Hindawi Publishing Corporation
Journal of Chemistry
Volume 2014, Article ID 217596, 15 pages
http://dx.doi.org/10.1155/2014/217596

Review Article

Fused Imidazopyrazoles: Synthetic Strategies and Medicinal Applications

Rizk E. Khidre,[1,2] Bakr F. Abdel-Wahab,[3,4] and Othman Y. Alothman[5]

[1] *Chemical Industries Division, National Research Centre, Dokki, Giza 12622, Egypt*
[2] *Chemistry Department, Faculty of Science, Jazan University, Saudi Arabia*
[3] *Applied Organic Chemistry Department, National Research Centre, Dokki, Giza 12622, Egypt*
[4] *Chemistry Department, Faculty of Science, Shaqra University, Al Dawadmi, Saudi Arabia*
[5] *Chemical Engineering Department, King Saud University, P.O. Box 800, Riyadh 11421, Saudi Arabia*

Correspondence should be addressed to Rizk E. Khidre; rizkarein@yahoo.com and Bakr F. Abdel-Wahab; bakrfatehy@yahoo.com

Received 7 June 2014; Accepted 18 July 2014; Published 14 August 2014

Academic Editor: Liviu Mitu

The current review summarizes the known synthetic routes of fused imidazopyrazoles. This review is classified into two main categories based on the type of annulations, for example, annulation of the imidazole ring onto a pyrazole scaffold or annulation of the pyrazole ring onto an imidazole scaffold. Some medicinal applications of imidazopyrazoles are mentioned.

1. Introduction

Over the past two decades, imidazopyrazole and related drugs have been attracting the attention of the medicinal chemists due to their considerable biological and pharmacological activities. Medicinal properties of imidazopyrazole derivatives include anticancer [1–11]; for example, 2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazoles have *in vivo* effects on the proliferation of mouse leukemic [1], and the same compound has antiviral activity in herpes simplex virus type 1-infected mammalian cells [12], and substituted imidazo[1,2-*b*]pyrazole (cephem derivatives) is used as antimicrobials [13–15]. Also, imidazo[1,2-*b*]pyrazole nucleus used as photographic dye-forming couplers comprise, useful in photographic materials and processes, have improved absorption [16–19]. In view of the above fact and in connection to our previous review articles about biologically active heterocyclic systems [20–25], we decided to prepare this review to present for the reader a survey of the literature of the different azoles linked directly with imidazole nucleus; also some of the medicinal applications are mentioned.

Fused imidazopyrazole refers to three isomers according to the conjunction between imidazole and pyrazole nucleus. The three isomers of imidazopyrazole are shown in Figure 1.

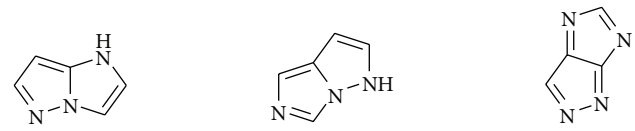
Today, there are several approaches available for the synthesis of imidazopyrazoles and they may be classified into two main categories:

(a) annulation of the imidazole ring onto a pyrazole scaffold;

(b) annulation of the pyrazole ring onto an imidazole scaffold.

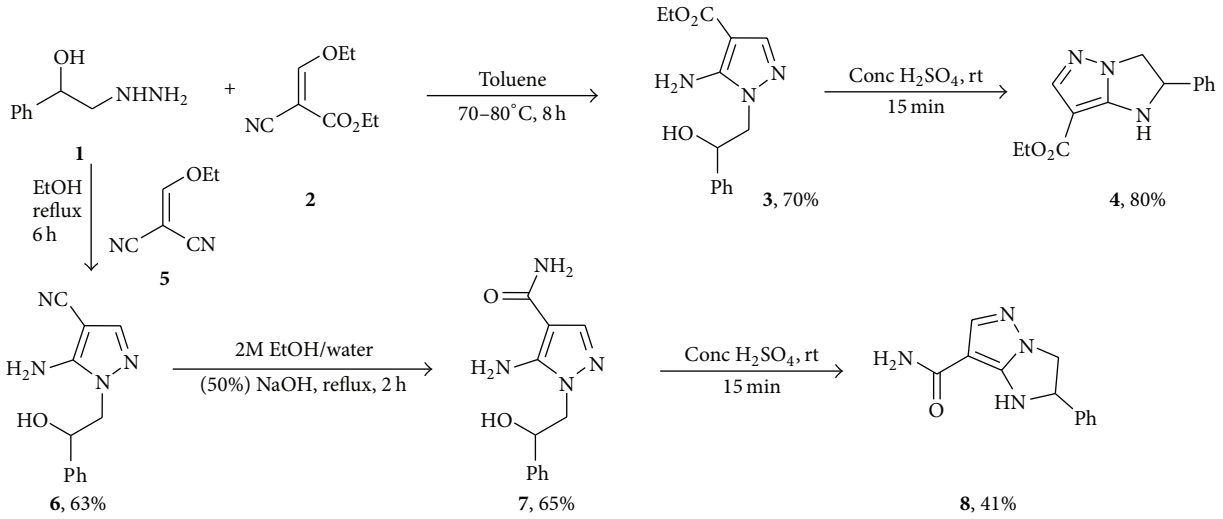
2. Synthesis by Annulation of the Imidazole Ring onto a Pyrazole Scaffold

2.1. Synthesis of Imidazo[1,2-b]Pyrazole. Ethyl 5-amino-1-(2-hydroxy-2-phenylethyl)-1*H*-pyrazole-4-carboxylate **3**, obtained by reaction of 2-hydrazino-1-phenylethanol **1** with ethyl (ethoxymethylene)cyanoacetate **2**, was treated with concentrated sulphuric acid at 0°C to give the 2-phenyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole-7-carboxylate **4**. Also, on condensation of **1** with ethoxymethylenemalononitrile in absolute ethanol the 5-amino-1-(2-hydroxy-2-phenylethyl)-1*H*-pyrazole-4-carbonitrile **6** was obtained and then hydrolysed in alkaline ethanol/water solution to form 5-amino-1-(2-hydroxy-2-phenylethyl)-1*H*-pyrazole-4-carboxamide **7**.



1*H*-Pyrazolo[1,5-*a*]imidazole (a) 1*H*-Imidazo[1,5-*b*]pyrazole (b) Imidazo[4,5-*c*]pyrazole (c)

Figure 1



Scheme 1

Finally, 2-phenyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole-7-carboxamide **8** was prepared by cyclization in the presence of concentrated sulphuric acid [26]. The synthesized 2-phenyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole derivatives were tested *in vitro* in order to evaluate their ability to interfere with human neutrophil functions. All tested compounds showed strong inhibition of fMLP-OMe-induced chemotaxis (Scheme 1) [26, 27].

The synthesis of imidazo[1,2-*b*]pyrazoles was reported; thus the condensation of the hydrazinoacetaldehyde synthon with electrophiles such as ethyl (ethoxymethylene)cyanoacetate **2** and 3-oxo-2-phenylpropanenitrile **9** gave ethyl 5-amino-1-(2,2-diethoxyethyl)-1*H*-pyrazole-4-carboxylate **10** and 1-(2,2-diethoxyethyl)-4-phenyl-1*H*-pyrazol-5-amine **12**, respectively. The latter compounds were cyclized in acid to produce imidazopyrazoles **11** and **13**, respectively. Similarly, ethyl 5-amino-1-(2,2-diethoxyethyl)-1*H*-pyrazole-4-carboxylate **14** was reacted with hydrazine followed by reaction with nitrous acid to afford 1*H*-imidazo[1,2-*b*]pyrazole-7-carbonyl azide **15** rearranged to produce carbamates **16** [28] (Scheme 2).

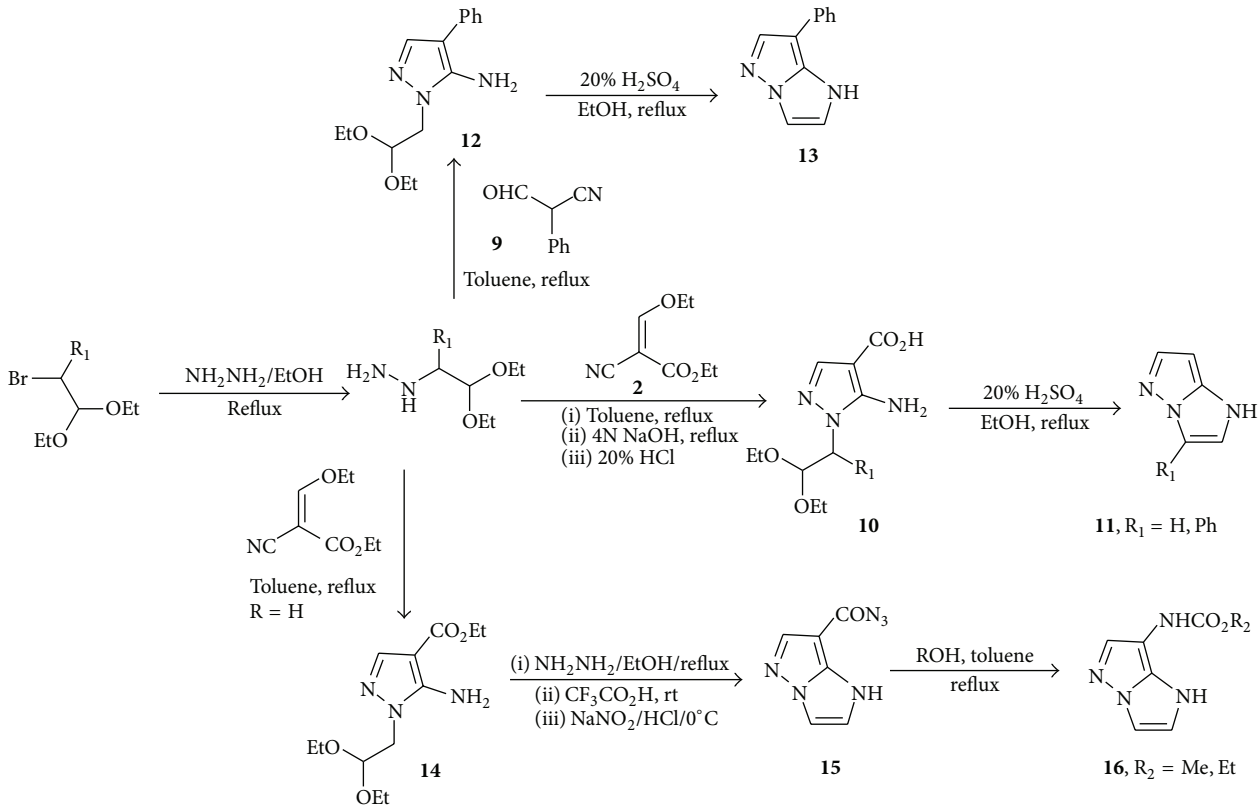
A series of 1*H*-imidazo[1,2-*b*]pyrazolecarboxylate derivatives were synthesized from reaction between ethyl cyanopyruvate sodium **17** and hydrazinoacetaldehyde diethylacetal in a biphasic water/chloroform in the presence of sulfuric acid to give ethyl 5-amino-1-(2,2-diethoxyethyl)-1*H*-pyrazole-3-carboxylate **18** followed by cyclization to give imidazopyrazole **19**. The synthesized compounds were evaluated *in vitro* for 5-HT3 receptor affinity. The biochemical data show significant activity for these derivatives (Scheme 3) [29]. On the other hand, imidazo[1,2-*b*]pyrazole-7-carbonitrile was prepared by the condensation of 2-hydrazinoacetaldehyde diethyl acetal with (ethoxymethylene)malononitrile **5**, which gave pyrazole followed by ring closure under acid-catalyzed hydrolytic conditions to afford imidazopyrazole **21** [30] (Scheme 3).

Amino-1-(2-hydroxyethyl)pyrazole **22** was formylated, treated with methanesulfonyl chloride and triethylamine, and then followed by cyclization with sodium hydride, to give 1-formyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole **23** [31] (Scheme 4).

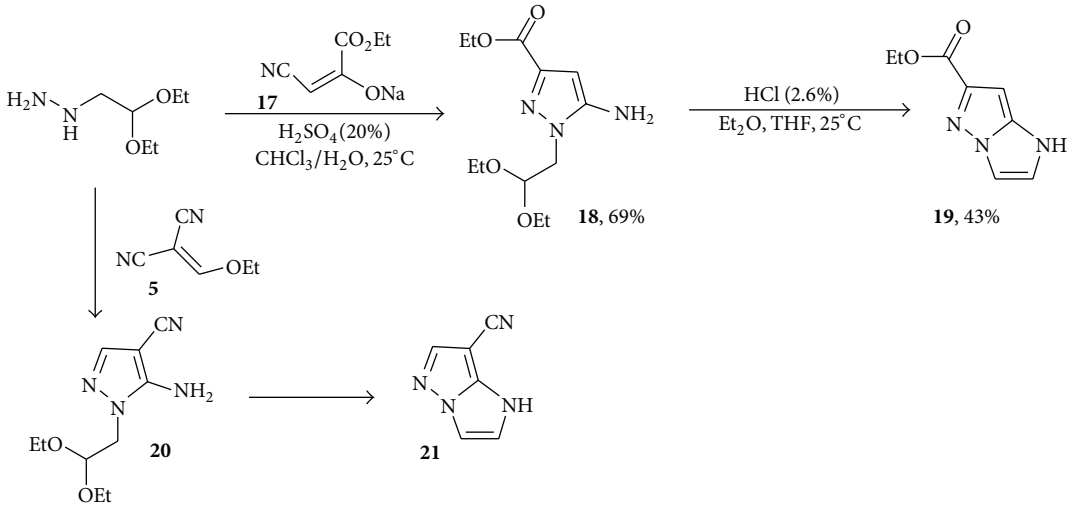
3-Amino-5-phenylpyrazoles **25** were reacted with 2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-2-oxo-*N*-phenylethanehydrazonoyl bromide **24** in boiling ethanol to give 3-phenylazo-2-(4-methyl-2-phenyl-thiazol-5-yl)-6-phenyl-5*H*- imidazo[1,2-*b*]pyrazoles **26** (Scheme 5) [32].

In the same fashion, it was reported that equimolar amounts of hydrazonoyl bromides **27** and **32** were reacted with 5-amino-3-phenyl-1*H*-pyrazole **25** in ethanol under reflux to afford the corresponding imidazo[1,2-*b*]pyrazoles **31** and **34**, respectively (Scheme 6) [33, 34].

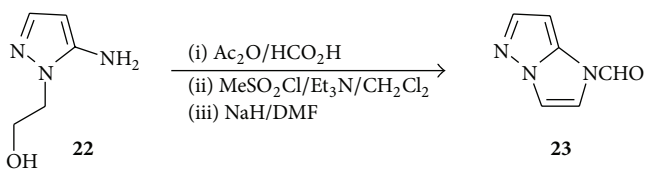
5-Aminopyrazole **25** was reacted with hydrazonyl halides such as 2-oxo-*N*′-arylpropanehydrazonoyl chlorides **35** [35–37] and 2-bromobenzofurylglyoxal-2-arylhydrazones **37** [38] in ethanol at reflux temperature to give 6-phenyl-3-(aryldiazenyl)-5*H*-imidazo[1,2-*b*]pyrazoles **36** and **38**, respectively (Scheme 7).



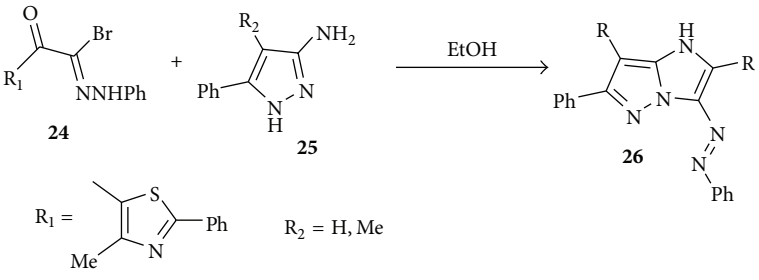
Scheme 2



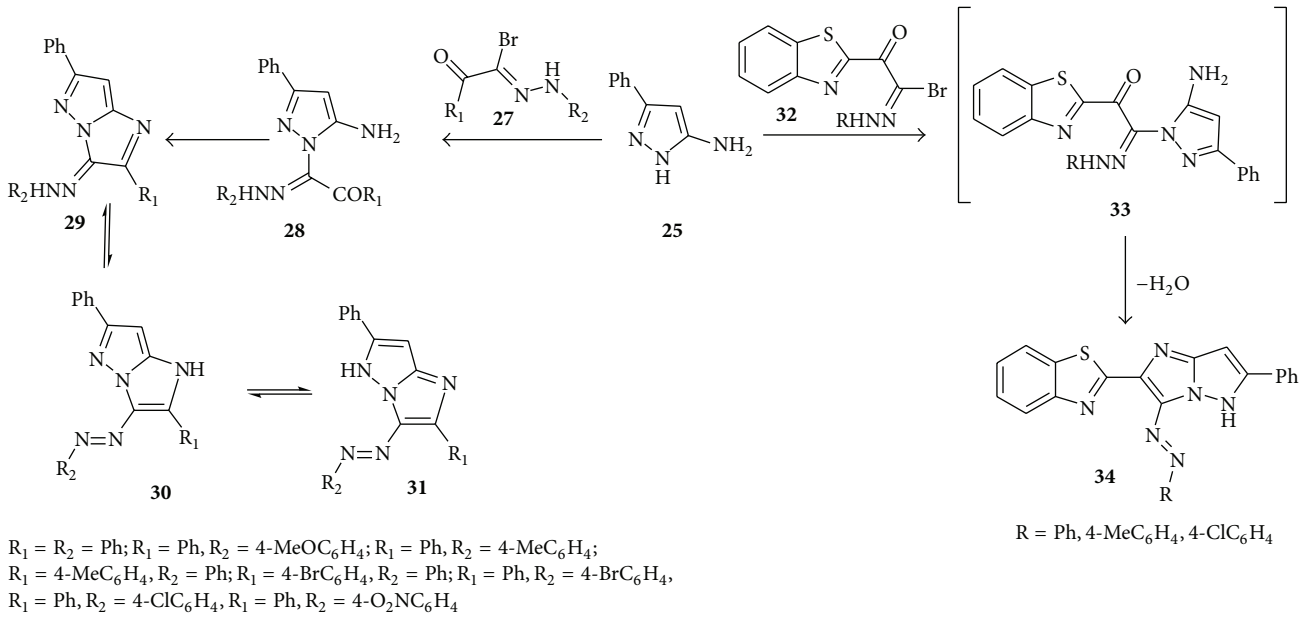
Scheme 3



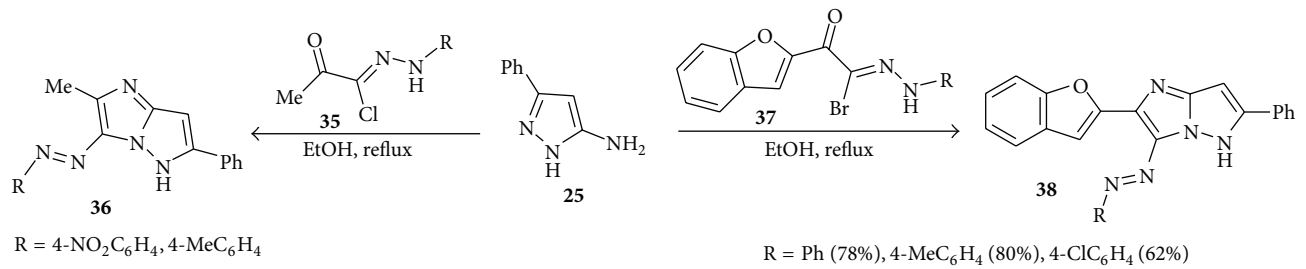
Scheme 4



Scheme 5



Scheme 6



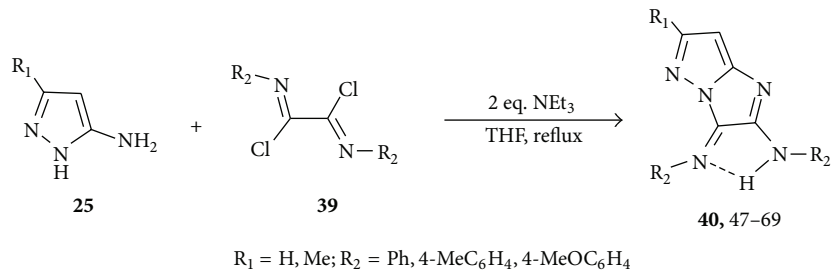
Scheme 7

Regioselective cyclization reaction between compound **25** and oxaldiimidoyl dichlorides **39** in THF in the presence of triethylamine afforded 3*H*-imidazo[1,2-*b*]pyrazoles **40** in good yields [39] (Scheme 8).

Appel's dehydration conditions of (2-oxo-1,2-diphenylethylidene)hydrazono)-*N*-phenylbutanamide **41**, prepared from reaction of benzil hydrazone with acetoacetanilide, led to azinoketimine **42** which underwent electrocyclic ring closure under the reaction conditions to give imidazo[1,2-*b*]pyrazole-2-one **49** and 1*H*-imidazo[1,2-*b*]pyrazole **50** [40] (Scheme 9).

In the same fashion, treatment of *N*-aziridinylimino carboxamides **52** prepared by the reaction of 1-amino-2-phenylaziridine **51** with acetoacetanilide in tetrahydrofuran at room temperature with a mixture of triphenylphosphine, carbon tetrachloride, and triethylamine (Appel's condition) in dichloromethane at reflux temperature led to the formation of 2,3-dihydro-1*H*-imidazo[1,2-*b*]-pyrazoles **56** (54–82%) as a major product [41] (Scheme 10).

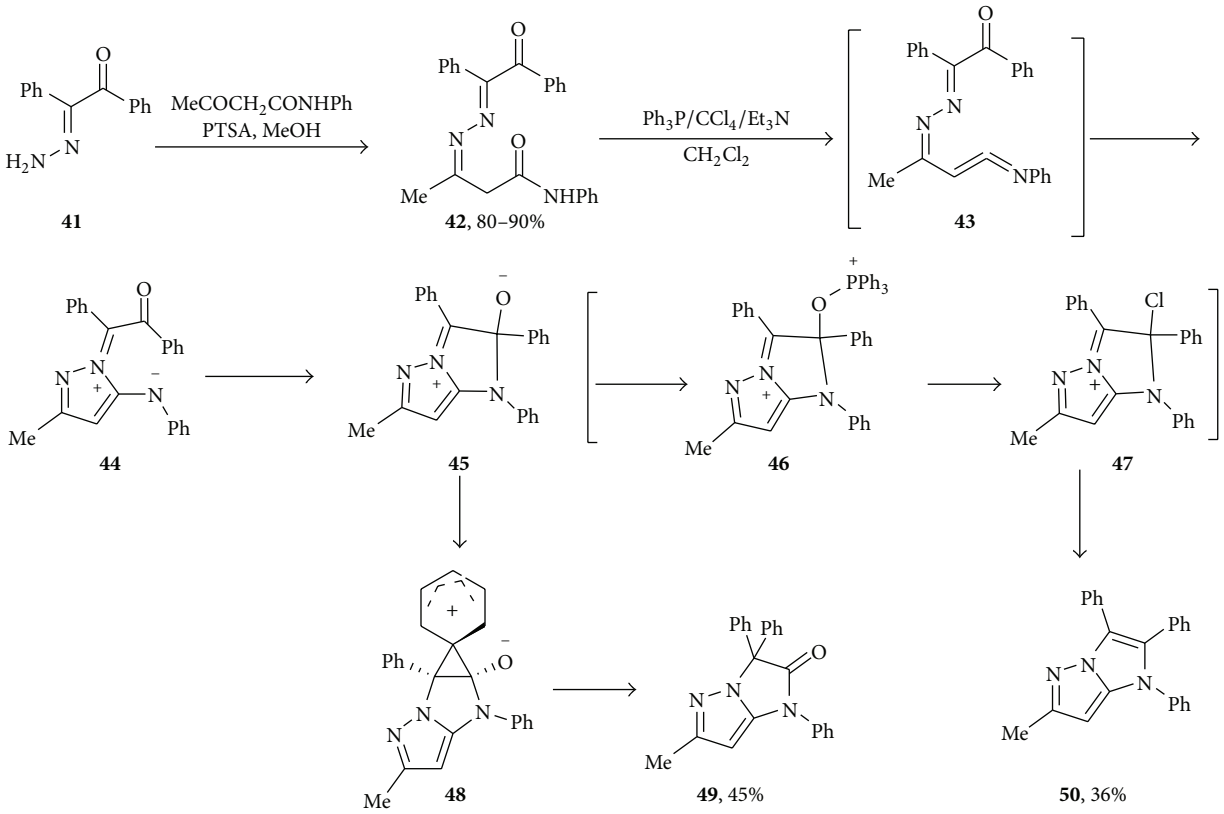
5-Amino-3-phenyl-1*H*-pyrazole **25** was reacted with hydroximoyl chloride **57** in ethanol at room temperature to give 3-nitroso-2-aryl-6-phenyl-1*H*-imidazo[1,2-*b*]pyrazoles **58** in 60–75% yields [30] (Scheme 11).



25 **39** **40,** 47–69

R_1 = H, Me; R_2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 8



41 **42**, 80–90% **43**

44 **45** **46** **47**

48 **49**, 45% **50**, 36%

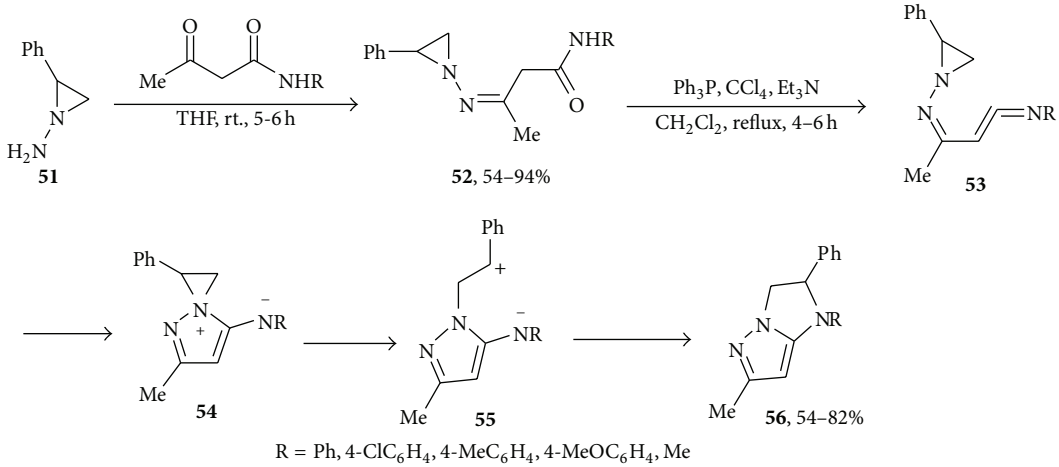
Scheme 9

Intermolecular aza-Wittig reaction of 5-(triphenylphosphoranylideneamino)-3-phenylpyrazole **60** with α-chloroketone, namely, 2-chloro-2-phenylacetophenone, chloroacetylchloride, and 1-chloro-1-(phenyldiazenyl)propan-2-one, afforded the imidazo[1,2-*b*]pyrazole derivatives **62**a–c *via* elimination of hydrogen chloride from the initially formed intermediate **61** [42] (Scheme 12).

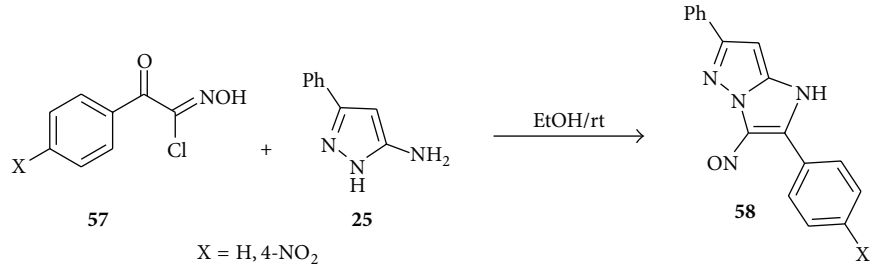
A series of 2-aryl-7-cyano/ethoxycarbonyl-6-methylthio-1*H*-imidazo[1,2-*b*]pyrazoles **65** have been synthesized in moderate to good yields, *via* reaction of 5-amino-4-cyano/ethoxycarbonyl-3-methylthio-1*H*-pyrazole **63** with either α-bromoacetophenones or α-tosyloxyacetophenones followed by cyclocondensation of the formed intermediate **64** under acidic conditions. Using α-tosyloxyacetophenones instead of α-bromoacetophenones in the previous reaction has such advantages that the reactions gave the final products in higher yields, became more eco-friendly as well as less time consuming, and avoided highly lachrymatory and toxic α-haloketones which are now not available commercially. Fungicidal activity of the synthesized compound was studied [43, 44] (Scheme 13).

3-Antipyrinyl-5-aminopyrazole **66** was reacted with either ethyl α-chloroacetoacetate or chloroacetyl chloride to yield 1-(2-hydroxy-3*H*-imidazo[1,2-*b*]pyrazole-3-yl)ethanone **67** and 3*H*-imidazo[1,2-*b*]pyrazole-2-ol **68**, respectively [45] (Scheme 14).

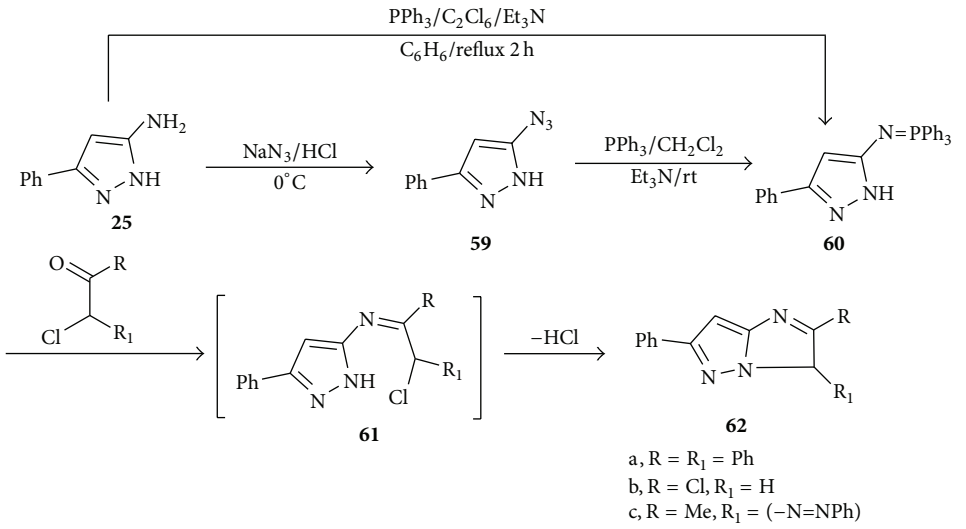
7-Chloro-6-methyl-2-phenyl-3-(phenylsulfinyl)-1*H*-imidazo[1,2-*b*]pyrazole **69**, useful as starting materials for color photograph couplers and dyes, was prepared from treating 5-amino-4-chloro-3-methyl-1*H*-pyrazole **68** with phenacyl



Scheme 10



Scheme 11

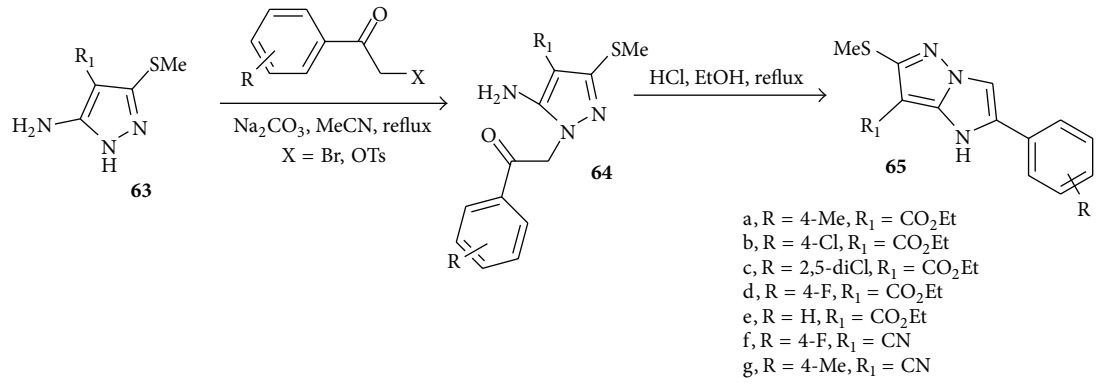


Scheme 12

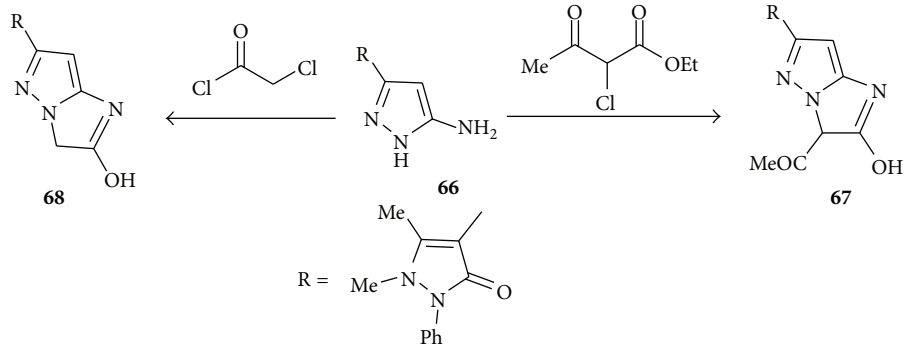
bromide in the presence of γ-collidine, reacting the product with PhSSPh in the presence of NaH and heating at 60° in the presence of HCl [46] (Scheme 15).

Ethyl 2-hydrazinylacetate hydrochloride **70** was reacted with 2-oxo-*N*′,2-diphenylacetohydrazonoyl cyanide **71** to afford 6-phenyl-7-(phenyldiazenyl)-1*H*-imidazo[1,2-*b*]pyrazole-2(3*H*)-one **72** [47] (Scheme 16).

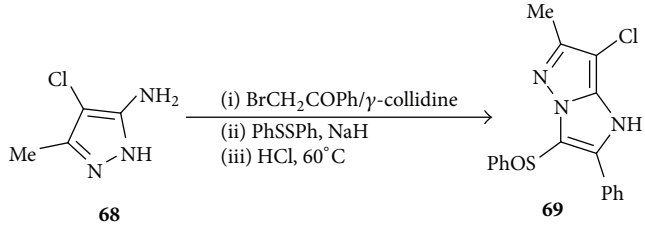
1*H*-Imidazo[1,2-*b*]pyrazole-7-carbonitrile derivatives, which are spleen tyrosine kinase (syk) inhibitors, are useful in the treatment of syk-mediated diseases. Thus, substituted imidazo[1,2-*b*]pyrazole-7-carbonitrile **76** was prepared by cyclocondensation of aminopyrazolecarbonitrile **73** with 3,4-dimethoxyphenyl isonitrile **74** and 2,4-dihydro-2-oxo-1*H*-benzo[d][1,3]oxazine-7-carbaldehyde **75** [35] (Scheme 17).



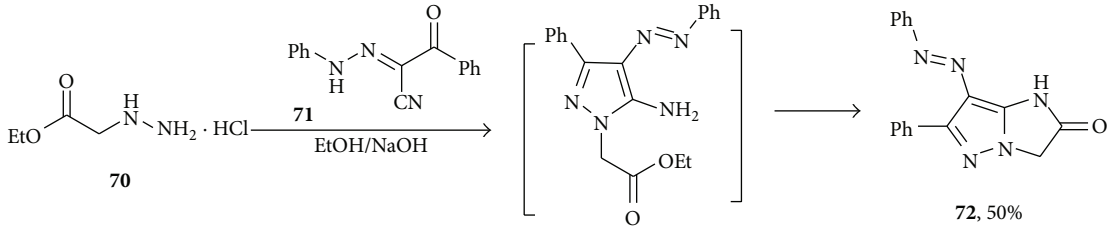
Scheme 13



Scheme 14



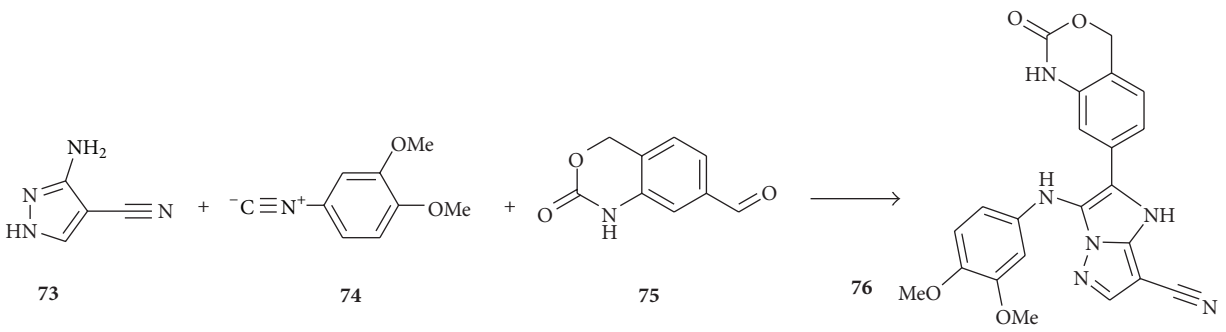
Scheme 15



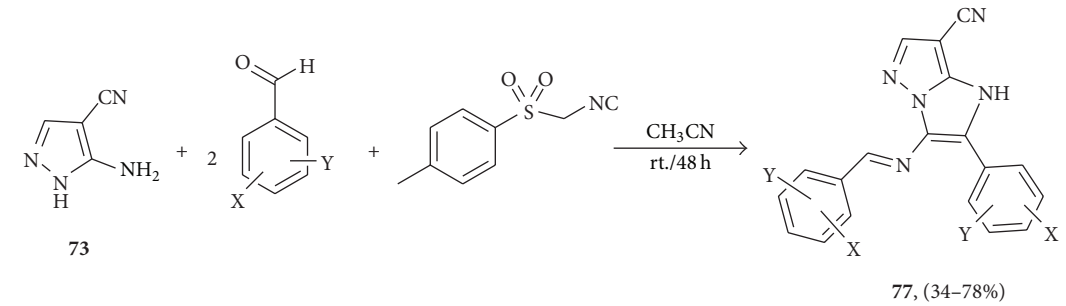
Scheme 16

In a recent report [36], 3-(benzylideneamino)-2-phenyl-5*H*-imidazo[1,2-*b*]pyrazole-7-carbonitriles **77** were synthesized, in moderate to high yields, from one-pot, four-component condensation reaction of aromatic aldehydes, toluene-4-sulfonylmethyl isocyanide, and 5-amino-1*H*-pyrazole-4-carbonitrile **73** in acetonitrile in the presence of p-toluenesulfonic acid as a catalyst at room temperature (Scheme 18).

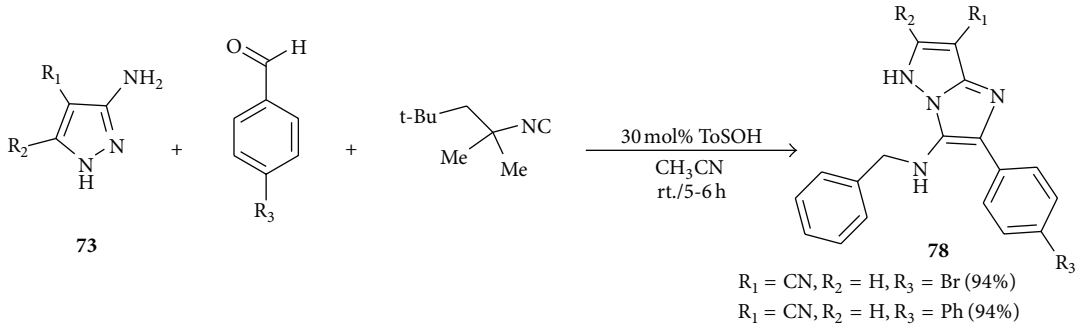
Similarly, A series of *N*-alkyl-2-aryl-5*H*-imidazo[1,2-*b*]pyrazole-3-amines **78** in good to high yields were synthesized by the three-component condensation of an aromatic aldehyde, aminopyrazole, and isocyanide in acetonitrile in



Scheme 17



Scheme 18



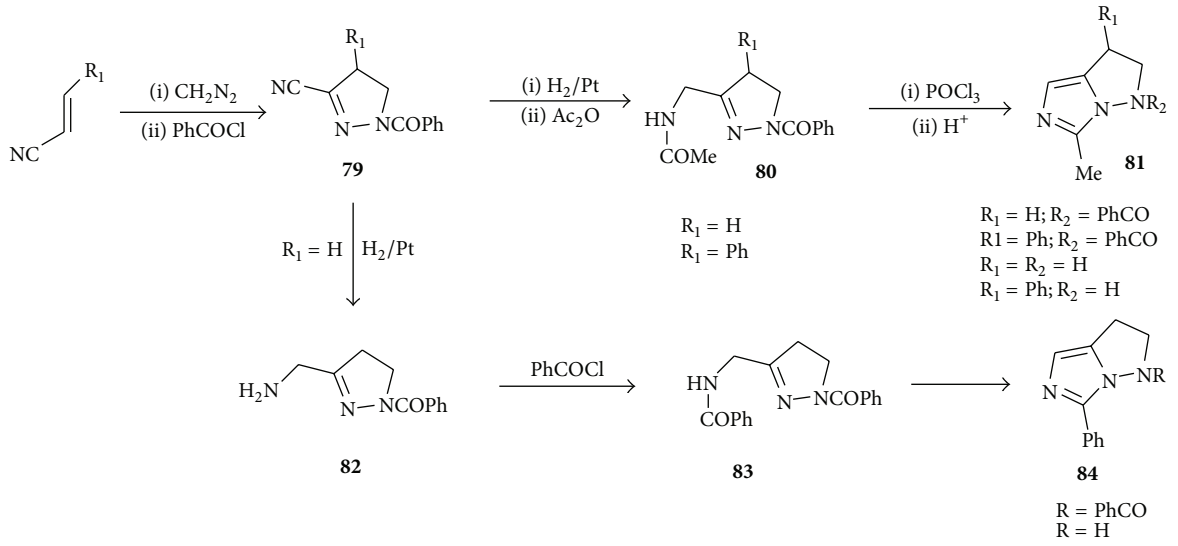
Scheme 19

the presence of 4-toluenesulfonic acid as a catalyst at room temperature [37] (Scheme 19).

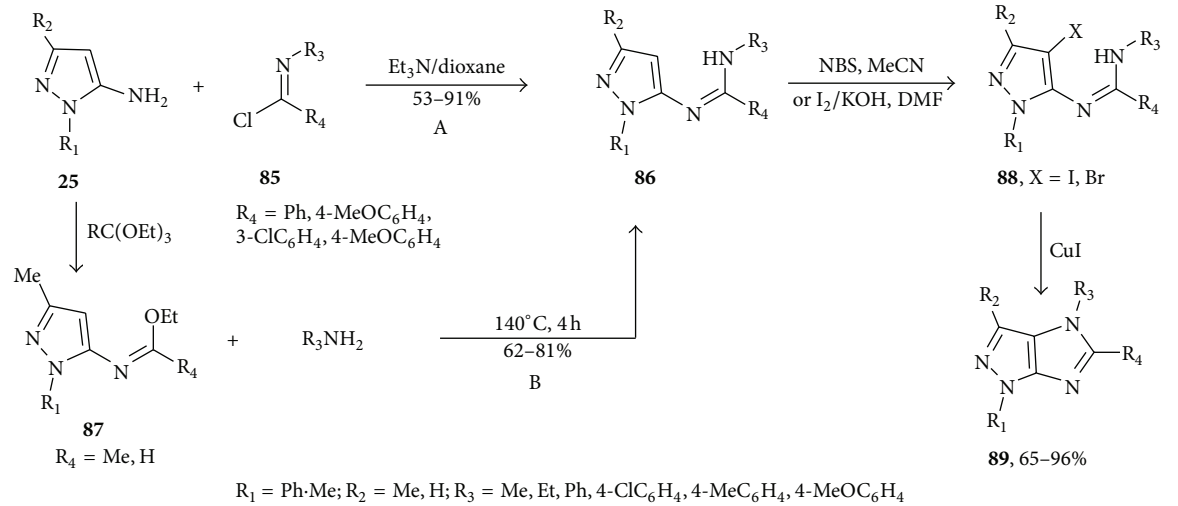
2.2. Syntheses of Imidazo[1,5-b]Pyrazole. 2,3-Dihydroimidazo[1,5-*b*]pyrazoles **84** containing a structurally heterocyclic system corresponding to cyclized histamine were prepared by cyclodehydration of substituted *N*-(3-pyrazolylmethyl)acetamides **80** or *N*-(3-pyrazolylmethyl)acetamides **83**, obtained by the catalytic hydrogenation of 1-benzoyl-4,5-dihydro-1*H*-pyrazole-3-carbonitriles **79** followed by acylation. These latter precursors **79** were conveniently obtained by the cycloaddition of substituted acrylonitriles with CH_2N_2 followed by *in situ* benzoylation using benzoyl chloride [48] (Scheme 20).

2.3. Imidazo[4,5-c]Pyrazole. Recently, imidazo[4,5-*c*]pyrazoles **89** were synthesized in 65–96% yields by cyclization of *N′*-(4-halopyrazol-5-yl)amidine **88** under the conditions of copper-catalyzed cross-coupling reactions. Compound **88** was obtained *via* two pathways: (A) the reaction of 5-aminopyrazoles **25** with imidoyl chlorides **85** in dry 1,4-dioxane at room temperature and (B) the reaction of imino esters **87** with substituted aniline, followed by halogenations using either NBS in boiling acetonitrile or elementary iodine in the presence of KOH at room temperature [49] (Scheme 21).

Nitrosation of compound **25** with sodium nitrite yielded the 4-nitrosopyrazoles **90**, which were reduced to the diamines **91** with hydrazine hydrate in the presence of palladized charcoal. Since **91** were often



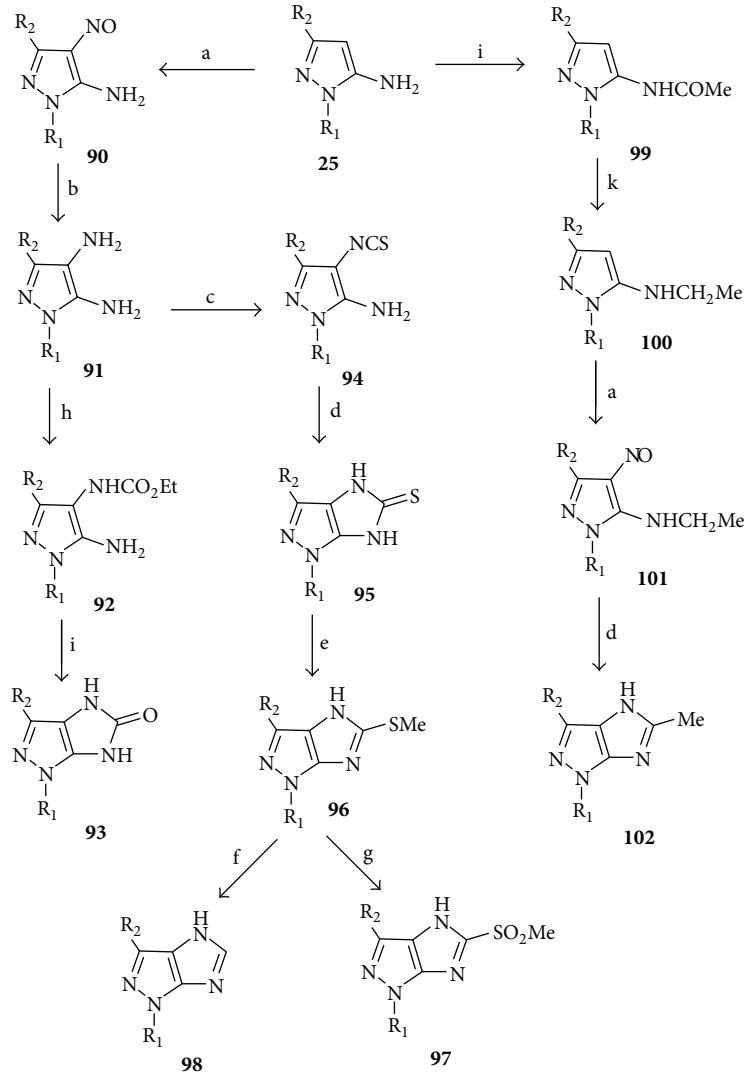
Scheme 20



Scheme 21

unstable during the usual work-up for isolation, they were directly reacted with thiophosgene to give the isothiocyanatopyrazoles **94**. Heating of **94** in pyridine gave the imidazo[4,5-*c*]pyrazole-5-thiones **95**. In order to obtain 5-substituted derivatives imidazo[4,5-*c*]pyrazole-5-thiones **95** were reacted with iodomethane in sodium hydroxide to give 5-methylthio derivatives **96**, which were subjected to hydrogen peroxide to yield 3-methyl-5-methylsulfonyl-1-phenylimidazo[4,5-*c*]pyrazoles **97**. Compound **96** was submitted to hydrogenolytic desulfurisation in the presence of Raney nickel, thus producing **98**. When heated at 200°C for 2 h, 5-amino-4-ethoxycarbonylaminopyrazole **92**, obtained by treatment of **91** with ethyl chloroformate, afforded imidazo[4,5-*c*]pyrazole-5-one **93**. The key step in the synthesis of 5-methylimidazo[4,5-*c*]pyrazole **102** was the intramolecular cyclodehydration in boiling pyridine of 5-ethylamino-4-nitrosopyrazole **101**, which was prepared from 5-acylaminopyrazole **100**. Reduction of **99** with $LiAlH_4$ afforded the 5-alkylaminopyrazole **100**. Nitrosation of **100** with amyl nitrite in the presence of hydrochloric acid yielded **101**. Imidazo[4,5-*c*]pyrazoles **93**, **95**, **96**, **97**, **98**, and **102,** which were considered of interest as potential herbicides, were examined for the preemergence, postemergence, and posttransplant control of weeds in rice against broadleaf and grass weed species. Some imidazo[4,5-*c*]pyrazoles have potential herbicidal activity against a wide range of weeds, with 5-thiomethyl **96** and 5-unsubstituted derivatives being the most efficient. No herbicidal activity was observed in the 5-methylsulfonylimidazo[4,5-*c*]pyrazole **97** and imidazo[4,5-*c*]pyrazolone **93** series [50] (Scheme 22).

Similarly, imidazo [4,5-*c*] pyrazoles **106** were synthesized by acylation 5-aminopyrazoles **25** either with benzoyl chloride or with acetic anhydride to give 5-acylaminopyrazoles



Scheme 22: Reagents: a, NO^+; b, N_2H_4, Pd/C; c, $CSCl_2$; d, reflux, pyridine; e, MeI; f, Raney Ni; g, H_2O_2; h, $ClCO_2Et$; i, heat at 200°C, 2 h; j, Ac_2O; k, $LiAlH_4$.

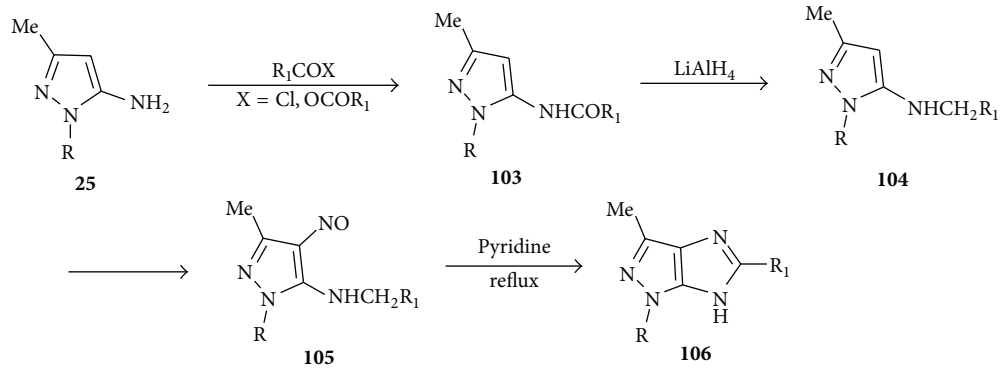
103. Reduction of compounds **103** with $LiAlH_4$ afforded the corresponding 5-alkylaminopyrazoles **104**. Nitrosation of compounds **104** with amyl nitrite in the presence of hydrochloric acid yielded 5-alkylamino-4-nitrosopyrazoles **105**. Cyclisation of compounds **105** to imidazo [4,5-*c*] pyrazoles **106** was achieved by heating **105** in boiling pyridine for 15–90 min [51] (Scheme 23).

3. Syntheses by Annulation of the Pyrazole Ring onto an Imidazole Scaffold

3.1. Synthesis of Imidazo[1,2-b]Pyrazole. 2,3-Dihydro-1*H*-imidazo[1,2-*b*]pyrazoles **112** and **113** were prepared by hydrazinolysis with 2,4-dinitrophenylhydrazine of ethyl 2-(1-(benzylideneamino)imidazolidin-2-ylidene)-2-nitroacetate **110** which was conveniently prepared from ethyl nitroacetate and *N*-benzylidene-2-(methylthio)-4,5-dihydro-1*H*-imidazol-1-amine **109** as described in Scheme 24 [52].

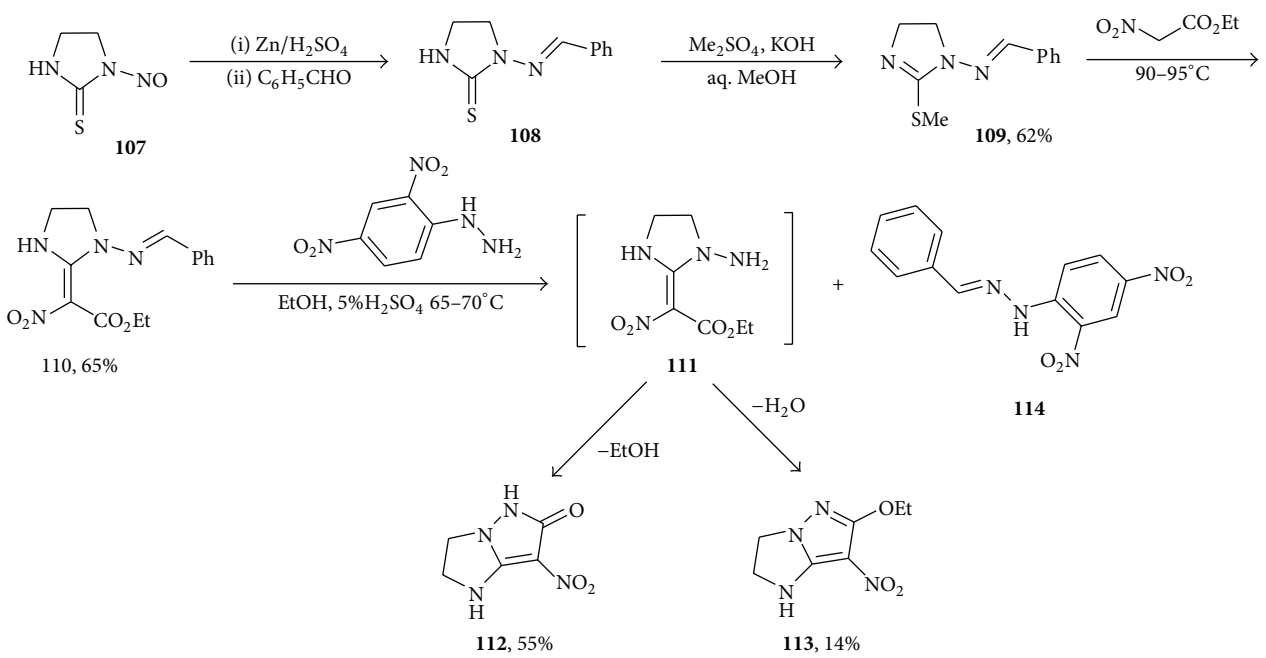
3.2. Synthesis of Imidazo[1,5-b]Pyrazole. Dihydro-1*H*-imidazo[1,5-*b*]pyrazole-4,6(2*H*,5*H*)-dione **119** was synthesized from treatment 1-(benzylideneamino)-5-(2-hydroxyethyl)hydantoin **117**, prepared from treated sodium salt of acetone semicarbazone **115** with α-bromo-γ-butyrolactone **116** and the reaction mixture was then subjected to acid hydrolysis followed by condensation with benzaldehyde, with $SOCl_2$ to give 1-benzylidene-2,3,3a,4,5,6-hexahydro-4,6-dioxo-1*H*-imidazo[1,5-*b*]pyrazolium chloride **118**. Next the latter salt was treated with MeOH and ether [53] (Scheme 25).

3.3. Synthesis of Imidazo[4,5-c]Pyrazole. 3-Amino-6-(β-D-ribofuranosyl)imidazo[4,5-*c*]pyrazole **125** was synthesized

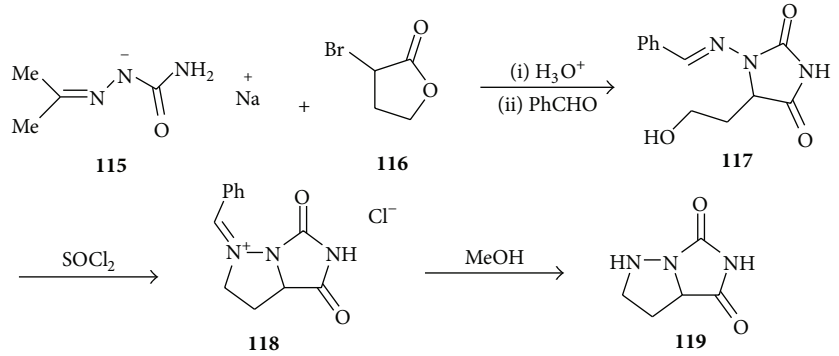


a: R = CH_3, R_1 = CH_3; b: R = CH_3, R_1 = C_6H_5; c: R = C_6H_5, R_1 = CH_3; d: R = R_1 = C_6H_5; e: R = 4-ClC_6H_4, R_1 = CH_3; f: R = 4-ClC_6H_4, R_1 = C_6H_5; g: R = 3-ClC_6H_4, R_1 = CH_3; h: R = 3-ClC_6H_4, R_1 = C_6H_5; i: R = 2-CiC_6H_4, R_1 = CH_3

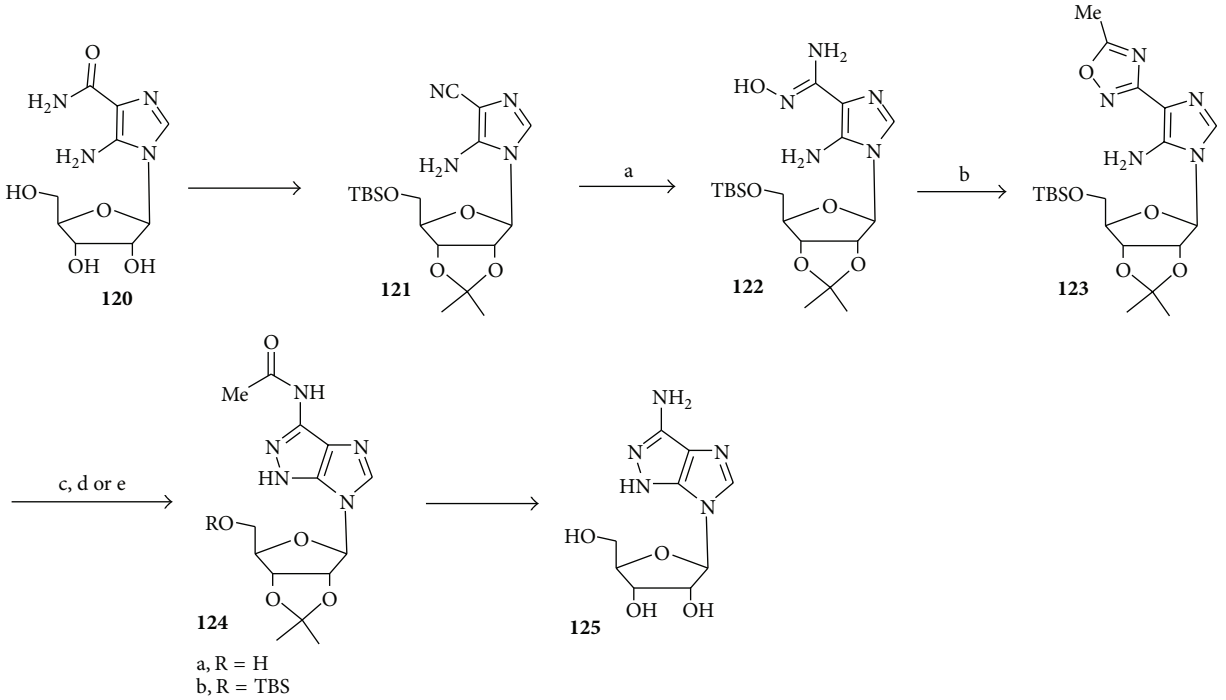
Scheme 23



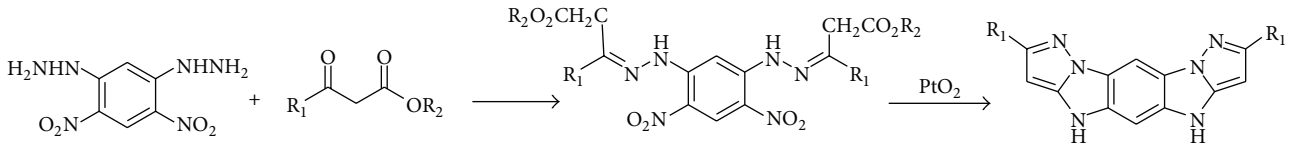
Scheme 24



Scheme 25

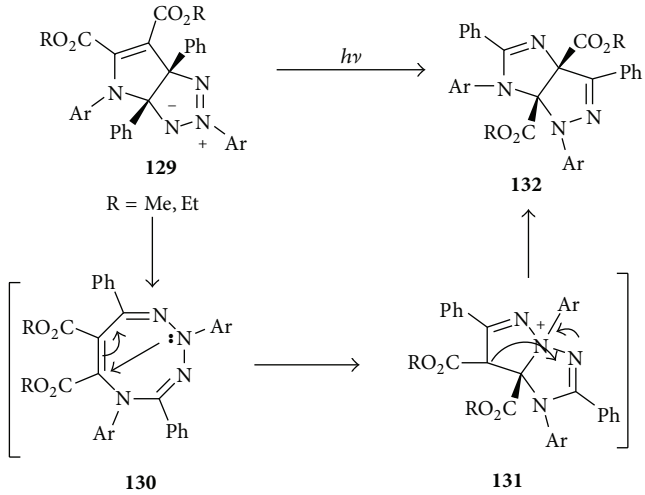


Scheme 26: Reagents and conditions: (a) NH_2OH, EtOH, reflux, 90 min, 70%; (b) (i) Na/EtOH, rt; (ii) $MeCO_2Et$, EtOH, reflux; (c) NaH, DMSO, 75–100°C, 15 min, **124**b: 74% from **123**; (d) (i) NaH, DMF, 75–100°C, 15 min; (ii) TBAF, THF, 0°C, rt, overnight, **124**a: 43% from **123**; (e) (i) NaH, DMF, 75–100°C, 15 min; (ii) TBSCl, imidazole, cat. DMAP, DMF, rt, 8 h, **124**b: 55% from **123**.



R_1 = Ph, 2-$PhOC_6H_4$; R_2 = Me, Et

Scheme 27



Ar = Ph, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 28

via an N–N bond formation strategy by a mononuclear heterocyclic rearrangement (MHR). Thus, 5-amino-1-(5-*O*-tert-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-4-(1,2,4-oxadiazol-3-yl)imidazole **123,** synthesized from treatment of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide **122** with sodium ethoxideat room temperature followed by reaction with ethyl acetate at reflux temperature, underwent the MHR with sodium hydride in DMF or DMSO to afford the corresponding 3-acetamidoimidazo[4,5-*c*]pyrazole nucleosides **124** in good yields. Subsequent protecting group manipulations afforded the desired 3-amino-6-(β-D-ribofuranosyl)imidazo[4,5-*c*]pyrazole **125** as a 5:5 fused analog of adenosine. Compound **125** was evaluated for activity against two herpes viruses, herpes simplex virus type 1 (HSV-1) and human cytomegalovirus (HCMV), in a plaque reduction assay and an ELISA, respectively. Cytotoxicity was detected both in stationary human foreskin fibroblasts (HFF cells) and in growing KB cells. No activity was observed at the highest concentration tested (100 μM) against HCMV and HSV-1 [54] (Scheme 26).

4. Miscellaneous Methods

1,5-Dihydrazino-2,4-dinitrobenzene **126** was treated with β-ketoesters to give 65–95% corresponding dihydrazones **127**, which were subjected to reductive cyclization using PtO_2 catalyst to provide benzo [1,2-*b*:5,4-b′]bis (1*H*-imidazo[1,2-*b*]pyrazoles **128** in 47–54% yields [55] (Scheme 27).

Upon UV irradiation the substituted pyrrolo[2,3-*d*]-1,2,3-triazoles **129** (R = Me, Et; R_1 = Ph, substituted phenyl) were transformed to imidazo[4,5-*c*]pyrazoles **132** *via* intermediates 1,2,3,5-tetrazocine **130**. X-ray crystal structure of **132** (R = Me, Ar = 4-BrC_6H_4) is reported [56] (Scheme 28).

5. Conclusions

This review has attempted to summarize the synthetic methods, reactions, and medicinal application of imidazopyrazoles. Synthesis of imidazopyrazole derivatives may be *via* two categories: annulations of imidazole ring onto a pyrazole scaffold or annulations of pyrazole ring onto an imidazole scaffold.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publishing of this paper.

Acknowledgment

The authors would like to thank the Research Center of College of Engineering at King Saud University for supporting this work.

References

[1] R. Ganapathi and A. Krishan, "Effect of 2,3-dihydro-1H-imidazo[1,2-b]pyrazole on the proliferation of mouse leukemic and normal cells in vivo," *Cancer Research*, vol. 40, no. 4, pp. 1103–1108, 1980.

[2] L. M. Allen and J. T. Thornthwaite, "Studies on the pharmacology and cytokinetics of 2,3-dihydro-1H-imadazo[1,2-b]pyrazole (NSC 51143) with P815 mastocytoma cells," *Cancer Research*, vol. 40, no. 11, pp. 4059–4063, 1980.

[3] M. C. Henry, C. D. Port, E. Rosen, and B. S. Levine, "Preclinical toxicologic study of 2,3-dihydro-1H-imidazo[1,2-b] pyrazole (IMPY) in mice, dogs, and monkeys," *Cancer Treatment Reports*, vol. 64, no. 10-11, pp. 1031–1038, 1980.

[4] D. D. Shoemaker, O. C. Ayers, M. E. D'Anna, and R. L. Cysyk, "Studies on the disposition of 2,3-dihydro-1H-imidazo[1,2-b]pyrazole in rodents," *European Journal of Cancer and Clinical Oncology*, vol. 17, no. 4, pp. 391–396, 1981.

[5] H. L. Ennis, L. Möller, J. J. Wang, and O. S. Selawry, "2,3-Dihydro-1H-imidazo[1,2-b]pyrazole. A new inhibitor of deoxyribonucleic acid synthesis," *Biochemical Pharmacology*, vol. 20, no. 10, pp. 2639–2646, 1971.

[6] M. T. Ahmet, K. T. Douglas, J. Silver, A. J. Goddard, and D. E. Wilman, "Iron and haem complexation studies of 2,3-dihydro-1H-imidazo(1,2-b)pyrazole (IMPY, NSC 51143), a tumor cell ribonucleotide reductase inhibitor," *Anti-Cancer Drug Design*, vol. 1, no. 3, pp. 189–195, 1986.

[7] A. J. Goddard, R. M. Orr, J. A. Stock, and D. E. V. Wilman, "Synthesis and ribonucleotide reductase inhibitory activity of analogues of 2,3-dihydro-1H-imidazo[1,2-b]pyrazole (IMPY)," *Anti-Cancer Drug Design*, vol. 2, no. 3, pp. 235–245, 1987.

[8] A. Krishan, K. D. Paika, and E. Frei III, "Cell cycle synchronization of human lymphoid cells in vitro by 2,3 dihydro 1H imidazo[1,2 b]pyrazole," *Cancer Research*, vol. 36, no. 1, pp. 138–142, 1976.

[9] A. L. Sagone Jr., J. A. Neidhart, and R. M. Husney, "Effect of 2,3-dihydro-1H-imidazo[1,2-b]pyrazole (IMPY) on the metabolism of human red cells," *Investigational New Drugs*, vol. 1, no. 3, pp. 243–248, 1983.

[10] A. Sato, J. A. Montgomery, and J. G. Cory, "Synergistic inhibition of leukemia L1210 cell growth in vitro by combinations of 2-fluoroadenine nucleosides and hydroxyurea or 2,3-dihydro-1H-pyrazole[2,3-a]imidazole," *Cancer Research*, vol. 44, no. 8, pp. 3286–3290, 1984.

[11] C. L. Vogel, J. M. Denefrio, D. C. Padgett, and M. A. Silverman, "Phase I clinical trial of weekly iv 2,3-dihydro-1H-imidazo[1,2-b]pyrazole (IMPY)," *Cancer Treatment Reports*, vol. 64, no. 10-11, pp. R1153–R1156, 1980.

[12] J. C. Pelling and C. Shipman Jr., "Antiviral activity of 2,3-dihydro-1H-imidazo[1,2-b]pyrazole in herpes simplex virus type 1-infected mammalian cells," *Biochemical Pharmacology*, vol. 25, no. 21, pp. 2377–2382, 1976.

[13] H. Yamanaka, Y. Ogawa, and K. Itane, "Preparation of cephem derivatives as antibacterials," JP 05213971, 1993, http://worldwide.espacenet.com/singleLineSearch?locale=en_EP.

[14] K. Sakane, K. Kawabata, and Y. Inamoto, "Preparation of new cephem compounds," EP 427248, 1991, http://worldwide.espacenet.com/numberSearch?locale=en_EP.

[15] H. Yamanaka, Y. Ogawa, and K. Itane, "Preparation of cephem derivatives as antibacterials," JP 05213971, 1993, http://worldwide.espacenet.com/numberSearch?locale=en_EP.

[16] K. Sato, T. Kawagishi, and H. Kobayashi, "Silver halide color photographic material," Tech. Rep. JP 07134380, 1995, http ://worldwide.espacenet.com/numberSearch ?locale=en_EP.

[17] J. Bailey and D. N. Rogers, "Photographic color couplers, photographic materials containing them and method of forming dye images," WO 8602467, 1986, http://worldwide.espacenet.com/numberSearch?locale=en_EP.

[18] T. Ukai, T. Ito, T. Kawagishi, and H. Takei, "Photosensitive materials containing dyes," JP 60213937, 1985, http:// worldwide.espacenet.com/numberSearch?locale=en_EP.

[19] T. Sato, T. Kawagishi, and N. Furutachi, "Producing magenta images in silver halide color photographic materials," EP 119741, 1984, http://worldwide.espacenet .com/numberSearch?locale=en_EP.

[20] B. F. Abdel-Wahab and R. E. Khidre, "2-Chloroquinoline-3-carbaldehyde II: synthesis, reactions, and applications," *Journal of Chemistry*, vol. 2013, Article ID 851297, 13 pages, 2013.

[21] R. E. Khidre and B. F. Abdel-Wahab, "Application of benzoylaceteonitrile in the synthesis of pyridines derivatives," *Current Organic Chemistry*, vol. 17, no. 4, pp. 430–445, 2013.

[22] W. M. Abdou and R. E. Khidre, "Overview of the chemical reactivity of phosphonyl carbanions toward some carbon-nitrogen systems," *Current Organic Chemistry*, vol. 16, no. 7, pp. 913–930, 2012.

[23] B. F. Abdel-Wahab, M. F. El-Mansy, and R. E. Khidre, "Production of pyrans , pyridazines , pyrimidines , pyrazines and triazine compounds using benzoylacetonitriles as a precursor," *Journal of the Iranian Chemical Society*, vol. 10, no. 6, pp. 1085–1102, 2013.

[24] R. E. Khidre and B. F. Abdel-Wahab, "Synthesis of 5-membered heterocycles using benzoylacetonitriles as synthon," *Turkish Journal of Chemistry*, vol. 37, no. 5, pp. 1–27, 2013.

[25] R. E. Khidre, H. A. Mohamed, and B. F. Abdel-Wahab, "Advances in the chemistry of pyrazolopyrazoles," *Turkish Journal of Chemistry*, vol. 37, no. 1, pp. 1–35, 2013.

[26] C. Brullo, S. Spisani, R. Selvatici, and O. Bruno, "N-Aryl-2-phenyl-2,3-dihydro-imidazo[1,2-b]pyrazole-1-carboxamides 7-substituted strongly inhibiting both fMLP-OMe- and IL-8-induced human neutrophil chemotaxis," *European Journal of Medicinal Chemistry*, vol. 47, no. 1, pp. 573–579, 2012.

[27] O. Bruno, C. Brullo, F. Bondavalli et al., "2-Phenyl-2,3-dihydro-1H-imidazo[1,2-b]pyrazole derivatives: New potent inhibitors of fMLP-induced neutrophil chemotaxis," *Bioorganic and Medicinal Chemistry Letters*, vol. 17, no. 13, pp. 3696–3701, 2007.

[28] P. Seneci, M. Nicola, M. Inglesi, E. Vanotti, and G. Resnati, "Synthesis of mono- and disubstituted 1H-imidazo[1,2-b]pyrazoles," *Synthetic Communications*, vol. 29, no. 2, pp. 311–341, 1999.

[29] E. Vanotti, F. Fiorentini, and M. Villa, "Synthesis of novel derivatives of 1H-imidazo[1,2-b]pyrazole as potential CNS-agents," *Journal of Heterocyclic Chemistry*, vol. 31, no. 4, pp. 737–743, 1994.

[30] C. Parkanyi, A. O. Abdelhamid, J. C. S. Cheng, and A. S. Shawali, "Convenient synthesis of fused heterocycles from a-keto hydroximoyl chlorides and heterocyclic amines," *Journal of Heterocyclic Chemistry*, vol. 21, no. 4, pp. 1029–1032, 1984.

[31] H. Ohki, K. Kawabata, Y. Inamoto, S. Okuda, T. Kamimura, and K. Sakane, "Studies on 3'-quaternary ammonium cephalosporins-III. Synthesis and antibacterial activity of 3'-(3-aminopyrazolium)cephalosporins," *Bioorganic and Medicinal Chemistry*, vol. 5, no. 3, pp. 557–567, 1997.

[32] A. O. Abdelhamid, E. K. A. Abdelall, and Y. H. Zakic, "Reactions with hydrazonoyl halides 62: synthesis and antimicrobial evaluation of some new imidazo [1,2-a]pyrimidine, imidazo [1,2-a]pyridine, imdazo [1,2-b]pyrazole, and quinoxaline derivatives," *Journal of Heterocyclic Chemistry*, vol. 47, no. 2, pp. 477–482, 2010.

[33] A. M. Farag and K. M. Dawood, "One-pot synthesis of imidazo [1,2-b]pyrazole, imidazo[1,2-b]-1,2,4-triazole, imidazo[1,2-a]-pyridine, imidazo[1,2-a]pyrimidine, imidazo-[1,2-a]benzimidazole, and 1,2,4-triazolo-[4,3-a]benzimidazole derivatives," *Heteroatom Chemistry*, vol. 8, no. 2, pp. 129–133, 1997.

[34] A. S. Shawali, M. Sami, S. M. Sherif, and C. Parkanyi, "Synthesis of some derivatives of imidazo[1,2-a]pyridine, pyrazolo[1,5-b]imidazole, and 4-(3H)quinazolinone from α-ketohydrazidoyl bromides," *Journal of Heterocyclic Chemistry*, vol. 17, no. 5, pp. 877–880, 1980.

[35] J. Zhang, R. Singh, D. Goff, and T. Kinoshita, "1H- Imidazo[1,2-b]pyrazole-7-carbonitrile derivatives as spleen tyrosine kinase (syk) inhibitors and their preparation and use for the treatment of syk-mediated diseases," U.S. Pat. Appl. Publ., US 20100316649 A1 20101216, 2010.

[36] A. Rahmati, M. Eskandari-Vashareh, and M. Alizadeh-Kouzehrash, "Synthesis of 3-(benzylideneamino)-2-phenyl-5H-imidazo[1,2-b]pyrazole-7- carbonitriles via a four-component condensation reaction," *Tetrahedron*, vol. 69, no. 21, pp. 4199–4204, 2013.

[37] A. Rahmati and M. A. Kouzehrash, "Synthesis of N-alkyl-2-aryl-5 H-imidazo[1,2-b]pyrazol-3-amines by a three-component condensation reaction," *Synthesis*, no. 18, Article ID N49511SS, pp. 2913–2920, 2011.

[38] A. O. Abdelhamid, S. S. Ghabrial, M. Y. Zaki, and N. A. Ramadan, "Facile synthesis of fused heterocycles through 2-bromobenzofurylglyoxal-2-arylhydrazones," *Archiv der Pharmazie*, vol. 325, no. 4, pp. 205–209, 1992.

[39] P. Langer, J. Wuckelt, M. Döring, P. R. Schreiner, and H. Görls, "Regioselective anionic [3+2] cyclizations of isoxazole, pyrazole and 1,2,4-triazole dinucleophiles—efficient synthesis of 2,4-dihydroimidazo-[4,5-*b*]quinoxalines, 3*H*-imidazo[1,2-*b*]pyrazoles and 5*H*-imidazo[2,1-c]-[1,2,4]triazoles," *European Journal of Organic Chemistry*, no. 12, pp. 2257–2263, 2001.

[40] K.-J. Lee, H.-T. Kwon, and B.-G. Kim, "Synthesis of pyrazolo-fused heterocycles by a tandem Appel's dehydration/ electrocyclization methodology," *Journal of Heterocyclic Chemistry*, vol. 34, no. 6, pp. 1795–1799, 1997.

[41] K. Lee, D. Kim, and B. Kim, "Synthesis of pyrazole-fused heterocycles by thermal rearrangement of N-aziridinylimino ketenimines," *Journal of Heterocyclic Chemistry*, vol. 40, no. 2, pp. 363–367, 2003.

[42] M. A. Barsy and E. A. El-Rady, "Intermolecular aza-Wittig reaction: one-step synthesis of pyrazolo[1,5-a]pyrimidine and imidazo[1,2-b]pyrazole derivatives," *Journal of Heterocyclic Chemistry*, vol. 43, no. 3, pp. 523–526, 2006.

[43] M. Li, G. Zhao, L. Wen, W. Cao, S. Zhang, and H. Yang, "Utilization of hypervalent iodine in organic synthesis: a novel and facile two-step protocol for the synthesis of new derivatives of 1H-imidazo[1,2-b] pyrazole by the cyclocondensation involving α-tosyloxyacetophenones," *Journal of Heterocyclic Chemistry*, vol. 42, no. 2, pp. 209–215, 2005.

[44] L. Ming, Z. Guilong, W. Lirong, and Y. Huazheng, "Hypervalent iodine in synthesis: a novel two-step procedure for the synthesis of new derivatives of 1H-imidazo[1,2-b]-pyrazole

by the cyclocondensation between 5-amino-4-cyano-3-phenyl-1H-pyrazole and alpha-tosyloxyacetophenones or α-haloacetophenones," *Synthetic Communications*, vol. 35, no. 4, pp. 493–501, 2005.

[45] A. G. A. Elagamey, S. Z. A. Sowellim, and M. N. Khodeir, "Reactions with heterocyclic amidines (V). Synthesis of some new imidazo[1,2-b] pyrazole, pyrazolo [5,1-c]-1,2,4-triazine and pyrazolo [5,1-c]-1,2,4-triazole derivatives," *Archives of Pharmacal Research*, vol. 10, no. 1, pp. 14–17, 1987.

[46] T. Sato and M. Matsuoka, "Preparation of 1H-imidazo[1,2-b] pyrazole derivatives," JP 07278455 A 19951024, 1995.

[47] M. H. Elnagdi, E. A. A. Hafez, H. A. El-Fahham, and E. M. Kandeel, "Reactions with heterocyclic amidines. VIII. Synthesis of some new imidazo [1,2-b] pyrazole derivatives," *Journal of Heterocyclic Chemistry*, vol. 17, no. 1, pp. 73–76, 1980.

[48] I. Lantos, H. Oh, C. Razgaitis, and B. Loev, "Synthesis of 6-substituted-2,3-dihydro-1H-imidazo[1,5-b]pyrazoles," *Journal of Organic Chemistry*, vol. 43, no. 25, pp. 4841–4844, 1978.

[49] K. Liubchak, A. Tolmachev, and K. Nazarenko, "Synthesis of imidazo[4,5-c]pyrazoles via copper-catalyzed amidine cyclization," *The Journal of Organic Chemistry*, vol. 77, no. 7, pp. 3365–3372, 2012.

[50] C. B. Vicentini, M. Manfrini, M. Mazzanti, A. Scatturin, C. Romagnoli, and D. Mares, "Synthesis of a novel series of imidazo[4,5-c]pyrazole derivatives and their evaluation as herbicidal agents," *Archiv der Pharmazie*, vol. 332, no. 10, pp. 337–342, 1999.

[51] C. B. Vicentini, A. C. Veronese, P. Giori, B. Lumachi, and M. Guarneri, "A new general and efficient synthesis of imidazo[4,5-c]pyrazole derivatives," *Tetrahedron*, vol. 46, no. 16, pp. 5777–5788, 1990.

[52] K. Pilgram, "Synthesis of 2,3-dihydro-1H-imidazo[1,2-b]pyrazoles," *Journal of Heterocyclic Chemistry*, vol. 17, no. 7, pp. 1413–1416, 1980.

[53] J. G. Michels and G. C. Wright, "2,3-Dihydro-1H-imidazo[1,5-b]pyrazole-4,6(3aH,5H)-dione," *The Journal of Organic Chemistry*, vol. 34, no. 10, pp. 3213–3215, 1969.

[54] T.-C. Chien, D. A. Berry, J. C. Drach, and L. B. Townsend, "Synthesis of 3-aminoimidazo[4,5-c]pyrazole nucleoside via the N-N bond formation strategy as a [5:5] fused analog of adenosine," *Nucleosides, Nucleotides and Nucleic Acids*, vol. 24, no. 10–12, pp. 1971–1996, 2005.

[55] S. Hauptmann, H. Wilde, and M. Szymanowski, "Synthesis and dye formation from benzo [1,2-b:5,4-b′] bis (1H-imidazo[1,2-b] pyrazoles)," *Zeitschrift für Chemie*, vol. 28, no. 12, pp. 441–442, 1988.

[56] R. N. Butler, D. M. Colleran, D. F. O'Shea, D. Cunningham, P. McArdle, and A. M. Gilian, "New entry to the imidazo[4,5-c]pyrazole system through photochemically induced sequential transformations of substituted pyrrolo[2,3-d]-1,2,3-triazoles: X-ray crystal structure of a substituted 1,3a,6,6a-tetrahydro-imidazo[4,5-c]pyrazole," *Journal of the Chemical Society, Perkin Transactions 1*, no. 22, pp. 2757–2759, 1993.