Recent advances on the synthesis of azoles, azines and azepines fused to benzimidazole

Kamal M. Dawood,^{a,*} Nehal M. Elwan,^a and Bakr F. Abdel-Wahab^b

^aDepartment of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt

^bDepartment of Chemistry, Faculty of Science and Arts, King Abdulaziz University, Khulais Branch, Saudi Arabia

E-mail: dr_dawood@yahoo.com

Abstract

The current review article represents a survey covering the literatures on azoles, azines and azepines fused to the *a* face of a benzimidazole moiety since 1980. Synthetic routes leading to benzimidazole fused with different ring systems; five-, six-, and seven-membered heterocyclic rings, containing one-, two- and three-heteroatoms were reported utilizing simple reactive benzimidazole synthons

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1. Introduction

In the recent years, many biologically active fused benzimidazoles exhibiting interesting medicinal properties for the potential treatment of human diseases have been disclosed. For example, pyrrolobenzimidazoles,¹⁻⁵ thiazolobenzimidazoles,⁶ pyrimidobenzimidazoles,⁷ and pyridobenzimidazoles⁸ were reported as potent antitumor agents. Furthermore, pyrrolobenzimidazoles,⁹ pyridobenzimidazoles,¹⁰ were found to be useful in treating central nervous system disorder. Pyridobenzimidazoles have also anxiolytic activity in humans,¹¹⁻¹³ and pyrimidobenzimidazoles were anti-rheumatic agents.¹⁴ Also, 1,2,4-triazinobenzimidazoles were found to be aldose reductase inhibitors¹⁵ and to possess antimicrobial activity.¹⁶

There are a large number of pharmacologically interesting benzimidazole molecules fused to a five membered rings containing one heteroatom (pyrrolobenzimidazoles), two heteroatoms (pyrazolo-, imidazo-, oxazolo-, and thiazolo-benzimidazoles) and three heteroatoms (triazolo-, thiadiazolo- and oxadiazolo-benzimidazoles). Also, several benzimidazole moieties are fused to a six membered ring containing one heteroatom (pyridobenzimidazoles), two heteroatoms (pyrimido-, pyrazino-, thiazino-benzimidazoles) and three heteroatoms (triazinobenzimidazoles). Seven membered rings fused to benzimidazole (azepino-, diazepino-, triazepino- and thiazepino-benzimidazoles) are also well known.

As a continuation of our very recently published review article concerning the synthesis of benzimidazole-based polyheterocycles,¹⁷ herein we wish to publish our current review reporting the numerous publications declaring various synthetic routes to the benzimidazole-based triheterocycles that are mentioned above, since 1980, utilizing simple reactive benzimidazole synthons.

2. Synthesis of Azolo-fused-benzimidazoles

2.1. Pyrrolobenzimidazoles

3-Hydroxypyrrolo[1,2-*a*]benzimidazoles **3** were prepared by Michael-type addition of benzimidazole **1** to α,β -unsaturated carbonyl compounds **2** in refluxing dioxane in the presence of Et₃N (Scheme 1).¹⁸

Scheme 1

Treatment of 1-benzyl-1*H*-benzimidazole **4** with phenacyl bromide **5** gave the benzimidazolium salt **6**. An oxidant promoted 1,3-dipolar cycloaddition of **6** to activated alkenes was developed for the preparation of 4*H*-pyrrolo[1,2-*a*]benzimidazole derivatives **7** in moderate yields under mild conditions. In the presence of a suitable oxidant, alkenes could be used as dipolarophiles successfully. Moreover, $\text{CrO}_3/\text{Et}_3\text{N}$ has been proved to be a more effective dehydrogenating reagent than MnO_2 (Scheme 2).¹⁹

Scheme 2

Reaction of 1-benzyl-1*H*-benzimidazole **4** with 2-(bromoacetyl)thiophene **8** gave the benzimidazolium salt **9** which on treatment with activated acetylenes **10** resulted in the formation of thenoylpyrrolo[1,2-*a*]benzimidazole derivatives **11** (Scheme 3).²⁰

Scheme 3

Alkylation of 2-benzylbenzimidazole **12** with propargyl bromide **13** in refluxing ethanol gave

1-(2-propynyl)-2-benzylbenzimidazole **14** which upon treatment with KOH in THF at 20 °C gave pyrrolo[1,2-*a*]benzimidazole derivative **15** in 81% yield. Treatment of **14** with MeI in ethanolic KOH gave 2-methylpyrrolo[1,2-*a*]benzimidazole **16** (Scheme 4).²¹

Scheme 4

Fusion of 2-cyclopropylbenzimidazoles **17** with ammonium iodide at 150 °C with no solvent resulted in the formation of a mixture of the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazoles **18** and **19**. Yield and reaction time was greatly affected by the type of electron withdrawing and electron donating groups R¹ and R² (Scheme 5).²²

Scheme 5

The reaction of 2-benzyl-1-dialkylaminoethylbenzimidazoles **20** with phenacyl bromides **5** in refluxing acetone gave the quaternary salts **21** in high yields. Cyclization of the salts **21** proceeded smoothly upon boiling in water in the presence of sodium carbonate to give the pyrrolo[1,2-*a*]benzimidazoles **22** (Scheme 6).²³

Scheme 6

Rhodium-catalyzed microwave irradiation of *N*-allyl benzimidazoles **23** using 5 mol% of $[\text{RhCl}(\text{coe})_2]_2$ (coe = *cis*-cyclooctene) in the presence of tricyclohexylphosphine hydrochloride (HClPCy_3) gave the corresponding dihydropyrrolobenzimidazoles **24** in moderate to excellent yields after 20 min (Scheme 7).²⁴

Scheme 7

Cyclization of the amidine **25** with strong base such as sodium methoxide in DMF at 150 °C was reported to give the pyrrolo[1,2-*a*]benzimidazole **26** in 75% yield *via* loss of HF (Scheme 8).²⁵

Scheme 8

Pyrrolo[1,2-*a*]benzimidazolium salt **28** was prepared in high yield and selectivity from the catalytic ring closing of 1-(3-butenyl)-3-methylbenzimidazolium bromide **27** using nickel dicyclooctadiene, $\text{Ni}(\text{COD})_2$, as catalyst in DMF at 70 °C (Scheme 9).²⁶ The reaction proceeded

through azolium, C2–H, oxidative addition to Ni(0) followed by intramolecular insertion of the N-alkenyl double bond into the Ni hydride to give an intramolecularly bound carbene–Ni–alkyl intermediate **A**. Reductive elimination of the linked carbene and alkyl groups **B** gave the fused-ring azolium product **28** and regenerated the Ni(0) catalyst. The catalyst was formed *in situ* from Ni(COD)₂ and ligand L (where L = IMes, SMes, PPh₃, PCy₃, PCy₂(biphenyl), P(t-Bu)₃ in DMF.²⁶

Scheme 9

The *N*-arylpyrrolidine derivative **29** was cyclized to pyrrolo[1,2-*a*]benzimidazole **26** in low yield by heating in formic acid in the presence of hydrogen peroxide at 70 °C (Scheme 10).²⁷

Scheme 10

Treatment of 3-(*N*-pyrrolidinyl)-4-nitrotoluene **30** with ZnCl₂/Ac₂O followed by treatment with a mixture of Ac₂O, dimethylaminopyridine (DMAP) and Et₃N gave pyrrolo[1,2-*a*]benzimidazole **31** in 53% yield (Scheme 11).^{28,29}

Scheme 11

Cyclocondensation of 2-(1*H*-benzimidazol-2-yl)-4-chloro-3-oxobutanenitrile **32** in refluxing dioxane in the presence of triethylamine gave the pyrrolo[1,2-*a*]benzimidazol-2-one derivative **33** (Scheme 12).³⁰

Scheme 12

1-Carboxymethylbenzimidazolium chlorides **34** were converted into 4-methyl-4*H*-pyrrolo[1,2-*a*]benzimidazol-2(1*H*)-one derivatives **35** in fair yields by treating **34** with *N,N'*-carbonyldiimidazole (CDI) in DMF at room temperature followed by addition of Et₃N and heating the mixture at 70 °C for 5 h (Scheme 13).³¹

Scheme 13

Reaction of *o*-phenylenediamines **36** with maleic anhydrides **37** gave *N*-(*o*-aminophenyl)-maleimides **38** which were cyclized to give pyrrolobenzimidazoles **39** (Scheme 14).³²

Scheme 14

Cyclocondensation of γ -lactones **40** with *o*-phenylenediamine **36** in refluxing aq. HCl gave the benzimidazoles **41** which were cyclized by thionyl chloride in DMF to give pyrrolobenzimidazoles **42**. Pyrrolobenzimidazoles **44** were prepared by condensing *o*-phenylenediamine with 2-alkyl-4-oxopentanoic acid **43** at 180-200 °C (Scheme 15).³³

Scheme 15

Reaction of benzimidazolium salts **45** with aq. NaHCO₃ afforded the pyrrolobenzimidazole derivatives **46** (Scheme 16).³⁴

Scheme 16

Inaba *et al.* reported the ring-opening reaction of cyclopropane dicarboxylate **48** on heating with 2-chlorobenzimidazole **47** in *N*-methylpyrrolidine (NMP) at 120 °C using sodium hydride to provide the pyrrolo[1,2-*a*]benzimidazole derivative **49** in 56% yield (Scheme 17).³⁵

Scheme 17

Reaction of 1-but-3-enylbenzimidazole **50** with xanthates **51** using 10-camphorsulfonic acid (CSA) in dichloromethane (DCM) under reflux condition gave the pyrrolo[1,2-*a*]benzimidazole derivatives **52** in 37-57% yields. The reaction proceeded *via* radical chain mechanism initiated by a small amount of lauroyl peroxide to give **52** (Scheme 18).³⁶

Scheme 18

1,3-Dipolar cycloaddition reaction between fluorinated vinyl tosylate and the benzimidazolium salts **53** afforded 4*H*-pyrrolo[1,2-*a*]benzimidazoles **55** (Y = H) in 10-68% yields *via* elimination of TsOH and HF molecules from the 3+2 cycloadduct intermediates **54** (Scheme 19).³⁷ Benzimidazolium bromide **53** reacted also with 1-chloro-1,2,2-trifluoroethene to produce **55** (Y = F) in 45-80% yields *via* elimination of HCl and HF molecules from the intermediate **54** (Scheme 19).³⁸

Scheme 19

Condensation of ethyl 2-thienoylpyruvate **56** with *o*-phenylenediamine **36** in glacial acetic acid under reflux gave the corresponding 2-[(2-thienoyl)acetyl]benzimidazole **57**. Pyrrolo[1,2-*a*]benzimidazole derivative **58** was prepared in 58% *via* heating of compound **57** with phosphorus oxychloride on a water bath (Scheme 20).³⁹

Scheme 20

Reaction of 2-cyanomethylbenzimidazole **59** with hydrazonoyl halides **60** in the presence of triethylamine apparently led to the formation of pyrrolo[1,2-*a*]benzimidazoles **61** via the initial exocyclic *C*-attack (Scheme 21).⁴⁰ However, later Awadallah *et al.* repeated the above reaction and they found that the product was 3-arylazo-2-methylpyrrolo[1,2-*a*]benzimidazoles **62** rather than 2-arylazo-3-methylpyrrolo[1,2-*a*]benzimidazoles **61** based on X-ray crystallography via the initial endocyclic *N*-attack (Scheme 21).⁴¹

Scheme 21

Pyrrolo[1,2-*a*]benzimidazol-2-amine derivative **64** was prepared in a moderate yield by reaction of 2-cyanomethylbenzimidazole **59** with oxalbis(*p*-tolylimido)yl dichloride **63** in toluene in the presence of triethylamine at room temperature (Scheme 22).⁴² Furthermore, treatment of 2-methylbenzimidazole **65** with *n*-butyl lithium in THF at 0 °C followed by addition of **63** resulted in the formation of 1-arylimino-1*H*-pyrrolo[1,2-*a*]benzimidazole-2-amines **66** in moderate yields (Scheme 22).⁴³

Scheme 22

When a mixture of the benzimidazolium bromide **53** and methyl acrylate in DMF in the presence of triethylamine was treated with chromium trioxide, the 4-methylpyrrolo[1,2-*a*]benzimidazole-1,3-dicarboxylate **67** was isolated in a good yield (Scheme 23).⁴⁴

Scheme 23

Heating the benzimidazolium salts **68** with aqueous sodium carbonate in the presence of sodium bisulfite gave 2-phenylpyrrolo[1,2-*a*]benzimidazoles **69** in low yields (Scheme 24).⁴⁵

Scheme 24

Reaction of benzimidazole-2-carboxaldehyde **70** with *trans*-1-amino-2,3-diphenylaziridine **71** gave 1-[1-allyl-1*H*-benzimidazol-2-yl-methylidene]-2,3-diphenyl-1-aziridinamine **72** which underwent thermolysis facilitated intramolecular 1,3-dipolar cycloaddition followed by loss of N_2 to give the cyclopropapyrrolo[1,2-*a*]benzimidazole **73** (Scheme 25) in excellent yield.⁴⁶

Scheme 25

2.2. Pyrazolobenzimidazoles

1-Amino-3-alkylbenzimidazolethione **74** was transformed to 1-amino-3-alkyl-2-(methylthio)benzimidazolium salt **75** upon treatment with methyl iodide. The latter salt reacted with different active methylenes to give the corresponding 2-substituted methylenebenzimidazoline derivatives **76** which underwent base or acid catalyzed cyclization to give 2-aminopyrazolo[1,5-*a*]benzimidazoles **77** and pyrazolo[1,5-*a*]benzimidazol-2-ones **78**, respectively. Compounds **78** underwent *N*- and *O*-methylation when treated with methyl iodide under basic condition to give the corresponding pyrazolo[1,5-*a*]benzimidazoles **79** and **80** (Scheme 26).⁴⁷

Scheme 26

Acylation of 1-amino-2-methylbenzimidazole **81** with acetic anhydride gave the *N,N*-diacylated derivative **82**. The latter was alkylated with alkyl iodide to give benzimidazolium salts **83** which were cyclized with acetic anhydride to give pyrazolobenzimidazoles **85** in good yields. Pyrazolobenzimidazoles **85** were alternatively obtained *via* alkylation of 1-amino-2-methylbenzimidazole **81** with alkyl iodide to give benzimidazolium salts **84** followed by reflux in acetic anhydride (Scheme 27).⁴⁸ 3-(α -Bromoacetyl)pyrazolo[1,5-*a*]benzimidazole **86** was obtained by brominating 3-acetylpyrazolo[1,5-*a*]benzimidazoles **85** with bromine in AcOH (Scheme 27).⁴⁹

Scheme 27

Treatment of 1-amino-2-methylbenzimidazolium chlorides **87** with acetic anhydride in the presence of potassium carbonate under reflux afforded a mixture of pyrazolo[1,5-*a*]benzimidazoles **88** and pyrrolo[1,2-*a*]benzimidazoles **89** (Scheme 28).⁵⁰

Scheme 28

Pyrazolo[1,5-*a*]benzimidazoles **92** were prepared in moderate yields by reacting 1-aminobenzimidazole derivative **90** with phenacyl bromides **5** to form the thiadiazino-, and selenadiazino-benzimidazoles **91**, which underwent ring contraction to give **92** (Scheme 29).^{51,52}

Scheme 29

Ring contraction of 1,2,4-triazepino[2,3-*a*]benzimidazol-4-ones **93** in acetic anhydride afforded pyrazolo[1,5-*a*]benzimidazole derivatives **96** in low to high yields probably according to the mechanism depicted in Scheme 30.⁵³

Scheme 30

Free radical oxidation of anilinopyrazoles **97** by dibenzoyl peroxide or lead(IV) oxide resulted in the formation of the pyrazolo[1,5-*a*]benzimidazoles **98** in moderate yields (Scheme 31).⁵⁴

Scheme 31

4*H*-Pyrazolo[1,5-*a*]benzimidazoles **100** were prepared in moderate to good yields by hydrogenation of the hydrazones **99** in acetic acid containing Pt-metal (Scheme 32).⁵⁵

Scheme 32

When 5-amino-1-(*o*-chlorophenyl)pyrazoles **101** were heated with copper(II) oxide in DMF and anhydrous K_2CO_3 , the 4*H*-pyrazolo[1,5-*a*]benzimidazoles **102** were formed. Treatment of **102** ($R = \text{CN}$) with sodium azide gave 3-(tetrazol-5'-yl)-4*H*-pyrazolo[1,5-*a*]benzimidazole **103**. Basic hydrolysis of **102** ($R = \text{CO}_2\text{Et}$) led to 4*H*-pyrazolo[1,5-*a*]benzimidazole-3-carboxylic acid **104**. When **104** was heated above its melting point *in vacuo*, it smoothly decarboxylated to give the parent 4*H*-pyrazolo[1,5-*a*]benzimidazole **105** (Scheme 33).⁵⁶

Scheme 33

Flash vacuum pyrolysis (FVP) of 1-(2-azidophenyl)pyrazoles **106** or photolysis at 254 nm in ethanol and diethylamine gave the pyrazolo[1,5-*a*]benzimidazoles **105** in reasonable yields *via* the intermediate 2-(1-pyrazolyl)phenylnitrene **107** (Scheme 34).^{57,58}

Scheme 34

The hydrazine derivative **108** was cyclocondensed with ethyl 3-ethoxy-3-iminopropanoate hydrochloride **109** to give the ethoxypyrazolinone derivative **110** which was hydrogenated in acetic acid in the presence of Pd/C and then cyclized by refluxing in HOAc after removal of Pd/C to give the pyrazolobenzimidazole derivative **111** (Scheme 35).⁵⁹

Scheme 35

2.3. Imidazobenzimidazoles

Imidazo[1,5-*a*]benzimidazole derivative **113** was prepared by reaction of 2-aminomethylbenzimidazole **112** with acetic anhydride (Scheme 36).⁶⁰

Scheme 36

Reaction of 1,2-diaminobenzimidazole **114** with one equivalent of 1-phenyl-2-bromo-3-phenylpropanone **115** in methanol led to the formation of 2-phenyl-3-benzyl-9-aminoimidazo[1,2-*a*]benzimidazole **116** (Scheme 37).⁶¹

Scheme 37

Treatment of 2-aminobenzimidazole **117** with ethyl bromopyruvate **118** in THF at room temperature followed by reflux in ethanol gave the imidazo[1,2-*a*]benzimidazole **119** in low yield (Scheme 38).⁶²

Scheme 38

2-(Chloromethyl)imidazo[1,2-*a*]benzimidazole **122** was prepared by condensation of 1-methyl-2-aminobenzimidazole **120** with 1,3-dichloroacetone **121** (Scheme 39).⁶³

Scheme 39

Treatment of 2-aminobenzimidazole **117** with 2-bromoacetaldehyde diethylacetal in a solution of NaOMe in MeOH under reflux gave 2-amino-1-(2,2-diethoxyethyl)benzimidazole **123**. Refluxing the latter compound **123** in HCl afforded imidazo[1,2-*a*]benzimidazole **124** which on treatment with dimethyl sulfate in aq. NaOH gave a mixture of 1-methylimidazo[1,2-*a*]benzimidazole **125** and 9-methylimidazo[1,2-*a*]benzimidazole **126** (Scheme 40).⁶⁴

Scheme 40

When 2-aminobenzimidazole **117** was refluxed with 2-bromoacetylnaphthalene or 3-bromoacetylpyrazole derivatives **127** or **128** in ethanol, it afforded the 1*H*-imidazo[1,2-*a*]benzimidazole derivatives **129** and **130**, respectively, in good yields (Scheme 41).^{65,66}

Scheme 41

Photolysis of 1-(4,5-dihydro-1*H*-imidazol-2-yl)benzotriazole **131** in acetonitrile at 254 nm for 18 h gave dihydroimidazo[1,2-*a*]benzimidazole **133** in good yield. The reaction took place via the diradical intermediate **132** (Scheme 42).⁶⁷

Scheme 42

Treatment of the diimidoyl dichlorides **63** with 2-aminobenzimidazole **117** in refluxing THF in the presence of Et₃N resulted in the formation of the 3*H*-imidazo[1,2-*a*]benzimidazol-2-

amines **134** in good yield. Acylation of the latter **134** (Ar = 4-tolyl) with acetyl chloride in the presence $\text{NaN}(\text{SiMe}_3)_2$ at low temperature gave 9-acetyl-3*H*-imidazo[1,2-*a*]benzimidazole **135** in 53% yield (Scheme 43).⁶⁸

Scheme 43

2-Aminobenzimidazolium bromides **137** were formed by reaction of *o*-(*N*-aryl)phenylenediamines **136** with cyanogen bromide in ethanol at 150°C, followed by alkylation with ethyl bromoacetate in acetone at reflux. Condensation with acid anhydrides along with their respective sodium salts afforded the imidazo[1,2-*a*]benzimidazole esters **138** (Scheme 44).⁶⁹

Scheme 44

Treatment of hydrazonoyl bromides **139** with 2-aminobenzimidazole **117** in refluxing ethanol furnished 3-arylazo-1*H*-imidazo[1,2-*a*]benzimidazoles **140** (Scheme 45).⁷⁰

Scheme 45

2-Azidomethylbenzimidazole **141** reacted with benzoyl chlorides and gave the benzoyl(azidomethyl)benzimidazoles **142** which reacted with tributylphosphine to give the corresponding 3-aryl-9*H*-imidazo[1,2-*a*]benzimidazoles **143** (Scheme 46).⁷¹

Scheme 46

2,9-Disubstituted imidazo[1,2-*a*]benzimidazoles **145** were obtained regioselectively in good yields by heating a mixture of 2-aminobenzimidazole **117** and α -tosyloxy ketones **144** in acetic acid (Scheme 47).⁷²

Scheme 47

2.4. Oxazolobenzimidazoles

Reaction of 2-aminoxazoles **146** with *p*-benzoquinone **147** in acetic acid at 40-50°C for one hour gave the corresponding 6-hydroxyoxazolo[3,2-*a*]benzimidazoles **148** in moderate yields according to the mechanism shown in Scheme 48.⁷³

Scheme 48

Benzimidazo[2,1-*b*]benzoxazole **150** was prepared photolytically at 360 nm from 1-(2-benzoxazolyl)benzotriazole **149** (Scheme 49).⁷⁴

Scheme 49

3-Cyanomethylene-1,3-oxazolo[3,2-*a*]benzimidazole **153** was obtained by condensation of 2-alkylthiobenzimidazoles **151** with 4-hydroxy-4-methylpent-2-ynenitrile **152** in acetonitrile containing LiOH (Scheme 50).⁷⁵

Scheme 50

2,3-Dihydrooxazolo[3,2-*a*]benzimidazole derivatives **153** were also obtained by heating 2-aminobenzimidazoles **117** with 4-hydroxy-2-alkyenenitrile derivatives **152** in DMF probably according to the mechanism illustrated in Scheme 51.⁷⁶

Scheme 51

1-Substituted benzimidazoles **156** were readily annulated regio- and stereoselectively when treated with α,β -acetylenic- γ -hydroxy nitrile **152** under mild conditions, at 20-25°C without catalyst and without solvent, to form 3-cyanomethylene-2,2-dimethyl-1,3-oxazolo[3,2-*a*]benzimidazoles **157** in excellent yields (Scheme 52).⁷⁷

Scheme 52

The reaction of 2-chloro-1-phenacylbenzimidazole **158** with sodium benzoate, as a base, in DMF gave 2-phenyloxazolo[3,2-*a*]benzimidazole **159** in 76% yield (Scheme 53).⁷⁸

Scheme 53

Condensation of *o*-phenylenediamine **36** with (*S*)-lactic acid in 4*N* HCl at reflux gave 2-(hydroxyethyl)benzimidazole **160** in 85% yield. Heating the latter compound **160** with benzaldehyde dimethyl acetal using a catalytic amount of *p*-toluenesulfonic acid gave the oxazolo[3,4-*a*]benzimidazole derivative **161** (Scheme 54).^{79,80}

Scheme 54

Heating a mixture of 2-(hydroxymethyl)benzimidazole **162** and benzaldehyde dimethyl acetals **163** in dry toluene and a catalytic amount of *p*-toluenesulfonic acid for 48 h gave the oxazolo[3,4-*a*]benzimidazole derivatives **164** (Scheme 57).⁸¹

Scheme 55

2.5. Thiazolobenzimidazoles

Reaction of hydrazonoyl bromides **139** with benzimidazole-2-thiol **165** in ethanolic triethylamine solution at reflux gave the thiazolo[3,2-*a*]benzimidazoles **166** in good yields (Scheme 56).⁸²⁻⁸⁴

Scheme 56

Benzimidazole-2-thiol **165** reacted similarly with *bis*-hydrazonoyl chlorides **167** in refluxing ethanol in the presence of triethylamine to give 2,3-*bis*-(arylhrazono)-2,3-dihydrothiazolo[3,2-*a*]benzimidazoles **168** in high yields (Scheme 57).^{85,86}

Scheme 57

Refluxing of oxal-*bis*-(arylimido)yl dichlorides **63** in THF with benzimidazole-2-thiol **165** in the presence of Et₃N afforded the thiazolo[3,2-*a*]benzimidazole derivatives **170** (Scheme 58).⁶⁸

Scheme 58

When a mixture of benzimidazole-2-thiol **165** and the maleimide derivatives **171** was heated in acetic acid in the presence of sulfuric acid, it furnished the thiazolo[3,2-*a*]benzimidazole derivatives **173** in moderate yields *via* Michael-type addition followed by ring opening of the intermediate **172** (Scheme 59).⁸⁷

Scheme 59

Thiazolo[3,4-*a*]benzimidazoles **175** were prepared by heating a mixture of *o*-phenylenediamine, 2-mercaptoacetic acid and the appropriate carbonyl compounds **174** in benzene under conventional reflux or microwave irradiation (Scheme 60).⁸⁸⁻⁹²

Scheme 60

Condensation of 2-mercaptobenzimidazoles **165** with chloroacetic acid and acetic anhydride gave the thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones **177** in good yields.⁹³⁻⁹⁶ Reaction of **165** with α -bromoketones **5** followed by polyphosphoric acid (PPA) yielded the thiazolo[3,2-

a]benzimidazoles **179**.⁹⁷⁻¹⁰² Condensation of **165** with 1,2-dibromoethane in ethanol yielded the thiazolo[3,2-*a*]benzimidazole derivatives **180** (Scheme 61).¹⁰³

Scheme 61

2,3-Dihydrothiazolo[3,2-*a*]benzimidazole **182** was prepared by condensation of 2-(1,2-dibromoethyl)pyridine **181** in DMF with 2-mercaptobenzimidazole **165** (Scheme 62).¹⁰⁴⁻¹⁰⁶

Scheme 62

Treatment of benzimidazole-2-thiol **165** with 1,3-dichloroacetone **121** gave 1-(2-benzimidazolylthio)-3-chloro-2-propanone hydrochloride **183**. Cyclization of **183** in sulfuric acid followed by basic work up provided 3-chloromethylthiazolo[3,2-*a*] benzimidazole **184**.¹⁰⁷⁻¹⁰⁹ An efficient regioselective synthesis of 2-methoxycarbonylthiazolo[3,2-*a*]benzimidazoles **186** from benzimidazole-2-thiols **165** and α -chloroaldehyde ester **185** was reported (Scheme 63).¹¹⁰

Scheme 63

Treatment of 2-(allylthio)benzimidazole **187** with iodine in CHCl₃ and then with aqueous potassium hydroxide gave the thiazolo[3,2-a]benzimidazole **188** (Scheme 64).¹¹¹

Scheme 64

2-Methoxy-7-trifluoromethyl-2,3-dihydrothiazolo[3,2-a]benzimidazole **190** was prepared in 78% yield by the intermolecular cyclization of 1-(2,2-dimethoxyethyl)-2-mercaptobenzimidazole **189** using diethyl ether-boron trifluoride in dry dichloromethane (DCM) (Scheme 65).¹¹²

Scheme 65

The reaction between 2,3-dihydro-2,2,4-trimethyl-1H-1,5-benzodiazepine **191** and mercaptoacetic acid under reflux gave the thiazolobenzimidazole derivative **193** (Scheme 66).¹¹³

Scheme 66

The reaction of benzimidazole-2-thiol **165** with bromomalononitrile **194** in cold ethanolic potassium hydroxide solution afforded 2-dicyanomethylthiobenzimidazole **195** which underwent cyclization when treated with ethanolic sodium acetate at reflux to give 3-aminothiazolo[3,2-*a*]benzimidazole-2-carbonitrile **196** (Scheme 67).¹¹⁴ Heating benzimidazole-2-thiol **165** with acetophenones in acetic acid afforded 2-benzimidazolylthioacetophenone derivatives **197** in very good yield. Reaction of **197** in acetic anhydride afforded 2-benzoyl-3-methylthiazolo[3,2-*a*]benzimidazoles **198** in high yield (Scheme 67).¹¹⁵

Scheme 67

Treatment of thiazolinethione derivative **199** with iodomethane in anhydrous acetone at room temperature afforded quantitatively the thiazolium iodide **200**. Heating **200** in methanol then treatment of the cold product with aqueous sodium bicarbonate gave 3-methylthiazolo[3,2-*a*]benzimidazole **201** in 100% yield.¹¹⁶⁻¹¹⁸ Alternatively, 3-methylthiazolo[3,2-*a*]benzimidazole **201** was obtained in 95% by refluxing **202** in ethanolic KOH solution (Scheme 68).¹¹⁹

Scheme 68

Exposure of 1-alkynyl[4-(trifluoromethyl)phenyl](tetrafluoroborato)- λ^3 -bromanes **203** to benzimidazole-2-thiol **165** in dichloromethane (DCM) at 0 °C under argon resulted in a domino Michael addition–carbene rearrangement–cyclization reaction to produce directly 3-substituted thiazolo[3,2-*a*]benzimidazoles **204** in high yields (Scheme 69).¹²⁰ The epoxyphosphonate **205** reacted with **165** in refluxing toluene in the presence of tosyl alcohol to give the thiazolo[3,2-*a*]benzimidazole **206** in good yield (Scheme 69).¹²¹

Scheme 69

2.6. Triazolobenzimidazoles

Heating benzimidazole-2-thiol **165** with hydrazonoyl halides **207** in chloroform in the presence of Et₃N gave the 1,2,4-triazolo[4,3-*a*]benzimidazoles **210** through the spiro intermediate **208** which underwent ring opening to yield the thiohydrazide **209** (Scheme 70).¹²²

Scheme 70

Similarly, the hydrazonoyl bromides **211** reacted with 2-methylthiobenzimidazole **212** in refluxing ethanol in the presence of triethylamine to give 1,2,4-triazolo[4,3-*a*]benzimidazole derivatives **213** (Scheme 71).^{70,84,123,124}

Scheme 71

3-Arylazo[1,2,4]triazolo[4,3-*a*]benzimidazoles **215** were prepared from the reaction of 3-chloro-1,5-diarylformazans **214** with 2-methylthiobenzimidazole **212** in refluxing chloroform and triethylamine (Scheme 72).¹²⁵

Scheme 72

Bis-hydrazonoyl chlorides **168** reacted with 2-methylthiobenzimidazole **212** in 1:2 molar ratio in refluxing ethanol in the presence of triethylamine to give 1,1'-diaryl-3,3'-bi-1,2,4-triazolo[4,5-*a*]benzimidazoles **216** (Scheme 73).⁸⁵

Scheme 73

Reaction of 2-aminobenzimidazole **117** with the hydrazonoyl chloride **139** gave 1-phenyl-3-acetyl-1,2,4-triazolo[4,3-*a*]benzimidazole **217** (Scheme 74).¹²⁶

Scheme 74

1,3-Dipolar cycloaddition reaction of 1-acylbenzimidazoles **218** with two equivalents of hydrazonoyl chloride **207** in refluxing benzene and Et₃N gave the triazolobenzimidazole derivatives **219** (Scheme 75).¹²⁷

Scheme 75

Reaction of 2-hydrazinobenzimidazole **220** with aromatic aldehydes **221** in refluxing ethanol afforded the corresponding arylhydrazones **222** which, in turn, were cyclized upon heating in acetic acid to afford 3-aryl-9*H*-1,2,4-triazolo[4,3-*a*]benzimidazoles **223** (Scheme 76).¹²⁸

Scheme 76

Heating 4-methyl-1,5-benzodiazepin-2-one **224** in xylene induced rearrangement into the 1-(α -methylvinyl)benzimidazole **225**. Treatment of **225** with POCl₃ gave the 2-chlorobenzimidazole derivative **226** which on reaction with sodium methoxide followed by hydrazine then triethyl *ortho*-acetate afforded the 9-(α -methylvinyl)triazolobenzimidazole **228** (Scheme 77).¹²⁹

Scheme 77

Cyclisation of 2-hydrazinobenzimidazoles **220** with CS₂ and with triethyl orthoacetate gave the corresponding triazolobenzimidazoles **229** and **230**, respectively (Scheme 78).^{130,131}

Scheme 78

Cyclization of 1,2-diaminobenzimidazolium salt **231**, by boiling it in acetic anhydride in the presence of K₂CO₃ gave the triazolobenzimidazole derivative **232** (Scheme 79).¹³²

Scheme 79

2.7. Thiadiazolobenzimidazoles

Reaction of (1-amino-1*H*-benzimidazol-2-yl)methanol **233** with thionyl chloride at reflux afforded 3-chlorobenzimidazo[1,2-*c*]-1,2,3-thiadiazolium chloride **234**. Treatment of the salt **234** with sodium bicarbonate gave 3-chlorobenzimidazo[1,2-*c*]-1,2,3-thiadiazole **235** (Scheme 80).¹³³⁻¹³⁵

Scheme 80

Condensation of 2-amino-1,3,4-thiadiazoles **236** with *p*-benzoquinone **147** in acetic acid gave 6-hydroxy[1,3,4]thiadiazolo[3,2-*a*]benzimidazoles **238** (Scheme 81).¹³⁶

Scheme 81

The reaction of 1,3,4-oxadiazolinones **239** with phosphorus pentasulfide (P_4S_{10}) in refluxing xylene gave 1,3,4-thiadiazolo[3,2-*a*]benzimidazoles **240** probably according to the mechanism shown in Scheme 82.¹³⁷ After an induction period of approximately 10 hrs, the system, P_4S_{10} -refluxing xylene, generated H_2S which, in turn, was capable of reducing the nitro group.

Scheme 82

Amidation of 2-mercaptobenzimidazole **165** by *tert*-butyl isocyanate followed by cyclization gave 2-*tert*-butyl-1,2,4-thiadiazolo[4,5-*a*]benzimidazole **241** which on treatment with nitriles afforded the 1,2,4-thiadiazolo[4,5-*a*]benzimidazoles **242** (Scheme 83).¹³⁸⁻¹⁴⁰

Scheme 83

Thermal rearrangement of 1-(1,2,3-thiadiazol-5-yl)-1,2,3-benzotriazoles **243** afforded zwitterionic [1,2,3]thiadiazolo[3,4-*a*]benzimidazol-8b-ium-4-ides **244** (Scheme 84).¹⁴¹

Scheme 84

1,2,4-Thiadiazolo[2,3-*a*]benzimidazole derivative **246** was prepared in high yield from the reaction of 1,2,4-thiadiazol-3-(2*H*)-one **245** with 2-aminobenzimidazole **117** via rearrangement of the adduct **A** through hypervalent sulfur intermediates **B** (Scheme 85).¹⁴²

Scheme 85

2.8. Oxadiazolobenzimidazoles

Refluxing 2-(1-methylbenzimidazolyl)carbonylhydroximoyl chloride **247** with 2-methylthio-benzimidazole **212** in ethanol and triethylamine gave the benzimidazo[1,2-*d*]-1,2,4-oxadiazole **248** (Scheme 86).¹⁴³

Scheme 86

3. Synthesis of Azino-fused-benzimidazoles

3.1. Pyridobenzimidazoles

Treatment of *N*-(2-azidophenyl)imines **249** with trimethylphosphine in toluene gave the phosphazenes **250**. Reaction of **250** with ketenes led to the formation of the nonisolable ketenimines **A** which underwent [4+2] intramolecular cycloaddition to give the corresponding 3-aryl-3,4-dihydropyrido[1,2-*a*]benzimidazoles **251** (Scheme 87).¹⁴⁴

Scheme 87

Cyclocondensation and ring opening of triarylpyrylium salts **252** with 2-benzimidazoleacetonitrile **59** gave pyrido[1,2-*a*]benzimidazole-4-carbonitriles **253** via loss of acetophenones probably according to the mechanism depicted in Scheme 88.¹⁴⁵

Scheme 88

Acylation of arylhydroxylamines **254** gave the *N*-acetyl derivatives **255**, which on reaction with pyridine afforded the pyrido[1,2-*a*]benzimidazoles **256** (Scheme 89).¹⁴⁶

Scheme 89

Diels-Alder cycloaddition of 3-methylthiazolo[3,2-*a*]benzimidazole **201** with dimethyl acetylenedicarboxylate (DMAD) **257** in acetonitrile gave the pyrido[1,2-*a*]benzimidazole derivative **258** in 24% yield probably according to the mechanism outlined in Scheme 90.¹⁴⁷

Scheme 90

Cyclization of benzylidene-1*H*-benzimidazol-2-ylacetonitriles **259** with activated acetonitriles in ethanol in the presence of piperidine gave pyridobenzimidazoles **260**. Compound **259** reacted also with ethyl acetoacetate and with cyanoacetohydrazide to give the pyridobenzimidazole derivatives **261** and **262**, respectively (Scheme 91).¹⁴⁸⁻¹⁵⁰

Scheme 91

Michael-type addition of 2-benzimidazoleacetonitrile **59** to chalcone **263** in ethanol and piperidine led to the formation of pyridobenzimidazole **264**. Also, analogous reaction of **59** with ethyl 2-cyanoacrylate derivative **265** yielded the pyridobenzimidazole derivative **266** in 75% yield (Scheme 92).¹⁵¹⁻¹⁵³

Scheme 92

Treatment of 2-benzimidazoleacetonitrile **59** and benzylidinemalononitriles **267** in acetonitrile containing piperidine under reflux afforded the polysubstituted pyrido[1,2-*a*]benzimidazoles **269** in moderate to good yields *via* cyclization followed by loss of hydrogen from the intermediate **268** (Scheme 93).^{154,155}

Scheme 93

Heating a mixture of 2-benzimidazoleacetonitrile **59** and β -aminocrotonitrile **270** in the presence of ammonium acetate at 130-140 °C afforded 1-amino-3-methylpyrido[1,2-*a*]benzimidazole-4-carbonitrile **271** (Scheme 94).¹⁵⁶

Scheme 94

Treatment of 2-benzimidazoleacetonitrile **59** with the phenylacetylene derivative **272** produced the pyrido[1,2-*a*]benzimidazole-4-carbonitrile derivative **273** (Scheme 95).¹⁵⁷

Scheme 95

The reaction of heteroaryl enamines **274**, **275** and **276** with 2-benzimidazoleacetonitrile **59** was conducted in refluxing ethanol in the presence of piperidine to afford the corresponding pyrido[1,2-*a*]benzimidazoles **277-279** (Scheme 96).¹⁵⁸⁻¹⁶²

Scheme 96

Pyrido[1,2-*a*]benzimidazoles **282** and **283** were synthesized by reacting 2-benzimidazoleacetonitrile **59** with the enaminones **280** and **281**, respectively, in refluxing pyridine or ethanol/piperidine (Scheme 97).¹⁶³⁻¹⁶⁶

Scheme 97

Reaction of methyl 2-benzoyl-3-dimethylaminopropenoate **284** with 2-benzimidazoleacetonitrile **59** in refluxing acetic acid in the presence of ammonium acetate gave methyl 4-cyano-3-phenylbenzimidazo[1,2-*a*]pyridine-2-carboxylate **285**.¹⁶⁷ Heating a mixture of 3-(dimethylamino)-2-(phenylsulfonyl)acrylonitrile **286** with 2-benzimidazoleacetonitrile **59** in ethanol and piperidine afforded the pyrido[1,2-*a*]benzimidazole derivative **287** (Scheme 98).¹⁶⁸

Scheme 98

Treatment of 2-benzimidazoleacetonitrile **59** with cyanamide in the presence *s*-triazine gave the enaminonitrile derivative **288** which reacted again with **59** to give pyridobenzimidazole derivative **270** (Scheme 99).¹⁶⁹

Scheme 99

Reaction of 6-aryl-3-cyano-4-methylthio-2*H*-pyran-2-ones **289** with 2-benzimidazoleacetonitrile **59** in DMF and KOH at 30 °C led to the formation of the pyrido[1,2-*a*]benzimidazole derivatives **290** in moderate yields (Scheme 100).¹⁷⁰

Scheme 100

3-Formylchromenes **291** underwent ring opening when heated with 2-benzimidazoleacetonitrile **59** in ethylene glycol at 200-210 °C to give the pyridobenzimidazoles **292** in good yields.¹⁷¹ Similar ring transformation occurred on the reaction of 2-formylglycols **293** with **59** when heated in chlorobenzene/AcOH in the presence of piperidine, to furnish the pyridobenzimidazoles **294** in moderate yields (Scheme 101).^{172,173}

Scheme 101

7,8-Difluoro-3-methyl-1-oxo-4-cyano-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole **295A** was obtained in high yield by heating a mixture of 2-benzimidazoleacetonitrile **59** with ethyl acetoacetate at 140 °C in the presence of ammonium acetate.^{174,175} Pyrido[1,2-*a*]benzimidazol-1-ones **295B** ($R^1 = \text{H, Bz}$) were obtained by fusing 2-benzimidazoleacetonitrile **59** with ethyl β -aminocrotonates **296** in the presence of NH_4OAc at 140 °C (Scheme 102).¹⁷⁶

Scheme 102

Graebe-Ullmann thermolysis of 5-(1-benzotriazolyl)-spiro[2*H*-imidazo[4,5-*b*]pyridine-2,1'-cyclohexane] **297** followed by treatment with $\text{Na}_2\text{S}_2\text{O}_4$ in aq. THF gave 1,2-diaminopyrido[1,2-*a*]benzimidazole **298** in low yield (Scheme 103).¹⁷⁷

Scheme 103

Condensation of 2-benzimidazoleacetonitrile **59** with diethyl 2-oxosuccinate **299**, in ethanol and DMF in the presence of piperidine produced pyrido[1,2-*a*]benzimidazole derivative **300**. In addition, thermal condensation of **59** with diethyl ethoxymethylenemalonate **301** in diphenyl ether at 240-250 °C gave the pyrido[1,2-*a*]benzimidazole **302** (Scheme 104).¹⁷⁸ 3-Hydroxypyrido[1,2-*a*]benzimidazol-1-ones **304** were prepared by heating 2-benzimidazoleacetonitrile **59** with substituted malonate esters **303** (Scheme 104).^{179,180}

Scheme 104

Treatment of 1-aminobenzimidazoles **305** with α,β -unsaturated ketones **306** in the presence of zinc chloride as catalyst in refluxing acetone gave the corresponding pyridobenzimidazoles **307** via an intramolecular rearrangement of the intermediates **A** (Scheme 105).¹⁸¹

Scheme 105

Formation of 2-benzamido-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazoles **310** was achieved by the neat heating of 2-benzimidazoleacetonitrile **59** or ethyl 2-benzimidazoleacetate **308** with 4-ethoxymethylene-2-phenyl-5-oxazolinone **309** via loss of ethanol from the intermediates **A** (Scheme 106).^{8b,182}

Scheme 106

Reaction of 2-benzimidazoleacetonitrile **59** with sodium salts of 3-hydroxymethylene-2-alkanones **311** in piperidine acetate and aq. ethanol yielded the pyrido[1,2-*a*]benzimidazoles **312**. The other isomeric structure **313** was excluded based on the X-ray analysis (Scheme 107).¹⁸³

Scheme 107

2-(2-Hydroxyethyl)pyrido[1,2-*a*]benzimidazole-4-carbonitriles **315** were prepared from heating 2-benzimidazoleacetonitriles **59** with 2-acetylbutyrolactone **314** in the presence of ammonium acetate.¹⁸⁴ Condensation of **59** with ethyl 4-chloro-3-oxobutanoate **316** in refluxing DMF and ZnCl₂ led to 3-chloromethylpyrido[1,2-*a*]benzimidazol-1-one-4-carbonitrile **317** (Scheme 108).¹⁸⁵

Scheme 108

A highly efficient and regioselective annulation protocol for a series of pyrido[1,2-*a*]benzimidazoles **320** involving [3+3] cyclocondensation of 2-benzimidazoleacetonitrile **59** with a variety of α -oxoketene dithioacetals **318** has been reported (Scheme 109).¹⁸⁶

Scheme 109

Reaction of chloromethylenemalononitriles **321** with 2-(nitromethylene)-benzimidazole **322** yielded the 4-nitropyrido[1,2-*a*]benzimidazole derivative **323** (Scheme 110).¹⁸⁷

Scheme 110

Heating a mixture of 2-(2-arylhydrazono)malononitrile **324** with 2-benzimidazoleacetonitrile **59** in refluxing ethanol yielded the 2-arylazopyrido[1,2-*a*]benzimidazoles **325**.¹⁸⁸ However, condensation of the arylhydrazones **326** with 2-benzimidazoleacetonitrile **59** in refluxing acetic acid gave the 3-methyl-2-arylazopyrido[1,2-*a*]benzimidazoles **327** (Scheme 111).¹⁸⁹

Scheme 111

Heating of 2-benzimidazoleacetonitrile **59** with triethyl orthoformate gave the intermediate ethoxyacrylonitrile derivative **328** which upon treatment with hippuric acid derivatives **329** in refluxing acetic anhydride afforded the pyrido[1,2-*a*]benzimidazole derivatives **331** in high yields *via* loss of water molecule from the intermediate **330** (Scheme 112).¹⁹⁰

Scheme 112

Polysubstituted pyrido[1,2-*a*]benzimidazoles **332** were efficiently produced in moderate yields in a one-pot, four-component reaction of pyridine or 3-picoline, chloroacetonitrile, malononitrile, and aromatic aldehydes in refluxing acetonitrile as outlined in Scheme 113.¹⁹¹

Scheme 113

Alkylation of 4,7-dimethoxy-1*H*-benzimidazole **333** using 1-iodo-4-(phenylselenanyl)butane and sodium hydride gave the phenylselenide derivative **334**. Radical cyclisation of **334** gave the pyrido[1,2-*a*]benzimidazole derivative **335** using Bu₃SnH, 1,1'-azobis(cyclohexanecarbonitrile) (ACN) and camphorsulfonic acid (CSA) under reflux in toluene (Scheme 114).¹⁹²

Scheme 114

Pyrido[1,2-*a*]benzimidazole derivatives **339** were prepared by reaction of the 2-bromopyridinium salts **336** with pyridine to give the fused heterocyclic bromide salt **338** which upon heating in basic solution underwent recyclization to form **339** (Scheme 115).¹⁹³

Scheme 115

3-(*N*-Piperidyl)-2-nitroaniline **340** underwent Michael-type addition with acrylonitrile, followed by hydrogenation then condensation with 3-ethoxy-3-iminopropanoate hydrochloride **109** to give 1-(2-cyanoethyl)-2-(ethoxycarbonylmethyl)-4-(*N*-piperidinyl)benzimidazole **341**. Ethanolysis of the nitrile function and base-catalyzed cyclization of the resulted diester followed by amidation with 2,6-difluoroaniline gave the pyrido[1,2-*a*]benzimidazole derivative **342** (Scheme 116).^{194,195}

Scheme 116

Catalytic hydrogenation of *N*-cyanoethyl-2-nitroaniline **343** and subsequent reaction with ethyl 3-amino-3-ethoxyacrylate hydrochloride **109** followed by ethanolysis of the cyano group in

ethanolic HCl gave the diester intermediate **344**. The latter upon treatment with sodium ethoxide underwent Dieckmann cyclization to afford pyrido[1,2-*a*]benzimidazoles **345** (Scheme 117).^{196,197}

Scheme 117

The reaction of 2-amino-5-methylpyridine **346** with 1,2-cyclohexanediol **347** in the presence of a catalytic amount of $\text{RuCl}_2(\text{PPh}_3)_3$ **348** under reflux in diglyme for 24 h afforded 2-methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazole **349** in 74% yield (Scheme 118).¹⁹⁸

Scheme 118

Pyrido[1,2-*a*]benzimidazole derivative **351** was obtained by photochemical cyclization of 2-chloro-*N,N'*-di(2-pyridyl)-1,4-phenylenediamine **350** (Scheme 119).¹⁹⁹

Scheme 119

Photo-induced cyclization of haloarylpyridylamines **352** gave the pyrido[1,2-*a*]benzimidazoles **353** (Scheme 120).^{200,201}

Scheme 120

The *N*-heterocyclic carbene of complex **355** was found to be an active catalyst in the Rh(I)-catalyzed intramolecular coupling of the alkenyl group of 1-(2,2-dimethylbut-3-enyl)-1*H*-benzimidazole **354** to the C–H bond of the benzimidazole moiety to give 2,2-dimethyl-1,2,3,4-tetrahydropyrido[1,2-*a*] benzimidazole **356** (Scheme 121).^{202,203}

Scheme 121

Intramolecular radical addition of 2-thiophenoxybenzimidazole **357** was reported in the presence of cobaloxime **358** or $\text{Ph}_3\text{SnH/AIBN}$ to give 3,3-dimethyl-1,2,3,4-tetrahydropyrido[1,2-*a*] benzimidazole **360**. The yield of **360** was higher (81%) with using cobaloxime **358** than with $\text{Ph}_3\text{SnH/AIBN}$ (64%) (Scheme 122).²⁰⁴

Scheme 122

Palladium-catalyzed intramolecular cyclization of 2-anilinopyridine **361** ($X = \text{Br}; R = \text{H}$) using palladium acetate and Na_2CO_3 in DMF at reflux gave pyrido[1,2-*a*]benzimidazole **362** (R

= H) in 59% yield. Also, catalytic cyclization of **361** (X = H; R = H, Me) in a continuous-flow quartz reactor containing K-16, as a dehydrogenating catalyst, at 560-580 °C gave the pyridobenzimidazoles **362** (R = H, Me) in 10-27% yields (Scheme 123).²⁰⁶

Scheme 123

Condensation of 1,2-diaminobenzene **36** with the 5*H*-pyran-2,6-dione **363** gave the pyrido[1,2-*a*]benzimidazol-1-one **364**,²⁰⁷ while condensation of **36** with 6-hydroxy-4-methyl-2-oxo-3-pyridine-carbonitrile **365** in 85% orthophosphoric acid afforded 3-methyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole **366** (Scheme 124).²⁰⁸

Scheme 124

3.2. Pyrimidobenzimidazoles

Treatment of 2-aminobenzimidazole **117** with variety of enaminones **367**, **368** and **369** in refluxing pyridine gave the corresponding pyrimido[1,2-*a*]benzimidazoles **370**, **371** and **372**, respectively (Scheme 125).^{160,163,165,168,209-213}

Scheme 125

Meziane *et al* reported the microwave-assisted synthesis of the pyrimido[1,6-*a*]benzimidazoles **376**.²¹⁴ Thus, heating of ethyl 2-(benzimidazol-2-yl)acetate **308** with *N,N*-dimethylformamide diethylacetal (DMF-DEA) at 90°C under microwave irradiation for 15 minutes gave the enamine derivative **373** which on treatment with the isocyanates or isothiocyanates **374** led to the formation of the pyrimido[1,6-*a*]benzimidazole **376** in good yields (Scheme 126).²¹⁴

Scheme 126

Microwave assisted one-pot three component synthesis of 1,2-dihydro-pyrimido[1,2-*a*]benzimidazole-3-carbonitrile derivatives **379** were achieved in high yields. Thus, reaction of

carbonyl compounds **378**, malonodinitrile and 2-aminobenzimidazole **117** in water under microwave gave pyrimido[1,2-*a*]benzimidazoles **379** (Scheme 127).²¹⁵⁻²¹⁷

Carbonyl compd. = ArCHO, ArCOCH₃, cyclopentanone, cyclohexanone, α -tetralone

Ar = Ph, 4-ClC₆H₄, 4-BrC₆H₄, 4-FC₆H₄, 4-MeOC₆H₄, 4-MeC₆H₄, 2-ClC₆H₄, 2,4-Cl₂C₆H₃

Scheme 127

The pyrimido[1,2-*a*]benzimidazoles **381** were synthesized through reaction of 2-aminobenzimidazole **117** with tetracyanoethylene **380** in ethyl acetate at room temperature *via* loss of HCN and heterocyclization.²¹⁸ When 2-aminobenzimidazole **117** was treated with (*E*)-3-(diethylamino)acrylonitrile **382** in refluxing pyridine it gave pyrimido[1,2-*a*]benzimidazol-4-amine **383** in 57% yield (Scheme 128).²¹⁹

Scheme 128

Fusion of 2-aminobenzimidazole **117** with methyl cinnamates **384** gave the pyrimido[1,2-*a*]benzimidazoles **385** (Scheme 129).²²⁰ The acetylenic aldehydes **386** and 3-phenylpropynenitrile **388** reacted by conjugate addition to **117** giving the pyrimido[1,2-*a*]benzimidazoles **387** and **389**, respectively (Scheme 129).²²¹

Scheme 129

Refluxing chlorooxazinediones **390** with *o*-phenylenediamines **36** in THF in the presence of acetic acid gave pyrimidobenzimidazoles **391** in low yields (Scheme 130).²²²

Scheme 130

Photo-irradiation of *N,N'*-(chlorophenylene)bis[dimethylpyrimidinamines] **392** gave pyrimidobenzimidazoles **393** (Scheme 131).²²³

Scheme 131

Photochemical cyclization of (2-chloroanilino)pyrimidines **394** in aqueous acetonitrile gave pyrimido[1,2-*a*]benzimidazoles **395** (Scheme 132).^{224,225}

Scheme 132

Reaction of ethyl 2-[(1*H*-benzimidazol-2-yl)sulfinylmethyl]-4-dimethylamino-5-pyrimidine-carboxylate **396** with alkanethiols in the presence of hydrochloric acid gave the pyrimido[1,2-*a*]benzimidazole-3-carboxylate **403** according to the mechanism shown in Scheme 133.²²⁶

Scheme 133

Treatment of 2-vinylbenzimidazoles **404** with bromine in chloroform gave 2-(1,2-dibromoethyl)-1*H*-benzimidazoles **405**. Reaction of the latter compounds with benzonitriles and with aryl isocyanates under basic conditions yielded 1-phenylpyrimido[1,6-*a*]benzimidazole **407** and 2-phenylpyrimido[1,6-*a*]benzimidazole-3-one **408**, respectively (Scheme 134).²²⁷

Scheme 134

Reaction of ethyl benzimidazole-2-acetate **308** with alkyl isocyanates gave the corresponding pyrimido[1,6-*a*]benzimidazoles **410** in excellent yields *via* loss of ethanol from **409** (Scheme 135).²²⁸

Scheme 135

Abdelhamid *et al.* reported the synthesis of pyrimido[1,6-*a*]benzimidazole-4-carbonitriles **413** from the reaction of 2-(1-ethoxycarbonyl)benzimidazolylacetonitrile **411** with isothiocyanates in the presence of KOH followed by HCl (Scheme 136).^{229,230}

Scheme 136

Treatment of 2-benzimidazoleacetonitriles **59** or methyl 2-benzimidazoleacetate **308** with chloroalkyl isocyanates or carbodiimides **414** ($Y = O, N-Ar'$), in benzene in the presence of ethyl diisopropylamine furnished the pyrimido[1,6-*a*]benzimidazoles **416** via cyclization and loss of HCl from the benzimidazolium salt intermediate **415** (Scheme 137).²³¹

Scheme 137

Reaction of ethyl 2-(1*H*-benzimidazol-2-yl)-2-cyanoacetate **417** with guanidine sulfate **418** in dry pyridine and sodium methoxide gave 1-amino-3-hydroxypyrimido[1,6-*a*]benzimidazole-4-carbonitrile **419** (Scheme 138).²³²

Scheme 138

2-Benzimidazoleacetonitrile **59** and its ester **308** reacted with *N*-acyl imidates **420** under microwave irradiation in open vessels to give the corresponding pyrimido[1,6-*a*]benzimidazoles **421** (Scheme 139).²³³

Scheme 139

Badawey *et al.* reported the reaction of 1*H*-benzimidazoles **59** and **308** with ethoxycarbonyl isocyanate **422** at room temperature to afford the intermediate **423**, which was readily cyclized in boiling bromobenzene to the corresponding 1,3-dioxypyrimido[1,6-*a*]benzimidazole-4-carbonitrile **424** in excellent yields (Scheme 140).²³⁴

Scheme 140

The reaction of 2-aminobenzimidazole **117** with sulfones **425** proceeded at room temperature in acetonitrile to give tetrahydropyrimido[1,2-*a*]benzimidazol-2-ol **426**. Aromatization of the latter compounds **426** was performed under reflux in acetic acid *via* elimination of water and sulfinic acid to give **427**. One-step procedure for the preparation of **427** in high yields from 2-aminobenzimidazole **117** and the sulfones **425** under reflux in water was also reported (Scheme 141).²³⁵ Condensation of 2-aminobenzimidazole **117** with diethyl ethoxymethylenemalonate **301** in dry methanol afforded 4-oxypyrimido[1,2-*a*]benzimidazole-3-carboxylate **428** (Scheme 141).²³⁶

Scheme 141

3-(Trichloromethyl)pyrimido[1,6-*a*]benzimidazole-4-carbonitrile **429** was prepared by heating of 2-benzimidazoleacetonitrile **59** with trichloroacetonitrile followed by triethyl orthoformate (Scheme 142).²³⁷ Reaction of dimethyl *N*-cyanodithioiminocarbonate **430** with 2-benzimidazoleacetonitrile **59** in the presence of KOH furnished 1-amino-4-cyano-3-(methylthio)pyrimido[1,6-*a*]benzimidazole **432** (Scheme 142).²³⁸

Scheme 142

The reaction of 2-aminobenzimidazole **117** with the benzylidene derivatives **433**, **267** and **434** in ethanol containing a catalytic amount of piperidine gave the corresponding pyrimido[1,2-*a*]benzimidazole derivatives **435**, **436** and **437**, respectively (Scheme 143).²³⁹⁻²⁴²

Scheme 143

The condensation of 2-aminobenzimidazole **117** with chalcones **263** and with phenylhydrazonomalononitrile **324** gave pyrimido[1,2-*a*]benzimidazoles **438** and **440**, respectively.²⁴³⁻²⁴⁶ Similar condensation of **117** with ethyl α -(*p*-tolylazo)- β -oxobutyrate **441** in absolute ethanol afforded the pyrimido[1,2-*a*]benzimidazole-4-one **442** (Scheme 144).²⁴⁷

Scheme 144

The reaction of the allenic nitriles **443** with 2-aminobenzimidazoles **117** in refluxing DMF led to 2-aminopyrimido[1,2-*a*] benzimidazole **445** in high yields (Scheme 145).²⁴⁸

Scheme 145

Reaction of 1-ethyl-2-aminobenzimidazole **446** and dimethyl acetylenedicarboxylate **257** at 130 °C afforded the methyl pyrimido[1,2-*a*]benzimidazol-4-carboxylate **447** in 59% yield. Similar treatment of **446** with diethyl (ethoxymethylene)malonate **301** gave ethyl 10-ethyl-4-oxo-4*H*-pyrimido[1,2-*a*]benzimidazol-3-carboxylate **448** in 71% yield (Scheme 146).⁶²

Scheme 146

Reaction of 2-aminobenzimidazole **117** with 4-hydroxy-2-alkynenitrile **152** in ethanol under reflux gave excellent yields of 2-amino-4-(1-hydroxyalkyl)pyrimido[1,2-*a*]benzimidazole **450**.⁷⁶ In addition, the pyrimidobenzimidazole-2,4-dione **452** was prepared in 30% yield by treating **117** with diethyl diallylmalonate **451** (Scheme 147).²⁴⁹

Scheme 147

Refluxing 3-isothiocyantobutanal **453** with *o*-phenylenediamines **36** in methanol at pH 5 gave the pyrimido[1,6-*a*]benzimidazole derivative **454** (Scheme 148).^{250,251}

Scheme 148

Cyclocondensation of (2-benzimidazolylmethyl)triphenylphosphonium chloride **455** with benzoyl isothiocyanates in the presence of triethylamine gave pyrimido[1,6-*a*]benzimidazole derivative **456** (Scheme 149).^{252,253}

Scheme 149

4-Amino-1*H*-1,5-benzodiazepine-3-carbonitrile **457** underwent ring opening when treated with hydroxylamine to yield 3-amino-3-(2-aminoanilino)-2-cyanopropenal oxime **458**. Treatment of **458** with diluted hydrochloric acid gave 2-(2-benzimidazolinylidene)-2-cyanoethanal-oxime **459**. Refluxing of **459** in triethyl orthoformate resulted in the formation of the pyrimido[1,6-*a*]benzimidazole derivative **460** (Scheme 150).²⁵⁴

Scheme 150

The pyrimido[1,2-*a*]benzimidazole derivative **461** was prepared in 75% yield by cyclocondensation of 4-(ethoxymethylene)-2-phenyloxazol-5(4*H*)-one **308** with 2-aminobenzimidazole **117** under solventless domestic microwave heating *via* loss of ethanol from the intermediate **461A** (Scheme 151).²⁵⁵

Scheme 151

1,2-Diaminobenzimidazole **462** reacted with diethyl ethoxymethylenemalonate **301** to give the pyrimido[1,2-*a*]benzimidazole derivative **463** (Scheme 152).²⁵⁶

Scheme 152

Pyrimido[1,2-*a*]benzimidazole derivatives **467-470**, which are useful as neoplasm inhibitors, immuno-modulators, and antiallergic agents, were prepared *via* reaction of 2-aminobenzimidazole Schiff's base **464** with active methylene compounds and with the cinnamoyl chlorides **465** (Scheme 153).²⁵⁷⁻²⁶¹

Scheme 153

3.3. Pyrazinobenzimidazoles

2-Acetylbenzimidazole **471** reacted with aromatic aldehydes to give 1-(benzimidazol-2-yl)-3-aryl-2-propenone **472**. Reaction of **472** with phenacyl bromides **5** in acetone in the presence of potassium carbonate gave 1-[1-(2-aryl-2-oxoethyl)benzimidazol-2-yl]-3-arylpropenones **473** which upon heating with ammonium acetate in acetic acid gave 1-(2-arylviny)-3-arylpyrazino[1,2-*a*]benzimidazole derivative **474**. Reaction of **471** with phenacyl bromides **5** gave 1-(2-aryl-2-oxoethyl)-2-acetylbenzimidazoles **475**, which were then reacted with anilines in acetic acid to give 1-methylene-2,3-diaryl-1,2-dihydropyrazino[1,2-*a*]benzimidazoles **476** (Scheme 154).²⁶²

Scheme 154

Pyrazino[1,2-*a*]benzimidazole **478** was prepared by heating 1-(2-pyrazinyl)benzotriazole **477** with polyphosphoric acid (PPA) at 180 °C (Scheme 155).²⁶³

Scheme 155

Pyrazino[1,2-*a*]benzimidazole derivatives **479-481** were obtained from the reaction of 2-aminomethylbenzimidazole **112** with diethyl oxalate, phenacyl bromide **5** and with dibromoethane, respectively (Scheme 156).⁶⁰

Scheme 156

Treatment of the 2-formylbenzimidazole **482** with primary amines and cyclohexyl isocyanide at 40 °C in methanol resulted in the formation of 3-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole-1-carboxamides **485** in good yields. Formation of **485** took place probably according to the mechanism depicted in Scheme 157.²⁶⁴

Scheme 157

3-Anilinopyrazinones **486** were easily converted into the pyrazino[1,2-*a*]benzimidazol-1(2*H*)-ones **487** by applying a microwave assisted Buchwald–Hartwig type cyclization using 10% Pd(PPh₃)₄ and anhydrous potassium carbonate in DMF at 150 °C and 150 Watts (Scheme 158).²⁶⁵

Scheme 158

3.4. Triazinobenzimidazoles

Treatment of ethyl 2-benzimidazolylacetate **308** with aryldiazonium salts in ethanolic sodium acetate solution yielded the arylhydrazones **488**. Heating the latter hydrazones with ethyl chloroformate in pyridine afforded the 1,2,4-triazino[4,5-*a*]benzimidazole derivatives **489** (Scheme 159).²⁶⁶

Scheme 159

1,2,4-Triazino[2,3-*a*]benzimidazole derivative **493** was obtained selectively by the reaction of diethyl (*E*)-2,3-dicyanobutenedioate **490** with 1,2-diamino-1*H*-benzimidazole **462** in dimethyl sulfoxide at room temperature as outlined in Scheme 160.²⁶⁷

Scheme 160

3-Oxopropanenitriles **494** coupled smoothly with 1*H*-benzimidazole-2-diazonium sulfate **495** to afford the corresponding hydrazones **496**. The latter hydrazones underwent intramolecular cyclization when heated in pyridine to give 1,2,4-triazino[4,3-*a*]benzimidazoles **497** in good yields (Scheme 161).^{268,269}

Scheme 161

Benzimidazole-2-diazonium salt **495** was coupled with 2-benzimidazoleacetonitrile **59** to yield the hydrazone **498** which was cyclized under refluxing pyridine to produce the 1,2,4-triazino[4,3-*a*]benzimidazole **499** (Scheme 162).²⁷⁰

Scheme 162

The diazotized 2-nitroanilines **500** were coupled with *N*-ethoxycarbonylcianoacetamide **501** to afford the corresponding hydrazones **502** which were cyclized into the nitrophenyltriazinediones **503**. The latter were reduced to the corresponding aminophenyltriazinedione derivatives **504** which were then converted into the 1,2,4-triazino[2,3-*a*]benzimidazoles **505** (Scheme 163).²⁷¹⁻²⁷⁴

Scheme 163

Heating benzoylpyruvic acid **507** with 1-amino-2-(*N*-methylamino)benzimidazole **506** produced the 1,2,4-triazino[2,3-*a*]benzimidazole derivative **508** (Scheme 164).²⁷⁵

Scheme 164

Heating 2-chloro-1-phenacylbenzimidazole **158**, in refluxing DMF, with aminoguanidine **509** or with hydrazine hydrate led to 3-phenyl-1,4-dihydro-1,2,4-triazino[4,3-*a*]benzimidazole **510** in 49 and 86% yields, respectively (Scheme 165).⁷⁸

Scheme 165

The reaction of 2-hydrazinobenzimidazoles **220** with diethyl 2-oxomalonate **511** and with α -keto acids **513** in refluxing ethanol gave the corresponding 1,2,4-triazino[4,3-*a*]benzimidazol-4(10*H*)-ones **412** and **514**, respectively.^{276,277} Refluxing of **220** with diethyl oxalate in ethanol gave the 1,2,4-triazino[4,3-*a*]benzimidazole-3,4-dione **515** (Scheme 166).¹²⁸

Scheme 166

Condensation of hydrazines with *N*-propargyl-2-chlorobenzimidazole **516** resulted in the formation of 1,2,4-triazino[4,3-*a*]benzimidazole derivatives **517** (Scheme 167).²⁷⁸

Scheme 167

Heating benzimidazole-1-acetonitriles **518** and hydrazine in methanol gave 3-hydrazino-1,2,4-triazino[4,3-*a*]benzimidazole **519** (Scheme 168).^{279,280}

Scheme 168

3.5. Thiazinobenzimidazoles

Michael-type addition of 2-mercaptobenzimidazole **165** to ethyl propiolate in the presence of clay catalyst gave 4-oxothiazino[3,2-*a*]benzimidazole **520**.²⁸¹ Alkylation of **165** with epichlorohydrin **521** in aqueous base gave the thiazino[3,2-*a*]benzimidazole derivative **522**.²⁸² On the other hand, reaction of 2-mercaptobenzimidazole **165** with acryloyl chlorides **523** in pyridine and acetone afforded the 4*H*-[1,3]thiazino[3,2-*a*]benzimidazol-4-ones **524** (Scheme 169).²⁸³

Scheme 169

Thiazino[3,2-*a*]benzimidazole derivatives **525** and **526** were prepared from the reaction of 2-mercaptobenzimidazoles **165** with 3-chloropropanoic acid and 1,3-dibromopropane, respectively (Scheme 170).^{284,285}

Scheme 170

Bromination of 2-(allylthio)benzimidazoles **527** led to 2-[(2,3-dibromopropyl)thio]benzimidazoles **528** which were converted into the thiazino[3,2-*a*]benzimidazoles **529-531** in reasonable yields (Scheme 171).^{286,287}

Scheme 171

Treatment of 1*H*-benzimidazol-2-ylmethanethiol **532** with tetracyanoethylene **380** gave 1-cyanodihydrothiazino[4,3-*a*]benzimidazole-2-carboxamide **533** (Scheme 172).²⁸⁸

Scheme 172

Heating 2-mercaptobenzimidazoles **165** with acetylenedicarboxylate esters **257** under microwave irradiation gave a mixture of 4-oxothiazino[3,2-*a*]benzimidazole-2-carboxylates **534** and **535** (Scheme 173).^{289,290}

Scheme 173

Reaction of 3-methylthiazolo[3,2-*a*]benzimidazole **201** with two equivalents of methyl propiolate in refluxing acetonitrile gave the 1,4-thiazino[4,3-*a*]benzimidazole derivative **540** in reasonable yield and the mechanism of this reaction is depicted in Scheme 174.²⁹¹

Scheme 174

4. Synthesis of Azepino-fused-benzimidazoles

4.1. Azepinobenzimidazoles

Treatment of 2-methylbenzimidazole **65** with ethyl 4-bromobutyrate in THF in the presence of NaH gave 1-(3-ethoxycarbonylpropyl)-2-methylbenzimidazole **541**. Hydrolysis of the latter using NaOH followed by quaternization using alkyl halides gave the benzimidazolium salts **542**. Treatment of the latter salts **542** with *N,N'*-carbonyldiimidazole (CDI) in acetonitrile at room temperature followed by addition of Et_3N and heating the mixture at 70°C gave 7,8,9,10-tetrahydro-5*H*-azepino[1,2-*a*]benzimidazol-7-one derivatives **543** (Scheme 175).^{31,292}

Scheme 175

N-(Haloaryl)amidines **544** underwent heterocyclization when heated in DMF in the presence of sodium methoxide to give the 7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole derivatives **545** in high yields (Scheme 176).^{25,293}

Scheme 176

3-Methoxy-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole **547** was prepared from the reaction of mixture of *N*-(2-(azepan-1-yl)-5-methoxyphenyl)acetamide **546**, formic acid and H₂O₂ at 40 °C as shown in Scheme 177.²⁹⁴

Scheme 177

Fusion of a mixture of γ -bromodipnone **549** and 1,2-dimethyl-1*H*-benzimidazole **548** on an oil bath at 110 °C for 30 min afforded 11-methyl-7,9-diphenyl-6*H*,11*H*-azepino[1,2-*a*]-5-benzimidazolium bromide **550** in reasonable yield (Scheme 178).²⁹⁵

Scheme 178

Treatment of 1*H*-2-phenylthiobenzimidazole **551** with NaH in THF followed by adding 5-iodo-1-(phenylselenenyl)pentane **552** under reflux gave 1-[5-(phenylselenenyl)pentyl]-2-(phenylthio)-1*H*-benzimidazole **553**. Refluxing the latter **553** in toluene using Bu₃SnH and AIBN

resulted in an intramolecular radical substitution of the intermediate **554** to give the 7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole **555** in low yield (Scheme 179).²⁹⁶

Scheme 179

The tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole **555** was alternatively synthesized in a good yield by lithiation of either the *N*-alkylated 1*H*-benzimidazole **556** or 2-methylbenzimidazole **557** using lithium diisopropylamide (LDA) in THF at -78 °C (Scheme 180).²⁹⁷

Scheme 180

Rhodium-catalysed reactions of *N*-(4-methylpent-4-enyl)-1,2-diaminobenzene **558** with hydrogen and carbon monoxide gave the 7,8,9,10-tetrahydro-7-methyl-6*H*-azepino[1,2-*a*]benzimidazole **561** in good yield. This product arises from initial highly regioselective aldehyde formation at the terminal carbon atom followed by cyclisation with subsequent oxidation to the benzimidazole **561** (Scheme 181).^{298,299}

Scheme 181

4.2. Diazepinobenzimidazoles

Reaction of 2-(ω-aminopropyl)benzimidazole **562** with carbon disulfide in alkaline ethanol gave the 1,3-diazepino[3,4-*a*]benzimidazole-2-thione **563** which on treatment with methyl iodide gave the 2-methylthio derivative **564** (Scheme 182).³⁰⁰

Scheme 182

4.3. Triazepinobenzimidazoles

Heating a mixture 1,2-diaminobenzimidazole **462** and 1,3-diketones **565** in polyphosphoric acid (PPA) at 110-115 °C or in the presence of ZnCl_2 at 240-250 °C gave the corresponding 1,2,4-triazepino[2,3-*a*]benzimidazole derivatives **566** in good yields (Scheme 183).³⁰¹

Scheme 183

When 1,2-diaminobenzimidazole **462** was treated with β -ketoesters **567** under reflux condition either in acetic acid or without solvent it gave the corresponding 1,2,4-triazepino[2,3-*a*]benzimidazol-4-ones **568** (Scheme 184).^{53,301-303}

Scheme 184

2-Chlorobenzimidazole **47** was condensed with β -bromoketones **569** to give 1-(2-benzoyl-ethyl)-2-chlorobenzimidazoles **570** which cyclized with hydrazines to give the corresponding 1,2,4-triazepino[4,3-*a*]benzimidazoles **571** (Scheme 185).³⁰⁴

Scheme 185

Reaction of 2-(benzylhydrazino)benzimidazole **572** with 4-phenyl-3-buten-2-one **573** in DMF in the presence of Et_3N gave 73% of 1-benzyl-3-methyl-5-phenyl-1,2,4-triazepino[4,3-*a*]benzimidazole **574** (Scheme 186).³⁰⁵

Scheme 186

Reaction of 2-hydrazonobenzimidazole **575** with tetracyanoethylene (TCNE) **380** gave the 1,2,4-triazepino[4,3-*a*]benzimidazole derivatives **576** (Scheme 187).³⁰⁶

Scheme 187

4.4. Thiazepinobenzimidazoles

Reaction of 2-mercaptobenzimidazole **165** with two equivalents of tetracyanoethylene **380** in ethyl acetate at room temperature gave the 1,3-thiazepino[3,2-*a*]benzimidazole derivative **577** in low yield (Scheme 188).³⁰⁷

Scheme 188

5. References

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Authors' Biographies

Kamal M. Dawood was born in 1965 in Kafr-Elsheikh, Egypt. He graduated from Cairo University, Egypt in 1987 then he carried out his MSc and PhD studies under the supervision of Professor Ahmad M. Farag, Cairo University. He received his PhD in 1995 in the applications of hydrazonoyl halides in heterocyclic chemistry. In 1997 he was awarded the UNESCO Fellowship for one year at Tokyo Institute of Technology (TIT) and collaborated with Prof. Toshio Fuchigami in the field of 'Electrochemical Partial Fluorination of Heterocyclic Compounds'. In 1999, he was awarded the JSPS (Japan Society for Promotion of Science) Fellowship for two years and worked again with Professor Fuchigami at TIT in the same field. He was awarded the Alexander von Humboldt Fellowship at Hanover University in 2004-2005 with Prof. Andreas Kirschning in the field of polymer supported palladium catalyzed cross coupling reactions and in 2007 and 2008 with Prof. Peter Metz at TU-Dresden, Germany, in the field of total synthesis of natural products. In 2002 he promoted to Associate Professor and in May 2007 he was appointed as Professor of Organic chemistry, Faculty of Science, Cairo University. In 2002 he received the Cairo University Award in Chemistry and in 2007 he received the State-Award in Chemistry. He is a member of the international Editorial Board of ISRN Organic Chemistry, part of the *International Scholarly Research Network* (ISRN), open access journals. He published more than 75 scientific papers and reviews in distinguished international journals. There are about 690 citations of his work from 1993 until 2010 (*h-index* 16).

Nehal M. Elwan was born in 1959 in Giza, Egypt. She graduated from Cairo University, Egypt in 1980 then she carried out her MSc and PhD studies under the supervision of Professors Hamdi M. Hassaneen and Ahmad S. Shawali (DSc.), Chemistry Department, Faculty of Science, Cairo University. She received her PhD in 1990 on the applications of hydrazonoyl halides in heterocyclic chemistry. In 1990 she was appointed as a lecturer of organic chemistry at Faculty of Science, Cairo University. In 1995 she was promoted to Associate Professor and in 2004 she was appointed as Professor of Organic chemistry, Faculty of Science, Cairo University. In 2005 she received the Cairo University Award in chemistry. Currently, she is the director of the Microanalysis Centre, Cairo University.

Bakr F. Abdel-Wahab was born in 1978 in Mansoura, Egypt. He is a researcher of organic chemistry at National Research Centre, Giza, Egypt. He has got his B.Sc. in 1999 from Chemistry Department, Faculty of Science, Mansoura University, Egypt. He received his M.Sc. in 2003 from Mansoura University under the supervision of Professor Fathy A. Amer. He has awarded his Ph.D. degree in 2007 from Ain-Shams University, Cairo under the supervision of Professor Maher A. El-Hashash (D.Sc). His current research interests cover the development and mechanistic aspects of organic reactions and their applications in medicinal chemistry. Currently, he is an assistant professor of organic chemistry at the Department of Chemistry, Faculty of Science and Arts, King Abdulaziz University, Khulais Branch, Saudi Arabia.