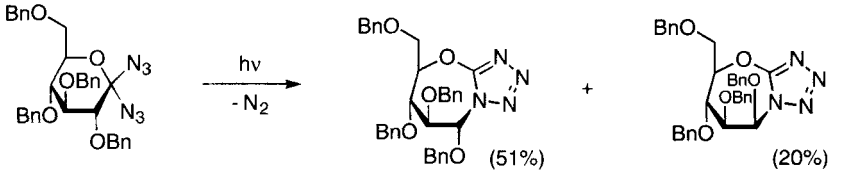


(16)

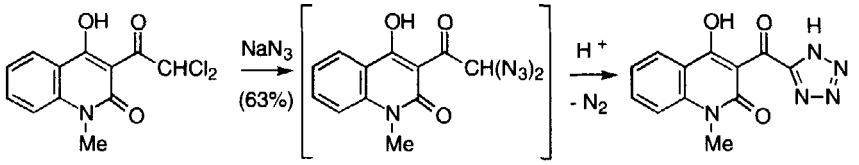
gem-Diazides have long been known to be precursors of 1,5-disubstituted tetrazoles; Götzky reported in 1931 that diazidodiphenylmethane decomposed to 1,5-diphenyltetrazole in 90% yield.[34] *gem*-Diazides may be prepared from *gem*-dihalides and cyclized (with loss of nitrogen) under thermal,[35] photolytic,[36] or protic acid[37] conditions (Eqs. 17-19).



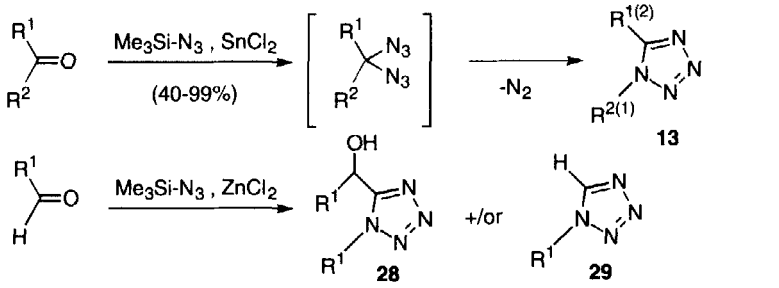
(17)



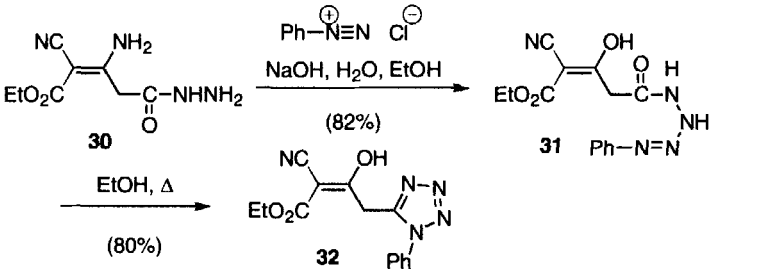
(18)



Nishiyama, Watanabe *et al.* reported a novel method for the formation of *gem*-diazides from carbonyl compounds and trimethylsilyl azide in the presence of Lewis acid (Eq. 20).[38] Though direct, the method is limited in that unsymmetrical ketones yielded mixtures of isomeric tetrazole products in most cases. Treatment of aliphatic aldehydes with equimolar trimethylsilyl azide produced an unexpected 1,5-disubstituted tetrazoles **28** (34-78% yield, Eq. 21). Excess trimethylsilyl azide led to the expected monosubstituted tetrazoles **29** (31-48%).



Tetrazenes (-C-N-N=N-N- or C-N-N-N=N- e. g. **31**) prepared by the reaction of acylhydrazines **30** with diazonium salts (Eq. 22), can be cyclodehydrated to the 1,5-disubstituted tetrazole **32**.[5,39]



Azide ion addition to nitrilium salts provides access to many 1,5-disubstituted tetrazoles.[5] Amer and Booth described studies concerning the addition of azide ion to aliphatic and aryl *N*-methylnitrilium triflate salts **33**.[40] The dichotomous results were explained in terms of the different rates of electrocyclization for the aliphatic *versus* arylimidoyl azide intermediate. The reaction of nitrilium salts **35** with covalent (organic) azides leads to 1,4,5-trisubstituted tetrazolium salts **36**.[41] Hydride reduction of, or nucleophilic addition to, the tetrazolium salts gave tri- or tetrasubstituted tetrazolines (**37** or **38** respectively) in good overall yield (Fig.2). A related approach has been accomplished by Collibee and Anselme for the preparation of 5-halo-1-phenyltetrazoles by reaction of

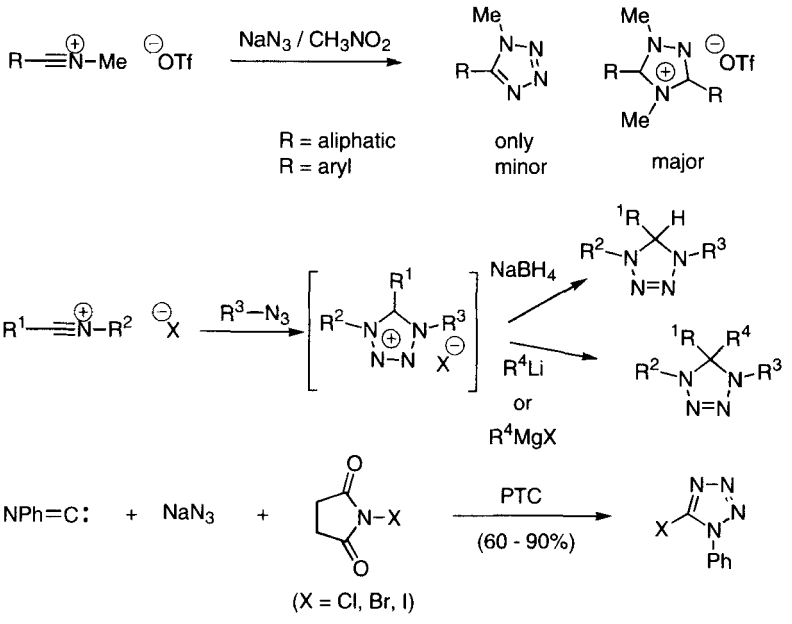


Fig. 2

phenylisonitrile with sodium azide and the corresponding *N*-halosuccinimides under phase-transfer catalysis (PTC) conditions in good yields.[42]

The Schmidt reaction[43] is another general and useful method for the preparation of 1,5-disubstituted tetrazoles.[4,5] Amides are common side-products due to hydrolysis of the nitrilium intermediate **35** (Fig. 3). The Schmidt reaction has been used extensively in the steroid field to prepare

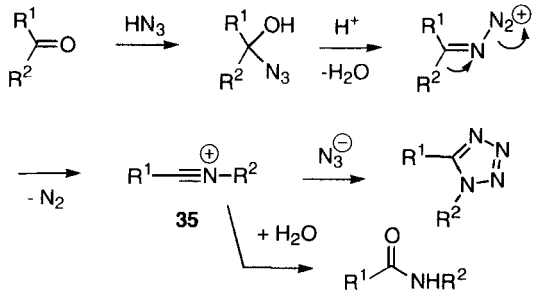
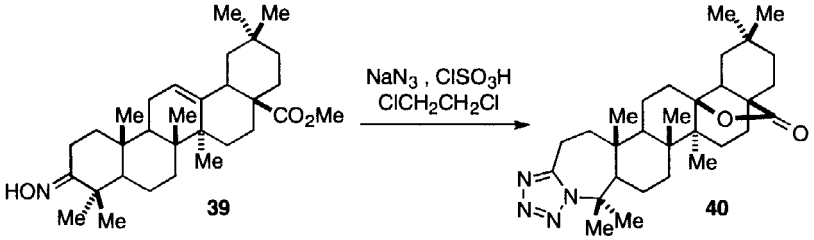


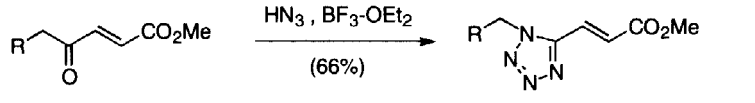
Fig. 3

tetrazole fused steroid derivatives[44,45] and recently on (+)-dihydrocarvone.[46] Rao *et al.* captured an intermediate nitrilium ion from a Beckmann rearrangement with azide ion to produce tetrazole **40** from steroid oxime **39** (Eq. 23).[47] Osman and coworkers have reported an extension of the Schmidt reaction to the synthesis of a novel tetrazole from an α,β-unsaturated γ-keto fatty acid.[48] Methyl 4-

oxo-(*E*)-2-octadecenoate **41** was treated with hydrazoic acid and boron trifluoride etherate to yield methyl 5-azanonadec-(*E*)-2-enoate (4,5-*D*)-tetrazole **42** as the major product (Eq. 24).



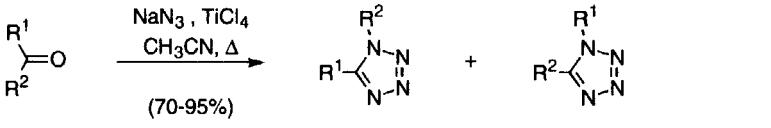
(23)



(24)

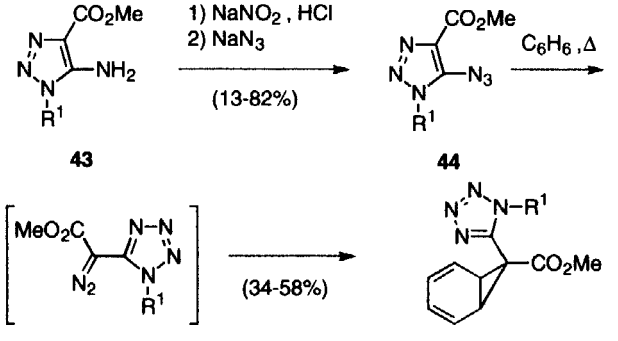
41 (R = CH_3-$(CH_2)_{13}$-) **42**

Suzuki and his group have found that treatment of both aliphatic and aromatic ketones with an excess of sodium azide in the presence of titanium(IV) chloride in boiling acetonitrile are converted to 1,5-disubstituted 1*H*-tetrazoles.[49] Unsymmetrical ketones afforded either one or both isomeric tetrazole products. The ratio of the isomers depended on the relative migratory aptitude of the substituent groups (Eq. 25).



(25)

L'abbé *et al.* reported the rearrangement of 5-azido-4-methoxycarbonyl-1-aryl-1,2,3-triazoles **44** to 5-(methoxycarbonyldiazomethyl)-1-aryltetrazoles **45**.[50] Further reaction yielded the cyclopropanes **46** derived from carbene intermediates formed by the thermal decomposition of the diazoalkyltetrazoles (Fig. 4).



43 **44** **45** **46**

Fig. 4

3. 2,5-Disubstituted Tetrazoles

In many circumstances, alkylation of 5-substituted-1*H*-tetrazoles is the most efficient route to 2,5-disubstituted tetrazoles and much of this work is summarized in earlier reviews.[2-5] The 1,5-isomers which may be formed as side products are usually separable by fractional crystallization or chromatography. A regiospecific preparation of 2,5-diaryl tetrazoles *via* acyclic formazans (-N=N-C=N-NH-) was described that expands the scope of this method. Shawli *et al.* prepared *N*-arenesulfonylbenzohydrazidoyl chlorides **48** from the *N*-arenesulfonylbenzohydrazides **47** and treated them with phenylhydrazine to give the hydrazidines **49** (Fig. 5).[51] Oxidation and base treatment provided the 2,5-diaryltetrazoles **51**.

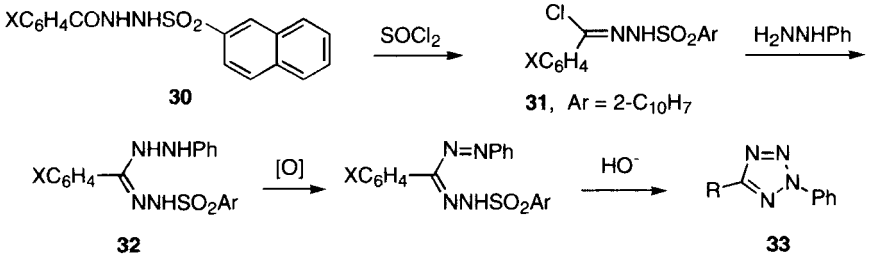
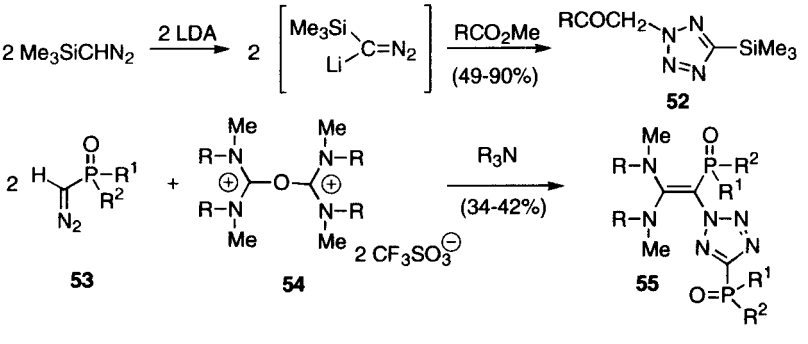


Fig. 5

Aoyama and Shiori have published a method for the conversion of methyl esters to 2-substituted-5-trimethylsilyltetrazoles **52** using lithium trimethylsilyldiazomethane.[52] 2-Aryl- and 2-alkyl-5-trimethylsilyltetrazoles are prepared in good yield (Eq. 26). Maas *et al.* showed that diazophosphoryl compounds **53** reacted with *bis*(formamidinium) ether **54**, in the presence of tertiary amine base, to yield 2-substituted-5-phosphoryltetrazoles **55** in moderate yield (Eq. 27).[53]

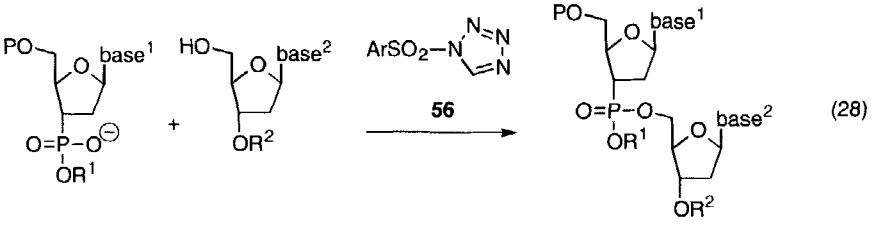


II. REACTIONS OF TETRAZOLES

Since the earlier reviews provided comprehensive overviews of the reactions of tetrazoles,[2-5] this section will focus on some novel reactions of tetrazoles as both reagent and substrate which have been reported during the last decade.

1. Tetrazoles as Reagents

Arylsulfonyltetrazoles **56** were introduced by Narang *et al.* as condensation agents for use in the synthesis of defined sequences of deoxyribooligonucleotides by the modified triester strategy (Eq. 28).[54] These reagents allowed for the rapid and efficient preparation of polydeoxyribonucleotides.[55-58] 1*H*-Tetrazole has been used to mediate the coupling of ribonucleotides and



phosphoramidites in the synthesis of oligoribonucleotides **60**.[59,60] The mechanism of this reaction has been studied. It is suggested that the tetrazole initially protonates the phosphoramidite **57** rapidly; this is followed by the formation of the tetrazolophosphane intermediate **58**, which is then attacked by the ribonucleoside **59** (Fig. 6).[61-63]

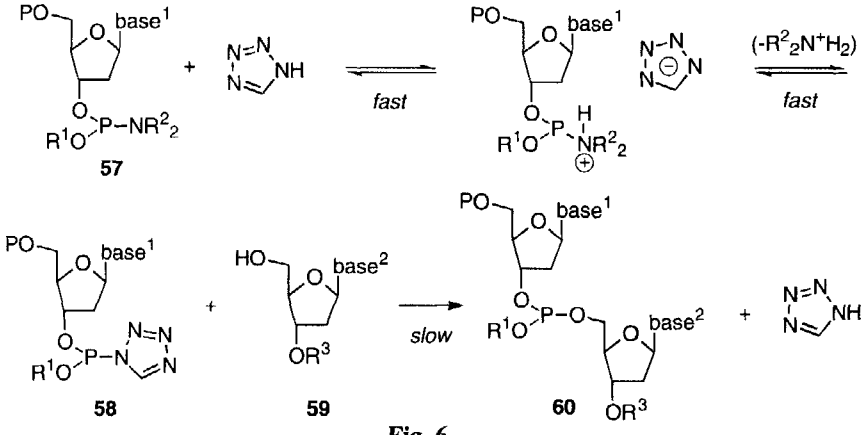
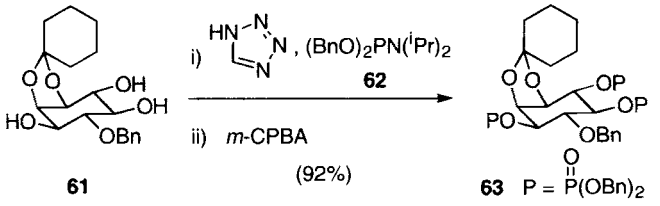
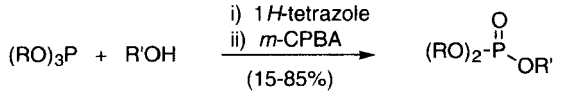


Fig. 6

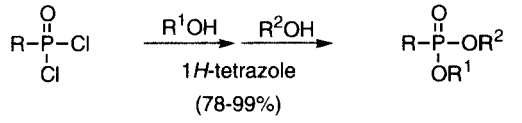
Fraser-Reid and others have reported that protected inositols can be phosphorylated by the use of *N,N*-diisopropyl dibenzyl phosphoramidate, 1*H*-tetrazole and *m*-CPBA under very mild conditions (Eq. 29).[64,65] This has become the method of choice for the introduction of the phosphate functionality in the synthesis of *myo*-inositol phosphates and related structures. 1*H*-Tetrazole is reported to catalyze the transesterification of trialkyl phosphites (Eq. 30).[66] An intermediate five-coordinate hydrophosphorane was observed by ^{31}P NMR. 1*H*-Tetrazole promoted the selective monoaddition of alcohols to phosphonic dichlorides thus leading to mixed phosphonate diesters in high yields (Eq. 31).[67]



(29)

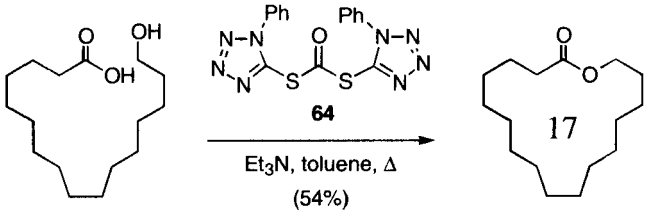


(30)

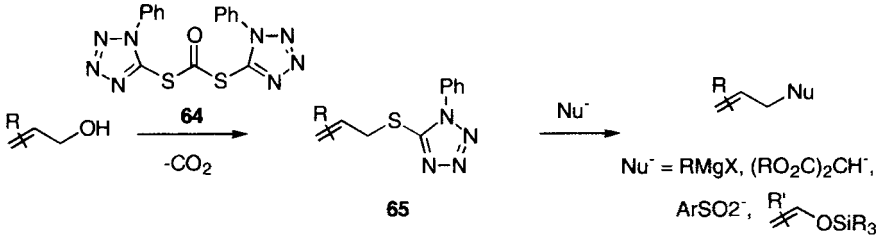


(31)

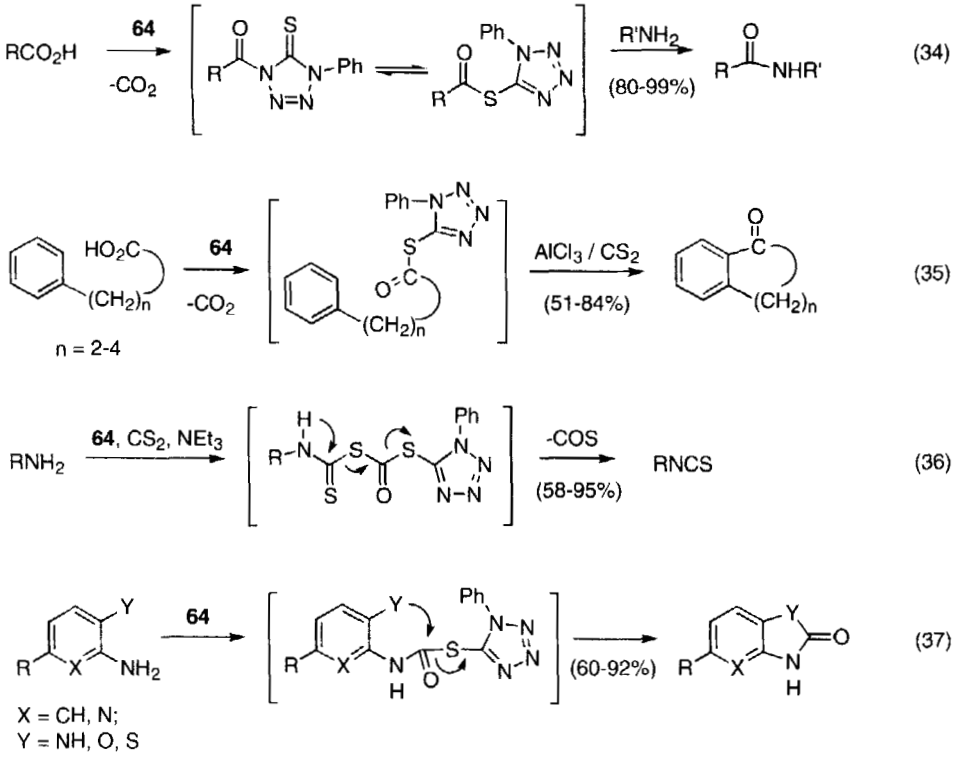
A new reagent, *S,S-bis*(1-phenyl-1*H*-tetrazol-5-yl) dithiocarbonate **64**, was introduced by Ogura for the esterification of carboxylic acids with alcohols in high yields.[68] Although it is unlikely that this reagent will supplant the more widely used esterification reagents, it may find use in macrolactonizations (Eq. 32). The scope of reactivity was expanded to include reaction with allylic and benzylic alcohols to produce sulfides **65** having the 5-mercapto-1-phenyltetrazolyl group which could then be coupled to nucleophiles such as Grignard reagents, malonate anions, silyl enol ethers, and aryl sulfinate (Eq. 33).[69] The reagent was applied to the formation of amides (including dipeptides), Friedel-Crafts type reactions, isothiocyanate syntheses, and carbonyl insertion reactions[70] as well as glycosidation of carbohydrates and sialic acid derivatives (Eqs. 34-37).[71]



(32)



(33)



bis(1-Methyl-1*H*-tetrazol-5-yl)disulfide **66** was demonstrated to be an excellent stoichiometric reagent for the preparation of symmetric, unsymmetric and cyclic disulfides under mild conditions and in aqueous solution.[72] Functional groups which are sensitive to other disulfide forming reagents such as iodine, are compatible (Fig. 7). Application of this method seems especially well suited for the preparation of cystine peptide disulfides (e. g., **67** and **68**).

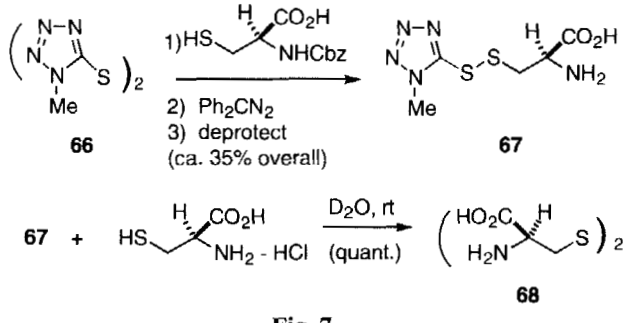
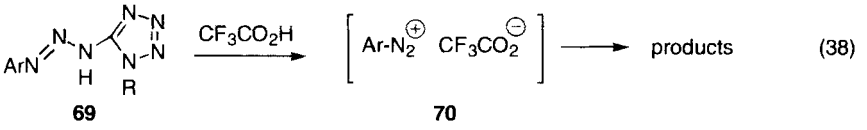


Fig. 7

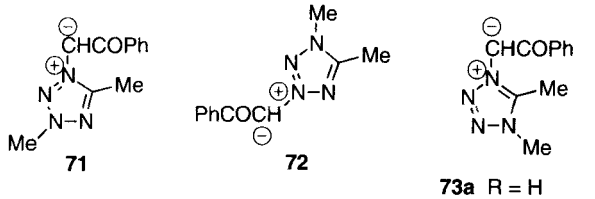
Butler *et al.* have reported 3-aryl-1-tetrazol-5-yltriazenes **69** are a stable source of aryldiazonium ions **70**, useful in the synthesis of biaryls, aryl halides, and azo dyes (Eq. 38).[73]



69 70

2. Reactions at the Ring Atoms

The synthesis and properties of the isomeric tetrazolium *N*-phenacylides have been investigated.[74] The 1,5-dimethyltetrazolium-3-phenacylide **72** showed a stronger electron-withdrawing influence than the 3,5-dimethyltetrazolium-1-phenacylide **71** as characterized by their relative reactivity toward alkali hydroxide and several electrophiles. The 1,5-dimethyltetrazolium-4-phenacylide **73a** could not be isolated, but when treated with acetic or benzoic anhydride in the presence of base afforded the stable ylides **73b** and **73c**. Higher 1-alkyl-5-methyltetrazolium-4-phenacylide homologues were also characterized.

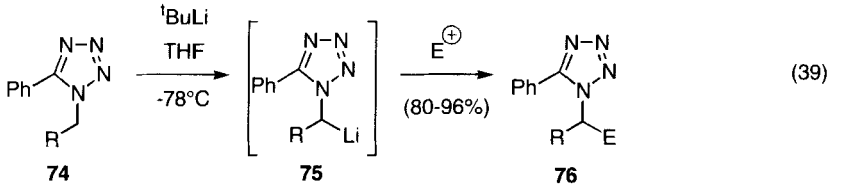


71 72

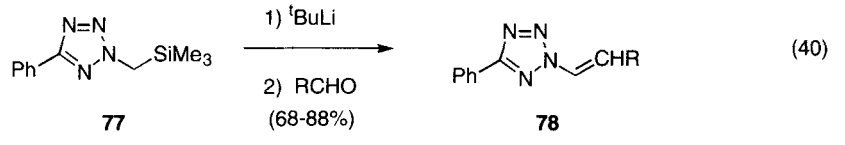
73a R = H
73b R = COMe
73c R = COPh

3. Reactions at the Substituents

Treatment of 1-alkyl- and 2-alkyl-5-phenyltetrazoles (i. e., **74**) with *t*-butyllithium at low temperature gave the "dipole-stabilized" α-lithioalkyl derivatives **75** (Eq. 39) which were reacted with a variety of electrophiles.[75] Metallation of 5-phenyl-2-(trimethylsilyl-methyl)tetrazole **77** followed by reaction with aliphatic aldehydes resulted in Peterson olefination to give 5-phenyl-2-alkenyltetrazoles **78** in good yield (Eq. 40).



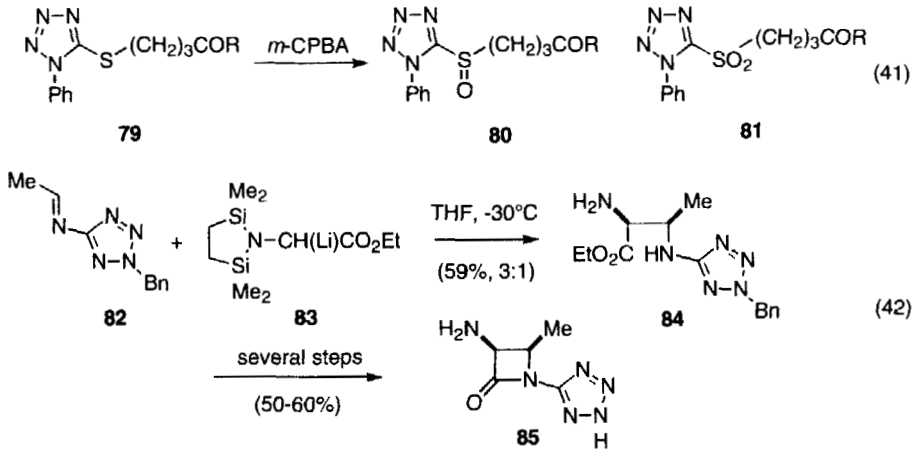
74 75 76



77 78

1-Phenyl-5-thioethers **79** were selectively oxidized with *m*-CPBA to the corresponding sulfoxides **80** or sulfones **81** in good yield (Eq. 41).[76] Imines derived from 5-amino-2-benzyltetrazole **82** were condensed with a glycine enolate **83** followed by cyclization to provide both *cis*- and *trans*-

substituted *N*-(tetrazol-5-yl) β-lactams **85** (Eq. 42).[77]



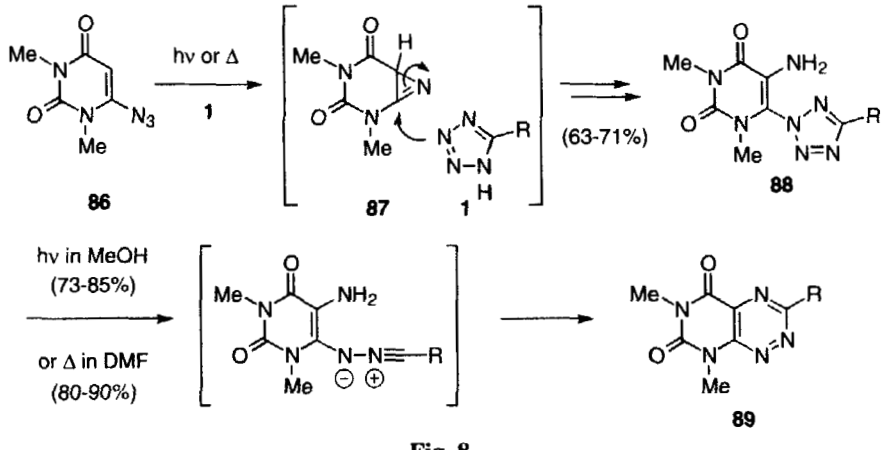
(41)

(42)

79 **80** **81** **82** **83** **84** **85**

4. Formation of Non-tetrazole Products

Senda *et al.* reported the use of 5-substituted tetrazoles **1** in a novel synthesis of fervenulins.[78] Thermolysis of 6-azido-1,3-dimethyluracil **86** in the presence of 5-substituted tetrazole **1** gave 3-substituted fervenulins **89** (Fig. 8). Interestingly, irradiation of **86** with **1** in tetrahydrofuran



86 **87** **1** **88** **89**

Fig. 8

gave uracil **88** which could be further transformed to **89** by irradiation in methanol or by heating in dimethylformamide, implicating **87** as an intermediate in the thermolysis of **86** to fervenulin **89**. Reaction of 1- and 2-hydrazonoyl-5-substituted tetrazoles **92** and **93**, readily obtained by the condensation of 5-substituted tetrazoles **90** with benzonitrile *N*-(*p*-nitrophenyl)imide **91**, gave high yields of substituted 1,2,4-triazoles **94** and **95** (Fig. 9).[79]

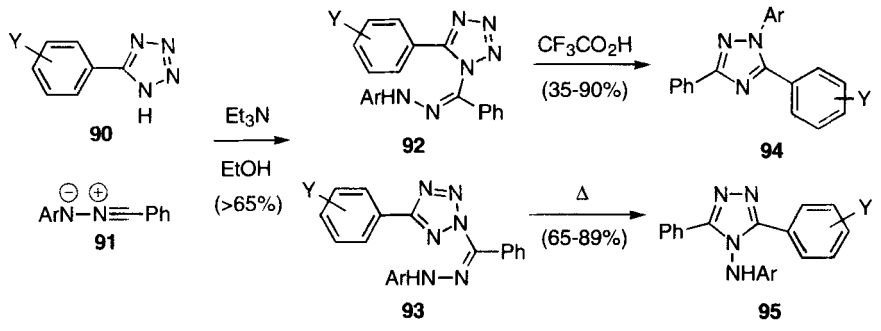


Fig. 9

Irradiation of 2-phenyltetrazole **96** in benzene gave phenylcyanamide **97** (27% yield) and unexpectedly the phenylhydrazone of *o*-aminobenzoyl cyanide **99** (53%). The structure of **99** was established by x-ray crystallographic analysis and a mechanism accounting for its formation was proposed (Fig. 10).[80]

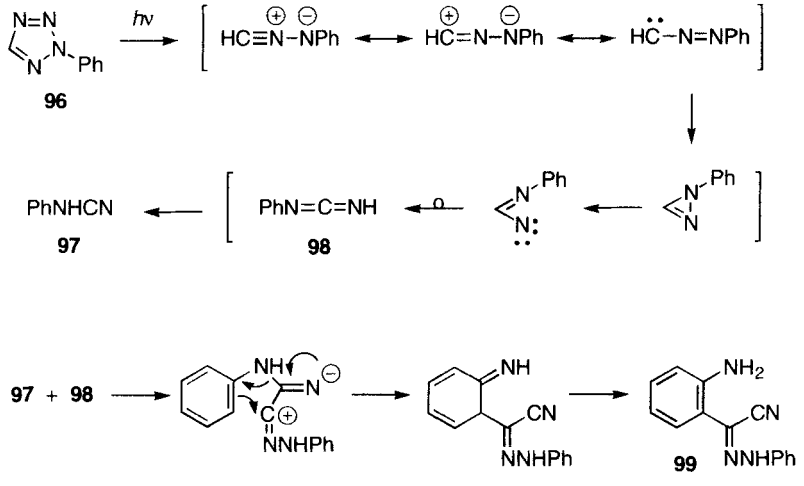


Fig. 10

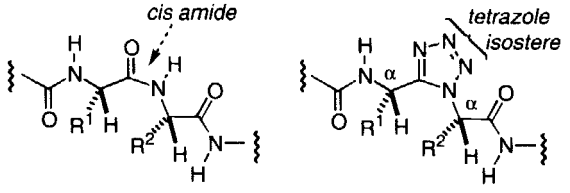
III. MEDICINAL CHEMISTRY OF TETRAZOLES

1. Structure / Function

The tetrazole ring has become familiar to medicinal chemists as an isosteric replacement for the carboxylic acid functional group. The groups have comparable acidity and the tetrazole ring has proved to be superior in resisting metabolic degradation. These features have led to the preparation of hundreds of compounds as potential therapeutic agents. The medicinal chemistry of tetrazoles has been reviewed[12] and Butler has compiled an extensive table[4] and an updated survey[5] of published

biologically active tetrazole compounds.

Marshall *et al.*[81] have proposed a new use for the tetrazole ring as a *cis* amide bond mimic within a peptide chain. Initial synthetic efforts[82] to prepare tetrazole dipeptide analogues resulted in racemization at one or both of the α-chiral centers (i.e., adjacent to the tetrazole ring); however more recent procedures[83,84] seem to have solved that problem. Incorporation of tetrazole dipeptide analogues into biologically active peptides such as somatostatin[85] and bradykinin[86,87] has been demonstrated. A different synthetic approach was used to prepare tetrazole analogues of deaminooxytocin[88] in which the LeuΨ[CN_4]-Gly-NH_2 fragment was synthesized *via* a non-regioselective *N*-alkylation of Cbz-Leu-tetrazole with methyl bromoacetate.[89]



2. Therapeutic Agents

a. Central Nervous System Activity

(Tetrazolylalkyl)piperazine- and (tetrazolylalkyl)piperidinecarboxylic acid derivatives (**100** and **101** respectively) were claimed as excitatory amino acid (EAA) receptor antagonists, useful in the treatment of neurological (epilepsy, stroke, and anxiety) and neurodegenerative (Alzheimer's and Huntington's diseases) disorders.[90] LY3000020 **102**, a conformationally constrained analogue of L-glutamic acid, was shown to be a potent α-amino-3-hydroxy-5-methyl-4-isoxazole-propanoic acid (AMPA) receptor agonist.[91] The enantiomer was devoid of activity at ionotropic EEA receptors. DL-Tetrazol-5-ylglycine **103** has proven to be an exquisitely potent and selective *N*-methyl-D-aspartate (NMDA) receptor agonist.[92]

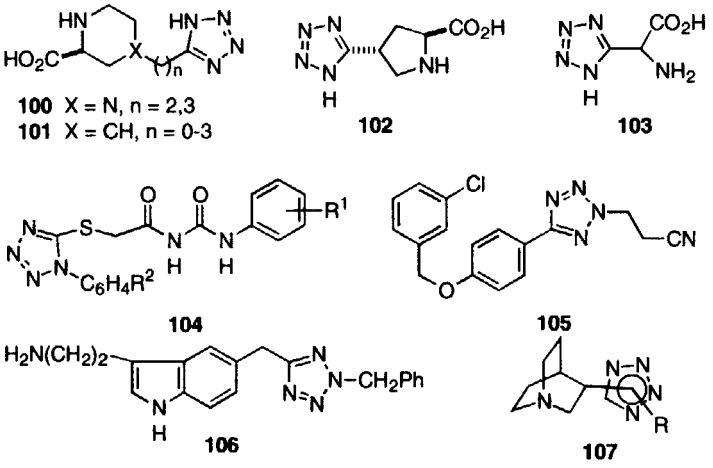


Fig. 11

Gupta *et al.* reported the synthesis and *in vitro* evaluation of 2-[(1-aryl-1*H*-tetrazol-5-yl)thio]-N-[(arylamino)carbonyl]acetamides **104** as acetylcholinesterase inhibitors.[93] 2,5-Disubstituted tetrazoles have been claimed as type B monoamine oxidase (MAO) inhibitors.[94] **105** inhibited type B MAO *in vitro* with a K_i of 0.73 nM and a selectivity coefficient for type B over type A of 1.03×10^5.

5-(Tetrazol-5-ylmethyl)-3-(2'aminoethyl)indole **106** and related compounds were claimed as seratonin (5-HT1) receptor agonists with IC_{50}'s of <1 μM, useful for the treatment of migraine.[95] Wadsworth and Jenkins detailed their studies regarding the syntheses and muscarinic activities of quinuclidin-3-yltetrazole derivatives **107**.[96] Structure-activity relationships (SAR) were coupled to electrostatic potential maps of these compounds to develop a model of the bound receptor-ligand complex.

b. Anti-inflammatory Activity

The anti-inflammatory activity of nonsteroidal tetrazole derivatives has been demonstrated in numerous cases. 2-(Tetrazol-5-yl)benzopyran **108**,[97] oxazole derivative **111**,[98] N-(aryl)tetrazol-5-yl carboxamides **110**,[99] and tetrazolylphenoxy-propoxyacetophenone **109**[100] were active in leukotriene (LT) receptor models. General structures **112**,[101] **113**,[102] and **114**,[103] were tested for inhibition of LTD_4 (Fig. 12).

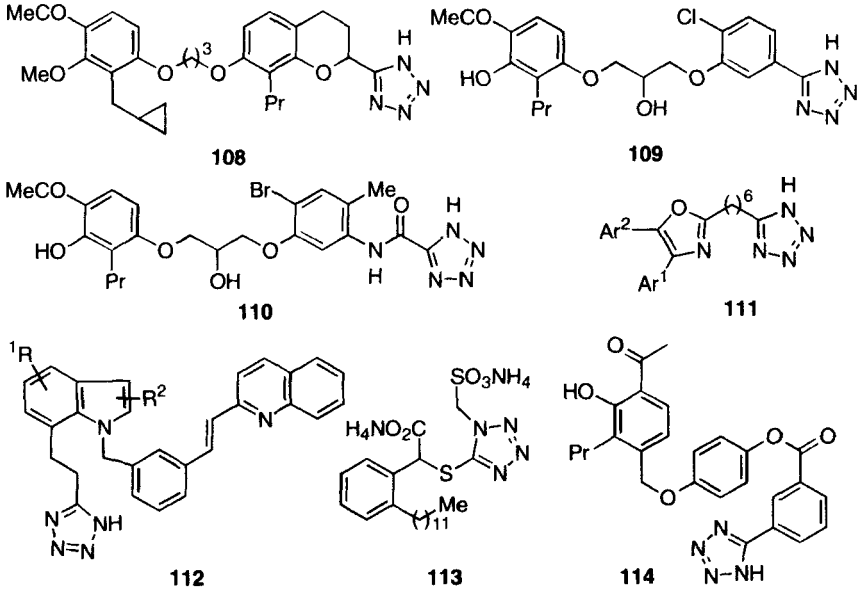


Fig. 12

Tetrazoles **115**,[104] 1,4-dihydro-3-pyridyltetrazoles **116**,[105] furyltetrazoles **117**,[106] and 2,5-disubstituted tetrazole **118**[107] showed anti-inflammatory activity against carrageenin induced rat paw edema. Other 5-monosubstituted tetrazoles **119**[108] and disubstituted tetrazoles **120-121**[109] and **122-123**[110] were tested for anti-inflammatory activity (Fig. 13).

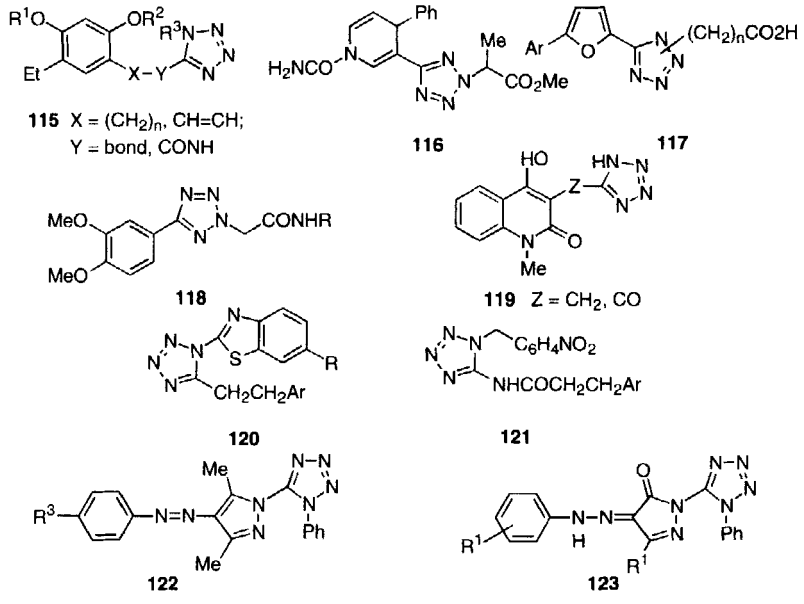


Fig. 13

c. Anti-allergic Activity

Disodium cromoglycate (DSCG, 1,3-*bis*(2-carboxychromon-5-yloxy)propan-2-ol disodium salt) **124**[111] and Zaprinast (M&B 22,948, 2-(*o*-propoxyphenyl)-8-azapurin-6-one) **125**[112] are potent inhibitors of reagin-mediated anaphylaxis (Fig. 14). Quantitative SAR studies suggest that for these

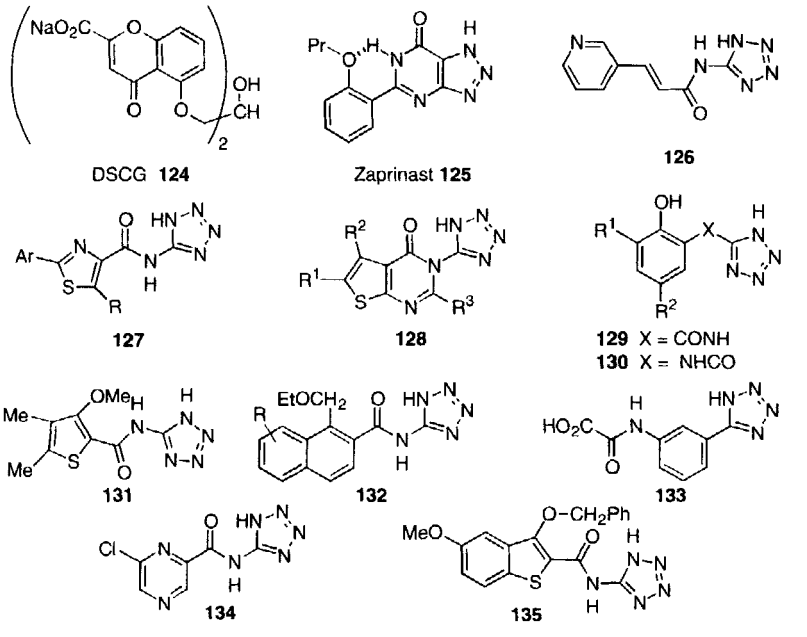


Fig. 14

compounds three important requirements are (i) an extended planar aromatic system with (ii) an acidic function capable of hydrogen bonding to (iii) a carbonyl group. Recently disclosed structures that fall into this class and show activity in the rat passive cutaneous anaphylaxis (PCA) test include: tetrazoylamides **126**,[113] tetrazolyl(carbamoylthiazoles) **127**,[114] tetrazolyl(thienopyrimidinones) **128**,[115] and the isomeric tetrazolylbenzamides **129** and (*o*-hydroxyphenyl)tetrazolylcarboxamides **130**.[116] Structurally similar compounds that were active in histamine release inhibition assays were reported; tetrazolyl(heteroaryl) carboxamides **131**,[117] tetrazolyl(naphthyl)carboxamides, **132**[118] *m*-(tetrazolyl)oxanilic acid **133**,[119] and tetrazolyl(pyrazine)carboxamides **130**[120] Tetrazolylcarboxamides exemplified by **135**[121] inhibited superoxide generation from neutrophils.

d. Anti-microbial Activity

A number of tetrazole-containing cephalosporin derivatives exhibit antibacterial activity (Fig. 15). Dax *et al.* reported the synthesis and activity of a novel "tetrazole-tethered" cephalosporin-quinolone hybrid **136** that showed cephalosporin-like *in vitro* activity but lacked quinolone activity.[122] Tetrazole-containing cephalosporin **137** showed activity against *Pseudomonas aeruginosa*.[123] The SAR of a series of compounds exemplified by the general structure **138** was investigated.[124] Excellent bactericidal activity was reported for **139** by Koh *et al.*[125] and the activity of a series of cephalosporanic acids **140** was tested.[126]

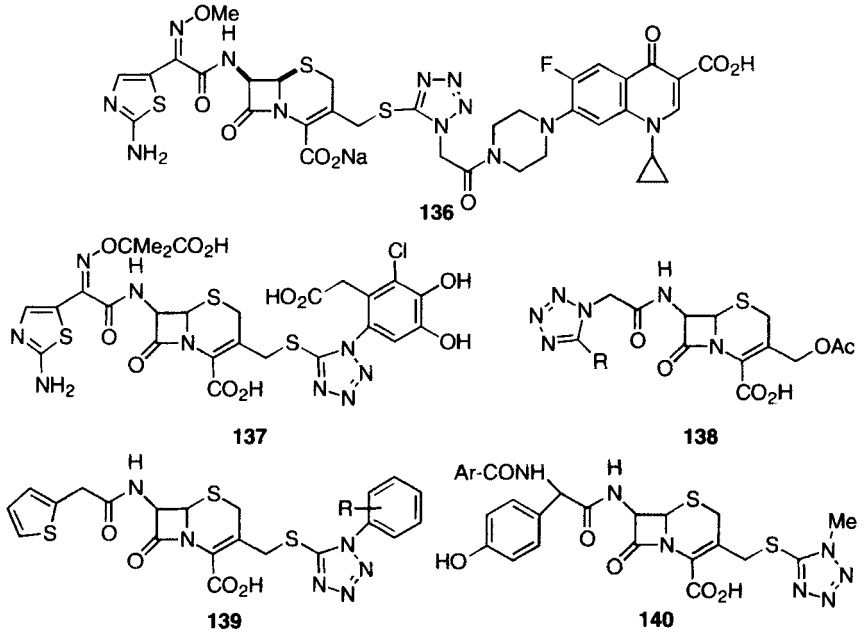


Fig. 15

Monocyclic β-lactams possessing a 5-tetrazolyl moiety at *N*-1, e. g. **141**, have been studied by Yoshida *et al.* as potential bactericidal agents (Fig. 16).[127] The effect of the oxyimino substituent and C-4 substitution on activity against Gram-negative bacteria was examined in detail. Other tetra-

zole derivatives reported to display anti-bacterial activity include 5-aryltetrazoles **142** and **144**[128,129] and 5-naphthyltetrazoles **143** and **145**.[130]

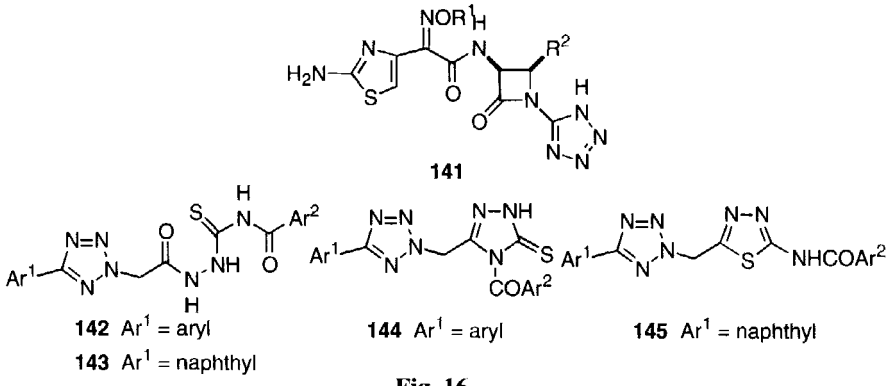


Fig. 16

Novel tetrazole oxathiolane nucleoside analogues **146** were prepared and found to be inactive against HIV-1 retrovirus (Fig. 17).[131] Virucidal activity was found in 6-(aminomethyl-5-tetrazolyl)benzothiazole **147**.[132] Tetrazolium salts **148** were found to be active against Ranikhet disease and tobacco mosaic virus.[133]

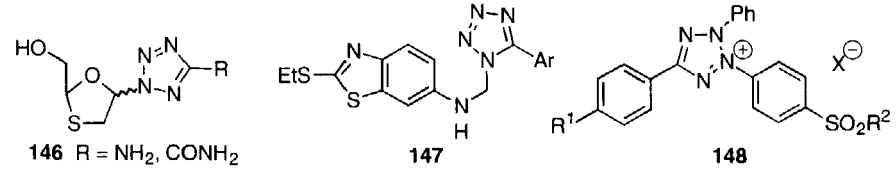


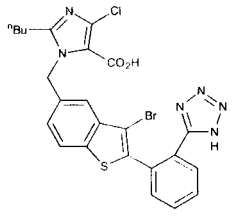
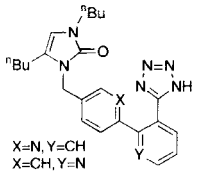
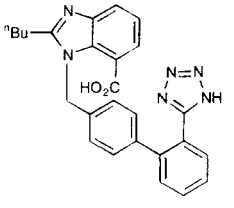
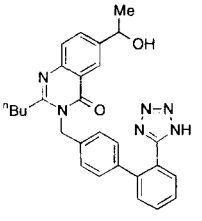
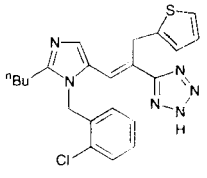
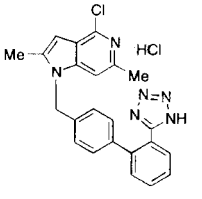
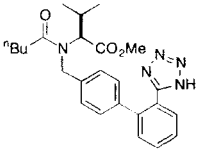
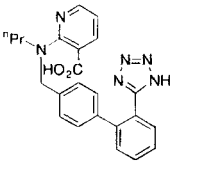
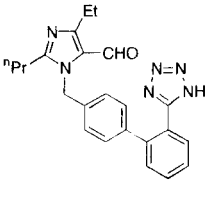
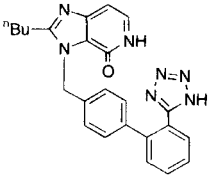
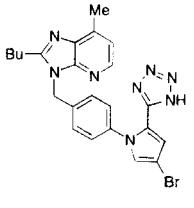
Fig. 17

e. Cardiovascular Activity

A tremendous amount of work has been done in the area of nonpeptide angiotensin II antagonist, and the tetrazole functional group is ubiquitous in the most potent of these compounds.[134] Table 1 displays representative examples disclosed recently by some of the major investigators in the field.

Tetrazole derivatives have been prepared to target other components of the cardiovascular system (Fig. 18). A large number of tetrazolyldiarylalkenoates were investigated as hypocholesteremics; **160** exhibited nanomolar inhibition of microsomal HMG-CoA reductase *in vitro*.[135] Tetrazole containing peptide inhibitors of renin were claimed by Raddatz *et al.*[136] Chucholowski *et al.* demonstrated that the tetrazolylureas **161** and -thioureas **162** decreased total cholesterol in rats through inhibition of acyl coenzyme A cholesterol acyltransferase.[137]

Table 1. Angiotensin II Antagonists

	Structure	Company	Ref	Structure	Company	Ref
149		*Glaxo*	138	**155**		*Searle*	144
150		*Takeda*	139	**156**		*American Cyanamid*	145
151		*SKB*	140	**157**		*ICI*	146
152		*Ciba-Geigy*	141	**158**		*Abbott*	147
153		*duPont*	142	**159**		*Merck*	148
154		*Fujisawa*	143				

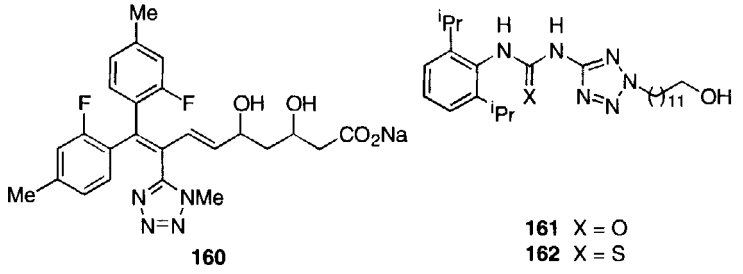


Fig. 18

f. Miscellaneous Activity

Both simple and complex derivatives of tetrazoles have been prepared as potential therapeutic agents for many other conditions (Fig. 19). Anti-ulcer activity has been explored by Uchida *et al.* in a series of 1,5-disubstituted tetrazole **163**[149] as well as by Ueda *et al.* with the more complex **164**.[150] Tetrazole containing compounds such as **165** have demonstrated blood glucose reduction in rats following oral administration.[151] Wolff *et al.* prepared tetrazolylamides **166** as anti-diabetic agents.[152] 6-Aryl-3-(5-tetrazolyl)pyridin-2(*H*)-one derivatives **167** have been claimed as cyclic AMP-dependent protein kinase agonists.[153] 2,4- and 2,5-*Bis*(tetrazolyl)pyridines **168** were prepared as fibrosuppressants and immunosuppressants.[154]

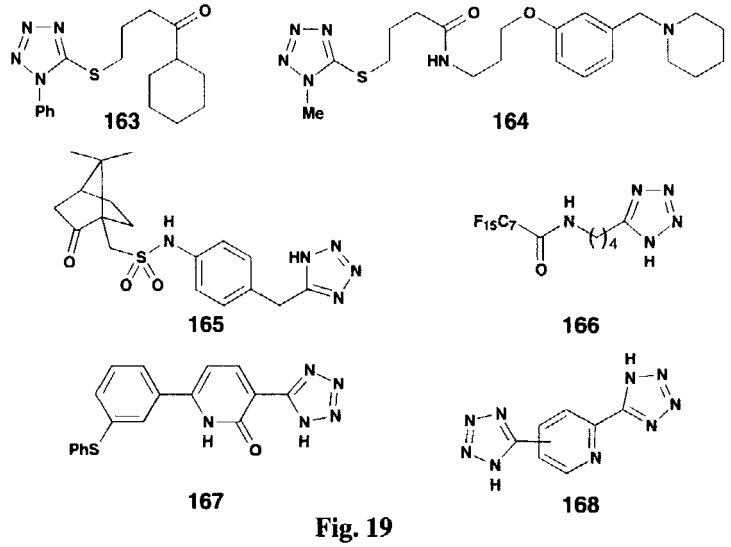


Fig. 19

IV. CONCLUSION

As evidenced by the volume of recent activity in the field, tetrazole chemistry remains to be an area of interest to many sectors of the chemical community. This survey has concentrated on aspects of tetrazole chemistry related to the contributions of and implications to the synthetic organic and medicinal chemist. This is not meant to minimize the importance of tetrazole derivatives to agri-

cultural use and nonbiological applications.

New methods of synthesis and improvements to existing procedures have been introduced that make the preparation many derivatives of tetrazoles facile and efficient. Tetrazole compounds have found new uses as reagents in synthesis. Strategies that utilize tetrazoles as starting materials for the preparation of both more complex tetrazole derivatives and non-tetrazole products have been recently published.

The application of the tetrazole moiety to problems of structure and function in peptides, as *cis*-amide bond isosteres, and medicinal chemistry, as an isosteric replacement for the carboxylate group, has exploded in recent years. Literally tens of thousands of structurally diverse compounds have been prepared and tested for biological activity against dozens of diseases. It is interesting to note that in cases where the carboxylate and 5-tetrazolyl groups were compared in otherwise identical molecules the observed activity might be similar or favor either one or the other functionality evidencing the subtle differences between the two "isosteric" groups.

Acknowledgment.- The author would like to thank B. Gregory Donner for his contributions to our initial foray into the synthesis of 1*H*-tetrazoles, the editors of this journal for their guidance in the preparation of this manuscript and H. Rumpelmeier.

REFERENCES

1. J. A. Bladin, *Ber.*, **18**, 1544 (1885).

2. F. R. Benson, *Chem. Rev.*, **41**, 1 (1947).

3. F. R. Benson, *Heterocyclic Compounds* , R. C. Elderfield, Ed.; John Wiley & Sons, Inc., New York, NY, 1967, Vol. 8, pp. 1-104.

4. R. N. Butler, *Adv. Heterocyclic Chem.*, **21**, 323-435 (1977).

5. R. N. Butler, *Comprehensive Heterocyclic Chem.*, K. T. Potts, Ed.; Pergamon Press, New York, NY, 1984, Vol. 5, pp. 791-838.

6. E. Lippmann and A. Könnecke, *Z. Chem.*, **16**, 90 (1976).

7. a) R. N. Butler, *Chem. Ind. (London)*, 371 (**1973**); b) M. Tisler, *Synthesis*, 123 (**1973**).

8. P. K. Kadaba, *ibid.*, 71 (**1973**).

9. A. I. Popov, *Coord. Chem. Rev.*, **4,** 463 (1969).

10. R. N. Butler, *Leicester Chem. Rev.*, **10,** 12 (1969).

11. F. Kurzer, L. E. A. Godfrey, *Angew. Chem. Int. Engl. Ed.*, **2,** 459 (1963).

12. H. Singh, A. S. Chawla, V. K. Kapoor, D. Paul, R. K. Malhotra, *Prog. in Med. Chem.*, **17,** 151 (1980).

13. W. G. Finnegan, R. A. Henry and R. Lofquist, *J. Am. Chem. Soc.*, **80,** 3908 (1958).

14. H. Behringer and K. Kohl, *Chem. Ber.*, **89,** 2648 (1956).

15. J. J. Yaouanc, G. Sturtz, J. L. Kraus, C. Chastel and J. Colin, *Tetrahedron Lett.*, **21,** 2689 (1980).

16. J. L. Kraus and G. Lajoie, Jr., *C. R. Seances Acad. Sci., Ser. 2*, **295,** 761 (1982).

17. B. E. Huff and M. A. Staszak, *Tetrahedron Lett.*, **34**, 8011 (1993).

18. J. G. Luitjen, M. J. Janssen and G. J. M. Van Der Kirk, *Recl. Trav. Chim. Pays-Bas,* **81,** 286 (1963).

19. S. J. Wittenberger and B. G. Donner, *J. Org. Chem.*, **58**, 4139 (1993).

20. a) N. D. Griffiths, B. J. W. F. Brynley and A. A. Thatcher, EP 32385 A1 12 Jun 1989; *CA,* **112**:35868x (1990); b) N. D. Griffiths, B. J. W. F. Brynley and A. A. Thatcher, DD 289526 A5 2 May 1991; *CA,* **116**:6564x (1992).

21. D. Kikelj and R. Neidlein, *Synthesis*, 873 (**1993**).

22. L. Bruché, L. Garanti and G. Zecchi, *Synth. Commun.*, **22**, 309 (1992).

23. J. V. Duncia, M. E. Pierce and J. B. Santella III, *J. Org. Chem.*, **56**, 2395 (1991).

24. E. W. Thomas, *Synthesis*, 767 (**1993**).

25. P. N. Gaponik, Y. V. Grigor'ev and V. P. Karavai, *Khim. Geterotsikl. Soedin.*, 566 (**1985**); *CA,* **103**:71260r (1985).

26. G. Litkei, T. Patonay, E. Patonay-Plei and V. P. Karavai, *Pharmazie*, **44**, 791 (1989); *CA,* **113**:23615v (1990).

27. R. T. Chakrasali, H. Iba and H. Junjappa, *Synthesis* 453 (1988).

28. a) R. W. Saalfrank, M. Fischer and U. Wirth, H. Zimmermann, *Angew. Chem. Int.. Eng. Ed*, **26,** 1160 (1987); b) R. W. Saalfrank, C.-J. Lurz, J. Hassa, D. Danion and L. Toupet, *Chem. Ber.*, **124**, 595 (1991); c) R. W. Saalfrank, C.-J. Lurz, U. Wirth, H. G. von Schnering and K. Peters, *J. Heterocyclic Chem.*, **28**, 1863 (1991).

29. S. Nagai, N. Kato, T. Veda, N. Oda and J. Sakakibara, *Heterocycles*, **24**, 907 (1986).

30. F. R. Atherton and R. W. Lambert, *Tetrahedron*, **39**, 2599 (1983).

31. (a) E. Zbiral and W. Schörkhuber, *Ann.*, 1870 (**1982**), (b) H. Knotz and E. Zbiral, *ibid.*, 1736 (**1986**).

32. D. Häbich, *Synthesis*, 358 (**1992**).

33. Y.-X. Ding and W. P. Weber, *ibid.*, 823 (**1987**).

34. S. Götzky, *Ber.*, **64,** 1555 (1931).

35. JP 59 98,023 [84 98,023] (Cl. C07C17/14), 06 Jun 1984; *CA*, **101**:171262v (1984).

36. M. Yokoyama, M. Matsushita, S. Hirano and H. Togo, *Tetrahedron Lett.*, **34**, 5097 (1993).

37. K. Faber and T. Kappe, *J. Heterocyclic Chem.*, **21,** 1881 (1984).

38. (a) K. Nishiyama and A. Watanabe, *Chemistry Lett.*, 455 (**1984**), (b) K. Nishiyama, M. Oba and A. Watanabe, *Tetrahedron*, **43**, 693 (1987).

39. S. M. Fahmy and R. M. Mohareb, *Synthesis*, 478 (**1983**).

40. M. I. K. Amer and B. L. Booth, *J. Chem. Res., Synop.*, 4 (**1993**).

41. B. Carboni and R. Carrié, *Tetrahedron*, **40**, 4115 (1984).

42. W. L. Collibee and J.-P. Anselme, Manuscript in preparation.

43. a) K. F. Schmidt, *Ber.*, **57**, 704 (1924); b) H. Wolff: *Organic Reactions;* Roger Adams Ed.; John Wiley & Sons, Inc.: New York, 1947; vol 3, pp. 307-336.

44. M. S. Ahmad, I. A. Ansari, S. A. Ansari and G. Moinubdin, *Indian J. Chem., Sect. B*, **24B**, 664 (1985).

45. M. S. Ahmad and Z. Alam, *ibid.*, **27B**, 1001 (1988).

46. A. Ahmed, B. K. Bairagi and M. A. Hai, *J. Bangladesh Chem. Soc.*, **3**, 239 (1990); *CA*, **114**:229163a (1991).

47. K. L. Rao, T. S. Ramaiah, K. S. Reddy, S. K. Ramraj and T. V. P. R. S. Rao, *J. Indian Chem. Soc.*, **62**, 137 (1985).

48. J. Mustafa, M. S. Ahmad, Jr., A. Rauf and S. M. Osman, *J. Am. Oil Chem. Soc.*, **61**, 555 (1984).

49. H. Suzuki, Y. S. Hwang, C. Nakaya and Y. Matano, *Synthesis*, 1218 (**1993**).

50. G. L'abbé, P. Van Stappen and S. Toppet, *Tetrahedron*, **41**, 4621 (1985).

51. H. M. Hassaneen, A. A. Fahmi, H. Abdelhamid, A. A. Yassin and A. S. Shawali, *J. Heterocyclic Chem.*, **21**, 797 (1984).

52. T. Aoyama and T. Shioiri, *Chem. Pharm. Bull. Jpn*, **30**, 3450 (1982).

53. G. Maas, H. Gümbel, G. Wise and M. Regitz, *Chem. Ber.*, **118**, 2105 (1985).

54. J. Stawinski, T. Hozumi, S. A. Narang, C. P. Bahl and R. Wu, *Nucleic Acids Res.*, **4**, 353 (1977).

55. T. Hirose, R. Crea and K. Itakura, *Tetrahedron Lett.*, 2449 (**1978**).

56. H. Takaku, M. Yoshida, M. Kato and T. Hata, *Chemistry Lett.*, 811 (**1979**).

57. (a) H. Takaku, T. Nomoto, Y. Sakamoto and T. Hata, *ibid.*, 1225 (**1979**), (b) H. Takaku, R. Yamaguchi, T. Nomoto and T. Hata, *Tetrahedron Lett.*, 3857 (**1979**).

58. H. Takaku and M. Yoshida, *J. Org. Chem.*, **46**, 589 (1981).

59. R. T. Pon, *Tetrahedron Lett.*, **28**, 3643 (1987) and references therein.

60. S. L. Beaucage and R. P. Iyer, *Tetrahedron*, **49**, 10441 (1993).

61. P. J. Garegg, T. Regberg, J. Stawinski and R. Strömberg, *Chem. Scr.*, **26**, 63 (1986).

62. B. H. Dahl, J. Nielsen and O. Dahl, *Nucleic Acids Res.*, **15**, 1729 (1987).

63. S. Berner, K. Mühlegger and H. Seliger, *Nucleosides & Nucleotides*, **7**, 763 (1988).

64. K.-L. Yu and B. Fraser-Reid, *Tetrahedron Lett.*, **29**, 979 (1988).

65. W. Tegge and C. E. Ballou, *Proc. Natl. Acad. Sci. USA*, **86**, 94 (1989).

66. Y. Watanabe, S. Maeharaand S. Ozaki, *J. Chem. Soc. Perkin Trans. 1*, 1879 (**1992**).

67. K. Zhao and D. W. Landry, *Tetrahedron*, **49**, 363 (1993).

68. K. Takeda, K. Tsuboyama, H. Takayanagi and H. Ogura, *Synthesis*, 560 (**1987**).

69. a) K. Takeda, K. Tsuboyama, K. Torii, M. Murata and H. Ogura, *Tetrahedron Lett.*, **29**, 4105 (1988); b) K. Takeda, K. Torii and H. Ogura, *ibid.*, **31**, 265 (1990); c) K. Tsuboyama, K. Takeda, K. Torii and H. Ogura, *Chem. Pharm. Bull. Jpn*, **38**, 2357 (1990).

70. K. Takeda, K. Tsuboyama, H. Takayanagi, R. Shirokami, M. Takeura and H. Ogura, *ibid.*, **37**, 2334 (1989).

71. a) K. Takeda, K. Tsuboyama, K. Torii, K. Furuhata, N. Sato and H. Ogura, *Carbohydrate Research*, **203**, 257 (1990); b) K. Tsuboyama, K. Takeda, K. Torii, M. Ebihara, J. Shimizu, A. Suzuki, N. Sato, K. Furuhata and H. Ogura, *Chem. Pharm. Bull. Jpn*, **38**, 636 (1990); c) K. Furuhata, K. Takeda and H. Ogura, *ibid.*, **39**, 817 (1991); d) M. Nakamura, K. Takeda, H. Takayanagi, N. Asai, N. Ibata and H. Ogura, *ibid.*, **41**, 26 (1993).

72. M. Ohtani and M. Narisada, *J. Org. Chem.*, **56**, 5475 (1991).

73. R. N. Butler, P. D. O'Shea and D. P. Shelly, *J. Chem. Soc. Perkin Trans. 1*, 1039 (**1987**).

74. a) D. Moderhack and D.-O. Bode, *ibid.*, 1483 (**1992**); b) D. Moderhack and A. Lembcke, *ibid.*, 1157, 2009 (**1986**).

75. a) C. J. Moody, C. W. Rees and R. G. Young, *ibid.*, 323 (**1991**); b) C. J. Moody, C. W. Rees and R. G. Young, *Synlett*, 413 (**1990**).

76. M. Uchida, M. Komatsu, S. Morita, T. Kanbe, K. Yamasaki and K. Nakagawa, *Chem. Pharm. Bull. Jpn*, **37**, 958 (1989).

77. M. Klich and G. Teutsch, *Tetrahedron Lett.*, **25**, 3849 (1984).

78. K. Hirota, K. Maruhashi, T. Asao and S. Senda, *Heterocycles*, **15**, 285 (1981).

79. R. N. Butler and K. J. Fitzgerald, *J. Chem. Soc. Perkin Trans. 1*, 1587 (**1988**).

80. N. Koga, G. Koga, J. P. Springer, B. H. Arison and J.-P. Anselme, *Chem. Commun.*, 610 (**1983**).

81. G. R. Marshall, C. Humblet, N. Van Opdenbosch and J. Zabrocki, *Peptides: Synthesis-Structure-Function;* Proc. 7th American Peptide Symposium, D. H. Rich, E. Gross, Eds.; Pierce Chemical Company: Rockford, IL, 1981; p 669.

82. K.-L. Yu and R. L. Johnson, *J. Org. Chem.*, **52**, 2051 (1987).

83. J. Zabrocki, G. D. Smith, J. B. Dunbar, Jr., H. Iijima and G. R. Marshall, *J. Am. Chem. Soc.*, **110**, 5875 (1988).

84. G. D. Smith, J. Zabrocki, T. A. Flak and G. R. Marshall, *Int. J. Peptide Protein Res.*, **37**, 191 (1991).

85. J. Zabrocki, U. Slomczynska and G. R. Marshall, In *Peptides: Chemistry, Structure and Biology*; J. Rivier, G. R. Marshall, Eds.; ESCOM: Leiden, 1990; pp 195-197.

86. J. Zabrocki, G. D. Smith, J. B. Dunbar, Jr., K. W. Marshall, M. Toth and G. R. Marshall, In *Peptides 1988: Proceedings of the 20th European Peptide Symposium;* G. Jung, E. Bayer, Eds.; Walter de Gruyter: Berlin, 1989; pp 295-297.

87. J. Zabrocki, J. B. Dunbar, Jr., K. W. Marshall, M. V. Toth and G. R. Marshall, *J. Org. Chem.*, **57**, 202 (1992).

88. M. Lebl, J. Slaninova and R. L. Johnson, *Int. J. Peptide Protein Res.*, **33**, 16 (1990).

89. G. Valle, M. Crisma, K.-L. Yu, C. Toniolo, R. K. Mishra and R. L. Johnson, *Coll. Czech. Chem. Commun.*, **53** 2863 (1988).

90. a) P. L. Ornstein, EP 330353 A1 30 Aug 1989; *CA*, **112**:118825g (1990); b)P. L. Ornstein, US 4902687 A 20 Feb 1990; *CA*, **113**:78420h (1990).

91. J. A. Monn, M. J. Valli, R. A. True, D. D. Schoepp, J. D. Leander and D. Lodge, *Biorg. & Med. Chem. Lett.*, **3**, 95 (1993).

92. a) D. D. Schoepp, C. L. Smith, D. Lodge, J. D. Millar, J. D. Leander, A. Sacaan and W. H. W. Lunn, *Eur. J. Pharmacol.*, **203**, 237 (1991); b) W. H. W. Lunn, D. D. Schoepp, D. O. Calligaro, R. T. Vasileff, L. J. Heinz, C. R. Salhoff and P. J. O'Malley, *J. Med. Chem.*, **35**, 4608 (1992).

93. A. K. S. Gupta, T. Bhattacharya and A. Rastogi, *Indian J. Chem.*, **24B**, 578 (1985).

94. R. Milcent, L. Lebreton, F. Mazouz and C. Burstein, FR 2631827 A1 1 Dec 1989; *CA*, **113**:191368k (1990).

95. R. Baker, V. G. Matassa and L. J. Street, EP 497512 A2 5 Aug 1992; *CA*, **118**:38924x (1993).

96. H. J. Wadsworth, S. M. Jenkins, B. S. Orlek, F. Cassidy, M. S. G. Clark, F. Brown, G. J. Riley, D. Graves, J. Hawkins and C. B. Naylor, *J. Med. Chem.*, **35**, 1280 (1992).

97. S. W. Djuric, D. J. Fretland and S. S. T. Yu, WO 9211252 A1 9 Jul 1992; *CA*, **117**:234018y (1992).

98. M. Barreau, M. Kryvenko, M. P. Lavergne and A. Techer, WO 9119714 A1 26 Dec 1991; *CA*, **116**:151775w (1992).

99. a) A. Beck, A. Sallmann and P. Wenk, US 4808604 A 28 Feb 1989; *CA*, **111**:153809f (1989); b) A. Beck, A. Sallmann and P. Wenk, EP 222962 A1 27 May 1987; *CA*, **107**:176045k (1987).

100. A. Nohara and Y. Maki, US 4672073 A 9 Jun 1987; *CA*, **107**:217632v (1987).

101. J. Gilmore and A. Todd, EP 469833 A1 5 Feb 1992; *CA*, **116**:214508j (1992).

102. J. G. Gleason, R. F. Hall and I. Uzinskas, WO 9118889 A1 12 Dec 1991; *CA*, **116**:174152e (1992).

103. a) F. P. Carr, R. D. Dilliard, W. S. Marshall and D. E. McCullough, EP 305085 A1 1 Mar 1989; *CA*, **111**:115183q (1989); b) R. D. Dilliard, D. E. McCullough and F. P. Carr, EP 288189 A1 26 Oct 1988; *CA*, **110**:75524x (1989).

104. V. Wazir, G. B. Singh, S. Singh, R. Gupta and P. L. Kachroo, *J. Indian Chem. Soc.*, **68**, 305 (1991).

105. P. Kumar and E. E. Knaus, *Drug Des. Delivery*, **7**, 287 (1991).

106. a) L. Janda, Z. Voticky, J. Svetlik, J. Grimova and E. Maturova, *Coll. Czech. Chem. Commun.*, **49**, 1505 (1984); b) L. Janda, Z. Voticky, J. Jakubcova, J. Svetlik, J. Grimova and E. Maturova, *ibid.*, **49**, 1699 (1984).

107. K. Pande, M. Tandon, T. N. Bhalla and J. P. Barthwal, *Indian J. Chem.*, **23B**, 1133 (1984).

108. K. Faber and T. Kappe, *J. Heterocycl. Chem.*, **21**, 1881 (1984).

109. R. Gupta, H. Singh, S. Sudan and P. L. Kachroo, *Natl. Acad. Sci. Lett.*, **15** 15 (1992).

110. M. A. Moustafa, H. M. Eisa, A. A. El-Emam and M. A. Metwally, *Arch. Pharmacal. Res.*, **13**, 204 (1990).

111. a) J. S. G. Cox, *Nature (London)*, **216**, 1328 (1967); b) J. B. L. Howell and R. E. C. Altounyan, *Lancet*, **2**, 539 (1967); c) M. C. S. Kennedy, *Acta Allerg. (Kbh.)*, **22**, 487 (1967).

112. B. J. Broughton, P. Chaplen, P. Knowles, E. Lunt, S. M. Marshall, D. L. Pain and K. R. H. Wooldridge, *J. Med. Chem.*, **18**, 1117 (1975).

113. V. Bernareggi, F. Bonifacio, M. Fano, L. Trabella, G. Battigelli and D. Montagna, EP 384450 A1 29 Aug 1990; *CA*, **114**:247282t (1991).

114. J. Yoshinaga, T. Shogaki, T. Kakita, H. Ozeki, N. Sugimoto and Y. Kato, EP 262873 A1 6 Apr 1988; *CA*, **109**:54782u (1988).

115. A. P. Vinogradoff, N. P. Peet and S. Sunder, EP 234557 A1 2 Sep 1987; *CA*, **108**:21900g (1988).

116. R. E. Ford, P. Knowles, E. Lunt, S. M. Marshall, A. J. Penrose, C. A. Ramsden, A. J. H. Summers, J. L. Walker and D. E. Wright, *J. Med. Chem.*, **29**, 538 (1986).

117. Austrian Patent AT 387966 B 10 Apr 1989; *CA*, **111**:194772g (1989).

118. D. T. Connor, P. C. Unangst and R. J. Weikert, EP 279466 A2 24 Aug 1988; *CA*, **109**:231035a (1988).

119. SA. Sawaki, Y. Ootake, T. Hashimoto, T. Abe and Y. Horio, EP 256507 A2 24 Feb 1988; *CA*, **108**:221708n (1988).

120. Y. Itoh, H. Kato, E. Koshinaka, N. Ogawa and K. Mitani, EP 227026 A1 1 Jul 1987; *CA*, **108**:21924t (1988).

121. D. T. Connor, R. J. Sorenson, M. D. Mullican and D. O. Thueson, EP 299457 A2 18 Jan 1989; *CA*, **111**:78009q (1989).

122. S. L. Dax, D. L. Pruess, P. L. Rossman and C.-C. Wei, *Bioorg. & Med. Chem. Lett.*, **3** , 209 (1993).

123. F. H. Jung, EP 447118 A2 18 Sep 1991; *CA*, **116**:6339c (1992).

124. H. Yamada, H. Tobiki, K. Jimpo, K. Gooda, Y. Takeuchi, S. Ueda, T. Komatsu, T. Okuda, H. Noguchi, K. Irie and T. Nakagome, *J. Antibiot.*, **36**, 532 (1983).

125. D. Koh, S. W. Park and Y. Kim, *Bull. Korean Chem. Soc.*, **8**, 189 (1987); *CA*, **108**:75055d (1988).

126. L. Janda and Z. Voticky, *Chem. Pap.*, **43**, 77 (1989); *CA*, **112**:77078v (1990).

127. a) C. Yoshida, K. Tanaka, R. Hattori, Y. Fukuoka, M. Komatsu, S. Kishimoto and I. Saikawa, *J. Antibiot.*, **39**, 215 (1986); b) C. Yoshida, K. Tanaka, Y. Todo, R. Hattori, Y. Fukuoka, M. Komatsu and I. Saikawa, *ibid.*, **39**, 90 (1986).

128. Z. Zhang, L. Chen and H. Wu, *Chem. Res. Chin. Univ.*, **7**, 193 (1991); *CA*, **117**:171334a (1992).

129. F. Xiaoming, C. Rong and C. Shaoyin, *Org. Prep. Proced. Int.*, **24**, 492 (1992).

130. F. Xiaoming and C. Rong, *Chem. Res. Chin. Univ.*, **8**, 315 (1992); *CA*, **119**:8746u (1993).

131. P. Faury, M. Camplo, A.-S. Charvet, J.-C. Chermann and J.-L. Kraus, *Nucleosides Nucleotides*, **11**, 1481 (1992).

132. E. Holbova and M. Uher, *Chem. Zvesti*, **36**, 253 (1982); *CA*, **97**:92209d (1982).

133. D. D. Mukerjee, S. K. Shukla, H. N. Verma and L. P. Awasthi, *Acta Pharm. Jugosl.*, **31**, 151 (1981); *CA*, **96**:85475p (1981).

134. P. Bühlmayer, *Current Opinion in Therapeutic Patents*, 1693 (**1992**).

135. a) J. J. Wright and S. Y. Sit, DE 3805801 A1 8 Sep 1988; *CA*, **110**:114836x (1989); b) J. J. Wright, S. Y. Sit, N. Balasubramanian and P. J. Brown, DE 3805789 A1 15 Sep 1988; *CA*, **110**:154302 (1989); c) S. Y. Sit and J. J. Wright, US 4870187 A 26 Sep 1989; *CA*, **112**:139037s (1990); d) S. Y. Sit and J. J. Wright, US 4897490 A 30 Jan 1990; *CA*, **113**:211987s (1990).

136. P. Raddatz, J. Gante, C. J. Schmitges, K. O. Minck, J. Sombroek and G. Hoelzemann, DE 3626130 A1 11 Feb 1988; *CA*, **109**:93623n (1988).

137. A. W. Chucholowski and A. D. White, WO 9117150 A1 14 Nov 1991; *CA*, **116**:128930j (1992).

138. B. C. Ross, D. Middlemiss, D. I. C. Scopes, T. I. M. Torquil, K. S. Cardwell and M. D. Dowle, EP 430709 A2 5 Jun 1991; *CA*, **115**:136104n (1991).

139. T. Naka and K. Nishikawa, EP 425921 A1 8 May 1991; *CA*, **115**:159142n (1991).

140. R. M. Keenan and J. Weinstock, EP 425211 A1 2 May 1991; *CA*, **115**:183309t (1991).

141. T. Schmidlin, F. Ostermayer and P. Buehlmayer, EP 490820 A2 17 Jun 1992; *CA*, **117**:150992y (1992).

142. a) P. E. Aldrich, M. E. Pierce and J. J. V. Duncia, EP 291969 A2 23 Nov 1988; *CA*, **110**:212826p (1989); b) D. J. Carini, WO 9200977 A2 23 Jan 1992; *CA*, **116**:174158m (1992).

143. T. Oku, S. Hiroyuki, H. Kayakiri and H. Tanaka, EP 480204 A1 15 Apr 1992; *CA*, **117**:26566y (1992).

144. D. B. Reitz and R. E. Manning, EP 508393 A1 14 Oct 1992; *CA*, **118**:59715v (1993).

145. A. M. Venkatesan and J. I. Levin, EP 497150 A1 5 Aug 1992; *CA*, **118**: 101979m (1993).

146. M. P. Edwards, R. J. Pearce and B. B. Masek, EP 511791 A2 Nov 1992; *CA*, **118**: 124546g (1993).

147. a) M. Winn, B. De, T. M. Zydowsky, D. J. Kerkman, J. F. De Bernardis, S. H. Rosenberg, K. Shiosaki, F. Z. Basha, A. S. Tasker, et al., EP 475206 A2 18 Mar 1992; *CA*, **118**:234077n (1993); b) M. Winn, B. De, T. M. Zydowsky, R. J. Altenbach, F. Z. Basha, S. A. Boyd, M. E. Brune, S. A. Buckner, D. Crowell, I. Drizin, A. A. Hancock, H.-S. Jae, J. A. Kester, et al., *J. Med. Chem.*, **36**, 2676 (1993).

148. W. Mederski, J. Sombroek, P. Schelling, N. Beier and I. Lues K. O. Minck, EP 505893 A1 30 Sep 1992; *CA*, **118**:254907m (1993).

149. a) M. Uchida, M. Komatsu, S. Morita, T. Kanbe and K. Nakagawa, *Chem. Pharm. Bull. Jpn*, **37**, 322 (1989); b) M. Uchida, M. Komatsu, S. Morita, T. Kanbe, K. Yamasaki, K. Nakagawa, *ibid.*, **37**, 958 (1989).

150. I. Ueda, K. Ishii, K. Sinozaki, M. Seiki and M. Hatanaka, *ibid.*, **39**, 1430 (1991).

151. a) K. L. Kees, US 4764623 A 16 Aug 1988; *CA*, **109**:190431f (1988); b) K. L. Kees, US 4845231 A 4 Jul 1989; *CA*, **111**:232835q (1989).

152. H. P. Wolff, R. Heck, H. F. Kuehnle and P. Freund, DE 4040619 A1 25 Jun 1992; *CA*, **117**:131208f (1992).

153. R. A. Porter, K. J. Murray, B. H. Warrington and H. D. Prain, WO 9206085 A1 16 Apr 1992; *CA*, **117**:90296n (1992).

154. G. Schubert, E. Baader, M. Bickel and V. Guenzler-Pukall, EP 498334 A1 12 Aug 1992; *CA*, **117**:212509g (1992).

(Received March 8, 1994; in revised form June 15, 1994)