Synthetic routes to benzimidazole-based fused polyheterocycles

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Abstract
The review article represents a survey covering the synthetic strategies leading to benzimidazole-based fused polyheterocyclic systems utilizing simple reactive benzimidazole synthons since 1980. The polyheterocyclic systems are classified based on the number of rings; tetra-, penta-, hexa- and hepta-fused ring systems. Among each polyheterocyclic system, further classification according to the number of heterotoms; two-, three-, four-, five-, six- and seven heteroatoms is considered.

Keywords: Polyheterocycles, fused benzimidazoles, synthesis, cyclization

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1. Introduction

There is a growing interest over the past years for the synthesis of benzimidazole-based heterocycles due to the crucial role of benzimidazole unit in the functions of biologically important molecules.\textsuperscript{1-3} Benzimidazole-based ployheterocycles has exhibited interesting biological properties. For example, benzimidazoquinazolines,\textsuperscript{4,8} benzimidazoisoquinolines\textsuperscript{9} and benzimidazo[2,1-a]isoindolones\textsuperscript{10} were reported as potent antitumor agents. Benzimidazo[2,1-b]quinazolines are potent immuno-suppressors\textsuperscript{11} and benzimidazo[2,1-b]benzo[f]isoquinoline ring system\textsuperscript{12} is present in pharmacologically active compounds. Isoindolo[2,1-a]benzimidazoles are also known to be sedatives and tranquilizers.\textsuperscript{13} There have been a number of practically important routes to benzimidazole-based polyheterocycles, \textit{e.g.} (i) the reaction of benzaldehyde derivatives with benzimidazoles containing an activated methylene group at position 2, (ii) the reaction of coumarins with \textit{o}-phenylenediamines, (iii) the reaction of 2-azidoanilines with substituted cinnamaldehydes, (iv) the reaction of 2-(2-aminoaryl(hetaryl))benzimidazoles with haloketones, (v) the reaction of \textit{o}-phenylenediamines with phthalic anhydrides, (vi) metal-catalyzed cyclization of alkynylaniline derivatives and (vii) the reaction of 2-(hydroxymethylene)-3-keto steroids with functionalized benzimidazoles. Such reactions provide convenient strategies for synthesis of annulated benzimidazole polyheterocycles. This review covers the literature from 1980 to 2009.

2. Tetracyclic fused benzimidazoles

2.1. With two heteroatoms

2.1.1. Isoindolo-benzimidazoles. The preparation of isoindolo[2,1-a]benzimidazol-11-one derivatives was mostly performed from the condensation reaction of \textit{o}-phenylenediamines with phthalic anhydrides. Thus, heating a mixture of \textit{o}-phenylenediamines 1 with phthalic anhydrides 2 in acetic anhydride at 140-150 °C gave 11\textit{H}-isoindolo[2,1-a]benzimidazol-11-one derivatives 3 (Scheme 1).\textsuperscript{14,15}

![Scheme 1](image-url)
Heating of 2-nitro-3-methylaniline 4 and phthalic anhydride 2 in \( n \)-amyl alcohol gave \( N \)-(2-nitro-3-methylphenyl)phthalimide 5. Reaction of 5 with iron powder in 50\% aqueous acetic acid at 100 °C gave 6-methyl-11-oxoisindolo[2,1-\( \alpha \)]benzimidazole 6 (Scheme 2).\(^\text{16}\)

![Scheme 2](image)

The isoindolobenzimidazolone derivative 8 was obtained similarly from heating of phthalic anhydride 2 with the pyridyl-phenylenediamine derivative 7 (Scheme 3).\(^\text{17}\)

![Scheme 3](image)

The hydroxyisoindolobenzimidazole derivatives 10 and 12 were synthesized from \( o \)-phenylenediamine 1 and 3-benzylidenephthalide 9 and with the 1,2-di(trifluoroacetyl)benzene 11, respectively (Scheme 4).\(^\text{18,19}\)

![Scheme 4](image)
Condensation of \( o \)-phenylenediamine 1 with \( o \)-acylbenzoic acids 13 in refluxing toluene using a catalytic amount of \( p \)-toluenesulfonic acid (PTSA) under azeotropic condition for removal of water, led to the formation of isoindolobenzimidazoles 14 in reasonable yields (Scheme 5).\(^{20,21}\) Similar condensation of 1 with aroylcyclohexane-carboxylic acids 15 gave the hexahydroisoindolobenzimidazoles 16 (Scheme 5).\(^{22,23}\)

\[
\begin{align*}
\text{Ar} &= \text{Ph, 4-MeC}_6\text{H}_4 \\
R = \text{H, Me, Ph, 4-MeC}_6\text{H}_4
\end{align*}
\]

Scheme 5

Reaction of dibenzo\([b,f]\)[1,4]diazocine-6,11-(5\(H\),12\(H\))-dione 17 with 2-azidobenzoyl chloride 18 in DMF and Na\(\text{H}\) afforded only 30\% yield 4b-[(2-azidobenzoyl)oxy]-5\(H\)-isoindolo[2,1-\(a\)]benzimidazol-11(4b\(H\))-one 19 via transannular cyclization (Scheme 6).\(^{24}\)

\[
\begin{align*}
\text{NaH} & \quad \text{DMF, rt} \\
R = \text{H, Me, Ph, 4-MeC}_6\text{H}_4
\end{align*}
\]

Scheme 6

The parent 11\(H\)-isoindolo[2,1-\(a\)]benzimidazole could also be obtained via an intramolecular aryl radical cyclization as shown in Scheme 7. Thus, heating a mixture of 2-chlorobenzimidazole 20, arenethiol and 2-iodobenzyl iodide 21 in DMF in the presence of KOH / KO\(\text{Bu}^+\) under reflux gave a quantitative yield of the 2-arythio-1-benzyl-1\(H\)-benzimidazole derivative 22. Five-membered cyclisation with the radical precursor 22 using tris-(trimethylsilyl)silane (TTMSS) in toluene at reflux afforded a low yield (20\%) of the cyclised product 11\(H\)-isoindolo[2,1-\(a\)]benzimidazole 23 via a homolytic aromatic substitution by aryl radical at C-2 of benzimidazole ring (Scheme 7).\(^{25}\)
Scheme 7

7-Methoxy-11H-isoindolo[2,1-a]benzimidazole 25 was prepared in 90% yield from palladium-catalyzed annulation of 2-(4-methoxy-2-nitrophenyl)-2,3-dihydro-1H-isoindole 24 by heating in DMF using bis-(dibenzylideneacetone)palladium [Pd(dba)$_2$] and 1,10-phenanthroline at 120 °C and the solution was saturated with CO under pressure (Scheme 8).

Scheme 8

2.1.2. Benzimidazo[2,1-a]isoquinolines. Condensation of o-phenylenediamine 1 with 2-(2-phenylethynyl)benzaldehyde 26 in refluxing nitrobenzene resulted in an oxidative cyclization to give 6-phenylbenzimidazo[2,1-a]isoquinoline 29 via the intermediates 27 and 28 (Scheme 9).
Direct, efficient syntheses of the benzimidazo[2,1-α]isoquinolines 32 have been achieved with 2-bromoarylaldehydes 30, terminal alkynes 31, and 1,2-phenylenediamines 1 by a microwave-accelerated tandem process in which a Sonogashira coupling, 5-endo cyclization, oxidative aromatization, and 6-endo cyclization could be performed in a single synthetic operation (Scheme 10).²⁸

![Scheme 10](image)

Heating of N-(5-methoxy-2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline 33 in acetic acid resulted in an intramolecular cyclization to give the benzimidazo[2,1-α]isoquinoline-N-oxide 34 which upon deoxygenation via heating with PCl₃ in chloroform gave the benzimidazo[2,1-α]isoquinoline derivative 35 (Scheme 11).²⁹

![Scheme 11](image)

The reaction of 2-azidoaniline 36 with aromatic aldehydes gave N-(2-azidophenyl)imines 37 which upon reaction with trimethylphosphine followed with diphenylketene 38, the corresponding 6,11-dihydrobenzimidazo[1,2-b]isoquinolines 40 were isolated in excellent yields via a formal [4+2] intramolecular cycloaddition of ketenimine with imine function of the intermediates 39. Refluxing of 40 with Pd/C in toluene gave benzimidazo[1,2-b]isoquinolines 41 in good yields (Scheme 12).³⁰,³¹
Scheme 12

2-Benzimidazoleacetonitrile 42 condensed with 2-haloaromatic esters 43 in refluxing acetonitrile containing K$_2$CO$_3$ to give the benzimidazo[1,2-$\alpha$]isoquinolones 44 (Scheme 13).$^{32-34}$

Scheme 13

Benzimidazo[1,2-$\alpha$]isoquinolines 46 were prepared in reasonable yield by condensing 2-benzimidazoleacetonitrile 42 with ethyl cycloalkanone-2-carboxylates 45 in the presence of ammonium acetate at 140 °C (Scheme 14).$^{35,36}$

Scheme 14
Refluxing of isochroman-1,3-dione 47 with o-phenylenediamine 1 in acetic acid gave 11H-benzimidazo[1,2-a]isoquinolin-11-one 48 (Scheme 15).\(^{37}\)

![Scheme 15](image)

Substituted 5H-benzimidazo[1,2-b]isoquinolin-11-ones 50 were synthesized in good yields (53-83%) by refluxing, in n-amyl alcohol, the appropriate o-phenylenediamine 1 with α-(o-carboxyphenyl)acetonitriles 49 (Scheme 16).\(^{38}\)

![Scheme 16](image)

### 2.1.3. Benzimidazo[1,2-α]quinolines

Photochemical cyclization of arylidene-1H-benzimidazol-2-ylacetonitriles 51 yielded the bezimidazo[1,2-α]quinoline derivatives 52 (Scheme 17).\(^{39}\) Highly fluorescent 7-(diethylamino)benzimidazo[1,2-α]quinoline-3-carbonitrile 53 was prepared in 75% yield by cyclization of the arylidene-1H-benzimidazol-2-ylacetonitrile 51 (X = OMe, R = NEt\(_2\)) under refluxing o-dichlorobenzene in the presence of piperidine and acetic acid (Scheme 17).\(^{40}\)

![Scheme 17](image)
2-N-Ethylamino-5-methylbenzimidazo[1,2-α]quinoline 55 was formed in 18% yield when 7-diethylamino-4-methylcoumarin 54 reacted with α-phenylenediamine 1 in the presence of polyphosphoric acid (PPA) at 240 °C (Scheme 18).41

Scheme 18

Arylidene-1H-benzimidazol-2-ylacetonitriles 56 underwent an intramolecular cyclization when heated in DMF containing triethylamine to give the benzimidazo[1,2-α]quinoline-6-carbonitriles 57 (Scheme 19).42,43

Scheme 19

Microwave irradiation of 2-(N,N-dimethylamino)methylene-5,5-dimethylcyclohexane-1,3-dione 58 and 2-benzimidazoleacetonitrile 42 in iso-propanol and a catalytic amount of piperidine led to the formation of tetrahydrobenzimidazo[1,2-α]quinoline derivative 59 (Scheme 20).44

Scheme 20
Room-temperature reactions of polyfluorobenzoyl chlorides 61 with 2-benzoylmethylbenzimidazole 60 in dichloromethane in the presence of triethylamine afforded tetracyclic imidazoquinolines 63 in 73-81% yields via the intermediate 62 (Scheme 21).\(^{45}\)

![Scheme 21](image)

**Scheme 21**

2.1.4. **Fused macroheterocycles with two heteroatoms.** Chlorocyclohepta[b]pyrroles 64 reacted with \(\sigma\)-phenylenediamine 1 to give 2-(2-aminoanilino)cyclohepta[b]pyrroles 65 in good yields. Treatment of 65 (R = H) with polyphosphoric acid (PPA) afforded cycloheptapyrrolobenzimidazole 66 (R = H) in good yields and when 65 (R = CO\(_2\)Et) was treated with TsOH in \(n\)-butanol under reflux the ester derivative 66 (R = CO\(_2\)Et) was obtained (Scheme 22).\(^{46}\)

![Scheme 22](image)

**Scheme 22**

Treatment of pyrido[1,2-\(a\)]benzimidazole 67 with dimethyl acetylenedicarboxylate 68 in benzene for 5 h at 20 °C gave the bis-pyridobenzimidazole derivative 69 in 44% yield (Scheme 23).\(^{47}\)

![Scheme 23](image)
Scheme 23

The reaction of Baylis–Hillman acetate 71 with 2-substituted benzimidazoles 70 in DMF and K₂CO₃ at room temperature gave the benzimidazole-attached Baylis–Hillman adducts 72 in 67–89% yields. The tetracyclic compounds containing eight-membered ring; benzoazocino-benzimidazole derivatives 73 were formed, in 36–48% yields, from the intramolecular palladium catalyzed cyclization of 72. Similarly, the seven-membered ring compounds 76 were obtained from the reaction of 71 with 2-unsubstituted benzimidazoles 74 in DMF and K₂CO₃ at room temperature to give the adducts 75. Intramolecular Pd-catalyzed cyclization of 75 resulted in the formation of benzo[3,4]azepino[1,2-a]benzimidazole derivatives 76 in reasonable yields. The latter results show that 2-position of benzimidazole is more reactive than that of 7-position (Scheme 24).

Scheme 24

2.2. With three heteroatoms
2.2.1. Pyrrolo-[3',4':3,4]pyrrolo[1,2-a]benzimidazoles. Condensation of 2-cyanomethyl-benzimidazoles 42 with dichloromaleimide derivative 77 afforded the (1H-benzimidazol-2-yl)-(3-pyrrolyl)acetonitriles 78. Intramolecular cyclization of 78 gave 1,3-dioxo-1,3-dihydropyrrolo[3',4':3,4]pyrrolo[1,2-a]benzimidazoles 79 (Scheme 25).
Scheme 25

2.2.2. Pyrrolo[3',4':3,4]pyrido[1,2-α]benzimidazoles. Condensation of 2-benzimidazole-acetonitrile 42 with ethyl 4-chloro-3-oxobutanoate 80 led to 3-chloromethylpyrido[1,2-α]benzimidazole-4-carbonitrile 81 which upon amination with primary amines yielded pyrrolo[3',4':3,4]pyrido[1,2-α]benzimidazoles 82 (Scheme 26).\(^{50}\)

Scheme 26

2.2.3. Furo[3',2':5,6]pyrido[1,2-α]benzimidazoles. Furo[3',2':5,6]pyrido[1,2-α]benzimidazole derivatives 84 were prepared by reaction of the hydroxy aldehyde 83 with activated alkyl halides in the presence of K₂CO₃ (Scheme 27).\(^{51}\)

Scheme 27

2.2.4. Pyrano[4,3-d]pyrido[1,2-α]benzimidazoles. Reaction of 6-aryl-3-cyano-4-methylthio-2H-pyran-2-ones 85 with 2-cyanomethyl-benzimidazole 42 in DMF and KOH at 30 °C led to the formation of pyrano[4,3-d]pyrido[1,2-α]benzimidazoles 86 in low yields (7-20%) (Scheme 28).\(^{52}\)
2.2.5. Thieno[2,3-b]pyrido[1,2-a]benzimidazoles. Badawy et al reported the reaction of chloropyrido[1,2-a]benzimidazole derivatives 87 with thiourea in refluxing ethanol to give thieno[2,3-b]pyrido[1,2-a]benzimidazole derivatives 88. Treatment of 87 with anilines in refluxing DMF gave the 1H-pyrrolo[2,3-b]pyrido[1,2-a]benzimidazole derivatives 89 (Scheme 29).53

Scheme 29

2.2.6. Benzimidazo[2,1-b]-1,3-benzothiazine. Reaction of benzimidazole-2-thiol 90 with pentafluorobenzoyl chloride 61 in pyridine at room temperature for 30 minutes gave 1,2,3,4-tetrafluoro-12H-benzimidazo[2,1-b][1,3]benzothiazin-12-one 91 in 50% yield (Scheme 30).54

Scheme 30

2.2.7. Benzimidazo[1,2-c]quinazolines. The benzimidazo[1,2-c]quinazoline derivatives 94 were obtained in high yields from the cyclocondensation reaction of 2-(2-aminophenyl)benzimidazole 92 with ortho-esters in dimethylacetamide (DMA) under microwave irradiation.55 The same
product 94 (R = H) was prepared from treatment of 2-(2-nitrophenyl)benzimidazole derivative 93 with triethyl-orthoformate in the presence of TiCl₄-Zn (Scheme 31).66,67

![Scheme 31](image)

Scheme 31

6-Cyanobenzimidazo[1,2-c]quinazoline 97 was prepared in 50% yield by treatment of 2-(2-aminophenyl)benzimidazole 92 with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) 95, in chloroform at room temperature in the presence of pyridine, via the intermediate 96 (Scheme 32).68

![Scheme 32](image)

Scheme 32

The cyano group in position 2 of the benzothiazole ring is very reactive and its transformation into acid, amide, amidine and imidate may be easily realised. Thus, microwave irradiation of 2-cyanobenzothiazole 98 with 2-(2-aminophenyl)benzimidazole 92 at 220 °C (150 Watt), in the presence of graphite, resulted in the formation of 6-(2-benzothiazolyl)benzimidazo[1,2-c]quinazolines 99 in good yields (Scheme 33).69

![Scheme 33](image)

Scheme 33
The 6-mercaptobenzimidazo[1,2-c]quinazoline 100 was easily accomplished by the reaction of 92 with carbon disulphide in the presence of methanolic potassium hydroxide either under microwave irradiation at 60 °C or conventional heating (Scheme 34).\(^{60,61}\) Compound 100 was alternatively prepared by cyclization of 3-(2-aminophenyl)-4-oxoquinazoline-2-thione 101 in refluxing DMF in the presence of acetic acid (Scheme 34).\(^{62}\)

![Scheme 34](image)

Mahana et al. reported the conversion of 1H-2-benzimidazol-2-ylbenzanilides 102 into 6-arylbenzimidazo[1,2-c]quinazolines 94 under microwave irradiation using SiO\(_2\)-MnO\(_2\) (95 : 5 mixture) as solid inorganic support (Scheme 35).\(^{63}\)

![Scheme 35](image)

Benzimidazo[1,2-c]quinazolines 103 was readily prepared in high yield by reduction of 2-(2-nitrophenyl)benzimidazole 93 followed by reaction of the obtained 2-(2-aminophenyl)benzimidazole 92 with aldehydes in ethanol/acetic acid mixture (Scheme 36).\(^{64}\)

![Scheme 36](image)
2-(o-Arylideneaminophenyl)benzimidazoles 104 were synthesized via the condensation between 2-(o-aminophenyl)benzimidazole 92 and various aldehydes in refluxing ethanol in the presence of catalytic amount of acetic acid. Oxidative cyclization of 2-(o-arylideneaminophenyl)-benzimidazoles 104 using potassium permanganate in refluxing acetone resulted in the formation of 6-arylbenzimidazo[1,2-c]quinazolines 94 (Scheme 37).  

Scheme 37

Benzimidazo[1,2-c]quinazoline 106 derivative was prepared by the reaction of the benzoyl chloride derivative 105 with 2-(2-aminophenyl)benzimidazole 92 in acetic acid / acetic anhydride mixture (Scheme 38).  

Scheme 38

Condensation of 2-(2-aminophenyl)benzimidazole 92 with 4-arylideneoxazolin-5-ones 107 in acetic acid resulted in the formation of the 6-arylidene-benzimidazo[1,2-c]quinazolines 108 (Scheme 39).  

Scheme 39
Heating a mixture of 2-(2-aminophenyl)benzimidazole 92 and chloroacetylchloride in glacial acetic acid on water-bath at 60 °C gave 6-chloromethylbenzimidazo[1,2-c]quinazoline 109 in 68% yield (Scheme 40).  

\[
\text{Scheme 40}
\]

Reductive cyclization of 1-acetyl-2-(2-nitrophenyl)benzimidazole 110 in the presence of iron powder and HCl in refluxing ethanol produced benzimidazo[1,2-c]quinazoline 94 (R = Me) in 46% yield (Scheme 41).  

\[
\text{Scheme 41}
\]

2.2.8. Benzimidazo[1,2-b]cinnolines. The pyrolysis of arylhydrazonobenzotriazoles 111 resulted in the formation of the benzimidazo[1,2-b]cinnoline derivatives 116 via intramolecular nucleophilic addition involving the arylhydrazono group and the ketone carbonyl moiety followed by cyclization and subsequent elimination of H\(_2\)O and N\(_2\) from the intermediates 112-115 according to the mechanism outlined in Scheme 42.  

2.2.9. Pyridopyridobenzimidazoles. Reaction of 2-chloronicotinoyl chloride 117 with 2-benzimidazoleacetonitrile 42 gave the conjugated nitrile 118 in 97% yield, which was then cyclized on heating to give the corresponding fused tetraheterocyclic system 119 in high yield (Scheme 43).

Scheme 43

2.2.10. Fused macroheterocycles with three heteroatoms. The synthesis of 5H-benzimidazo[1,2-d]-1,4-benzodiazepin-6(7H)-ones 121 was readily accomplished by reaction of 2-(2-aminophenyl)-1H-benzimidazole derivatives 92 and 2-bromoacetyl bromide via the intermediate 120, under microwave irradiation conditions at 300 W in THF and sodium carbonate (Scheme 44).
Scheme 44

2.2.11. Benzimidazo[2,1-b]benzoxazoles. Benzimidazo[2,1-b]benzoxazole 123 was prepared photolytically at 360 nm from 1-(2-benzoxazolyl)benzotriazole 122 (Scheme 45).\textsuperscript{73}

Scheme 45

2.3. With four heteroatoms

2.3.1. Pyrazolo[3,4:4',3']pyrrolo[1,2-a]benzimidazoles. Treatment of hydrazonoyl chlorides 124 with 2-cyanomethylbenzimidazol 42 in ethanolic sodium ethoxide solution at room temperature afforded ethyl 5-amino-1-aryl-4-(benzimidazol-2-yl)pyrazole-3-carboxylate 125. Heating 125 in chloroform in the presence of triethylamine yielded 1-amino-2-arylpyrazolo[3,4:4',3']pyrrolo[1,2-a]benzimidazoles 126 \textit{via} loss of ethanol (Scheme 46).\textsuperscript{74}
Condensation of pyrazolybenzimidazoles 127 with dimethylformamide-dimethylacetal (DMF-DMA) at 100~105 °C led to the formation of pyrazolo[3,4:3',4']pyrrolo[1,2-a]benzimidazole derivatives 128 in 80% yield (Scheme 47).75

\[
\begin{align*}
\text{Condensation reaction} \\
\text{ Scheme 47}
\end{align*}
\]

Refluxing the benzimidazole-2-Eschenmoser hydrazone 129 in benzene for three hours gave 3,3a,4,10b-tetrahydropyrazolo[3',4:3,4]pyrrolo[1,2-a]benzimidazole 130 in 56% yield via the 1,3-dipolar intramolecular [3+2] cycloaddition with thermal cleavage of 129 to generate trans-stilbene (Scheme 48).76

\[
\begin{align*}
\text{Refluxing reaction} \\
\text{ Scheme 48}
\end{align*}
\]

2.3.2. **Pyridazino-pyrrolo-benzimidazoles.** Treatment of 4,5-dichloropyridazine 131 2-cyanomethylbenzimidazoles 42 in the presence of potassium carbonate led to the formation of pyridazino-pyrrolo-benzimidazoles 133 via loss of HCl from the intermediate 132 (Scheme 49).77

\[
\begin{align*}
\text{Treatment reaction} \\
\text{ Scheme 49}
\end{align*}
\]
Treatment of 2-aminobenzimidazoles 134 with 2-chloronicotinic acid 135 in DMF, in the presence of K$_2$CO$_3$, gave the amides 136 which upon reflux in benzene and pyridine afforded the 5-oxopyrido[3',2':5,6]pyrimido[1,2-$a$]benzimidazoles 137 (Scheme 50).

\[
\text{134} \quad \text{R = H, Me, Bz} \\
\text{135} \quad \text{Cl} \\
\text{136} \quad \text{Cl} \\
\text{137} \quad \text{R = H, Me, Bz} \\
\]

**Scheme 50**

2.3.3. **Pyrazolo[4.3:5,6]pyrido[1,2-$a$]benzimidazoles.** The condensation of 5-chloro-4-formylpyrazoles 138 with 2-benzimidazoleacetonitrile 42 in pyridine-DMF mixture led to the pyrazolo[4.3:5,6]pyrido[1,2-$a$]benzimidazoles 139 in high yields (Scheme 51).

\[
\text{42} \quad \text{Ph} \\
\text{138} \quad \text{R = Me, Ph} \\
\text{139} \quad \text{Ph} \\
\]

**Scheme 51**

Pyrazolo[4',3':5,6]pyrido[1,2-$a$]benzimidazoles 141 were prepared by the condensation of pyridobenzimidazoles 140 with hydrazines (Scheme 52).

\[
\text{140} \quad \text{R = CHO, CN} \\
\text{141} \quad \text{R$^1$ = H, NH$_2$; R$^2$ = H, Ph} \\
\]

**Scheme 52**
2.3.4. **Imidazo[4',5':5,6]pyrido[1,2-α]benzimidazoles.** Heating a mixture of the diaminopyridobenzimidazole 142 and formic acid in the presence of aq. HCl at reflux condition followed by neutralization with Et₃N gave 60% yield of 1H-imidazo[4',5':5,6]pyrido[1,2-α]benzimidazoles 143 (Scheme 53).

![Scheme 53](image)

**Scheme 53**

2.3.5. **Oxazolo[4',5':5,6]pyrido[1,2-α]benzimidazoles.** The condensation of 2-amino-1-hydroxypyrido[1,2-α]benzimidazole 144 with acetic anhydride at reflux yielded 2,4-dimethyloxazolo[4',5':5,6]pyrido[1,2-α]benzimidazole 145 which was used as fluorescent brighteners for polyester fibers (Scheme 54).

![Scheme 54](image)

**Scheme 54**

2.3.6. **Pyrimido-pyrido-benzimidazoles.** Treatment of 2-benzimidazoleacetonitrile 42 with arylidenemalononitrile 146 in ethanol containing piperidine gave 1-aminopyrido[1,2-α]benzimidazole-2,4-dicarbonitriles 147 which upon heating with dimethylformamide-dimethylacetal (DMF-DMA) in dioxane gave the corresponding N,N-(dimethylaminomethylene)amino derivatives 148. Condensation of 148 with hydrazine hydrate in ethanol at room temperature afforded 3-amino-4-imino-5-aryl-6-cyanopyrimido[5`4:5,6]pyrido[1,2-α]benzimidazoles 149 (Scheme 55).
Scheme 55

1-Aminopyrido[1,2-a]benzimidazole-2,4-dicarbonitiles **147** underwent cyclocondensation reaction when heated with formamide to yield the pyrimido[5',4':5,6]pyrido[1,2-a]benzimidazoles **150** in 83-93% yields (Scheme 56).\(^{86,87}\)

```
\[
\begin{array}{c}
\text{Ar} = \text{C}_6\text{H}_5, 4-\text{ClC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4 \\
\end{array}
\]
```

Scheme 56

Reaction of 2-cyanomethylbenzimidazoles **42** with ethyl 4-chloro-2-methylthio-5-pyrimidine-carboxylate **151** in refluxing DMF in the presence of K\(_2\)CO\(_3\) led to the formation of the 3-methylthio-5-cyano-12-oxopyrimido[4',5'-4,5]pyrido[1,2-a]benzimidazoles **152** in 85-88% yields via the intermediate **152** (Scheme 57).\(^{88}\)

```
\[
\begin{array}{c}
\text{Ar} = \text{Ph}, 4-\text{ClC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4 \\
\end{array}
\]
```
7-Methyl-3-(methylthio)-5-oxo-6-cyanopyrimido[4',5':5,6]pyrido[1,2-\textit{a}]benzimidazole 156 was prepared from the reaction of 2-benzimidazoleacetonitrile 42 with 4-bromo-2-methylsulfanyl-5-pyrimidinoyl chloride 154 in the presence of \(N,N\)-dimethylbenzylamine followed by intramolecular cyclization of the intermediate 155 (Scheme 58).

**Scheme 58**

### 2.3.7. Pyrido-pyrimido-benzimidazoles

2-Aminonicotinic acid 157 reacted with aromatic acid chlorides in pyridine to give 2-arylpyrido[2,3-\textit{d}][1,3]oxazin-4-ones 158. Treatment of the latter compounds 158 with \(o\)-phenylenediamines 1 in pyridine gave the 6-arylpyrido[2',3':4,5]pyrimido[1,6-\textit{a}]benzimidazoles 159 (Scheme 59).

**Scheme 59**

Compounds 159 were alternatively accomplished by refluxing 2-(2-amino-3-pyridyl)benzimidazole 160 with aromatic aldehydes in acetic acid to give 5,6-dihydropyridopyrimidobenzimidazoles 161. Oxidation of the latter compounds 161 with KMnO\(_4\) in acetone afforded 6-arylpyrido[2',3':4,5]pyrimido[1,6-\textit{a}]benzimidazoles 159 (Scheme 60).

Scheme 61


Scheme 62

![Scheme 63](image)

Scheme 63

2.3.11. Fused macroheterocycles with four heteroatoms. Cycloalkano-1,2,4-triazepino[2,3-a]benzimidazolones 171 were prepared in low yields by condensing 1,2-diaminobenzimidazole 170 with 5 equivalents of ethyl cycloalkanone-2-carboxylates 45 at reflux temperature (Scheme 64).95

![Scheme 64](image)

Scheme 64

2.4. With five heteroatoms
2.4.1. 1,3-Thiazolo[4',5':4,5]pyrimido[1,6-a]benzimidazoles. Reaction of 2-benzimidazoleacetonitrile 42 with arylisothiocyanates in the presence of elemental sulfur and Et₃N in DMF at room temperature gave moderate yields of the thiazolylbenzimidazole derivatives 172. Treatment of the latter compounds with carbon disulfide in DMF under reflux followed by S-alkylation afforded the thiazolo[4',5':4,5]pyrimido[1,6-a]benzimidazole-2(3H)-thiones 173 in 50-65% yields (Scheme 65).96,97
2.4.2. Pyrimido[4’,5’:4,5]thiazolo[2,3-a]benzimidazoles. When 3-aminothiazolo[3,2-a]benzimidazole-2-carbonitrile 174 was treated with formamide and with acetic anhydride at 100 °C it gave the tetracyclic; pyrimido[4’,5’:4,5]thiazolo[2,3-a]benzimidazoles 175 and 176, respectively (Scheme 66). When the thiazolo[3,2-a]benzimidazole 174 was allowed to react with carbon disulphide followed with alkyl iodides in EtOH and KOH it gave the corresponding dialkylthio derivatives of pyrimido[4’,5’:4,5]thiazolo[2,3-a]benzimidazole 177 (Scheme 66).

Reaction of 3-aminothiazolo[3,2-a]benzimidazole-2-carboxamide 178 with aromatic carboxylic acids or with their chlorides afforded the corresponding pyrimido-fused derivatives 179 (Scheme 67).
2.4.3. Triazolo[4,5-b]pyrido[1',2'-a]benzimidazoles. Condensation of 2-(arylhydrazone)-3-iminobutanenitrile 180 with 2-benzimidazoleacetonitrile 42 in acetic acid furnished the corresponding 3-methylpyrido[1,2-a]benzimidazoles 181. Treatment of compounds 181 with cupric acetate in DMF resulted in their oxidative cyclization to give the S-triazolo[4,5-b]pyrido[1',2'-a]benzimidazoles 182 (Scheme 68).  

![Scheme 68](attachment:Scheme-68.png)


![Scheme 69](attachment:Scheme-69.png)

2.4.5. 1,3,4-Oxadiazolo[2',3':2,3]pyrimido[1,6-a]benzimidazoles. The 1,3,4-oxadiazolo[2',3':2,3]pyrimido[1,6-a]benzimidazoles 187 were prepared by treatment of 2-acetonyl-1H-benzimidazolehydrazones 185 with trifluoroacetic anhydride in dioxane at room temperature via loss of water from the intermediate 186 (Scheme 70).  

![Scheme 70](attachment:Scheme-70.png)
Scheme 70

2.4.6. Pyrimido[4',5':4,5]pyrimido[1,2-α]benzimidazole. Intramolecular cyclocondensation of pyrimidobenzimidazolylurea derivatives 188 under the action of K₂CO₃ in refluxing DMF gave the pyrimido[4',5':4,5]pyrimido[1,2-α]benzimidazole derivatives 189 in good yields (Scheme 71).¹⁰⁵

Scheme 71

2.4.7. Pyridazino-pyrimido-benzimidazoles. Reaction of 2-benzimidazoleacetonitrile 42 with arylhydrazones 190 gave the benzimidazolypyriridazines 191 in 90-99%, which were cyclized by acyl chlorides or anhydrides to give 80-94% of the pyridazinopyrimidobenzimidazoles 192 (Scheme 72).¹⁰⁶
2.4.8. Benzimidazo[2′,1′:2,3][1,3]thiazino[6,5-d]pyrimidine. Synthesis of 5H-benzimidazo[2′,1′:2,3][1,3]thiazino[6,5-d]pyrimidine 194 was reported via the cyclocondensation between 2-methylthiopyrimidine-5-carboxaldehyde 193 and 2-mercaptobenzimidazole 90 in DMF at 30-50 °C (Scheme 73).\(^{107}\)

![Scheme 73](image)

2.4.9. Thiadiazino[3′,4′:5,4]pyrrolo[1,2-a]benzimidazole. Reaction of (3,5-dichloro-4H-1,2,6-thiadiazin-4-ylidene)propanedinitrile 195 with 1,2-diaminobenzene 1 in ethanol at 20 °C gave 4-chloro-5-cyano-1,2,6-thiadiazino[3′,4′:5,4]pyrrolo[1,2-a]benzimidazole 198 via loss of HCl and NH\(_3\) molecules as shown in Scheme 74.\(^{108}\)

![Scheme 74](image)

2.4.10. Fused macroheterocycles with five heteroatoms. Reaction of the 1,3-diazepino[3,4-a]benzimidazole-2-thione 199 with acid hydrazides 200 in refluxing butanol gave the tetracyclic triazolo-diazepino-benzimidazole derivatives 201 (Scheme 75).\(^{109}\)
Scheme 75

Treatment of the pyrazoles 202 with cyanogen bromide afforded the 2-amino-1-(5 pyrazolyl)benzimidazoles 203 which upon treatment with 1,2-dibromoethane in the presence of 18-crown-6 in DMF and K₂CO₃ gave the pyrazolo[2,3-a]triazepino[3,2-a]benzimidazoles 204 (Scheme 76).¹¹⁰

Scheme 76

Reaction of the pyrazoles 202 with carbon disulfide yielded the 2-mercapto-1-(5 pyrazolyl)benzimidazoles 205. When compounds 205 were treated with 1,2-dibromoethane in the presence of 18-crown-6, the pyrazolo[3,2-d][1,3,5]thiadiazepino[3,2-a]benzimidazoles 206 were obtained (Scheme 77).¹¹⁰

Scheme 77

Synthesis of the tetracyclic 1,3,5-triazino[1,2-a]benzimidazolium derivatives 210 starting from the methylbenzhydrylamine (MBHA) resin-bound benzimidazoles 207 was reported. Thus,
treatment of 207 with triphenylphosphine at room temperature to give the iminophosphorane intermediates 208 which upon heating with halogenoalkyl isocyanates followed by resin-cleavage using anhydrous HF and anisole at 0 °C gave 210 as outlined in Scheme 78.\textsuperscript{111}

![Scheme 78](image)

\( n = 1, 2 \quad X = \text{Cl, Br} \quad \bullet = \text{MBHA resin} \quad R = \text{butyl, hexyl, cyclohexyl, 3-methoxypropyl}

\textbf{Scheme 78}

\textbf{2.5. With six heteroatoms}

\textbf{2.5.1. Benzimidazo[1,2-\(c\)]pyridazino[4,3-\(e\)]-1,2,3-triazines.} Diazotization of 6-aminobenzimidazolylpyridazine 188 using sodium nitrite in acetic acid at 0-20 °C for 12 h followed by subsequent heating of the intermediate diazonium salt 211 yielded the benzimidazo[1,2-c]pyridazino[4,3-\(e\)]-1,2,3-triazine 212 in 68% yield (Scheme 79).\textsuperscript{112}

![Scheme 79](image)

\( \text{Ar} = 4-\text{MeC}_6\text{H}_4 \)

\textbf{Scheme 79}

\textbf{2.5.2. Triazolo-triazino-benzimidazoles.} Treatment of 2-chloro-1-cyanomethylbenzimidazole 213 with hydrazine in boiling methanol gave 3-hydrazino-1,2,4-triazino[4,3-\(a\)]benzimidazole 214. Reaction of 214 with carboxylic acids gave the triazolotriazinobenzimidazoles 215 in 70-
75% yield (Scheme 80)\(^{113}\)

Scheme 80

Triazinone derivative 216 was converted into its thio-analogue 217 using phosphorus pentasulphide which was subsequently S-methylated then hydrazinated followed by cyclization via its reflux with formic acid to form 4-methyl-1,2,4-triazolo[4',3':4,5][1,2,4]triazino[2,3-\(a\)]benzimidazole 218 (Scheme 81)\(^{114,115}\)

Scheme 81

2.5.3. Pyridazino[6,5-\(a\)]-1,2,4-triazino[2,3-\(a\)]benzimidazoles. Heating the ketone derivative 219 with arylhydrazines produced the arylhydrazones 220 which upon boiling in POCl\(_3\) underwent cyclization into the pyridazino[6,5-\(e\)]-1,2,4-triazino[2,3-\(a\)]benzimidazoles 221 (Scheme 82)\(^{116}\)

Scheme 82
3. Pentacyclic fused benzimidazoles

3.1. With two heteroatoms
Reaction of 2-benzimidazoleacetonitrile 42 with 2-dimethylaminomethylene-1,3-indandione 222 and with 2-dimethylaminomethylene-3-(phenylhydrazono)-indan-1-one 223 yielded the pentacyclic indeno-pyrido-benzimidazoles 224 and 225, respectively (Scheme 83).\(^{117}\)

![Scheme 83](image)

The preparation of 5-methyl-5,6-dihydrobenzimidazo[2,1-\(a\)]benzo[\(f\)]isoquinolines 229 is achieved conveniently in three steps as shown in Scheme 84. Thus, heating of 1-bromo-2-naphthoic acid 226 with \(o\)-phenylenediamines 1 in polyphosphoric acid (PPA) gave 2-(1-bromo-2-naphthyl)-1\(H\)-benzimidazoles 227 which underwent \(N\)-allylation with sodium hydride and 3-bromoprop-1-ene in THF to give 1-allyl-2-(1-bromo-2-naphthyl)benzimidazoles 228 in 68–88% yield. \(Bu_3SnH\) mediated cyclization of 228 in refluxing toluene afforded compounds 229 (Scheme 84).\(^{118}\)

![Scheme 84](image)
(5,6-Dihydrobenzimidazo[1,2-b]benzo[f]isoquinolin-7-yl)-acetonitriles 235 were synthesized by the ring transformation of 4-((piperidin-1-yl)-2-oxo-5,6-dihydro-2H-benzo[h]chromene-3-carbonitriles 230 with 2-benzimidazoleacetonitrile 42 in the presence of powdered KOH in DMF. In this reaction, the carbanion formed \textit{in situ} attacks at C-10b with ring opening and loss of carbon dioxide to give 232 followed by ring closure involving the ring nitrogen of benzimidazole and C-4 of the chromene ring to yield 235 in good yields \textit{via} loss of piperidine as depicted in Scheme 85.\cite{119}

Scheme 85

Treatment of 1,8-naphthoic anhydride derivative 236 with \textit{o}-phenylenediamine 1 in glacial acetic acid gave the pentacyclic fused system; 7H-benzimidazo[2,1-\textit{a}]benzo[\textit{d,e}]isoquinolin-7-ones 237 (Scheme 86).\cite{120}
Scheme 86

3.2. With three heteroatoms
3.2.1. Thieno[2,3-b]pyrido[1,2-a]benzimidazoles. Heating benzimidazolyl-benzothiophene derivative 238 in di(p-bromophenyl)ether at reflux produced the benzothieno[2,3-b]pyrido[1,2-a]benzimidazole derivative 239 (Scheme 87).121

Scheme 87

3.2.2. Indolo[2,3-b]pyrido[1,2-a]benzimidazoles. Heating a mixture of ethyl benzimidazole-2-acetate 240 with the malonate esters 241 gave ethyl 3-hydroxy-1-oxo-pyrido[1,2-a]benzimidazole-4-carboxylates 242. Heating the latter compounds 242 with POCl₃ gave the corresponding 1,3-dichloro derivatives 243. Compound 243 (R = H, R¹ = Ph) was quantitatively converted into the 1-azido-3-chloropyrido[1,2-a]benzimidazole derivative 244 when treated with sodium azide in DMF. Refluxing the azido derivative 244 in bromobenzene gave the indolo[2,3-b]pyrido[1,2-a]benzimidazole derivative 245 (Scheme 88).122
3.2.3. Benzimidazo-pyrido-isoquinolines. 3-Chloroisoquinoline-4-carboxaldehydes 246 were condensed with 2-benzimidazoleacetonitrile 42 in DMF to give the benzimidazo-pyrido-isoquinolines 247 (Scheme 89).\(^{123}\)

\[
\text{Scheme 89}
\]

3.2.4. Indeno[1,2:4,5]pyrimido[1,2-\(a\)]benzimidazoles. Reaction of 2-arylideneindandiones 248 with 2-aminobenzimidazole 134 in refluxing ethanol yielded indeno[1,2:4,5]pyrimido[1,2-\(a\)]benzimidazole-13-ones 249 in high yields (Scheme 90).\(^{124,125}\)
Scheme 90

3.3. With four heteroatoms

2-Amino-3-(benzimidazol-2-yl)thiochroman-4-one 251 was prepared by cyclocondensation of methyl thiosalicylate 250 with 2-benzimidazoleacetonitrile 42. Acylation of 251 with acid chlorides gave the benzimidazobenzothiopyranopyrimidines 252 (Scheme 91).106,126

Scheme 91

Treatment of 2,3,5-trimethyl-1,4-benzoquinone 254 with 2-benzimidazoleacetonitrile 42 gave 2-amino-3-(2-benzimidazolyl)benzofuran 257 via the intermediates 255 and 256. Treatment of compound 257 with acid anhydrides or acid chlorides afforded the benzofuro-pyrimido-benzimidazoles 258 (Scheme 92).127
Scheme 92

4-Chloro-3-nitrocoumarin 259 underwent cyclization when treated with 2-mercaptobenzimidazole 90 to give the coumarino-thiazolo-benzimidazole 260 (Scheme 93).\textsuperscript{124}

Scheme 93

Treatment of 1,5-dibromo-2,4-dinitrobenzene with pyrrolidine afforded 261, which was converted to 262 by reduction followed by acylation. Heating of 262 with formic acid at 70 °C in the presence of H\textsubscript{2}O\textsubscript{2} underwent cyclization into 3H,7H-1,2,8,9-tetrahydropyrrolo[1,2-a]-pyrrolo[1′,2′:1,2]imidazo[4,5-f]benzimidazole 263 in low yield (Scheme 94).\textsuperscript{128-130}

Scheme 94
Photochemical irradiation of 4,6-dichloro-1,3-(N,N'-di(2-pyridyl)benzenediamine 264 in 80% aq. t-butanol gave the linear fused-pentacyclic system 265 in 47% yield (Scheme 95).\textsuperscript{131,132}

\begin{center}
\includegraphics[width=0.5\textwidth]{sri95}

Scheme 95
\end{center}

Coupling of 2-dimethylaminomethylene-1-benzosuberone 266 with 2-aminobenzimidazole diazonium salt 267 gave 9,10-dihydro-8H-benzo[6',7']cyclohepta[1',2'-e]benzimidazo[2,1-c][1,2,4]triazine 270. The formation of the 270 is assumed to proceed via Japp–Klingemann-type cleavage of dimethylaminomethylene moiety from the intermediate 268 then loss of water from 269 (Scheme 96).\textsuperscript{133}

\begin{center}
\includegraphics[width=0.5\textwidth]{sri96}

Scheme 96
\end{center}

Reaction of 2-hydrazinobenzimidazole 271 with tetracyanoethylene (TCNE) 272 gave the 1,2,4-triazepino[1,2-\textalpha]benzimidazole derivs 273 that react with dicyanomethyleneindane-1,3-dione 274 to form the indeno-1,2,4-triazepino[1,2-\textalpha]benzimidazole derivative 275 in 83% yield (Scheme 97).\textsuperscript{134}
Scheme 97

3.4. With five heteroatoms

Treatment of the enaminone 276 with 2-aminobenzimidazole 134 in refluxing ethanol in the presence of piperidine resulted in the formation of pyrido[2'',3'':2',3']-7H-thiopyrano[4',5':4,5]pyrimido[1,2-\(\alpha\)]benzimidazole 278 via the initial attack of the endocyclic-NH of 134 to the exocyclic enamine moiety of 276 followed by the loss of dimethylamine and water molecules from the intermediate 277 (Scheme 98).\(^{135}\)

Scheme 98

Heating 2-amino-3-(2-benzimidazolyl)-1,8-naphthyridine 279 with aromatic aldehydes in acetic acid at reflux gave 6,7-dihydro-7-arylbenzimidazo[1',2':1,6]pyrimido[4,5-\(b\)][1,8]naphthyridines 280 which upon oxidation with KMnO\(_4\) in acetone afforded 7-arylbenzimidazo[1',2':1,6]pyrimido[4,5-\(b\)][1,8]naphthyridines 281 (Scheme 99).\(^{136}\)

\(R = \text{Ph, 4-MeC}_6\text{H}_4, 2\text{-thienyl}\)

Scheme 99
Reaction of 2-chloromethylbenzimidazole 282 with 2-pyridinethione derivative 283 gave the theino[2,3-b]pyridine derivative 284. Reaction of 284 with triethyl orthoformate, acetic anhydride, 4-chlorobenzaldehyde and carbon disulfide led to the formation of pyrido[3',2':4,5]pyrimido[1,6-a]benzimidazole derivatives 285, 286, 287 and 288, respectively, in very high yields (Scheme 100).

Scheme 100

Synthesis of the pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole derivative 291 was reported from the reaction of lactam 290 with 2-fluoronitrobenzene 289 using KOH in dimethoxyethane (DME) in the presence of tetrabutylammonium fluoride, via elimination of HF followed by reduction of the nitro group then water elimination (Scheme 101).

Scheme 101
3.5. With six heteroatoms
Treatment of 3-methylthio-pyrimido[1,6-α]benzimidazole-4-carbonitrile 292 with hydrazine hydrate in refluxing ethanol gave the pyrazolo[3′,4′:4,5]pyrimido[1,6-α]benzimidazole derivative 293. Reaction of 293 with the benzylidene derivatives 146 yielded pyrimido[2″,1″:5′,6′]pyrazolo[3′,4′:4,5]pyrimido[1,6-α]benzimidazoles 294 (Scheme 102).\(^{139}\)

![Scheme 102]

\[
\text{Scheme 102}
\]

1,2,4-Triazolo-[2″,3″:6′,1′]pyrimido[4′,5′:2,3]pyrido[1,2-α]benzimidazoles 295 and 296 were synthesized by refluxing 3-amino-4-imino-5-aryl-6-cyanopyrimido[5′,4′:5,6]-pyrido[1,2-α]benzimidazole 149 with acetic anhydride and with ethyl chloroformate, respectively (Scheme 103).\(^{85}\)

![Scheme 103]

\[
\text{Scheme 103}
\]

3.6. With seven heteroatoms
Heating 2-methyl-3H-pyrimido[4′,5′:4,5]thiazolo[3,2-α]benzimidazol-4-one 176 in POCl\(_3\) followed by hydrazine hydrate gave 4-hydrazino-2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-α]benzimidazole 297. Refluxing the latter 297 with triethylorthoformate afforded 5-methyl-1,2,4-triazolo[4″,3″:3′,4′]pyrimidino[5′,6′:5,4]-thiazolo[3,2-α]benzimidazole 298 in 49% yield (Scheme 104).\(^{140}\)
Scheme 104

Synthesis of azolo[5'″,1''″:3',4'] [1,2,4] triazino[5',6':4,5] pyrimido[1,6-α] benzimidazoles 302 is performed in one-step by the reaction of ethyl 2-cyanomethyl-1H-benzimidazole-1-carboxylate 162 with the heterocyclic diazonium salts 299 via loss of ethanol from the intermediate 301 (Scheme 105).\(^\text{141}\)

Scheme 105

Copper catalyzed cyclocondensation of 2-bromobenzoic acid 303 and 2-aminobenzimidazole 134 in K₂CO₃ and DMF at reflux afforded pyrido[3',2':5,6] pyrimido[1,2-α] benzimidazol-5(6H)-one 304 (X = O) which up on treatment with phosphorus and sulfur in refluxing pyridine gave 5-thione analogue 304 (X = S). Treatment of 304 (X = S) with hydrazine in refluxing ethanol followed by nitrosation gave the fused hexaazapentacyclic system 305 (Scheme 106).\(^\text{142}\)

Scheme 106
Treatment of the pyrazolo[3',4':4,5]pyrimido[1,6-\textit{a}]benzimidazole derivative 293 with active methylene derivatives in the presence of sodium nitrite and acetic acid yielded triazino[2''',1''':5',6']pyrazolo[3',4':4,5]pyrimido[1,6-\textit{a}]benzimidazoles 306 (Scheme 107).\(^{139}\)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{Me} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\end{align*}
\]

\[
\text{X = CN, COMe; Y = CN, COMe, CO}_2\text{Et} \quad R = \text{NH}_2, \text{Me}
\]

Scheme 107

Heating benzimidazo[1,2-\textit{c}]quinazoline-6(5\textit{H})-thiones 100 with hydrazine hydrate in ethanol followed by adding triethylorthoformate at reflux gave benzimidazo[1,2-\textit{c}]-1,2,4-triazolo[4,3-\textit{a}]quinazoline 307 (Scheme 108).\(^{62,143}\)

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{1. N}_2\text{H}_4\text{.H}_2\text{O} & \quad 2. \text{HC(OEt)}_3 \\
\text{2. HC(OET)_3} & \quad \text{reflux}
\end{align*}
\]

Scheme 108

4. Hexa- and heptacyclic fused benzimidazoles

The pyrroloquinoline derivative 309 was prepared in good yield by treating 2-benzimidazoleacetonitrile 42 with methyl tetrahydroquinoline-2-carboxylate 308 in refluxing pyridine containing sodium \(t\)-butoxide. Cyclization of 309 was performed in refluxing acetic anhydride to give the hexacyclic fused system 310 (Scheme 109).\(^{144}\)
Scheme 109

Benzimidazole-2-diazonium salt 267 was coupled with 2-benzimidazoleacetonitrile 42 to yield the hydrazone 311 which was cyclized in refluxing pyridine to produce the 1,2,4-triazino[4,3-a]benzimidazole 312. Heating the latter with ethyl chloroformate in refluxing pyridine produced the fused polyheterocycle 313 (Scheme 110).

Scheme 110

Methylation of the mercaptobenzimidazo[1,2-c]quinazoline 100 with methyl iodide, in dimethylformamide, in the presence of sodium hydride gave the methylthio- derivative 314 in 95% yield. Thermal heating of benzimidazoquinazoline 314 and anthranilic acids 315, neat at 120 °C or in butanol at reflux for 48 h, cannot give more than 50% of the polyheterocyclic skeleton: 5a,10,14b,15-tetraaza-benzo[a]indeno[1,2-c]anthracen-5-ones 316. However, microwave irradiation of 315 with 314 on carbon graphite as support led to the formation of compounds 316 in good yields and in shorter times than for the purely thermal procedures (Scheme 111).
Scheme 111

Phenanthreno[9,10-\(e\)]-1,2,4-triazino[2,3-\(a\)]benzimidazole 318 was prepared by cyclocondensation of 1,2-diaminobenzimidazole 170 with phenanthrene-9,10-dione 317 in refluxing xylene (Scheme 112). 146

Scheme 112

Reaction of 2,5-\(bis\)(bromomethyl)benzene-1,4-dinitrile 319 with \(o\)-phenylenediamine 1 led to the formation of polycyclic skeleton 320 (Scheme 113). 147

Scheme 113

Diaminopyrrolobenzimidazole 321 underwent a condensation reaction with phenanthrene-9,10-dione 317 in acetic acid at reflux to give the hepta-fused-heterocyclic system 322 (Scheme 114). 148
**Scheme 114**

Reaction of 2-methylbenzimidazole 70 with 3-dicyanomethylidine-1-ethyl-2-oxoindoline 323, in ethyl acetate and Et₃N, afforded 1-amino-2-cyano-3,4-dihydro-1'-ethylspiro{benzimidazo[1,2-a]pyridine-3,3'-indolin}-2'-one 325. Reaction of 325 with o-phenylenediamine 1 in refluxing ethanol containing few drops of pyridine gave the benzimidazolyl spiroheterocycle 326 which reacts with triethylorthoformate to give the poly-fused heterocyclic system; 6,7-dihydro-1'-ethylspiro{benzimidazo[1',2':1,6]pyrido[2,3-d]benzimidazo[2'',1''-f]pyrimidine-6,3'-indolin}-2'-one 327 in 45% yield (Scheme 115).

**Scheme 115**

*Bis-hydrazone*yl chlorides 329 reacted with 2-methylthiobenzimidazole 328 in 1:2 molar ratio in refluxing ethanol in the presence of triethylamine and gave 1,1'-diaryl-3,3'-bi-1,2,4-
triazolo[4,5-a]benzimidazoles 331 via loss of two molecules of MeSH from the intermediate 330 (Scheme 116).\textsuperscript{150}

Scheme 116

Condensation of 3,5-di-(tert-butyl)-1,2-benzoquinone 332 with 2-methylbenzimidazoles 70 proceeded under reflux in o-xylene to yield the benzimidazolyldene derivative 333. Reaction of the latter 333 with another molecule of 2-methylbenzimidazole 70 then rearranged to give the intermediate 334 which upon oxidation by an excessive amount of the o-quinone 332 gave rise to the polycyclic fused benzimidazoles 337 (Scheme 117).\textsuperscript{151}

Scheme 117
Reaction of 3-β-acetoxy-17-chloro-16-formyl-5α-androst-16-ene 338 with 2-benzimidazoleacetonitrile 42 in refluxing ethanol in the presence of piperidine yielded the benzimidazopyridoandrostan derivative 339 in high yield (Scheme 118).  

Scheme 118

Treatment of 2-hydroxymethylene-3-androstanedione derivative 340 with 2-aminobenzimidazole 134 in refluxing ethanol gave the androstan[3,2-b]pyrimido[1,2-a]benzimidazole derivatives 341 in excellent yields (Scheme 119).  

Scheme 119

Cyclocondensation reaction of 2-bromo-3-cholestanone 342 with 2-mercaptobenzimidazole 90 under refluxing ethanol gave the cholestano-thiazolo-benzimidazole derivatives 343 (Scheme 120).  

Scheme 120
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 published about 75 scientific papers in distinguished international journals.

Bakr F. Abdel-Wahab was born in 1978 in Mansoura, Egypt. He is currently a researcher of organic chemistry at National Research Centre, Cairo, 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.