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Synthetic access to benzazolyl (pyrazoles, thiazoles, or triazoles)

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This review surveys data published in recent years on the synthesis of benzazoles linked directly with pyrazoles, thiazoles, or triazoles. Some of the commercial applications are mentioned.

Key Words: Biheterocycles, indolylpyrazoles, indolylthiazoles, indolyltriazoles, benzimidazolyltriazoles, triazolylbenzoisoxazoles

Introduction

The combination of benzazole directly with a pyrazole, thiazole, or triazole ring led to more biologically active targets, e.g., indolylpyrazoles are antitumor agents and also as Chk1 inhibitors[1] and benzothiazolylpyrazoles are useful as anti-inflammatory agents.[2] A thiazolyl indolequinone, BE 10988, isolated from culture broths of a *Streptomyces* strain, is known to increase DNA-topoisomerase complex formation and displayed significant anti-cancer activities.[3] Moreover, triazol-4-yl-indoles are agonists of 5-HT1-like receptors.[4–8] Despite this versatile importance and in connection with our previous review article about the chemistry of biazoles[9,10] and other active heterocyclic systems,[11–23] the benzazoles-based pyrazole, thiazole, and triazole have not been previously reviewed. The main purpose of this review is to present a survey of the literature of benzazolyl linked with some azole moieties; some of the commercial applications are mentioned.

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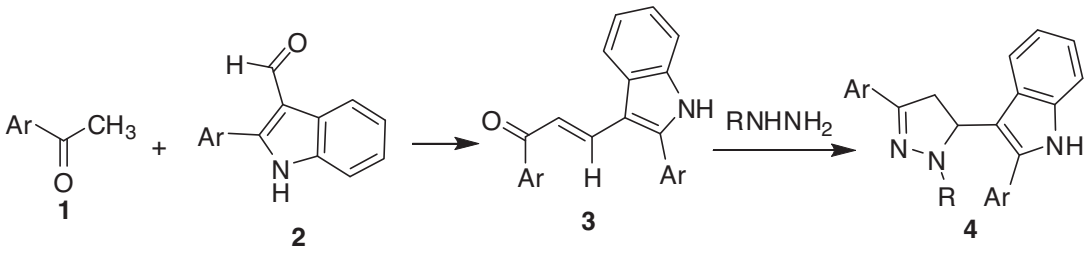
Benzazolylpyrazoles

Indolylpyrazoles

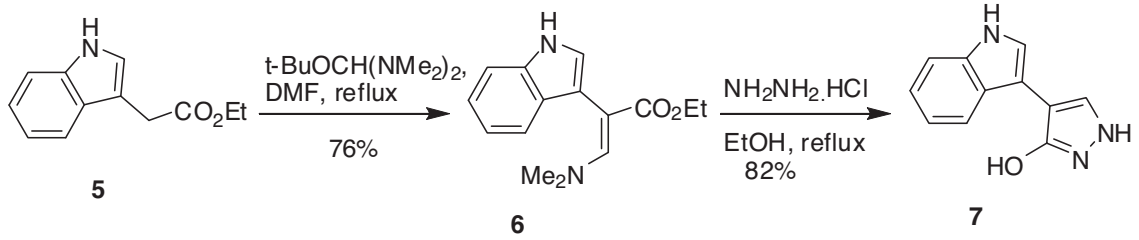
Interaction of chalcones or enamines and hydrazines

Indolylpyrazolines **4** were prepared by treating 1-(4-methoxyphenyl)ethanone **1** with 3-formyl-2-(4-methoxyphenyl)indole **2** and treating the resulting α, β-unsaturated ketones **3** with hydrazines. Compounds **4** inhibited monoamine oxidase activity.[24–31]



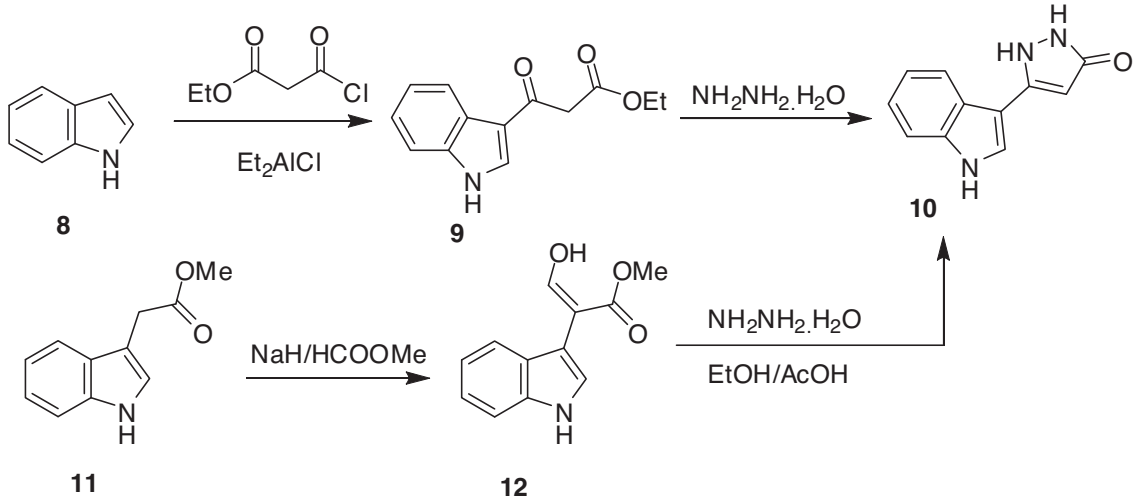
Ar = 4-$MeOC_6H_4$; R = 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2,4,6-$Me_3C_6H_2$, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-ClC_6H_4, 3-ClC_6H_4, 2,6-$Cl_2C_6H_3$, 2,4,6-$Cl_3C_6H_2$, 2,5-$Cl(O_2N)C_6H_3$, 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 2,4-$(O_2N)_2C_6H_3$

(*E*)-ethyl 3-(dimethylamino)-2-(1*H*-indol-3-yl)acrylate **6** was prepared, in 76% yield, in one step by heating of ethyl 2-(1*H*-indol-3-yl)acetate **5** and *tert*-butoxy-bis(dimethylamino)methane (Bredereck's reagent) in DMF under reflux for several hours. Indolyl substituted pyrazole **7** was obtained via the reaction of **6** with hydrazine.HCl.[32]



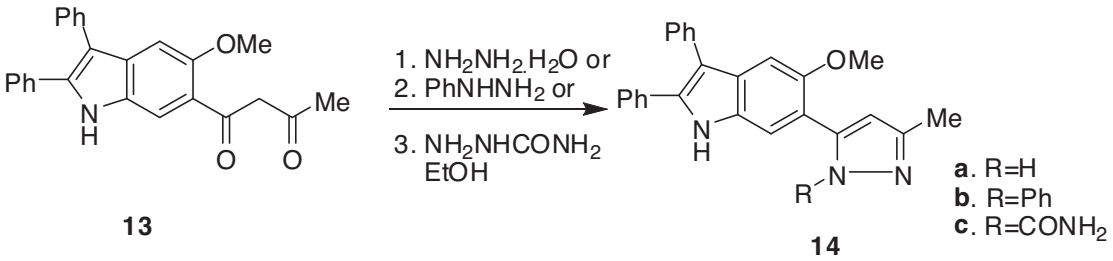
Reaction of dicarbonyl compounds with hydrazines

Ethyl 1-chloro-malonate was coupled to indole **8** in the presence of diethylaluminium chloride. Reaction of the resulting β-keto-ester **9** with hydrazine hydrates led to pyrazolone **10**. For alternative synthesis of compound **10**, formylation of commercial methyl 3-indolyl-acetate **11** with methyl formate after deprotonation with sodium hydride according to a method described with a phenyl substituent instead of an indole led to 3-hydroxy-acrylate **12** in a quantitative yield. Reaction of compound **12** with hydrazine hydrate in an acidic medium as described in non-aromatic series gave pyrazolone **10** in 74% yield.[33]



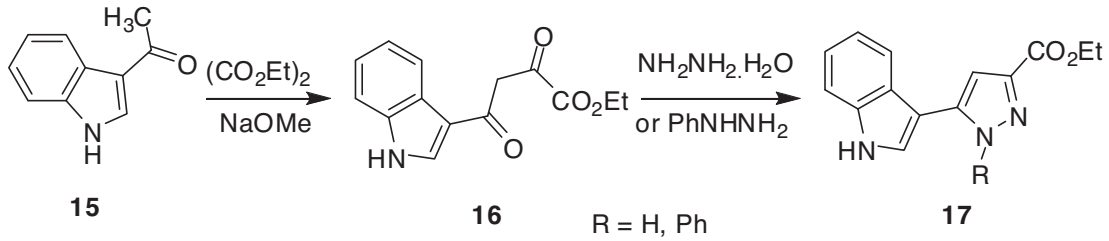
8 **9** **10** **11** **12**

Hydrazine hydrate, phenylhydrazine, and semicarbazide hydrochloride reacted with acetoacetyldiphenylmethoxyindole **13** to give the pyrazoles **14**.[34]



13 **14**

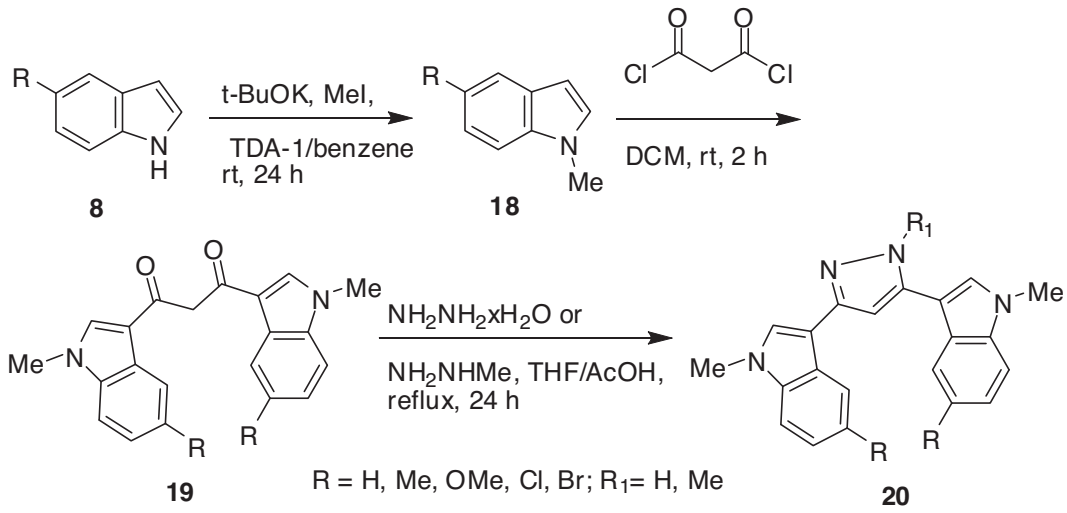
3-Acetylindole **15** condensed with diethyl oxalate in absolute methanol containing sodium methoxide at room temperature to give the ethyl indolebutyrate **16**. Cyclization of **16** with phenyl hydrazine and hydrazine hydrate gave the pyrazoles **17**.[35]



15 **16** **17**

The synthesis of 3,5-bis(3'-indolyl)pyrazoles **20** where a pyrazole central ring substituted the imidazole ring of nortopsentin was reported. The synthetic approach to the pyrazole compounds involved the indole derivatives of type **8**, which were converted into the corresponding *N*-methyl derivatives **18** using potassium *t*-butoxide, tris(3,6-dioxaheptyl)amine (TDA-1) as a catalyst, and methyl iodide in dry benzene (96–98%). Friedel-Craft reaction of the *N*-methylindoles **18** with malonyldichloride in dichloromethane yielded the expected 1,3-diketones of type **19** (45%-70%). The resulting symmetrical 1,3-diketones **19** were converted into corresponding

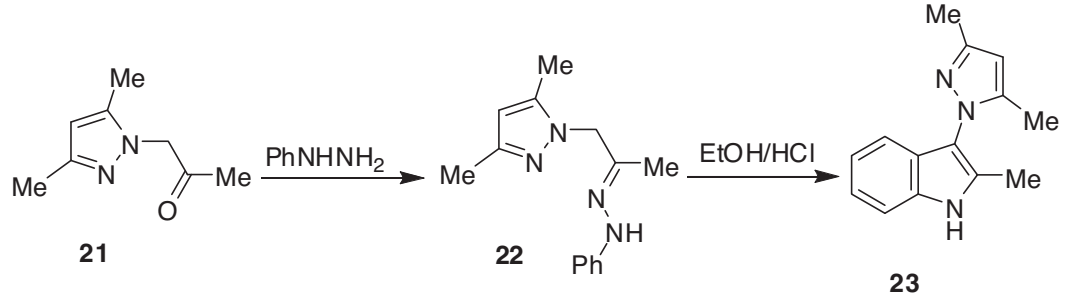
3,5-bis(3'-indolyl)-pyrazoles **20** using hydrazine monohydrate or methylhydrazine in refluxing acetic acid/THF (54%-92%).[36]



8 **18** **19** **20**

Miscellaneous methods

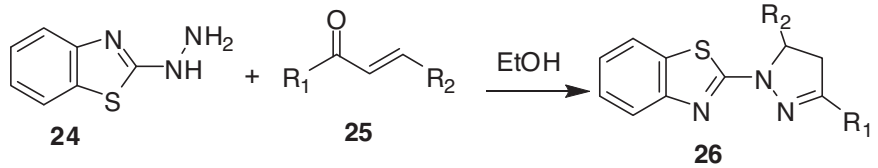
Condensation of dimethylpyrazolylacetone **21** with phenylhydrazine yielded a phenylhydrazone **22**, which was converted to the indolylpyrazole **23** upon treatment with ethanolic hydrochloric acid.[37]



21 **22** **23**

0.1. Benzothia(oxa)(imida)zoylpyrazoles

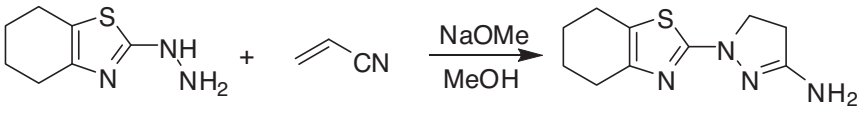
Pyrazol-1-ylbenzo[*d*]thiazole derivatives **26** were synthesized, in 50%-70% yields, by 2-hydrazinobenzothiazole **24** with chalcones **25** in absolute ethanol. Compounds **26** show fluorescent properties.[38–40]



24 **25** **26**

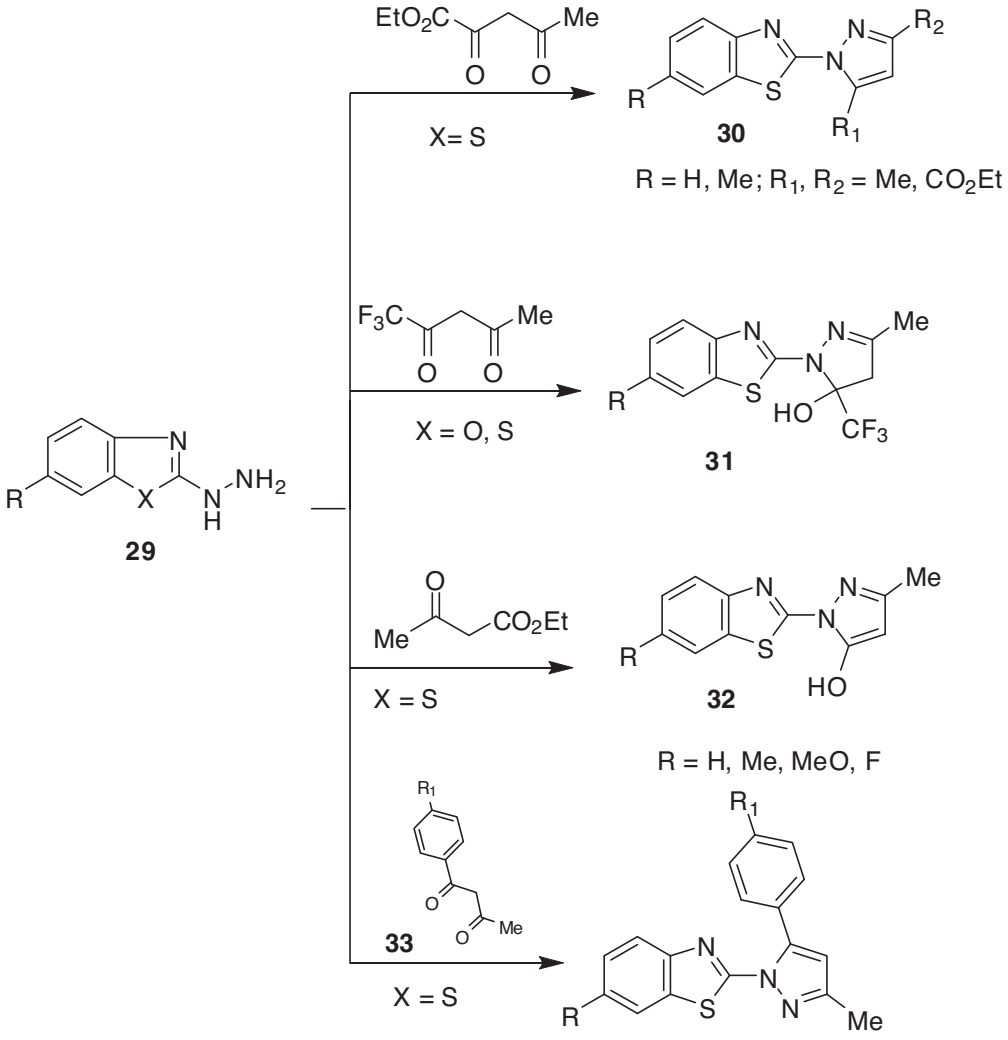
R_1= Ph, 4-MeOC$_6$H$_4$, 2-thienyl; R_2= Ph, 2-furyl, 2-thienyl, 4-tolyl, 4-N,N-dimethylphenyl

3-Amino-1-(4,5,6,7-tetrahydro-2-benzothiazolyl)-2-pyrazoline **28**, useful as an antiinflammatory agent, was prepared by refluxing of 2-hydrazinyl-4,5,6,7-tetrahydrobenzo[d]thiazole **27** with acrylonitrile in methanolic sodium methoxide.[2]



27 **28**

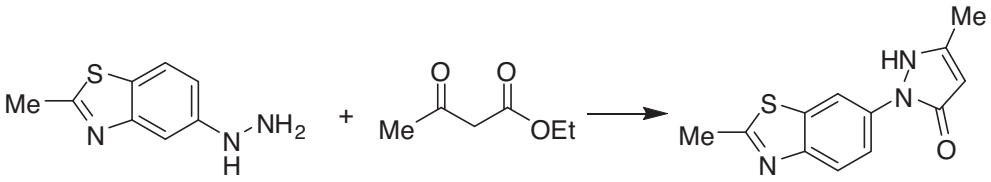
The reaction of 2-hydrazinobenzothiazoles (**29**, X=S) with ethyl 2,4-dioxovalerate gave mixtures of the isomeric benzothiazolylpyrazoles **30**. However, the reaction of (**29**, X= O, S) with 1,1,1-trifluoropentane-



29 **30** **31** **32** **33** **34**

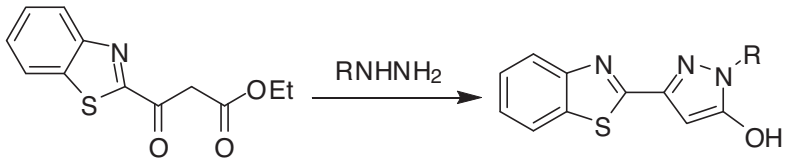
2,4-dione gave 1-(benzothiazol-2'-yl)-5-trifluoromethyl-3-methylpyrazoles **31** as the sole products.[41,42] In addition, hydrazinobenzothiazoles (**29**, X=S) reacted with ethyl 3-oxobutanoate to afford 1-(2-benzothiazolyl)-3-phenylpyrazoline **32**,[43–45] while 1-(2-benzothiazolyl)-5-aryl-3-methylpyrazoles **34** were prepared by condensing β-diketones **33** with 2-hydrazinobenzothiazoles (**29**, X=S).[46]

2-Methyl-5-benzothiazolylhydrazine **35** was reacted with ethyl 3-oxobutanoate at 130-135 °C for 25 min gave 91.2% 1-(2-methyl-6-benzothiazolyl)-3-methyl-5-pyrazolone **36**.[47]



35 **36**

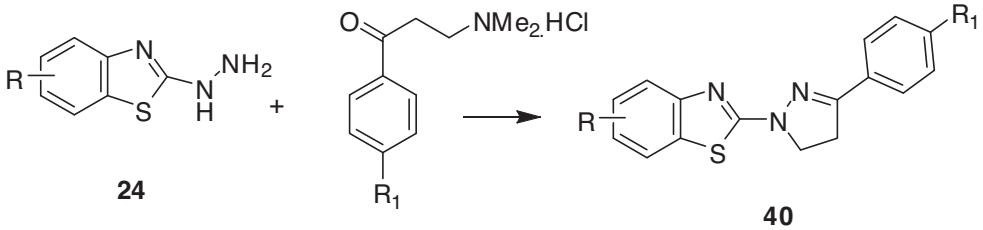
Condensation of ethyl 2-benzothiazoloylacetate **37** with hydrazines gave 3-(2-benzothaizolyl)-5-pyrazolones **38**.[48]



37 **38**

R = H, Me, Ph, p-ClC_6H_4, p-$O_2NC_6H_4$

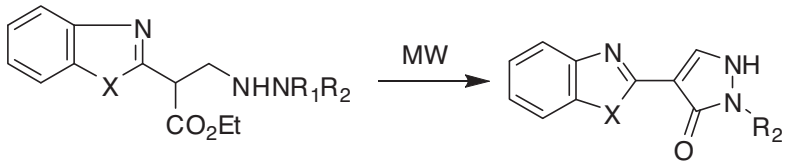
1-(2-Benzothiazolyl)-3-phenylpyrazoline derivatives **40** were prepared by cyclocondensation of hydrazinobenzothiazoles **24** with aminoketones **39**.[49]



24 **39** **40**

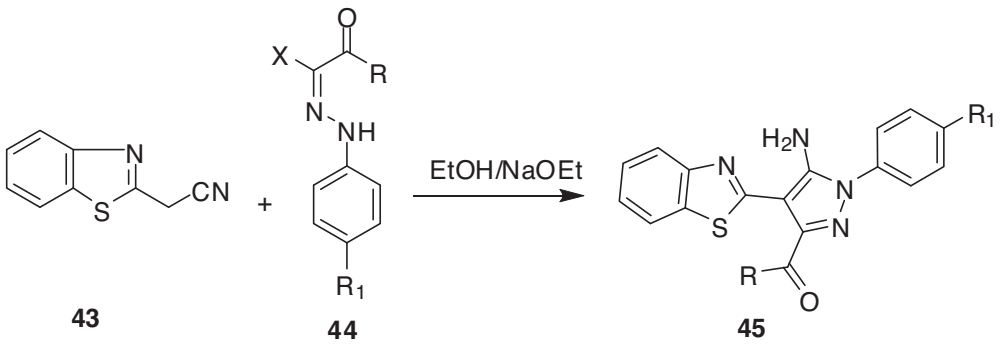
R = H, 4-Me, 6-Cl, 6-MeO, 6-Me, 6-Br; R_1 = H, Cl, Me, NO_2

1,2-Dihydropyrazol-3-ones **42** were prepared in good yields from ethyl β-hydrazino acrylates **41** by transamination and aza-annulation reactions under microwave irradiation.[50]



41 **42**

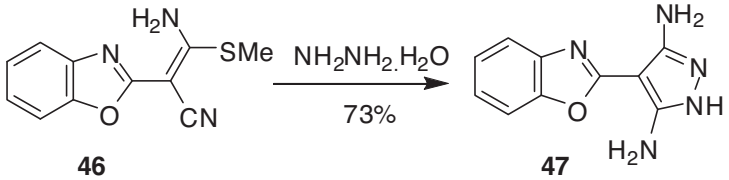
Reaction of 2-(cyanomethyl)benzothiazole **43** with hydrazonoyl halides **44** in ethanol in the presence of sodium ethoxide afforded 5-amino-4-(2-benzothiazolyl)pyrazoles **45**.[51]



43 **44** **45**

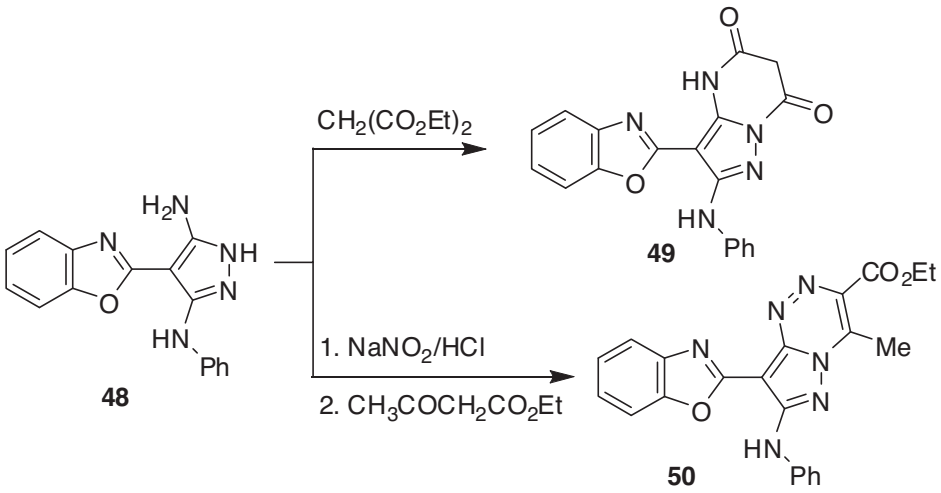
R = Me, EtO, MeO, PhNH; X= Cl, Br; R_1 = H, Me, Cl, Br

The benzoxazolylpyrazole **47** was prepared, in 73% yield, by condensing the cyanovinylbenzoxazole **46** with hydrazine hydrate.[52]

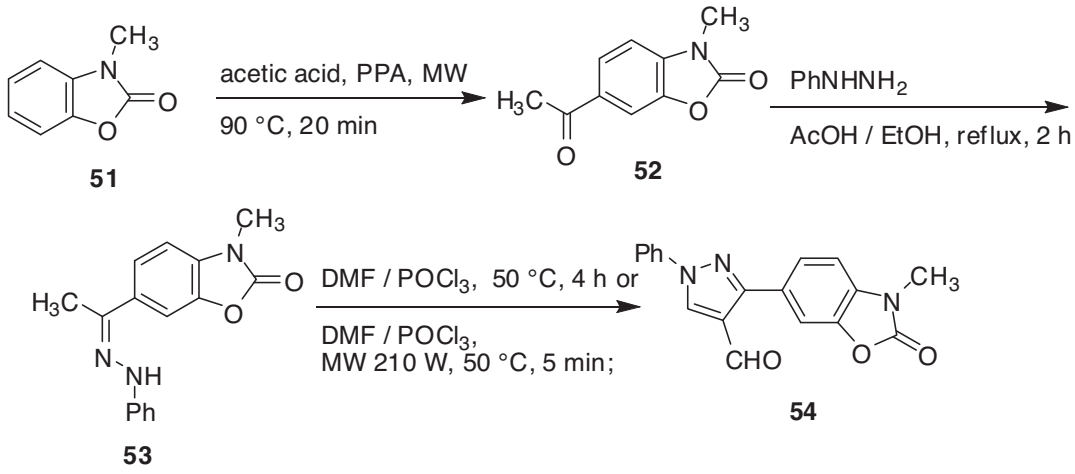


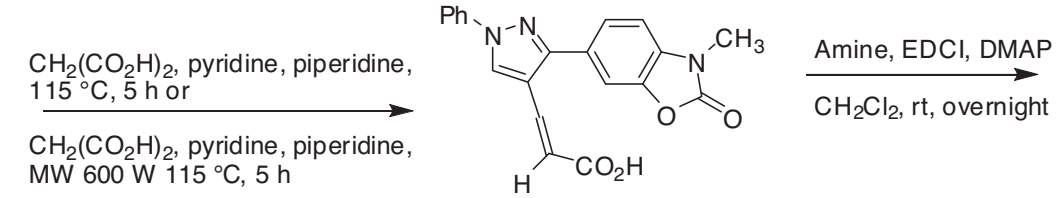
46 **47**

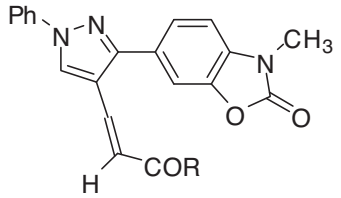
Pyrazolo[1,5-*a*]pyrimidines **49** and pyrazolo[5,1-*c*]-1,2,4-triazines **50** having a benzoxazole moiety are synthesized from *N*-[3-amino-4-(benzoxazol-2-yl)pyrazol-5-yl]phenylamine **48** by reaction with diethyl malonate or reaction of its diazonium chloride with ethyl 3-oxobutanoate.[53]



(*E*) -3-(3-(2,3-dihydro-3-methyl-2-oxo-3*H*-benzoxazole-6-yl)-1-phenyl-1*H*-pyrazole-4-yl)acrylamides **56** were synthesized and evaluated for their in vitro inhibitory activities on COX-1 and COX-2. Compound (**56** R= 4-pyridinyl) exhibited dual anti-inflammatory and antiplatelet activity with selective COX-2 inhibition. Thus, 3-methyl-2-oxo-3*H*-benzoxazole **51** was converted to 6-acetyl-3-methyl-2-oxo-3*H*-benzoxazole **52** via Friedel–Crafts acylation under microwave conditions. Subsequently, the hydrazone derivative **53** was generated by condensation with phenylhydrazine in the presence of acetic acid in refluxing ethanol. This hydrazone derivative was then reacted with phosphorus oxychloride and DMF using 2 different methods (conventional synthesis and microwave conditions), resulting in 1,3-diaryl pyrazole **54** with an aldehyde group at the 4 position. Knoevenagel condensation of 3-(2,3-dihydro-3-methyl-2-oxo-3*H*-benzoxazole-6-yl)-1-phenyl-1*H*-pyrazole-4-carboxy aldehyde **54** with malonic acid in pyridine, using both conventional and microwave irradiation methods, gave α,β-unsaturated carboxylic acid **55**. By treatment of **55** with appropriate amines in the presence of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDCI) and dimethylaminopyridine (DMAP), which was used as the carboxylate activator, the resulting amide derivatives **56** were prepared in 57%-83% yields.[54]







56

R = morpholin-1-yl, $NCH_2C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, CH_2(4-FC_6H_4), CH_2(4-ClC_6H_4), pyridine-4-yl, 4-$CH_3C_6H_4$, 4-$CF_3C_6H_4$, CH_2(4-$CH_3C_6H_4$), CH_2(4-$CF_3C_6H_4$)

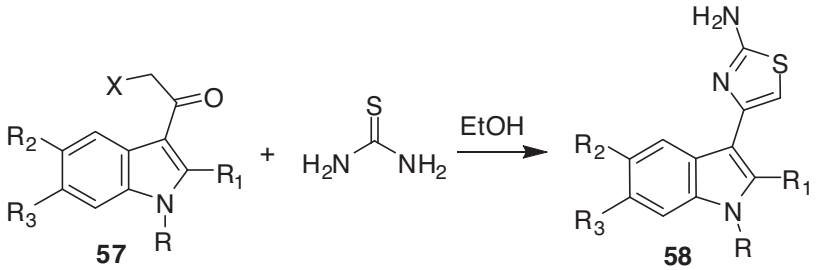
Benzazolylthiazoles

Indolylthiazoles

There are 2 important routes to synthesize indolylthiazoles: (*i*) cyclocondensation reaction between thioamides and α-haloketones and (*ii*) reaction of mercaptoacetic acids with Schiff bases.

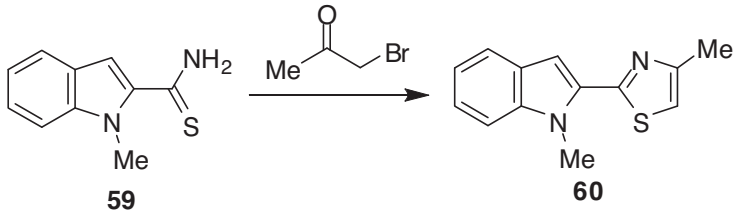
From thioamides

3-Haloacetyl-lindoles **57** were condensed with thiourea in dry ethanol to afford 3-(2-aminothiazol-4-yl)indoles **58**.[55–59]



a: R=H, alkyl; R_1= Me; R_2= MeO, R_3= X = Br
b: R=R_1=R_2=R_3=H; X = Cl

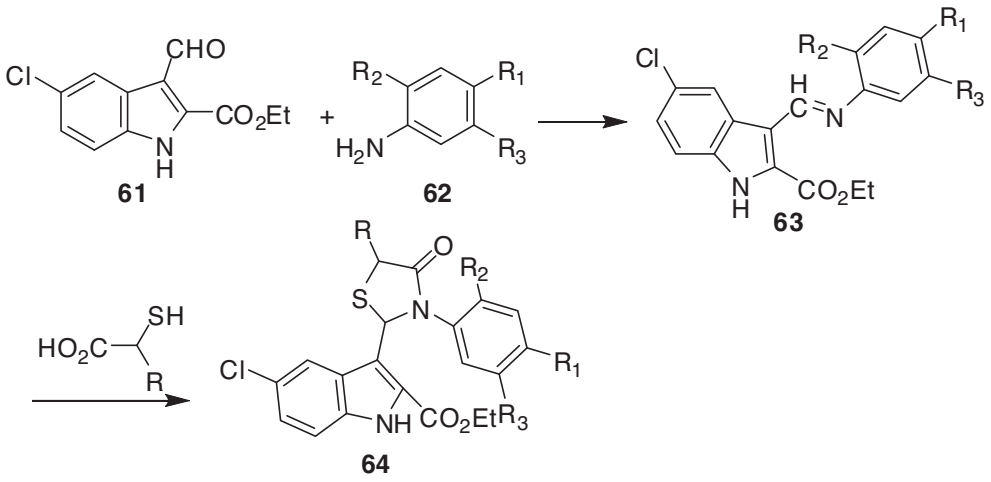
Treatment of 1-methylindole-2-thiocarboxamide **59** with bromoacetone gave indolylthiazoles **60**.[60]



59 **60**

From Schiff bases

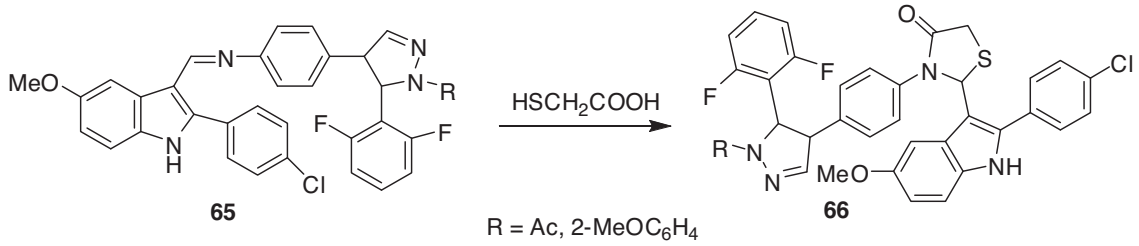
The reaction of 3-formyl-substituted-1*H*-indole-2-carboxylates **61** with substituted anilines **62** by conventional and microwave methods gave ethyl 3-(*N*-aryliminomethyl)-5-halo-1*H*-indole-2-carboxylates **63**. In a cyclocondensation reaction of these compounds with thiolacetic acid or substituted thioglycolic acid indolylthiazolidinones **64** were obtained.[61–63]



61 **62** **63** **64**

R_1= Cl, F; R_2=R_3= H; R_1= H, R_2= OH, R = R_3=H, Me

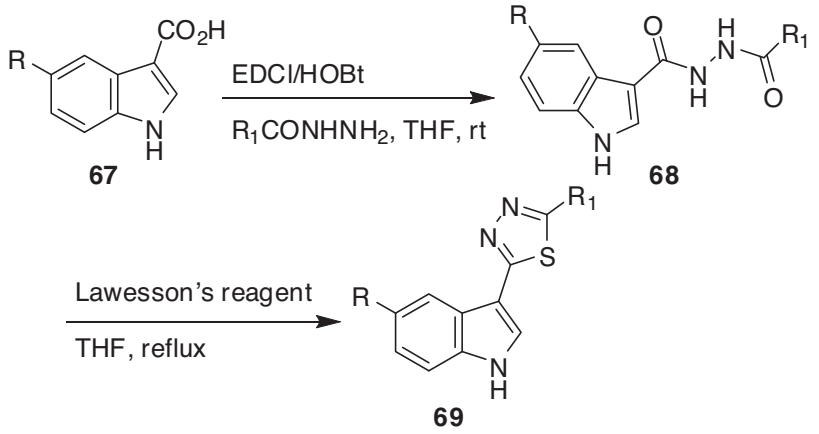
Indol-3'-yl-4'-oxo-1'-thiazolidines **66** has been synthesized by the condensation of thioglycolic acid with Schiff bases **65**.[64]



65 **66**

R = Ac, 2-MeOC$_6$H$_4$

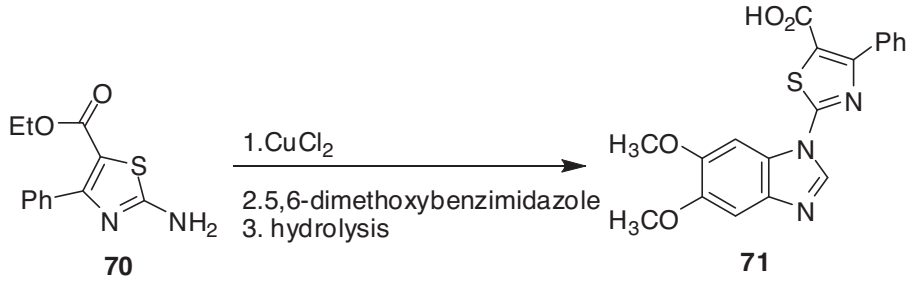
The reaction of indole-3-carboxylic acid **67** with aryl or heteroaryl hydrazides afforded the *N*,*N*'-diacylhydrazines **68**, which upon treatment with Lawesson's reagent resulted in the formation of indolyl-1,3,4-thiadiazoles **69** in good yields.[65]



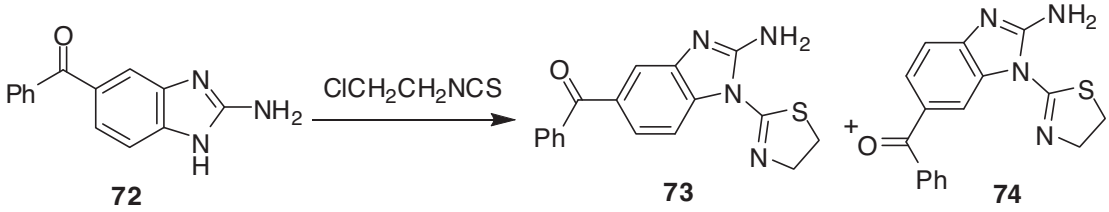
R= H, Br; R_1= Ph, benzyl, subs. phenyl, 3-pyridyl, 4-pyridyl

Benzimidazolylthiazoles

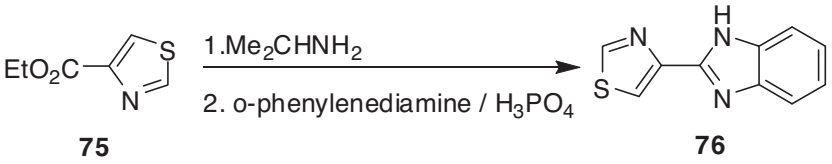
The preparation of 2-(benzimidazol-1-yl)thiazole-5-carboxylic acids **71**, whose amides and esters are useful as polo-like kinase 1 (PLK1) inhibitors for the treatment of cancer, has been reported. Sandmeyer reaction of 2-amino-4-phenylthiazole-5-carboxylic acid ethyl ester **70** with copper chloride followed by condensation with 5,6-dimethoxybenzimidazole and subsequent ester hydrolysis yielded thiazolecarboxylic acid **71**.[66]



(2-Amino-1*H*-benzo[d]imidazol-5-yl)(phenyl)methanone **72** reacted with 1-chloro-2-isothiocyanatoethane to give the 2-thiazolinylbenzimidazole isomers **73** and **74** respectively in good yields, which are useful as virucides.[67]

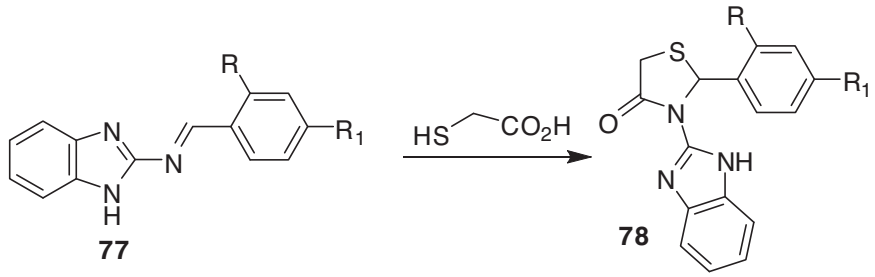


4-(2-Benzimidazolyl)thiazole **76**, useful as an anthelmintic and a medicinal fungicide, was prepared. Thus, ethyl 4-thiazolecarboxylate **75** was amidated by isopropyl amine, and cyclocondensation of the amide product with *o*-phenylenediamine in polyphosphoric acid afforded **76**.[68]



75 **76**

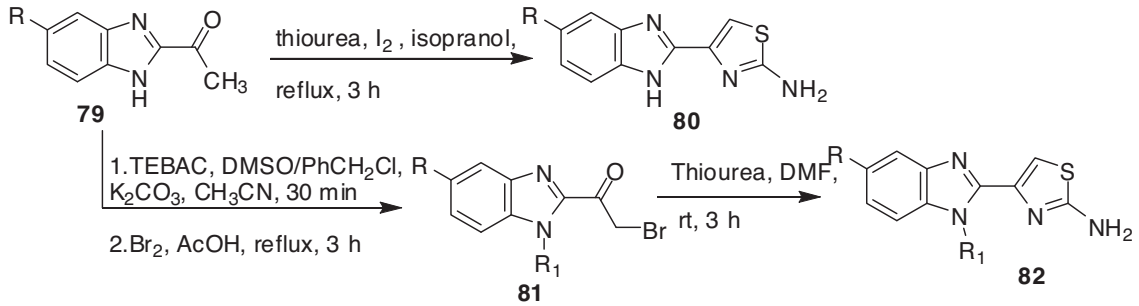
Treatment of arylideneaminobenzimidazoles **77** with thioglycolic acid gave 4-thiazolidinone **78**.[69,70]



77 **78**

R = H, R_1 = H, Cl, Br, OMe, NO_2, NMe_2; R = R_1 = OMe

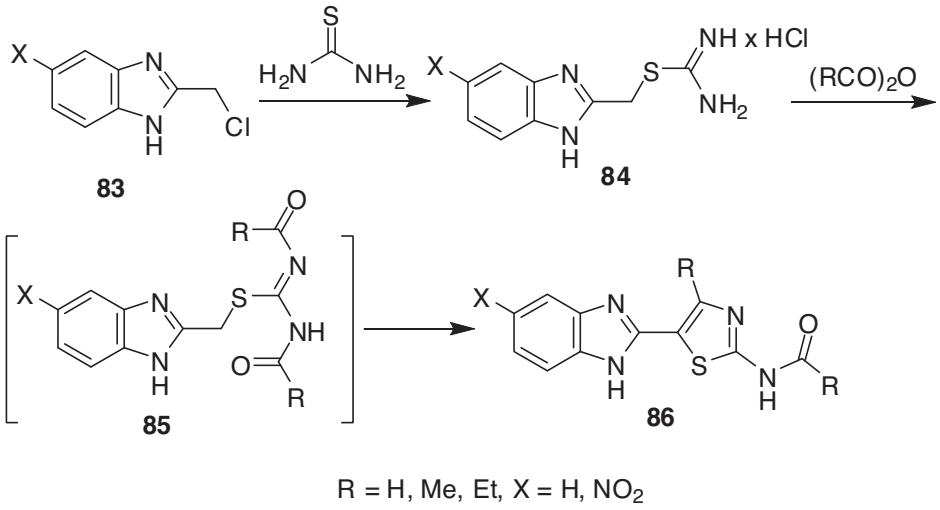
(Benz[d]imidazolyl)thiazolamines exhibited antibacterial activity comparable to std. streptomycin and benzyl penicillin and antifungal activity against fluconazole. Compounds **80** and **81** have been synthesized by the cyclocondensation of 2-acetylbenzimidiazoles **79** and 2-(bromoacetyl)-1-alkylbenzimidazoles **81** with thiourea. Thus, 2-acetyl benzimidazoles **79** on cyclocondensation reaction with thiourea under reflux in the presence of iodine and isopropanol gave 4-(1*H*- benz[d]imidazol-2yl)-1,3-thiazol-2-amines **80**. Similarly, the synthesis of 4-(1H-benz[d]imidazol-2yl)-3-alkyl-2,3-dihydro-1,3-thiazol-2-amine **82** was obtained by the cyclocondensation of 2-bromo-1-(1-alkyl-1*H*-benzo[d]imidazol-2-yl)-1-ethanone **81** with thiourea in DMF solvent under reflux. Compound **81** was achieved through α-bromination of acetyl group of 1-(1-alkyl-1*H*-benzo[d]imidazol-2-yl)-1-ethanone **79** with the mixture of molecular bromine and acetic acid.[71]



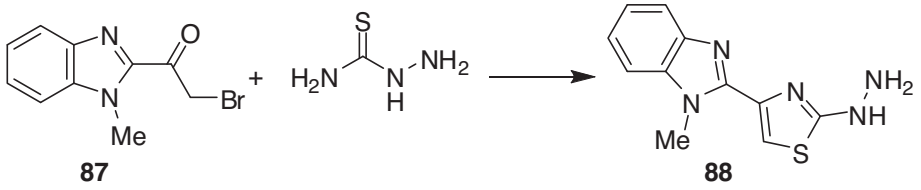
79 **80** **81** **82**

R = H, Me, Cl, NO_2; R_1 = H, Me, $PhCH_2$

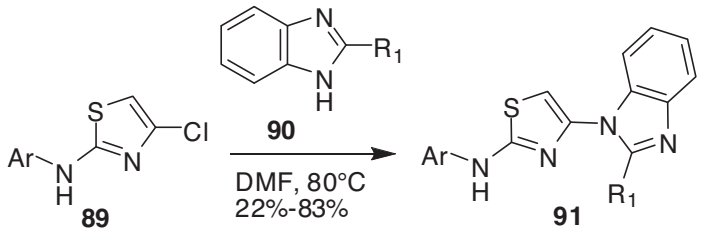
The synthesis of derivatives of 2-acylamino-5-(benzimidazol-2-yl)thiazoles **86** from 2-chloromethylbenzimidazoles **83** was achieved by the acylation of the corresponding thiuronium salts **84** followed by intramolecular cyclization of the intermediate diacetylthioureas **85**.[72,73]



2-Hydrazinyl-4-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)thiazole **88** was prepared by reaction of 2-bromoacetyl-1-methylbenzimidazole **87** and thiosemicarbazide.[74,75]



[4-(Imidazol-1-yl)thiazol-2-yl]phenylamines **91** were prepared from (4-chlorothiazol-2-yl)phenylamines **89** by nucleophilic aromatic substitution in DMF solution, using the respective benzimidazoles **90** in excess as reagents and bases.[76]



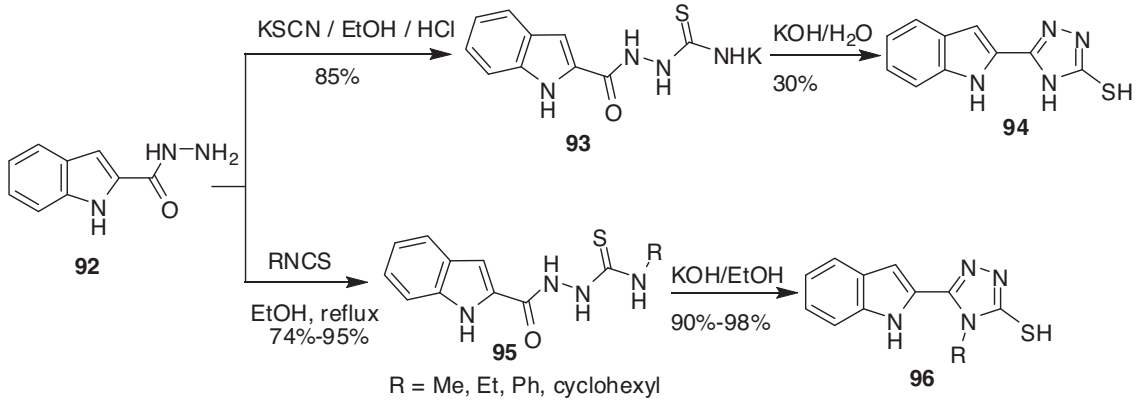
Ar = Ph, 4-BrC_6H_4, 4-$OMeC_6H_4$, 4-MeC_6H_4, 3-BrC_6H_4, 3-$OMeC_6H_4$
R_1= H, Me, 1-imidazolyl
Ar = 4-$NH_2SO_2C_6H_4$; R_1= Me

Benzazolyltriazoles

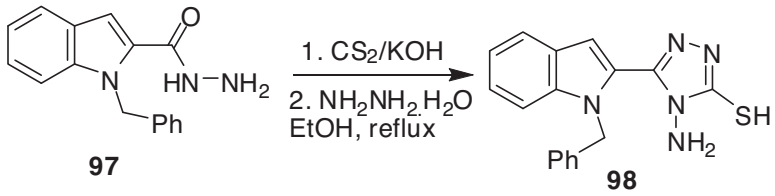
Indolyltriazoles

Indol-2-yltriazoles

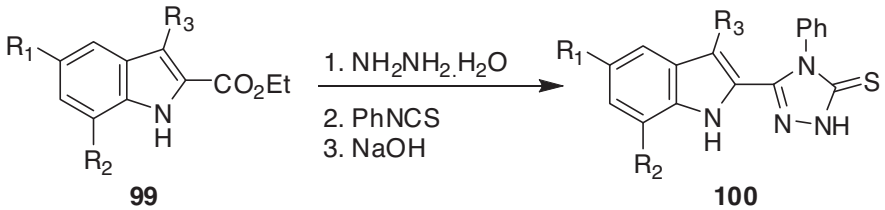
Reaction of hydrazide **92** with potassium thiocyanate in refluxing ethanol containing catalytic amounts of HCl gave the salt **93**, which was converted to **94** by heating in aqueous KOH followed by acidification with HCl in good yield. When **92** was refluxed with equimolar amounts of alkyl/arylisothiocyanates in ethanol the corresponding thiosemicarbazide derivatives **95** were obtained in high yields. Cyclization of **95** using an aqueous solution of KOH followed by neutralization with HCl furnished **96** in excellent yields.[77]



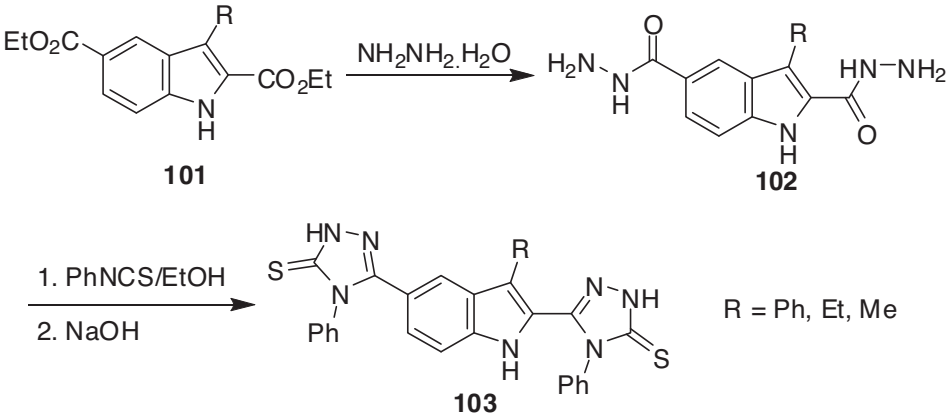
Reactions of indole hydrazide **97** with carbon disulfide in the presence of potassium hydroxide followed by treatment with hydrazine hydrate cyclized to give aminotriazolylindole **98**.[78]



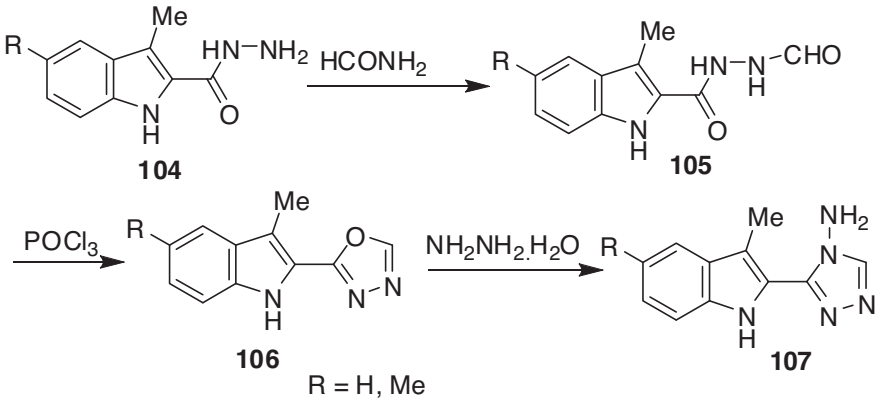
Ethyl substituted indole-2-carboxylates **99** were reacted with hydrazine hydrate followed by condensation with phenyl isothiocyanate and treatment with sodium hydroxide to yield 2-(5'-mercapto-4'-phenyl-1',2',4'-triazol-3'-yl)indoles **100**.[79–82]



Diethyl indole-2,5-dicarboxylates **101** were reacted with hydrazine hydrate to give the substituted indole-2,5-dicarbohydrazides **102**. Reaction of the latter with phenyl isothiocyanate followed by cyclization with sodium hydroxide afforded 2,5-bis(1-phenyl-5-mercapto-1,2,4-triazol-3-yl)indoles **103**.[83]

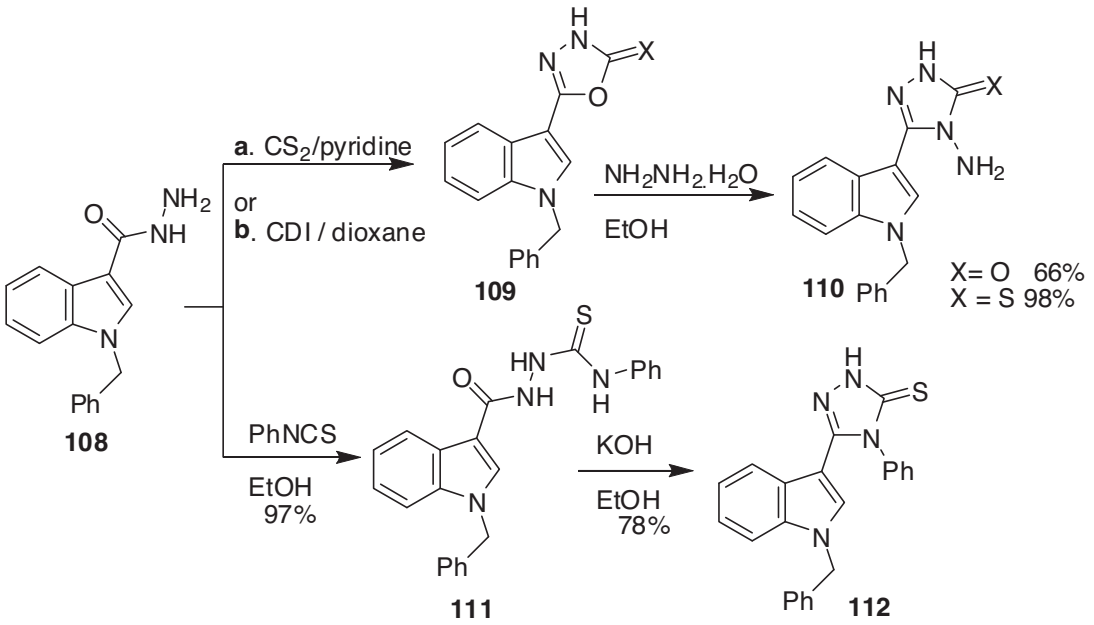


Substituted indole-2-carbohydrazides **104** are formylated using formamide to get *N*'-formylindole-2-carbohydrazides **105** in good yields, which are cyclized using phosphorus oxychloride to the corresponding 1,3,4- oxadiazolylindoles **106**. Treatment of **106** with hydrazine hydrate yields the 1,3,4-triazolylindoles **107**.[84]

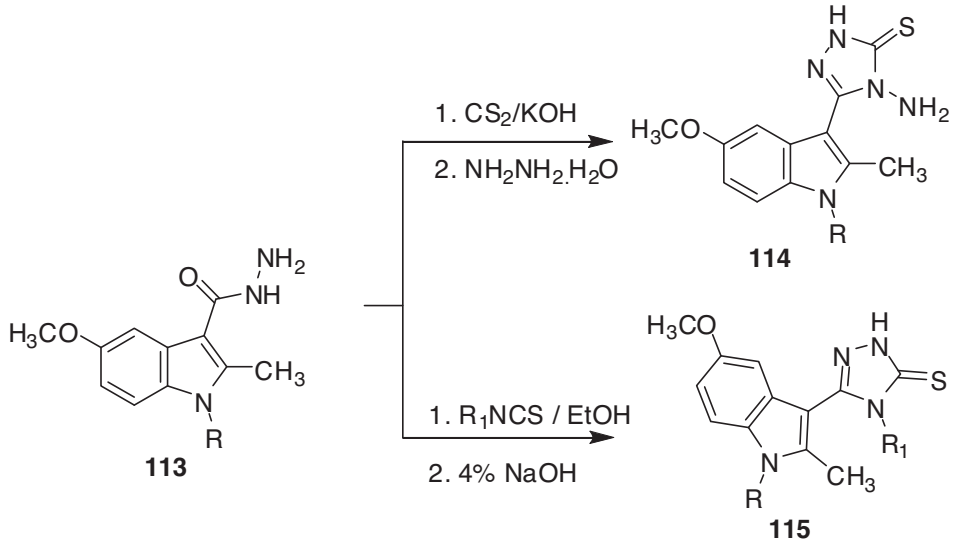


Indol-3-yltriazoles

Reaction of indole-3-carboxylic acid hydrazide **108** with carbon disulfide in boiling pyridine gave the corresponding oxadiazolthione (**109**, X=S) in 87% yield. Moreover, the oxadiazolone (**109**, X=O) was accomplished in 93% yield by treatment of the hydrazide **108** with 1,1'-carbonyldiimidazolyl (CDI) in refluxing dioxane. The amino triazolo derivatives **110** were obtained by treatment of oxadiazolo derivatives **109** with hydrazine hydrate via ring opening reaction. When compound **108** was reacted with phenyl isothiocyanate, *N*'-(1-benzyl-1*H*-indol-3-oyl)-N4-phenylthiosemicarbazide **111** was separated. The latter compound was cyclized by refluxing with an ethanolic potassium hydroxide solution to give the s-triazolthione **112**.[85,86]

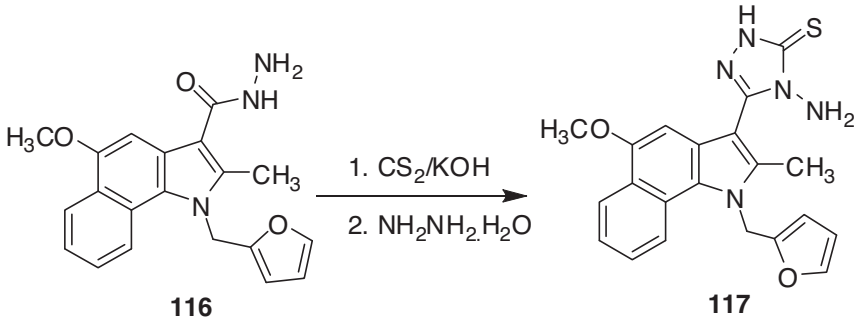


Indolyltriazoles **114** were prepared by reaction of hydrazides **113** with carbon disulfide and potassium hydroxide followed by cyclization with hydrazine hydrate. Furthermore, 3-(5-mercapto-1,2,4-triazol-3-yl)-5-methoxy-2-methylindoles **115** were prepared from reaction of hydrazides **113** with aryl isothiocyantes followed by heating with 4% NaOH.[87]



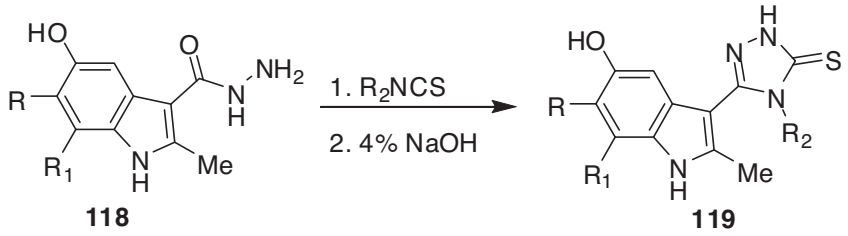
R = Ph, 4-MeC$_6$H$_4$, 2-furylmethyl; R$_1$ = Ph, allyl

Substituted 5-methoxy-3-hydrazinocarbonyl-2-methylindoles **116** were reacted with carbon disulfide in alc. KOH, followed by hydrazine hydrate to afford 5-methoxy-3-(5-mercapto-1,3,4-oxadiazol-2-yl)-2-methylindoles **117**.[87]



116 **117**

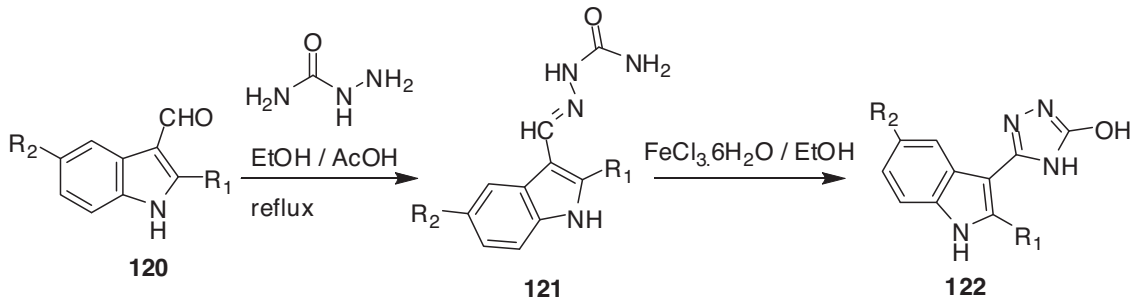
Substituted 2-methyl-5-hydroxyindole-3-carbohydrazides **118** were condensed with isothiocyanates followed by cyclization with 4% NaOH to give (1',3',4'-triazol-2'-yl)indoles **119**.[88]



118 **119**

R = R_1 = H, RR_1 = CH:CHCH:CH; R_2 = Me, Ph

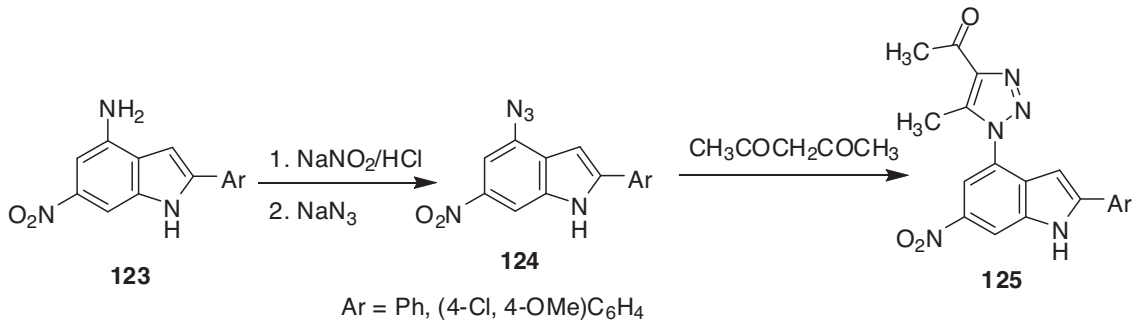
2,5-Disubstituted indol-3-carboxaldehydes **120** were condensed with semicarbazide in ethanol with a catalytic amount of glacial acetic acid to afford semicarbazones **121**. The semicarbazones **121** on reaction with ferric chloride hexahydrate in ethanol produced 3-hydroxy-5-(2',5'-disubstituted indol-3'-yl)-1,2,4-triazoles **122**.[89]



120 **121** **122**

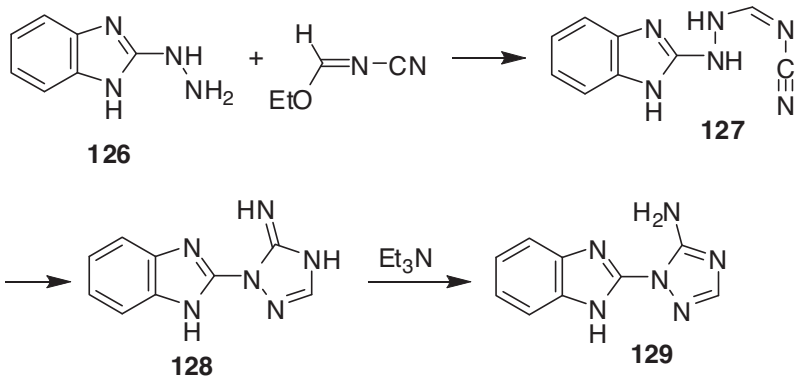
Indol-4-yltriazoles

The synthesis of 2-aryl-6-nitro-4-(vic-triazol-1-yl)-1H-indoles **125** was reported from 4-aminoindole derivatives **123** by diazotization followed by reaction with sodium azide to afford 5-azidoindole derivatives **124** and condensation of the latter with acetyl acetone.[90]

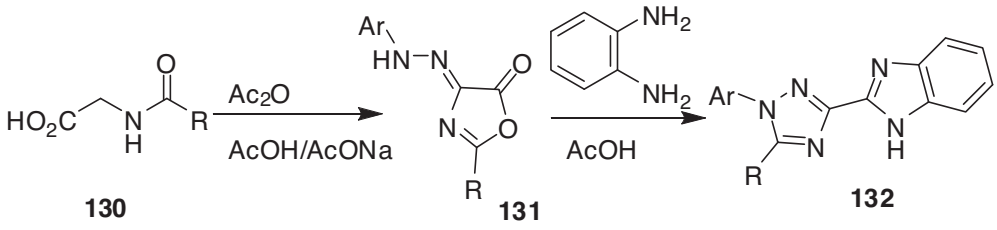


Benzimidazolyltriazoles

The interaction of ethyl *N*-cyanoformimidate with 2-hydrazinobenzimidazole **126** in triethylamine gave 1-(1*H*-benzo[d]imidazol-2-yl)-1*H*-1,2,4-triazol-5-amine **129**.[91,92]



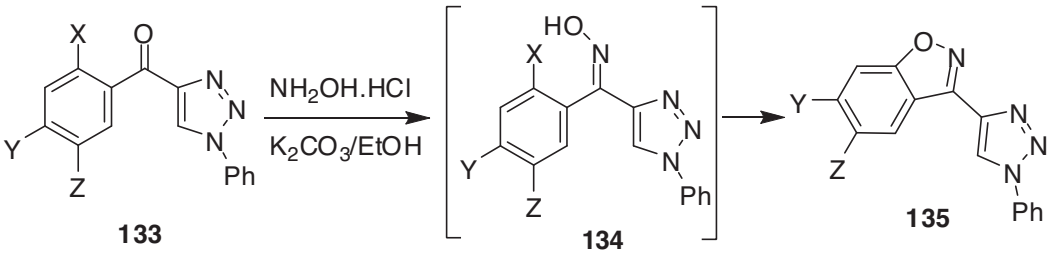
1,2,4-Triazolylbenzimidazoles **132** were prepared, in good yields, by action of acetic anhydride on *N*-acylglycines **130** followed by reaction with 1,2-phenylenediamine.[93]



R= Me; Ar= 4-HOC6H4 71%
R= Ph; Ar= 4-MeC6H4 78%

Triazolylbenzoisoxazoles

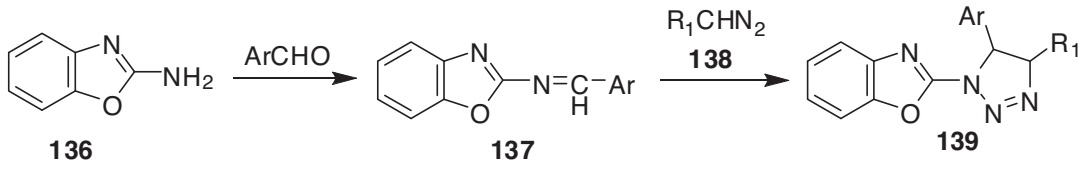
Aryl triazolyl ketones **133** were cyclized with hydroxylamine hydrochloride to yield 3-(1-phenyl-1,2,3-triazole-4-yl)benzisoxazoles **135**.[94]



X = halo; Y = H, halo, MeO; Z = H, halo

Benzoxazolyltriazoles

2-Aminobenzoxazole **136** was condensed with aromatic aldehydes to give the benzylideneaminobenzoxazoles **137**, which underwent cyclocondensation or cycloaddition with diazomethane (**138**, R_1 = Me) or 2-diazopropane (**138**, R_1 = Et) to give the triazolines **139**.[95]



Ar = [o-, m-, p-NO_2, p-MeO, p-Cl, p-HO, o-HO]C_6H_4; R_1 = H, Me

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