

Supplementary File

Benzimidazole(s): Synthons, Bioactive Lead Structures, Total Synthesis, and Profiling of Major Bioactive Categories

Lotfi M. Aroua^{1*}, Fahad M. Alminderej¹, Hind R. Almuhaylan¹, Abdulelah H. Alosaimi¹, Faten Medini², Hamdoon A. Mohammed³, Suliman A. Al-mahmoud³, Riaz A. Khan^{3*}, Nejib H. Mekni^{4,5}

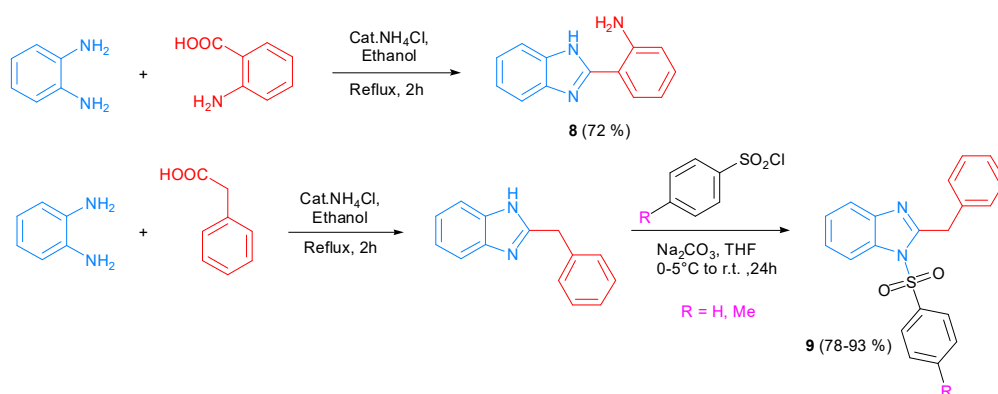
¹Department of Chemistry, College of Science, Qassim University, Box: 6644, Qassim 51452, Kingdom of Saudi Arabia, e-mail: lm.aroua@qu.edu.sa, aroua.lotfi@yahoo.com.

²Laboratory of Aromatic and Medicinal Plants, Biotechnology Center of Borj-Cedria, Carthage University, 2050, Tunis, Tunisia

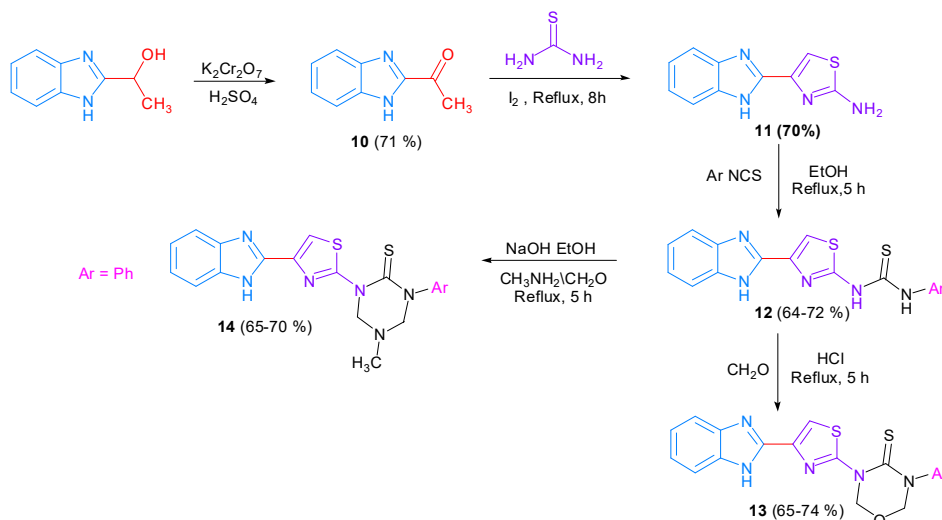
³Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, Qassim University, Qassim 51452, Saudi Arabia. ri.khan@qu.edu.sa

⁴Laboratory of Bio-Organic, Structural and Polymer Chemistry (LR99ES14), Department of Chemistry, Faculty of Sciences, University of Tunis El-Manar, El-Manar 2092, Tunis, Tunisia.

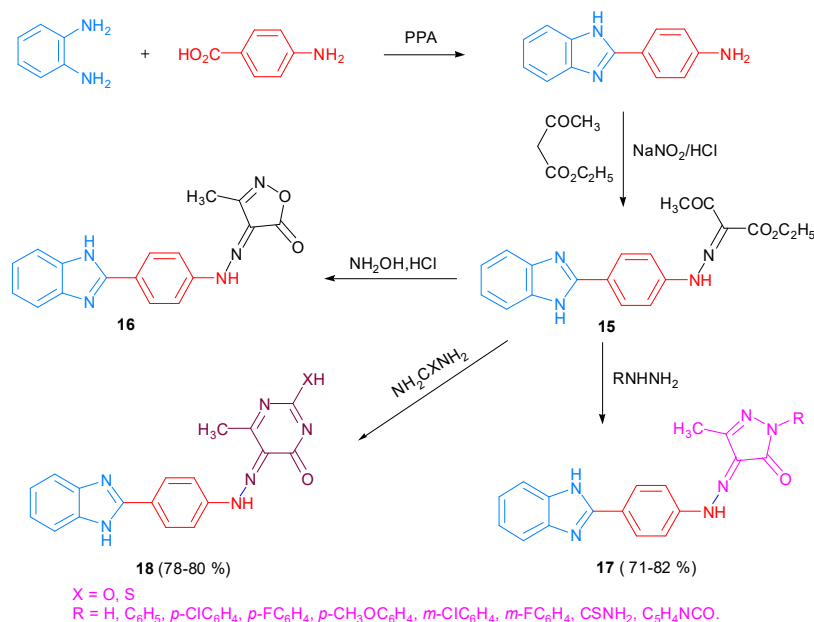
⁵Department of Fundamental Science, High Institute of Medical Technologies of Tunis, El Manar University, Tunis 1006, Tunisia



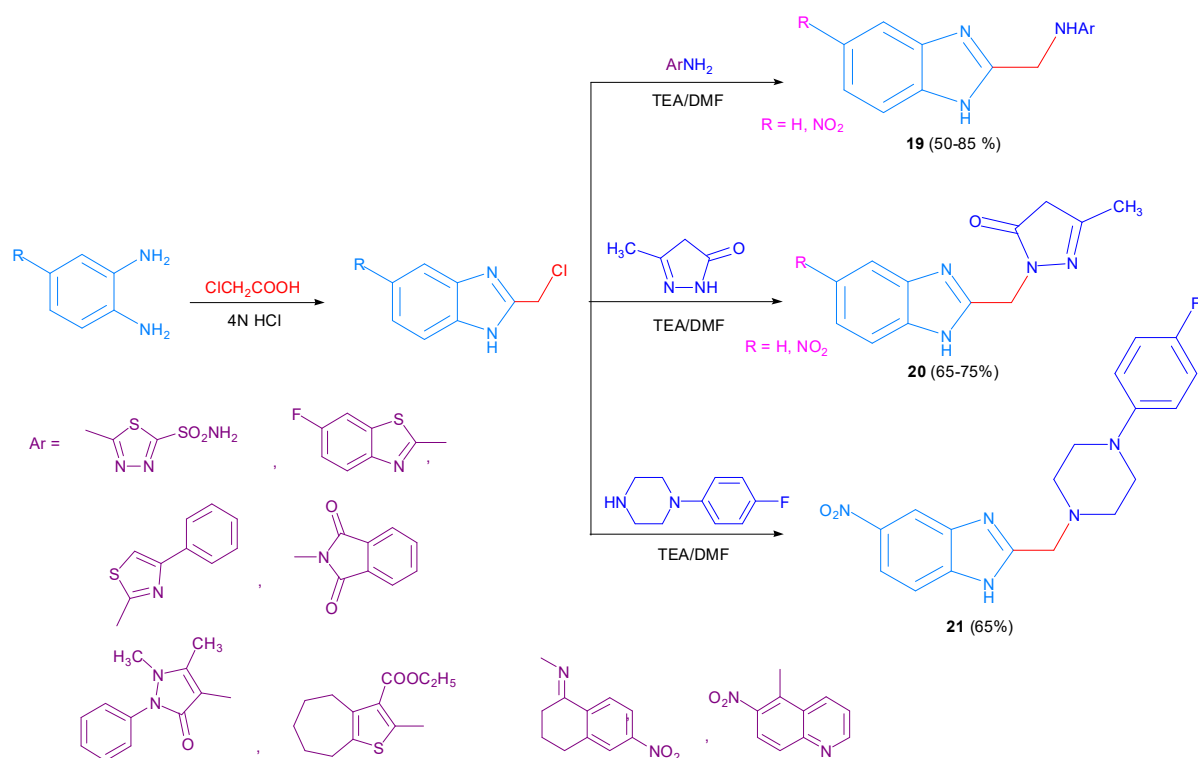
Scheme S-1. NH_4Cl -catalytic synthesis of the 2-(2-aminophenyl) and 2-benzyl-*N*-phenylsulfonyl benzimidazoles **8** and **9**.



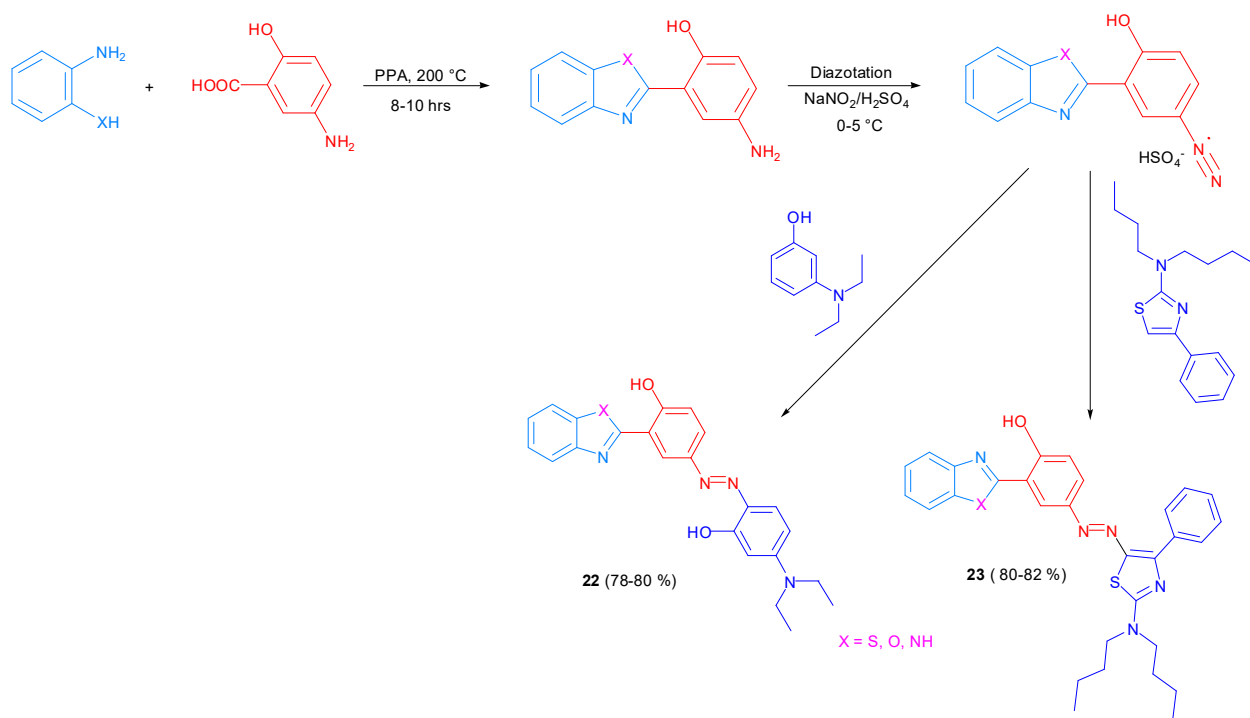
Scheme S-2. The synthetic route of the potential antibacterial 2-substituted benzimidazolyl *N*-5-aryl(1,3,5-triazinane-4-thione) **13**, and oxadiazinane-4-thione **14**.



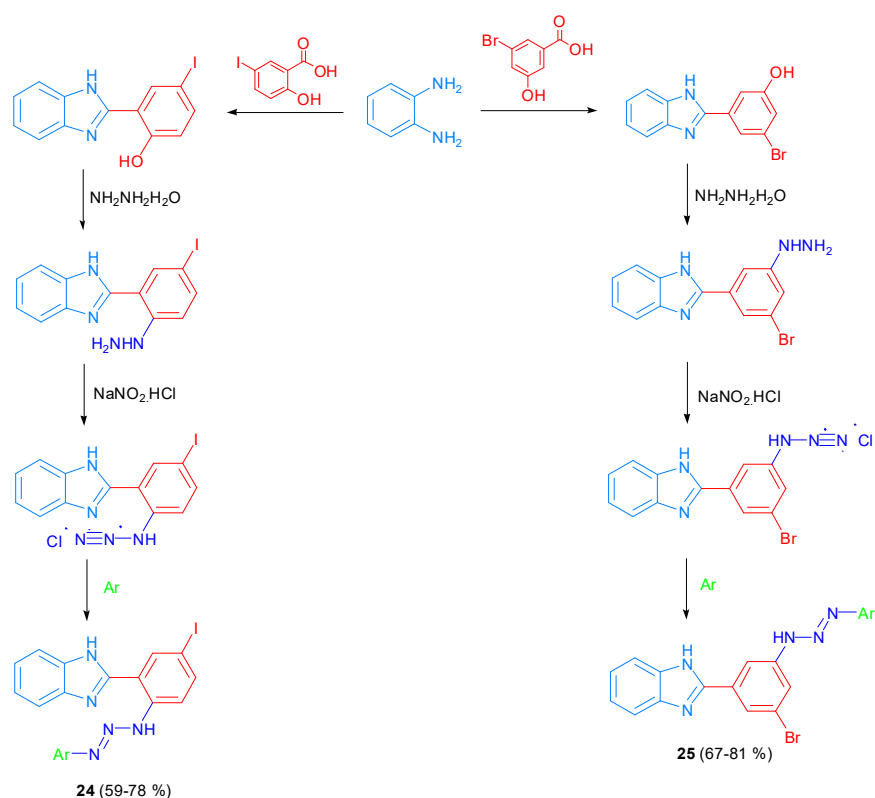
Scheme S-3. The synthesis sequence of 2-substituted benzimidazole isoxazole-5-one **16**, pyrazol-3-ones **17** and pyrimidin-4-one **18** derivatives.



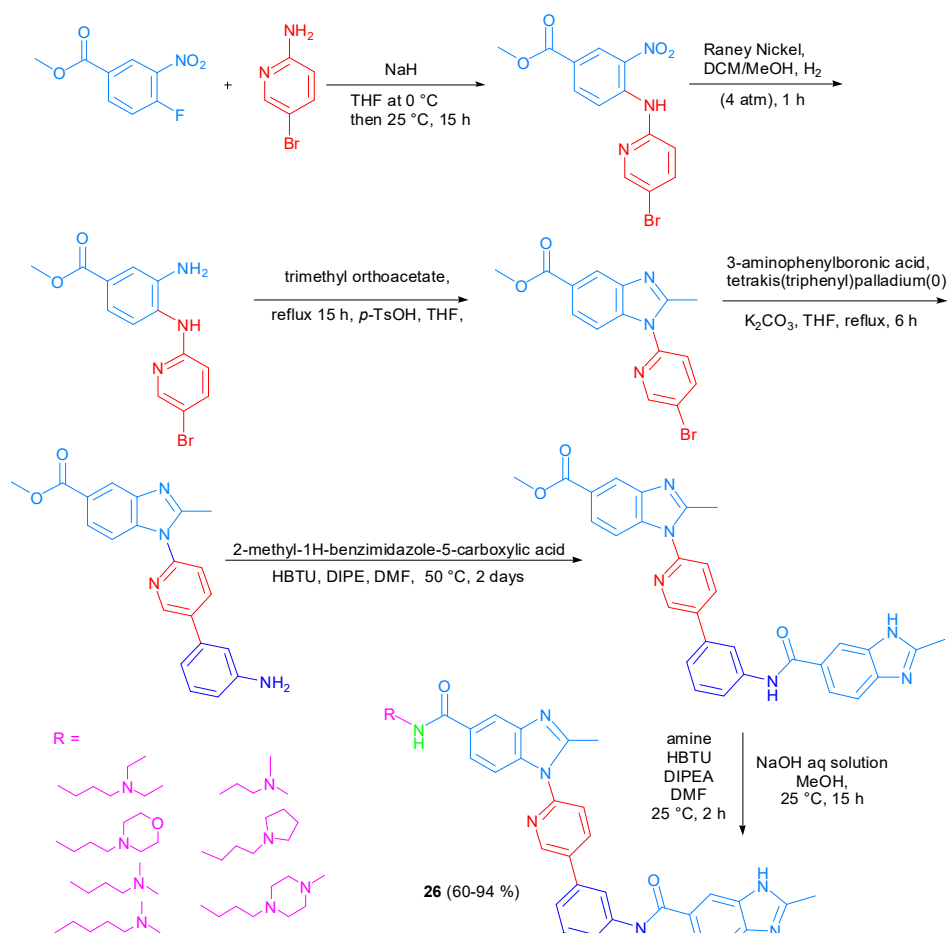
Scheme S-4. Synthesis approach of methylene *N*-aryl **19**, pyrazolo-3-ones **20** and (4-fluorophenyl) piperazin-2-substituted benzimidazoles **21**.



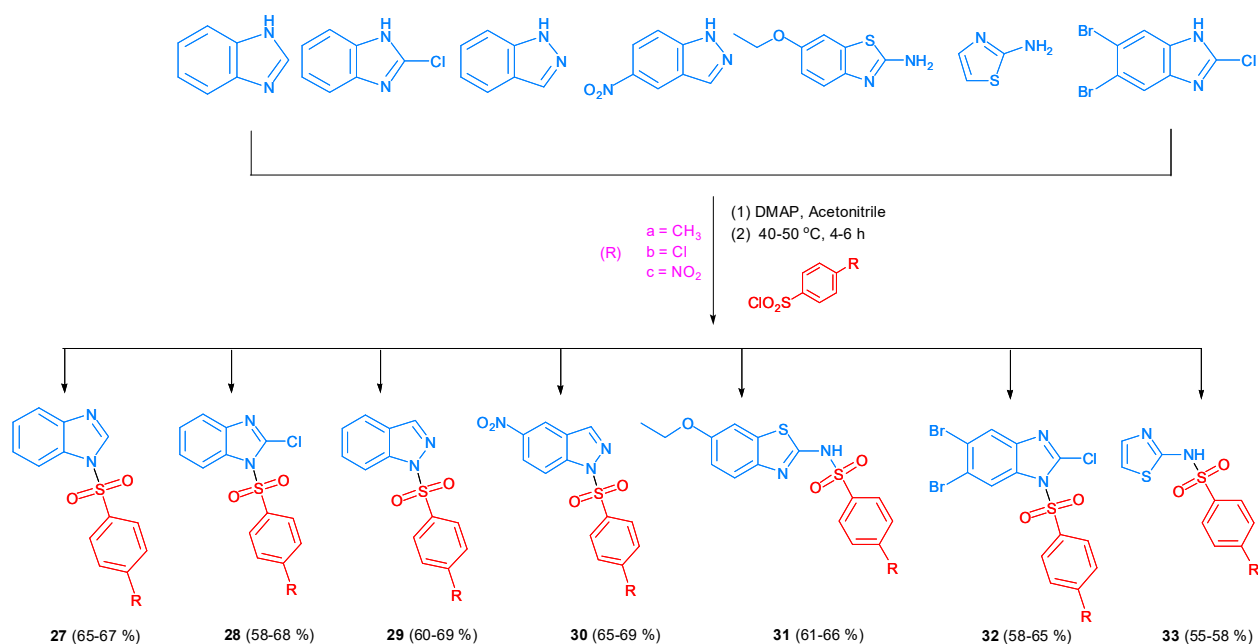
Scheme S-5. Synthesis of some *azo*-substituted benzimidazolyl, benzoxazolyl and benzothiazolyl polycyclic derivatives.



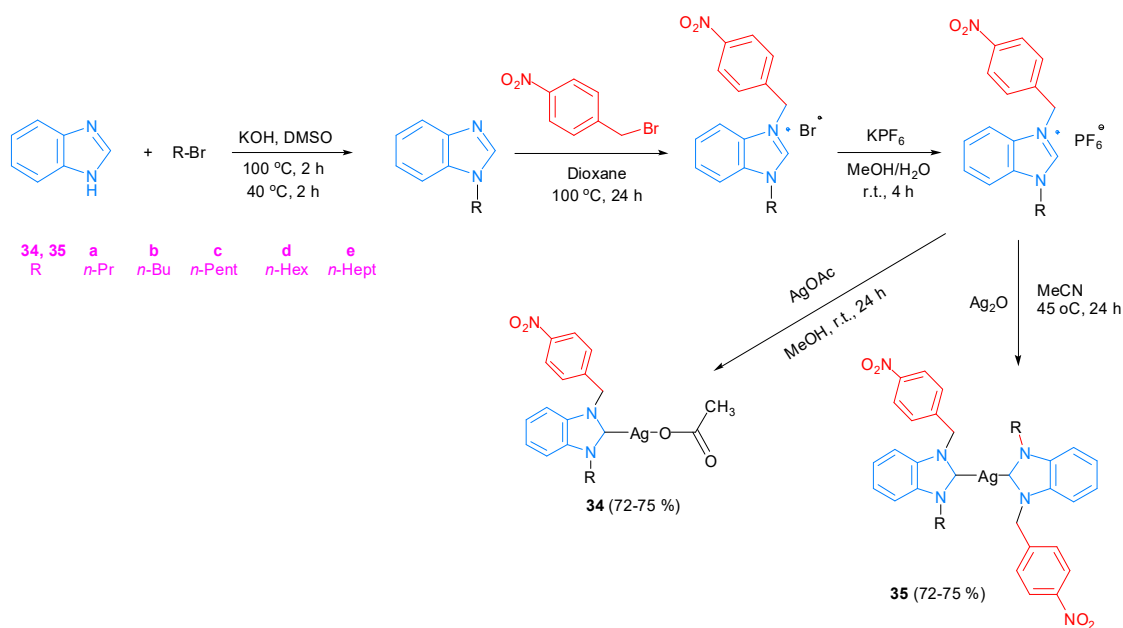
Scheme S-6. The synthesis process of benzimidazolyl 4 or 5-halo-benzo-aryl-triazines **24** and **25** from *o*-phenylenediamines.



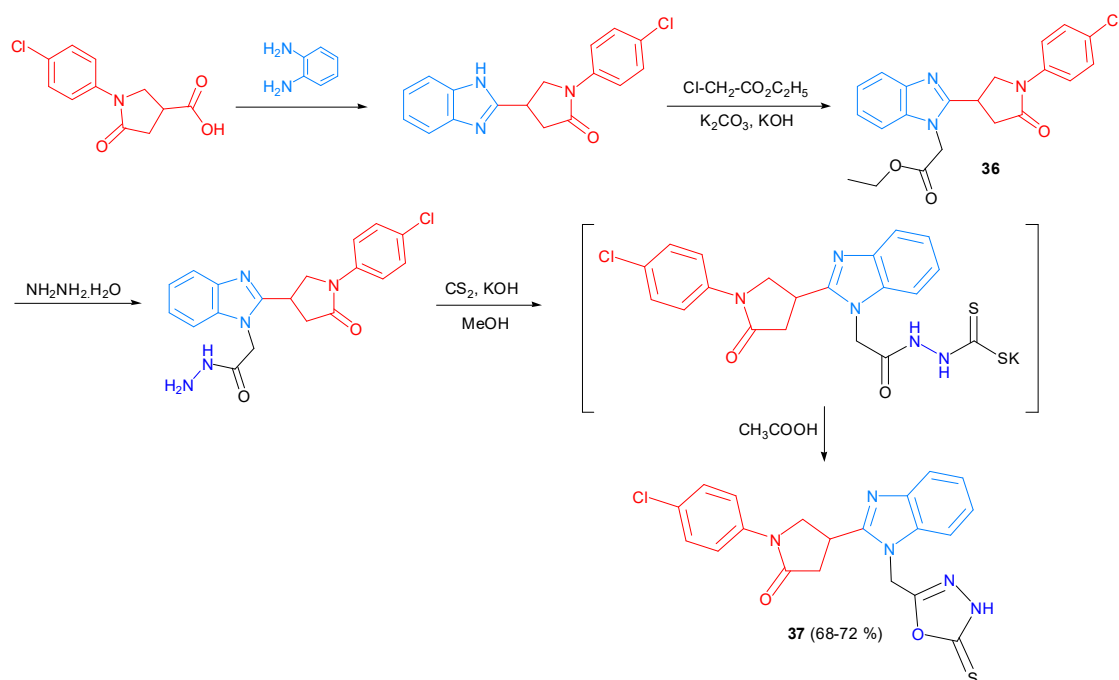
Scheme S-7. Synthesis of the bis(benzimidazolyl) carbamide derivatives, spaced from biarylpyridino-phenyl derivatives were accomplished via multi-steps approach.



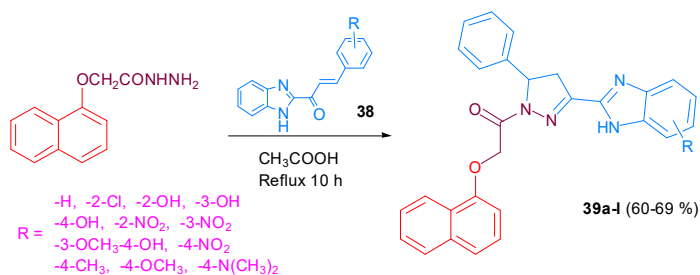
Scheme S-8. Synthesis series of *N*-sulfoxyamide benzimidazoles **27-33**.



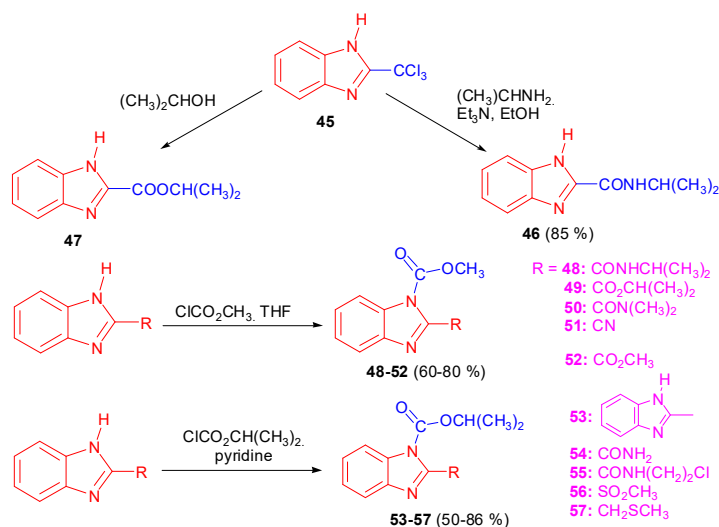
Scheme S-9. Synthesis of *N*-(*p*-nitrobenzyl)-*N*-alkyl NHC-silver(I) acetate and bis-NHC-silver(I) hexafluorophosphate complexes.



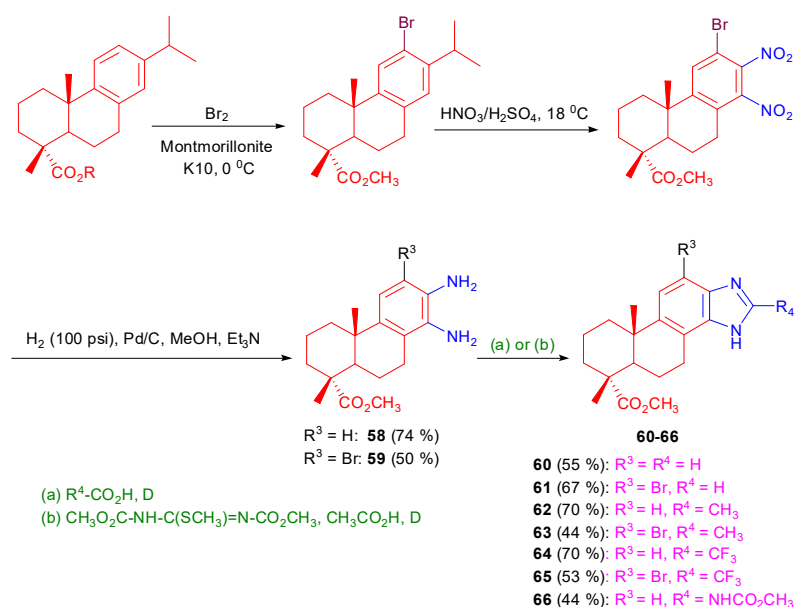
Scheme S-10. The route synthesis of 4-amino-5-[2-(1H-benzimidazol-2-yl)-3-(4-chloroanilino)propyl]-2,4-dihydro-3H-1,2,4-triazole-3-thione.



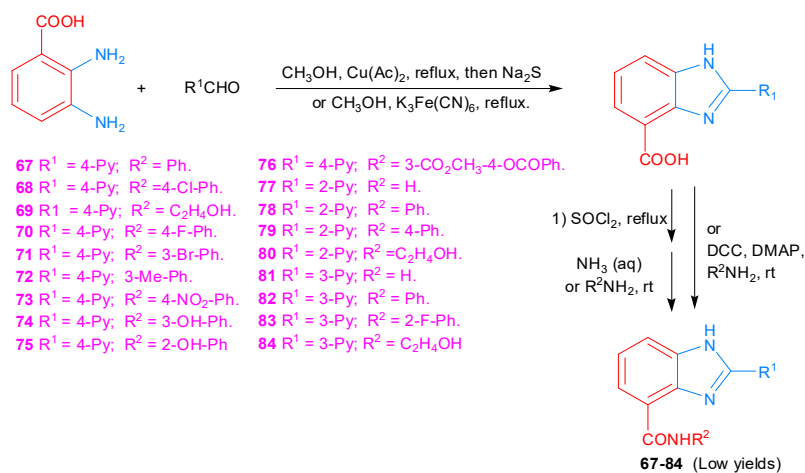
Scheme S-11. The synthetic approach of benzimidazole-pyrazole derivatives.



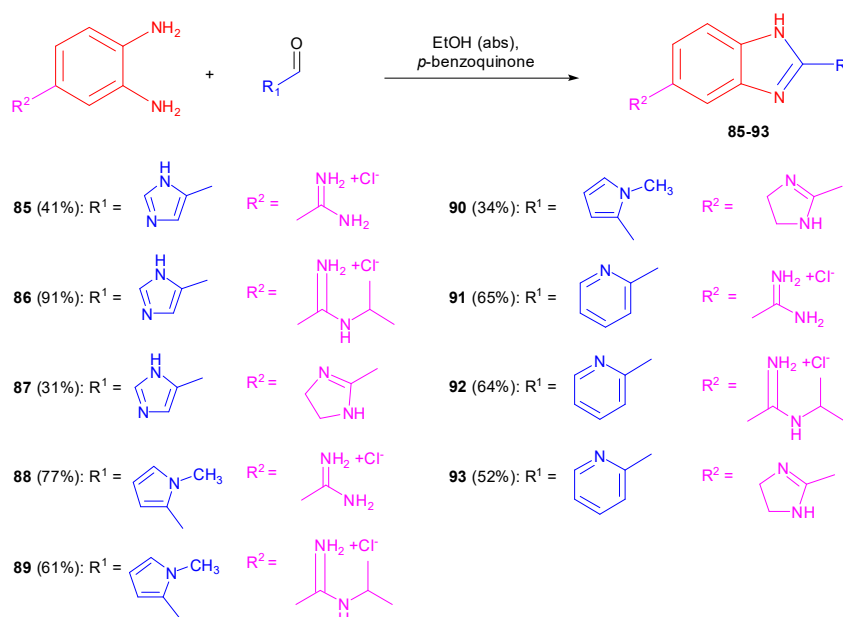
Scheme S-12. 2-substituted benzimidazole-N-carbamates synthetic conditions.



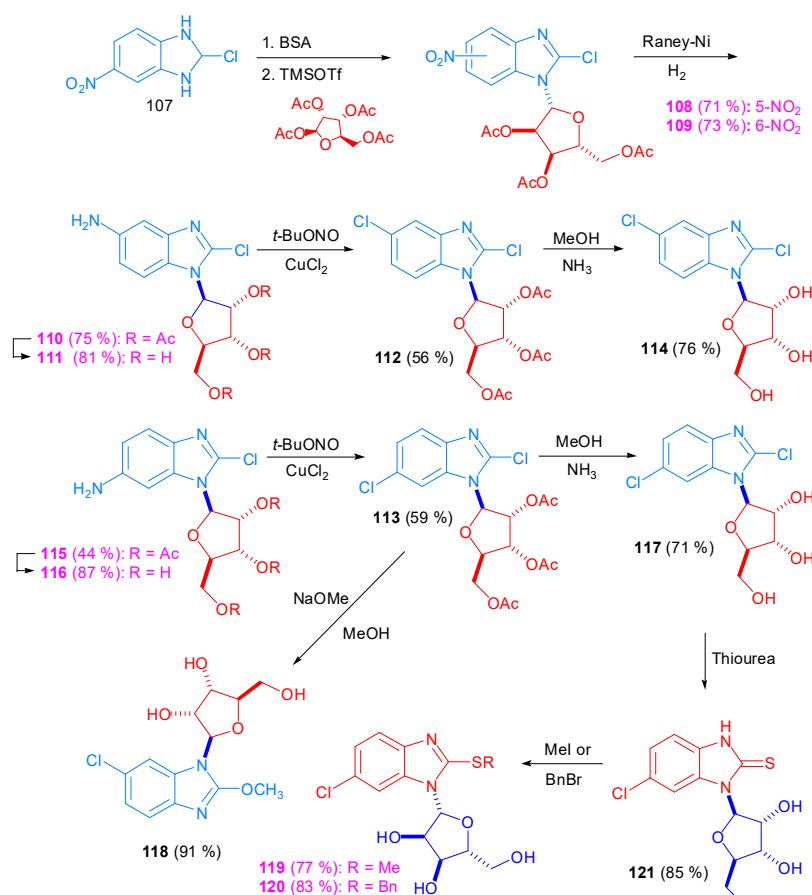
Scheme S-13. Synthetic pathway of tetracyclic fused benzimidazole, structural homologues of steroids **60-66** in four steps.



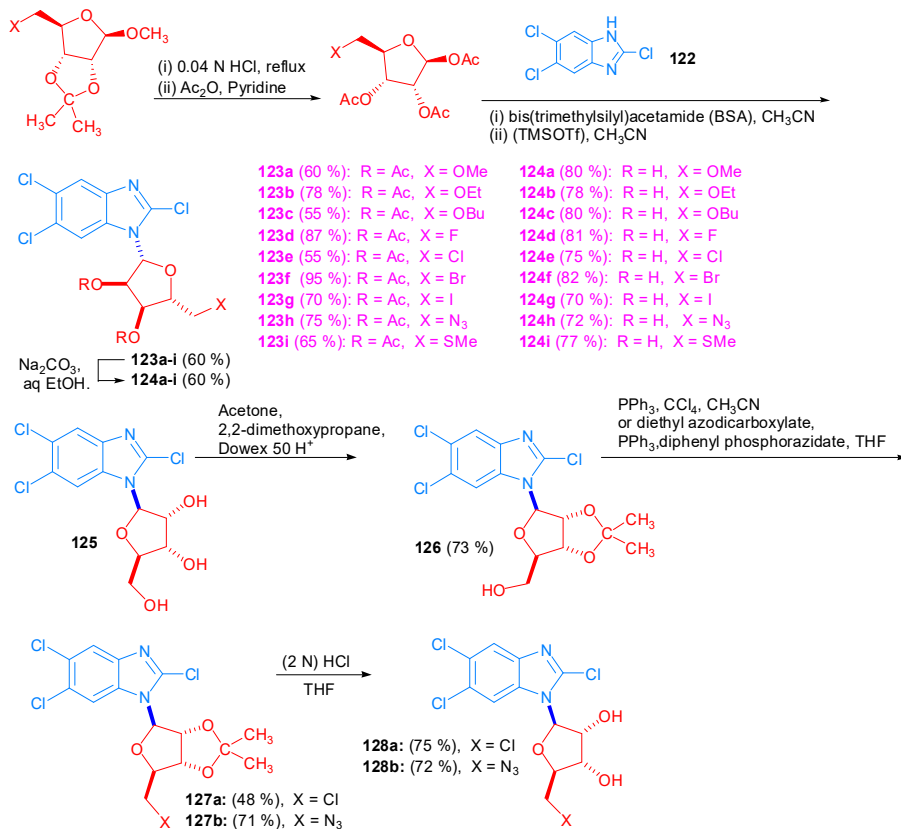
Scheme S-14. Condition route of 2-pyridin-2-, 3-, and 4-yl-1H-benzimidazole-4-carboxamide derivatives.



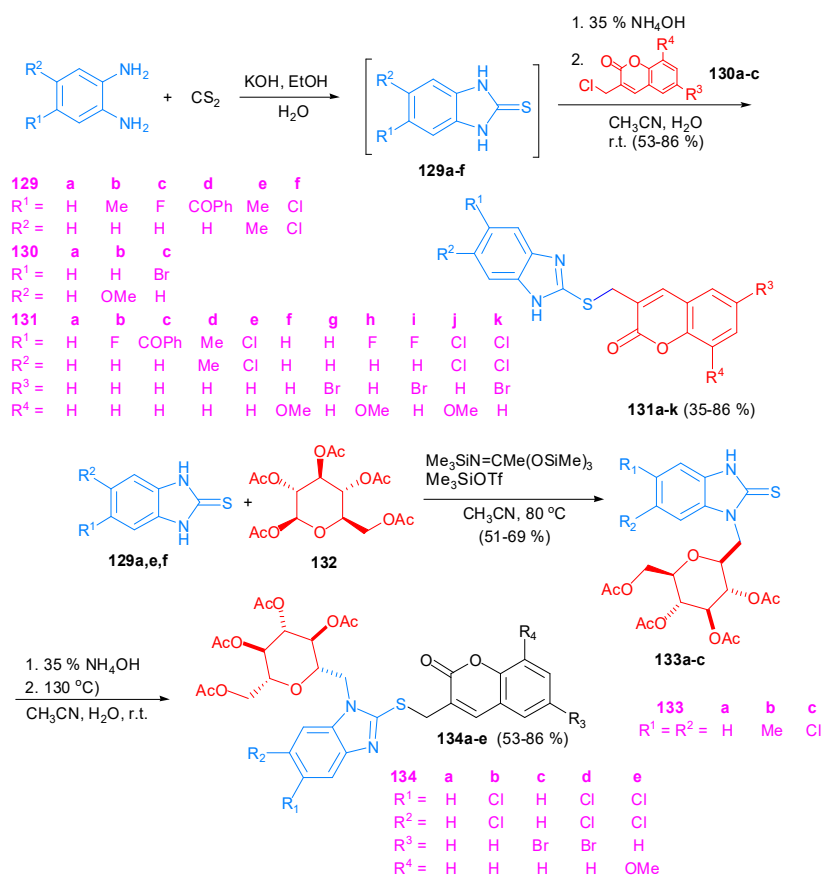
Scheme S-15. The condensation approach of imidazole, pyrrole and pyridine-1H-benzimidazole **85-93**.



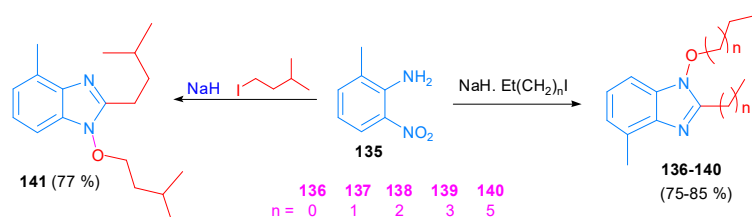
Scheme S-16. Synthesis of the *N*-ribose 5-chloro-2-methoxy, -2-thioalcoxy and 2-thione benzimidazole derivatives 102-113 from 2-chloro-4-nitrobenzimidazole 99.



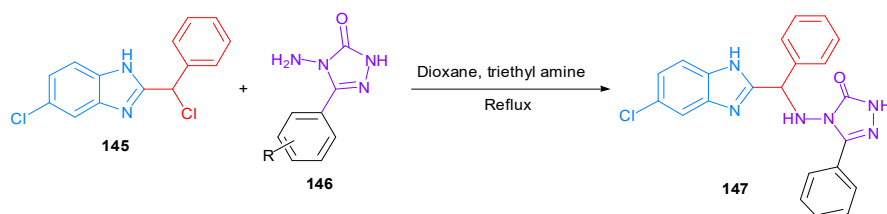
Scheme S-17. Synthesis of 5'-modified 2,5,6-trichlorobenzimidazoles.



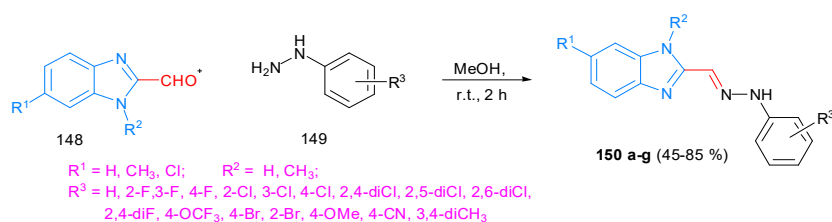
Scheme S-18. Synthesis condition of 2-sulfurmethylenecoumarin and 2-sulfurmethylenecoumarin *N*-(2,3,5-triacetatoxy-4-yl) benzimidazoles **131a-k** and **134a-e**.



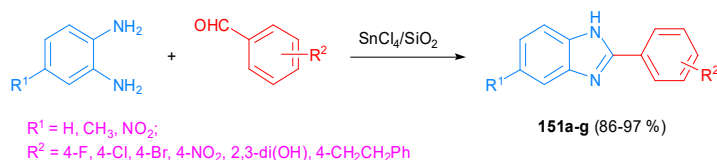
Scheme S-19: One step synthesis of the 1-alkoxy-2-alkylbenzimidazoles **136-141**.



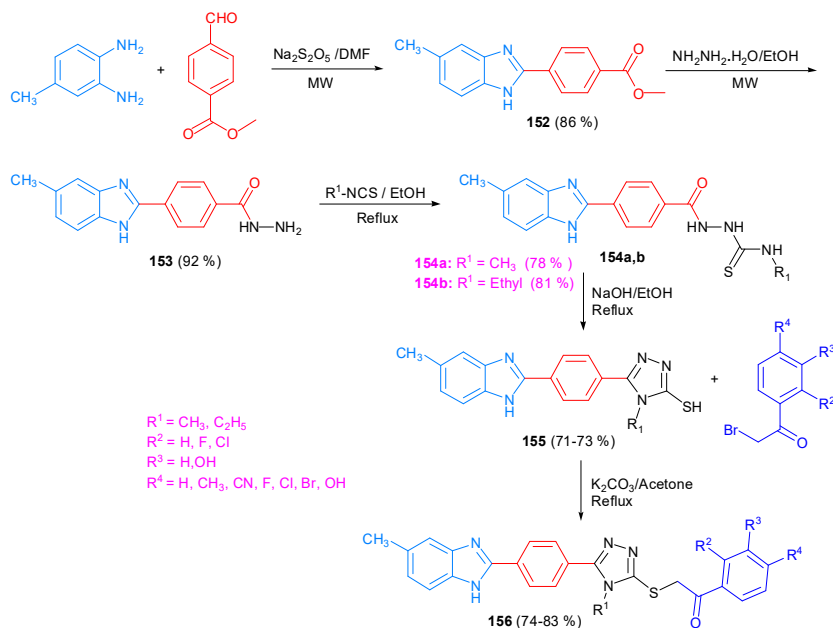
Scheme S-20. Synthesis of 4-amino-5-phenyl-2,4-dihydro-[1,2,4]triazol-3-one benzimidazole derivatives.



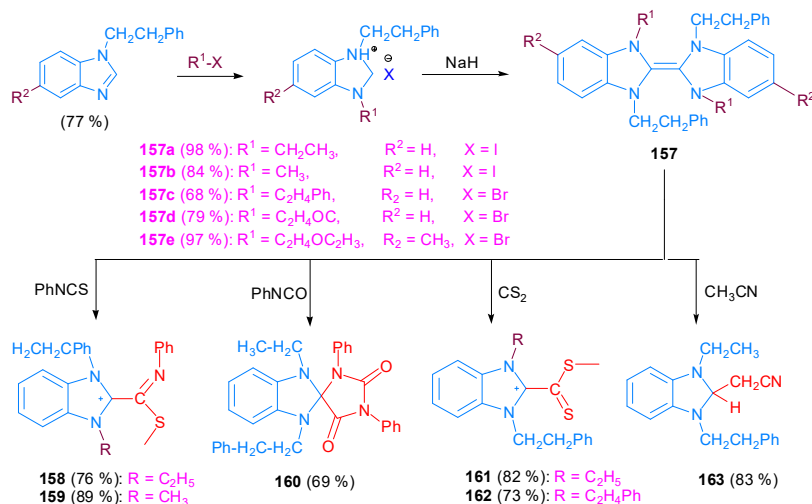
Scheme S-21. Benzimidazole based Schiff base derivatives **150**.



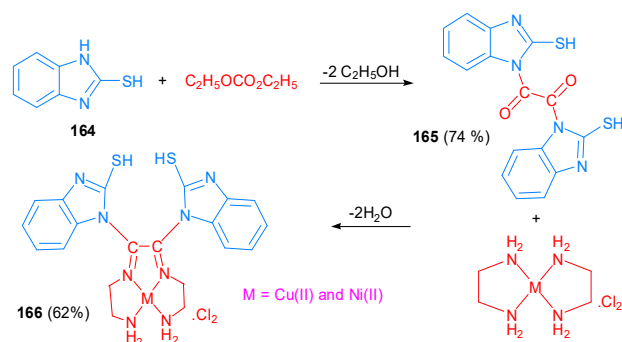
Scheme S-22. Microwave assisted and $\text{H}_2\text{SO}_4/\text{SiO}_2$ catalysed synthesis of 2-(substituted phenyl) 4-substituted benzimidazoles **151a-g**



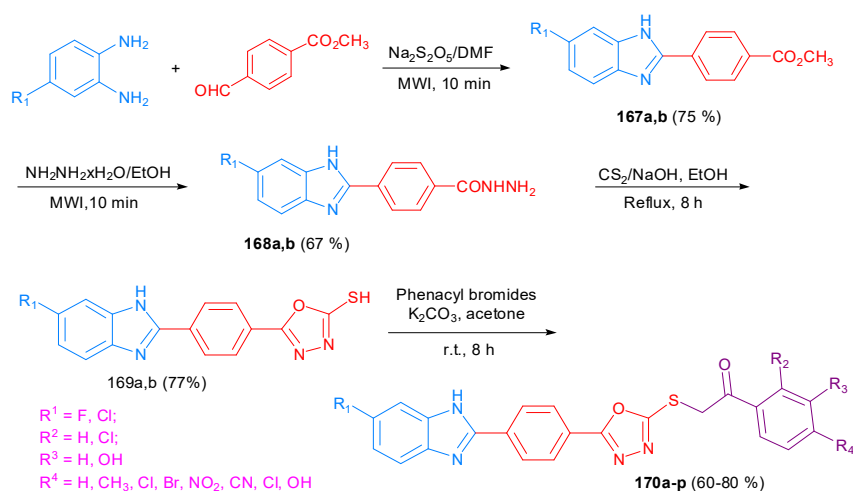
Scheme S-23. Synthesis strategy of the triazolo-benzimidazole compounds.



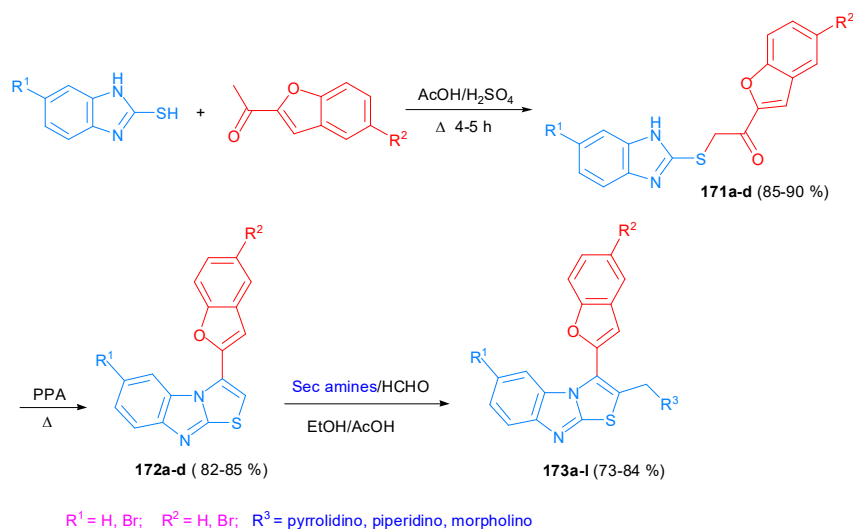
Scheme S-24. Synthetic route of various benzimidazolium *N*-phenyl methylthioformates **158, 159**, spirano-benzimidazolium **160**, methyl dithioformic esters **161, 162** and 2-ethane nitrile -1,3-disubstituted benzimidazole **163**.



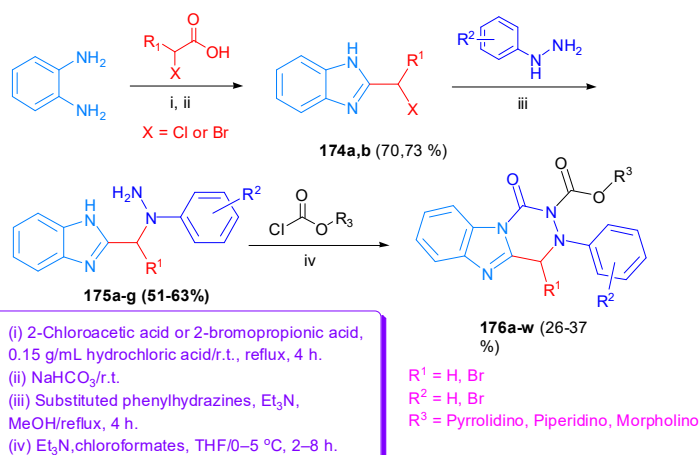
Scheme S-25. Synthesis of 1,2-bis-(2-mercapto-benzimidazol-1-yl)-ethane-1,2-dione and the corresponding diiminic bis(2-thiol benzimidazole) complexes.



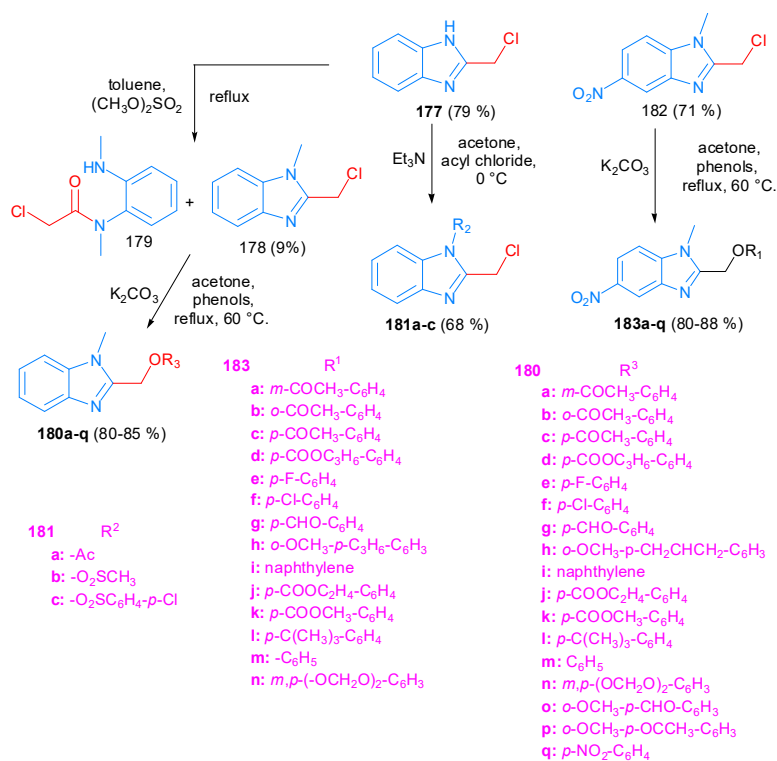
Scheme S-26. Four steps synthesized of targeted hybrid benzimidazole-thio-oxadiazole **170**.



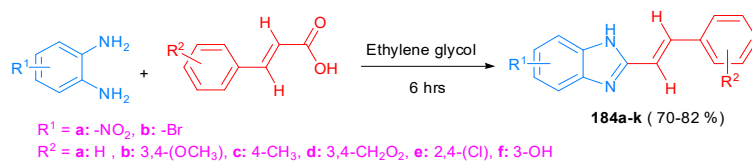
Scheme S-27. Three steps synthesis of fused benzimidazole-thiazole analogues.



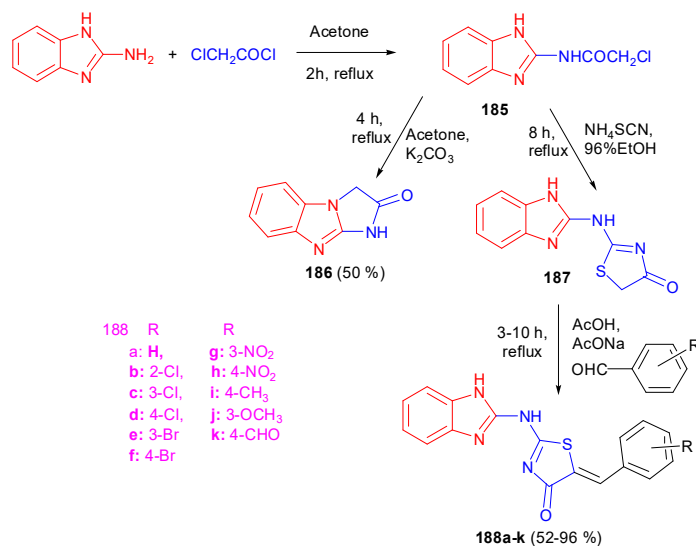
Scheme S-28. Three step synthesis of 1,2,4-triazol-3-one fused benzimidazole.



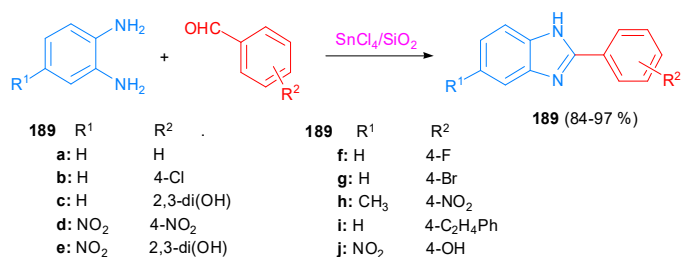
Scheme S-29. Synthesis of 2-chloromethyl-1H-benzimidazole derivatives **180a-q** and **183a-q** from *o*-phenylenediamines and chloromethyl acetic acid.



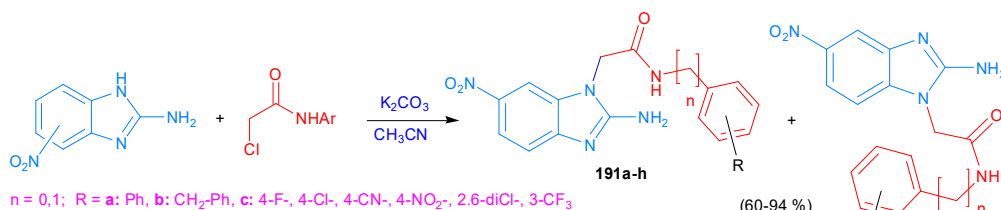
Scheme S-30. Synthesis of 2-styrylbenzimidazoles **184a-k** from substituted phenyl acrylic acids and substituted *o*-phenylenediamine.



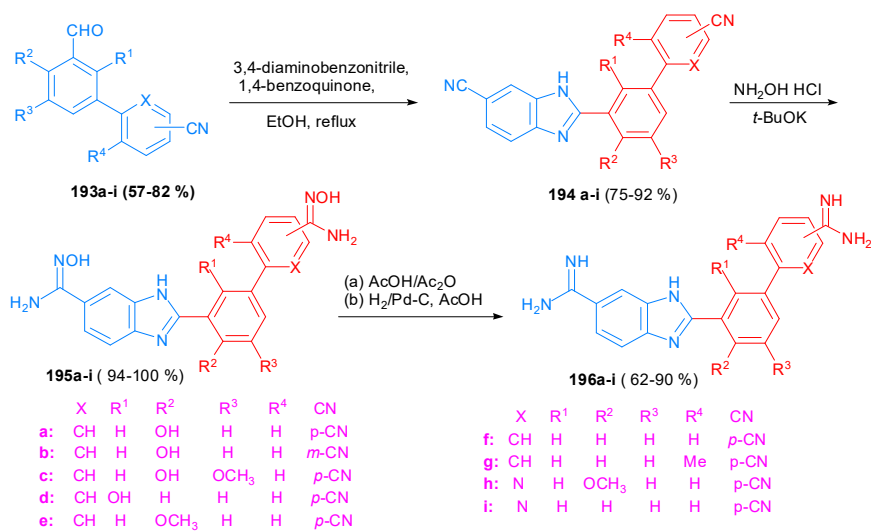
Scheme S-31. Synthetic approach targeted 2-benzimidazolylimino-5-arylidene-4-thiazolidinones **188**.



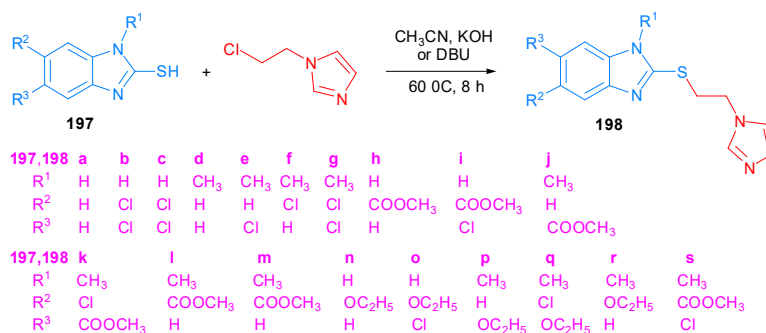
Scheme S-32. SnCl₄/SiO₂ catalysed synthesis of 2-substituted aryl-benzimidazoles.



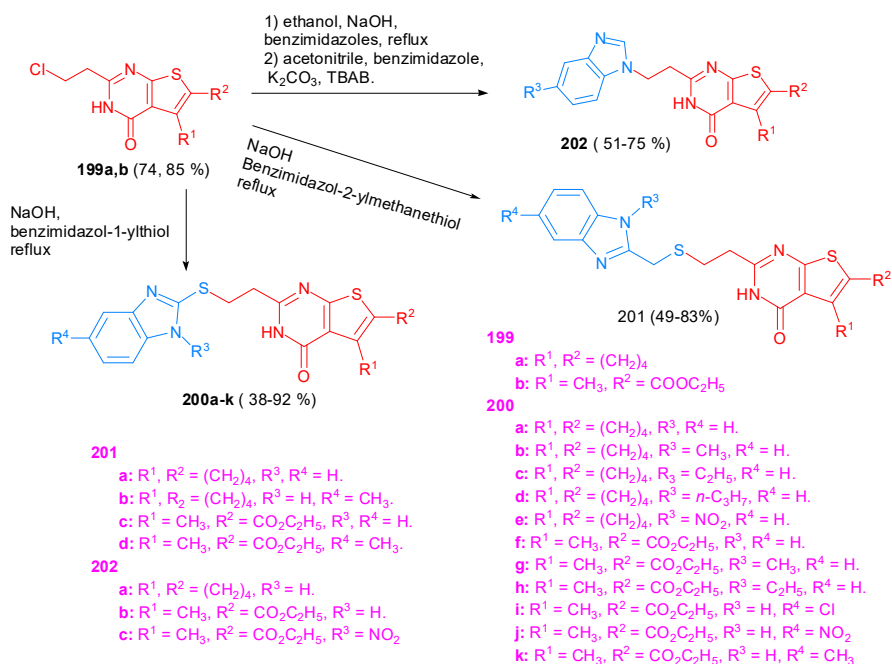
Scheme S-33. Synthesis mixture of regioisomers 4- and 5-nitro-3-aminobenzimidazole-*N*-arylacetamides products **191** and **192**.



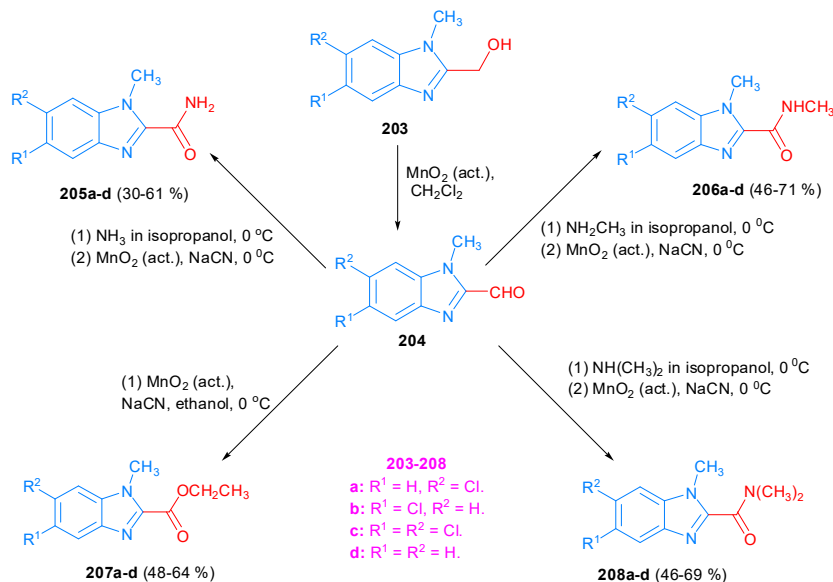
Scheme S-34. Three steps synthesis of biphenyls benzimidazole diamidines **196**.



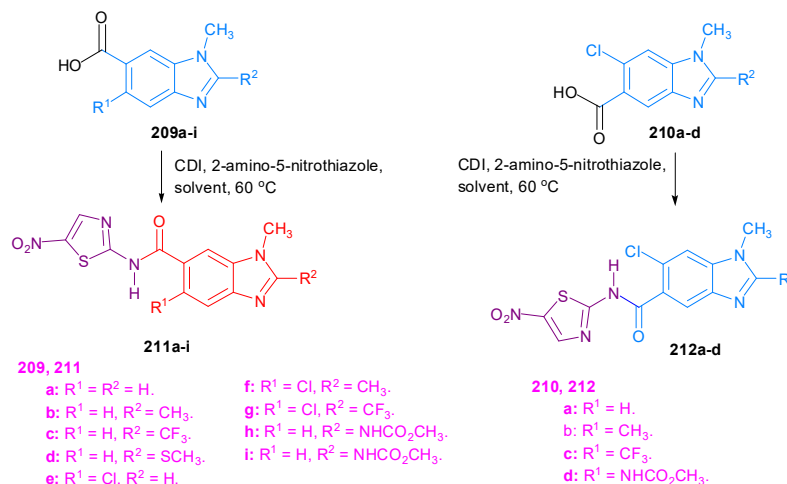
Scheme S-35. Synthetic approach of 2-{[2-(1*H*-imidazol-1-yl) ethyl] sulfanyl}-1*H*-benzimidazole **198**.



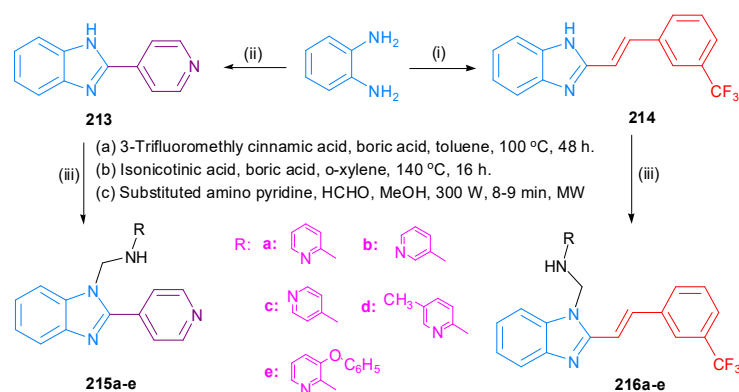
Scheme S-36. Synthesis of benzimidazole derivatives of thieno[2,3-d]-pyrimidin-4-ones



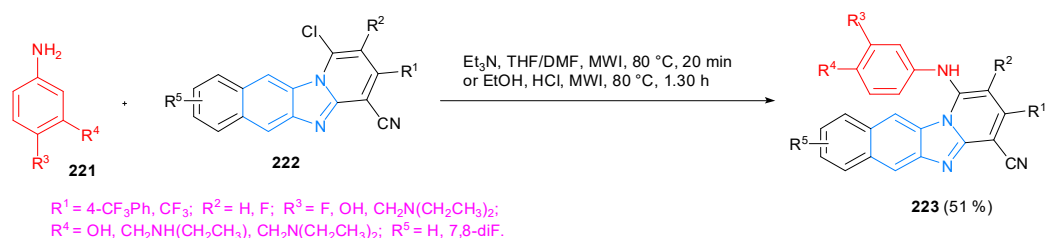
Scheme S-37. The synthetic process of *N*-methylated benzimidazole ester and amides **205a-d-208a-d**.



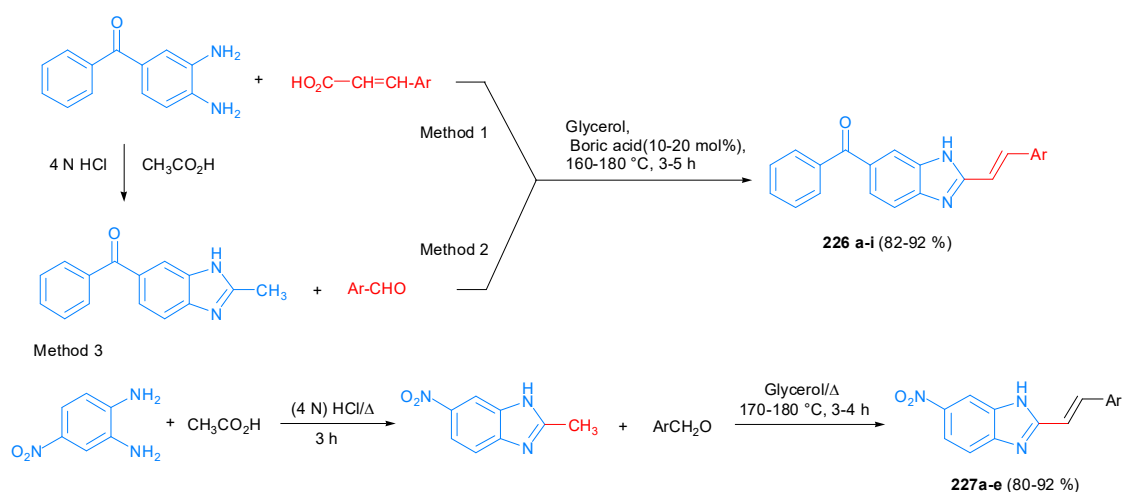
Scheme S-38. Synthetic approach of new benzimidazole-benzothiazole **211a-i** and **212a-d**.



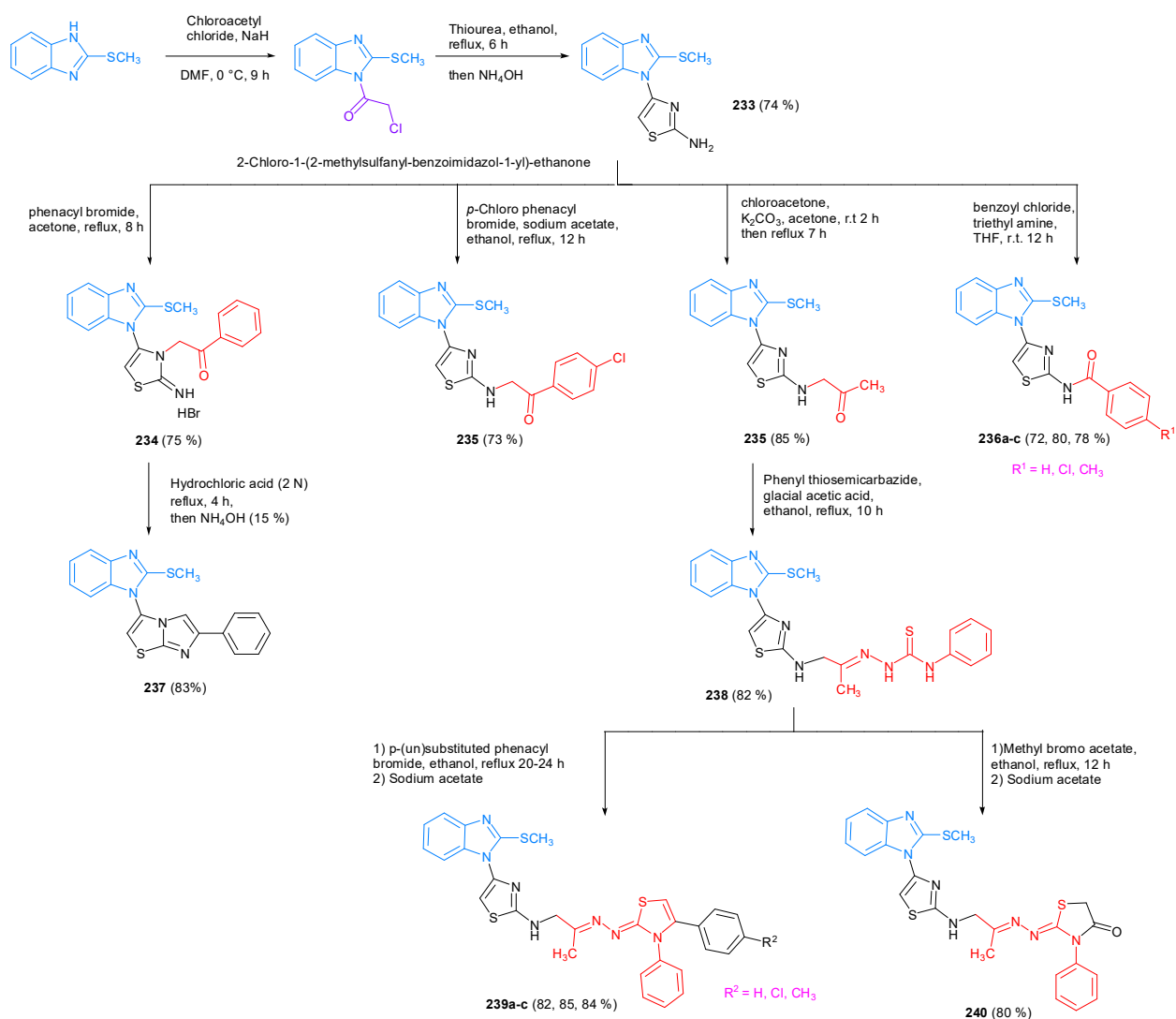
Scheme S-39. Synthesis of amino methyl *N*-substituted benzimidazole derivatives **215a-e** and **216a-e**.



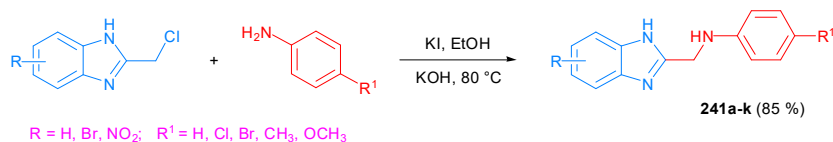
Scheme S-40. The microwave assisted synthesis of fused pyrido benzimidazole **223**.



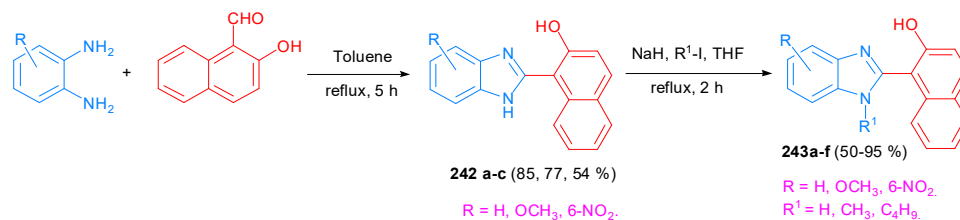
Scheme S-41. Synthesis of 2-styryl-benzoyl-1*H*-benzimidazol **226a-i** and the 5-nitro homologue structures **227a-e** via two methods.



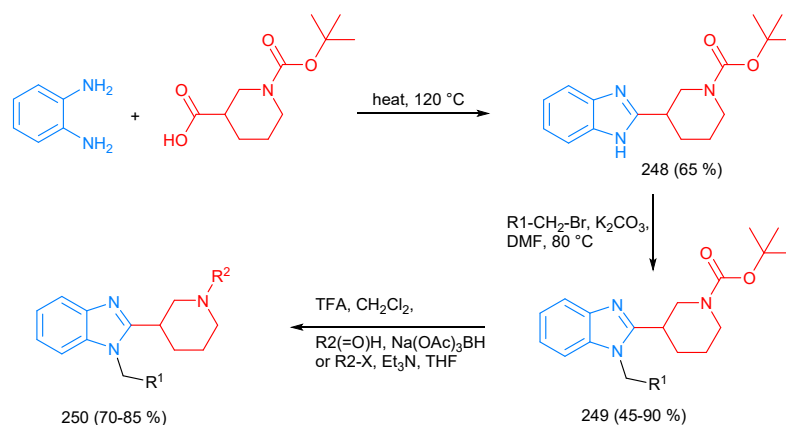
Scheme S-42. Conversion of 4-(2-methylthiobenzimidazol-1-yl)-thiazol-2-ylamine **233a-c** to corresponding benzimidazole derivatives bearing thiazole ring.



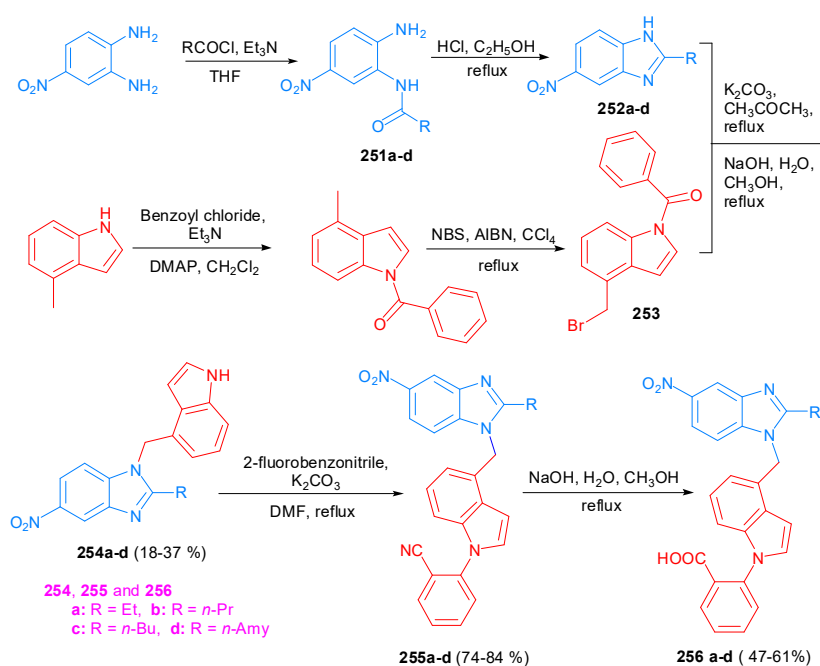
Scheme S-43. Substituted benzimidazol-2-methyl anilines **241a-k** prepared from the *N*-alkylation of 2-chloromethylbenzimidazole and *p*-substituted anilines.



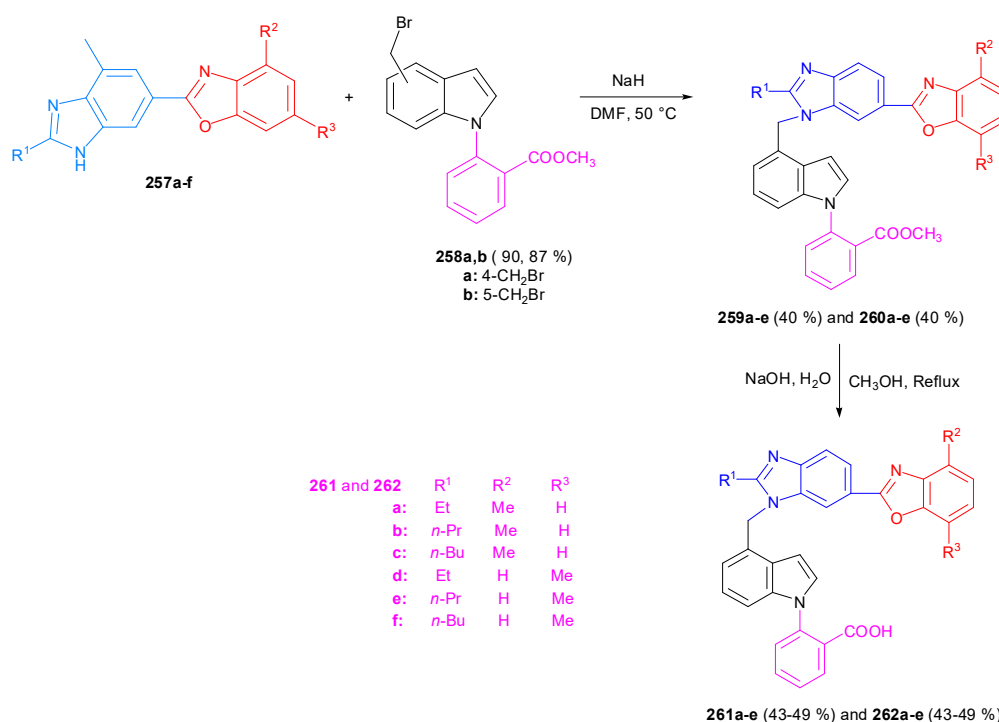
Scheme S-44. Synthesis of targeted substituted-2-(2-hydroxynaphthyl)-3-alkyl benzimidazoles **243a-f**.



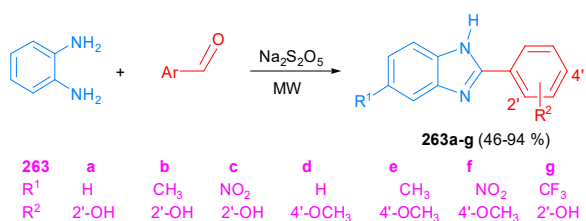
Scheme S-45. Double alkylated benzimidazole-piperidine derivatives **250**.



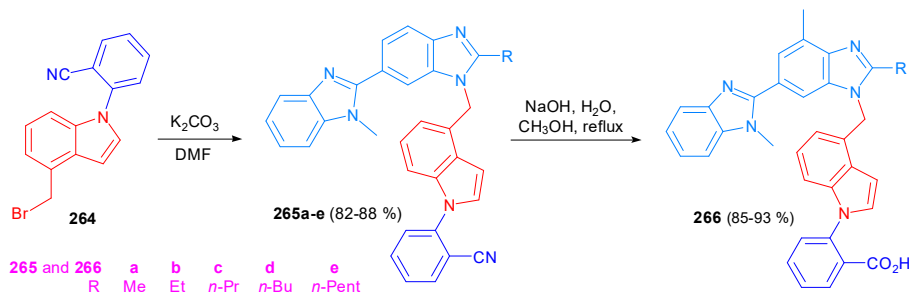
Scheme S-46. Synthesis of 1-(1*H*-indol-4-ylmethyl)-5-nitro-2-alkyl-1*H*-benzimidazole-benzoic acids **256**.



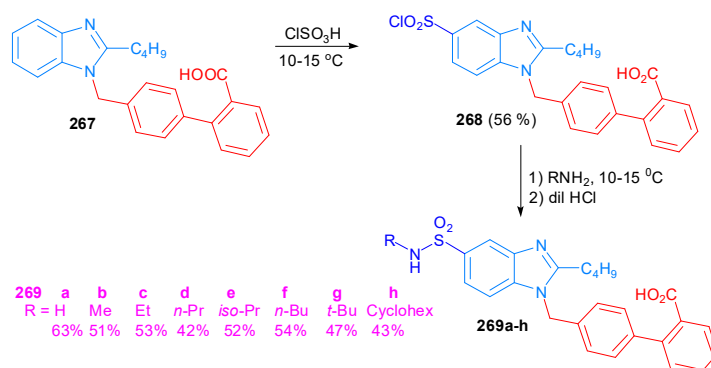
Scheme S-47. Synthesis of targeted benzimidazole-oxazole-indole carboxylic acid **261** and **262**.



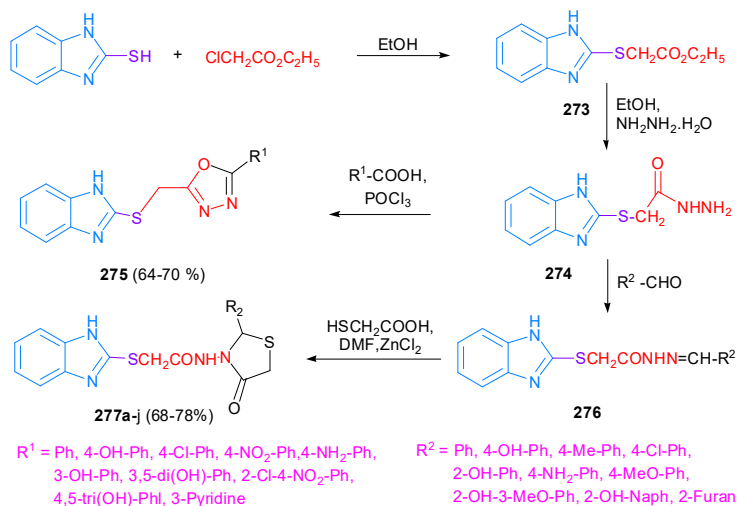
Scheme S-48. 2,5-disubstituted benzimidazoles **263** as *anti*-hypertensive agents.



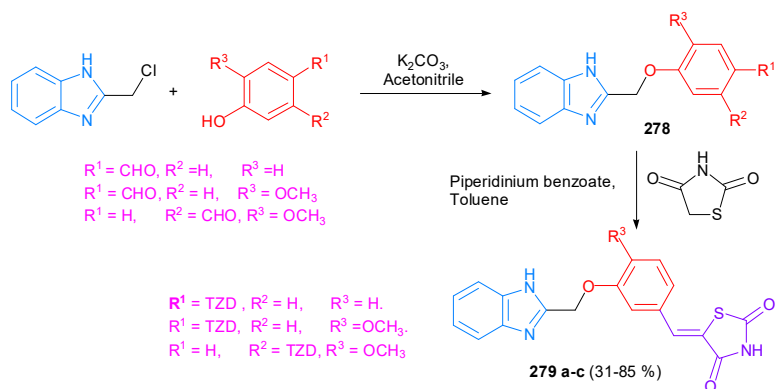
Scheme S-49. Reported series of bis-benzimidazole-indole-benzoic acids derivatives **266**.



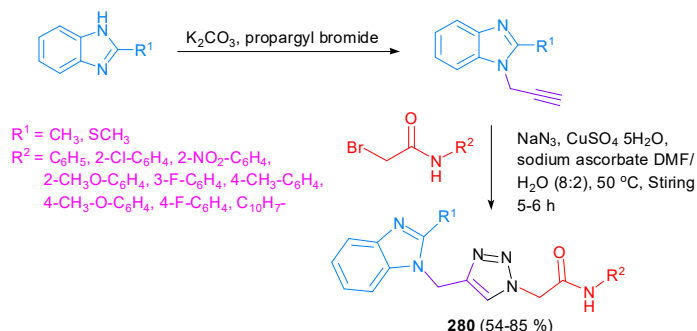
Scheme S-50. 4'-2-butyl-5-sulfamoylbenzimidazolemethyl-biphenyl-2-carboxylic acid **269**.



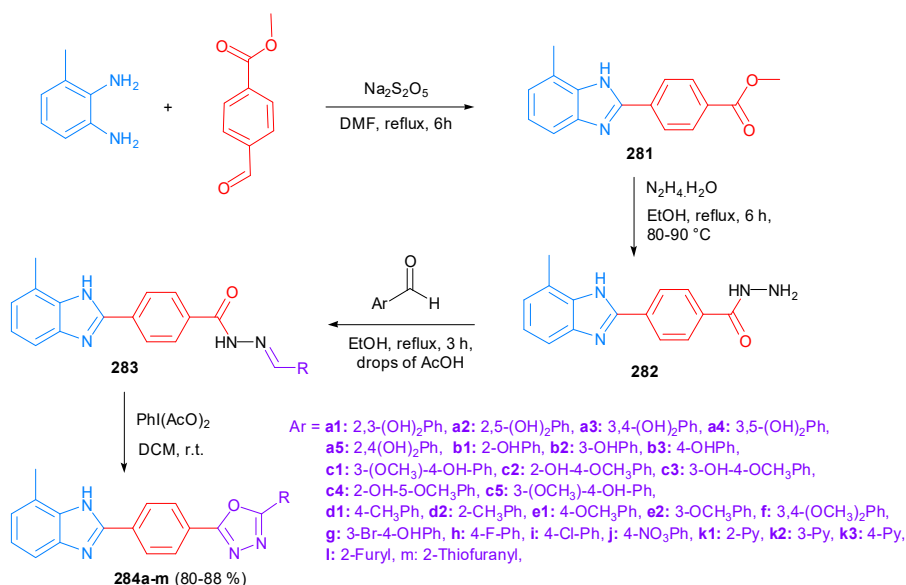
Scheme S-51. 2-mercapto-benzimidazole 1,3,4-oxadiazole **275** and 2-mercapto-benzimidazole thiazolidin-4-one **277** were cited as antidiabetic agents.



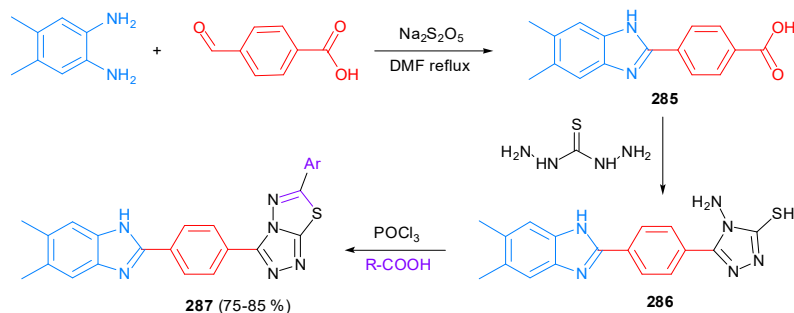
Scheme S-52. The predicted (5*Z*)-5-[3(4)-(1*H*-benzimidazol-2-yl-methoxy)benzylidene]-1,3-thiazolidine-2,4-diones **279**.



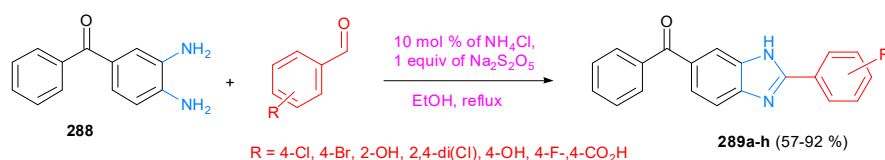
Scheme S-53. *N*-substituted-2-[4-(2-substituted-benzimidazol-1-ylmethyl)-[1,2,3]triazol-1-yl]-acetamide **280** synthesized via the Click Chemistry reaction.



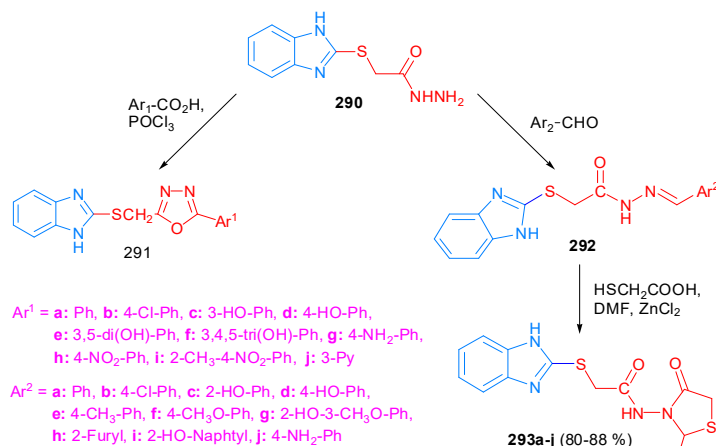
Scheme S-54. Hybrid Benzimidazole-oxadiazole as α -glucosidase inhibitor.



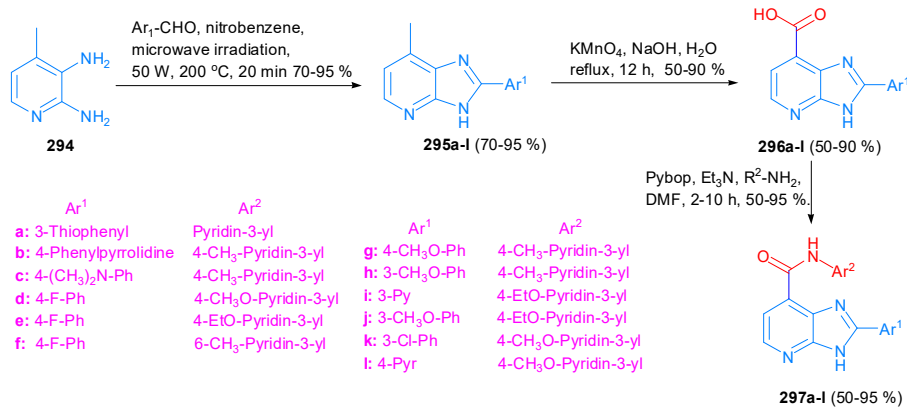
Scheme S-55. Fused bicyclic 6-substituted-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole benzimidazole derivatives **287** as β -glucuronidase inhibiting agents.



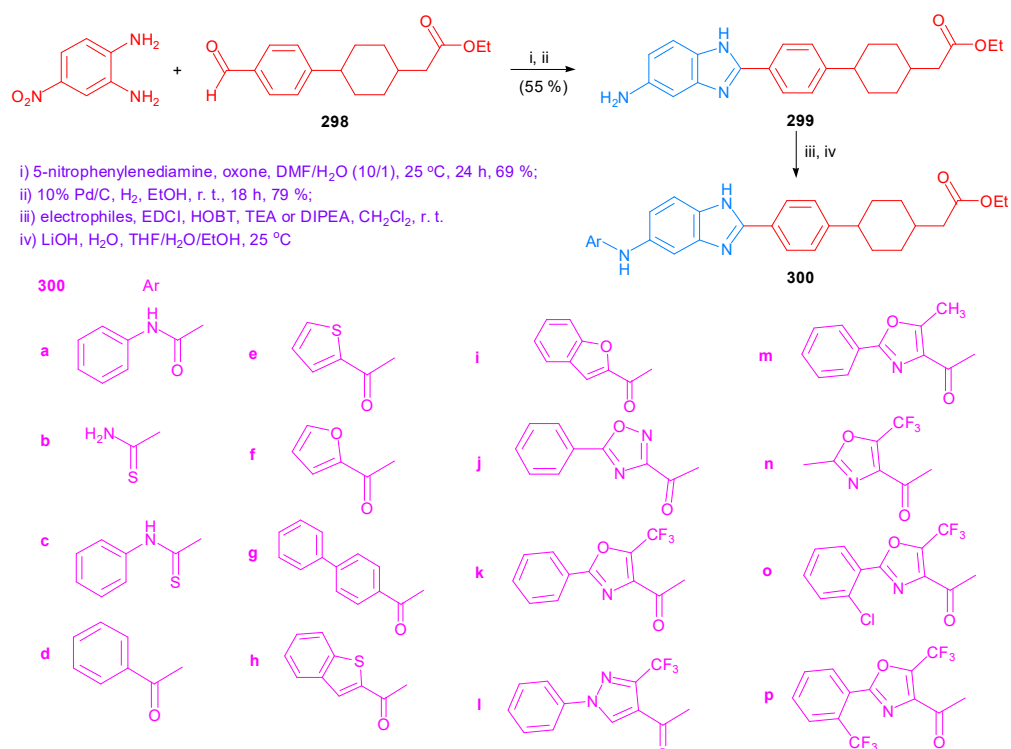
Scheme S-56. benzoyl aryl benzimidazoles were also synthesized using ammonium chloride, or a mixture of ammonium chloride and sodium metabisulfite as a catalyst.



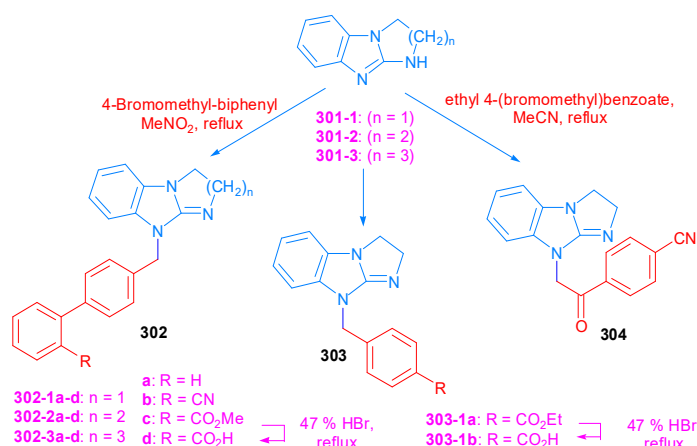
Scheme S-57. Benzoimidazol-2-yl-thio-*N*-2-methyl-4-oxothiazolidin-3-yl-acetamide **293**.



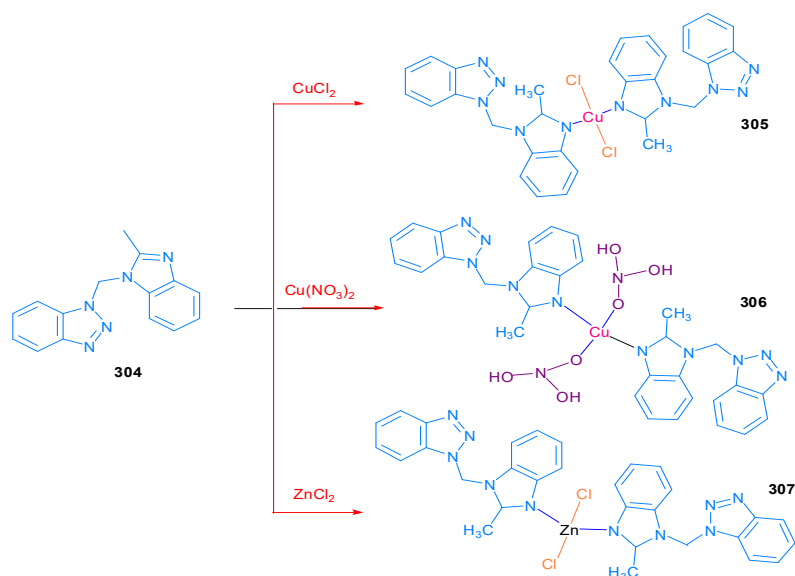
Scheme S-58. Synthesis approach of the 7-methyl-3*H*-imidazo[4,5-*b*] pyridine 2, benzimidazole analogues **297a-i**.



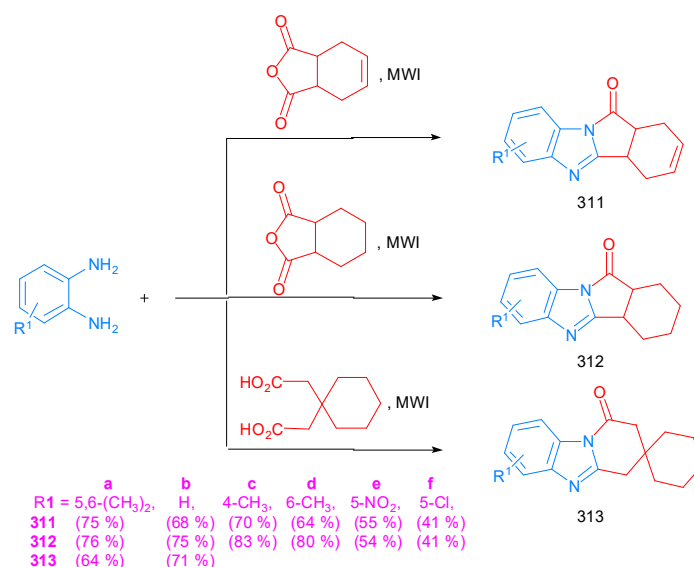
Scheme S-59. *N*-arylamine and arylthioamide benzimidazole phenylcyclohexylethyle ethanoates **300**.



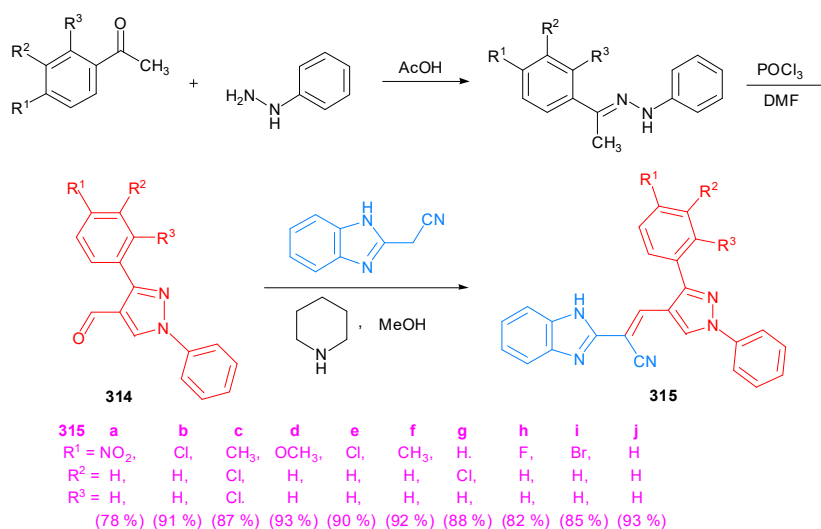
Scheme S-60. Synthesis of expected products *N*-benzyl, *N*-benzoyl and *N*-diphenyl benzimidazoles **302**, **303** and **304**.



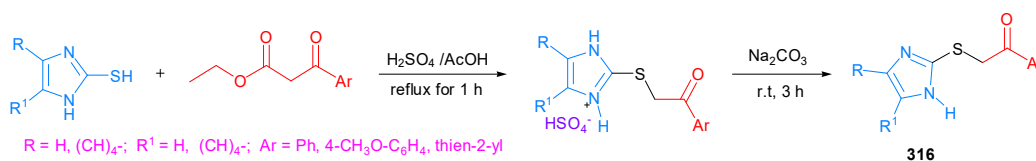
Scheme S-61. Synthesis of bidental complex species **305**, **306** and **307** from 1-(2-methyl-benzimidazol-1-yl)methyl-1*H*-benzotriazole and CuCl₂, Cu(NO₃)₂ and ZnCl₂ salts.



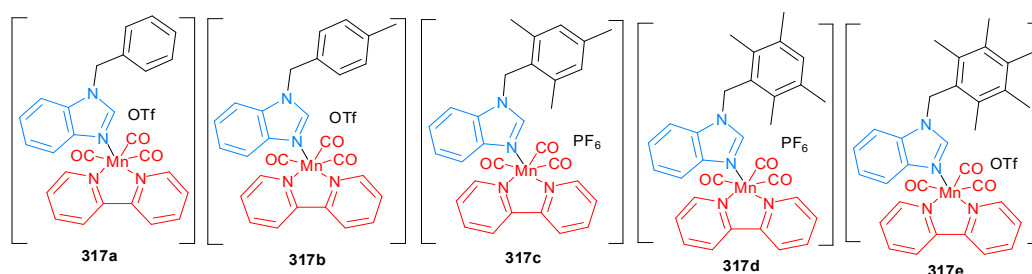
Scheme S-62. A one step microwave assisted of fused tetracyclic benzimidazole imidazolyl products **311**, **312** and **313**.



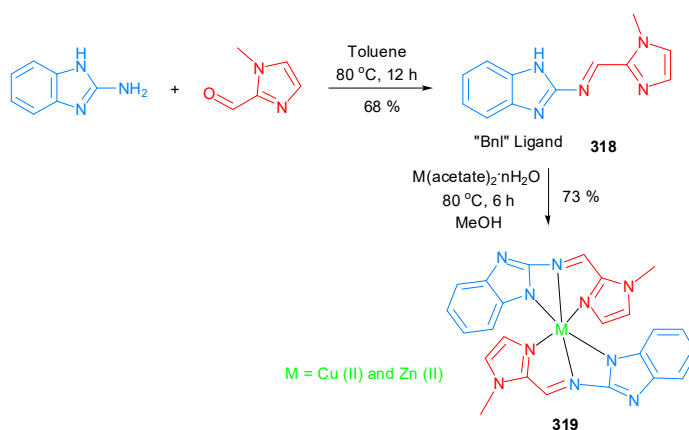
Scheme S-63. Synthesis of the hybrid cyano-benzimidazole-pyrazole compounds **315**.



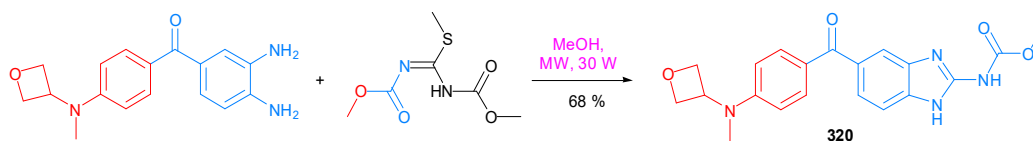
Scheme S-64. Identification of 2-((imidazole/benzimidazole-2-yl)thio)-arylethanones derivatives **316** as anticancer agents.



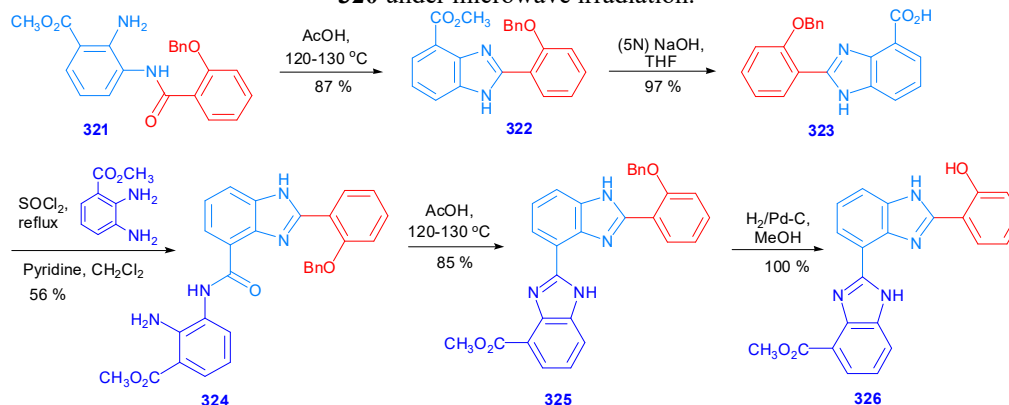
Scheme S-65. Hexacoordinated manganese complexes **317** of 1-benzyl-1*H*-benzimidazoles and 2,2'-bipyridine.



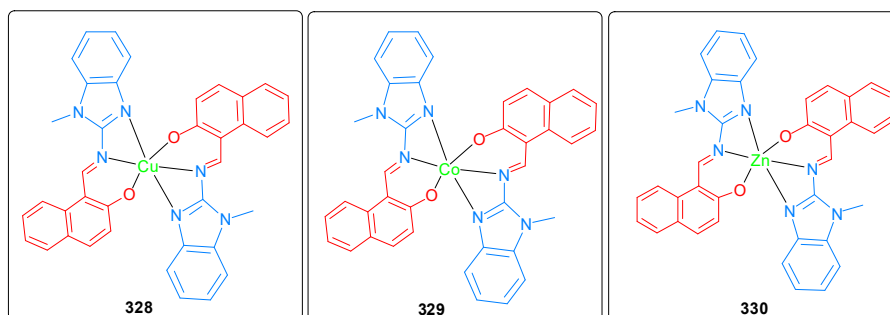
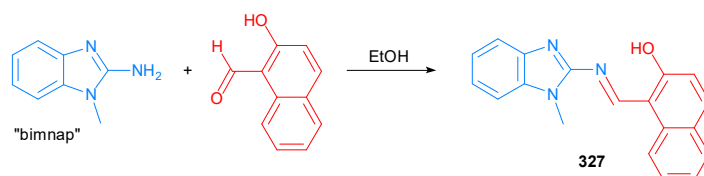
Scheme S-66. Copper (II) and zinc(II) complexes **319** elaborated from Schiff base **318** as ligand prepared from 2-amino-benzoimidazoles and 1-methyl-imidazole-2-carbaldehyde.



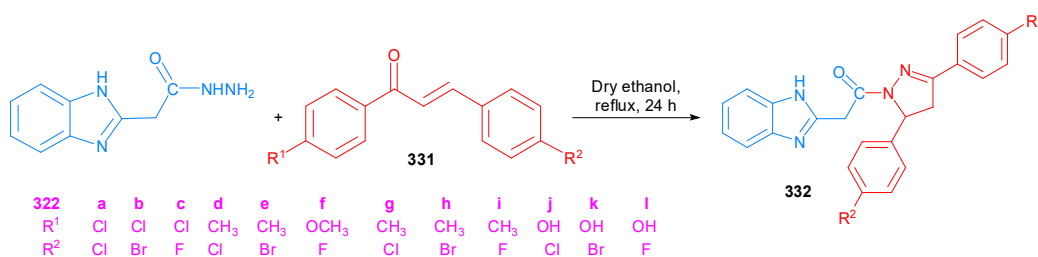
Scheme S-67. Synthesis of 5-[4-(methyl-oxetan-3-yl-amino)-benzoyl]-1*H*-benzoimidazol-2-yl}-methyl carbamate **320** under microwave irradiation.



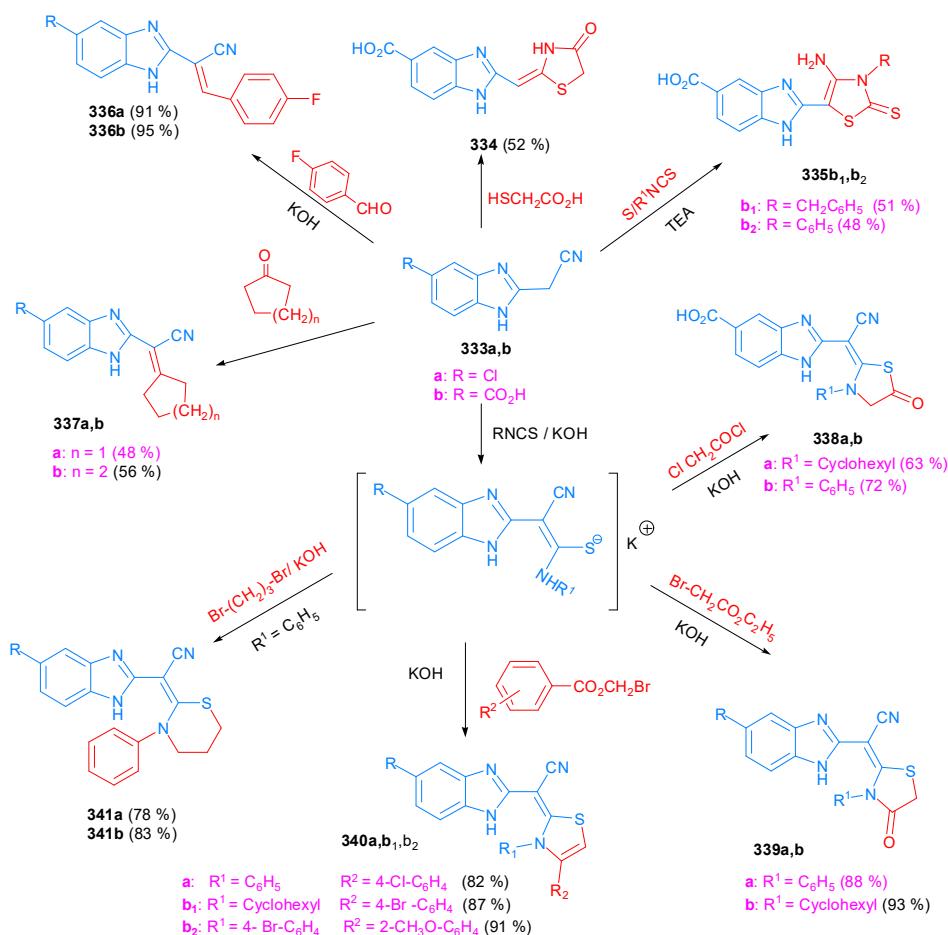
Scheme S-68. Synthesis of 2'-(2-hydroxyphenyl)-1*H*,1'*H*-[2,4']bibenzoimidazolyl-4-methyl carboxylate **326**.



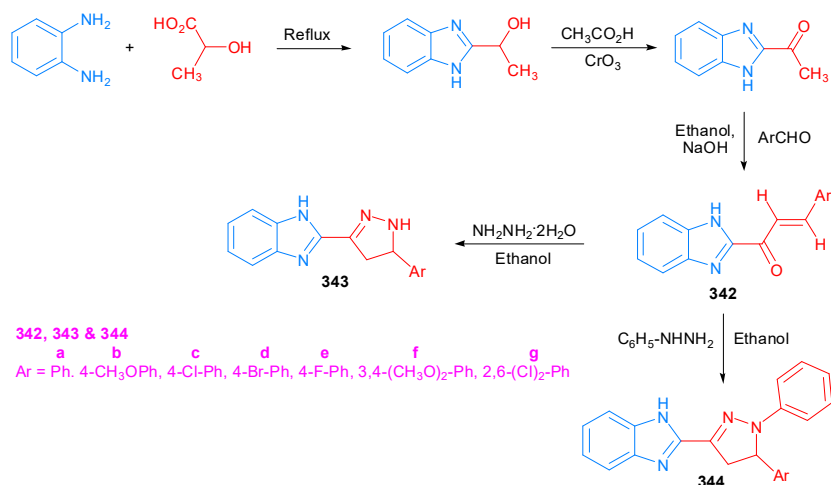
Scheme S-69. Schiff base **327** prepared from 2-aminobenzimidazole and 2-hydroxynaphthaldehyde, which was used to elaborate bidentate Cu(II), Co(II), and Zn(II) complexes **328**, **329** and **330**.



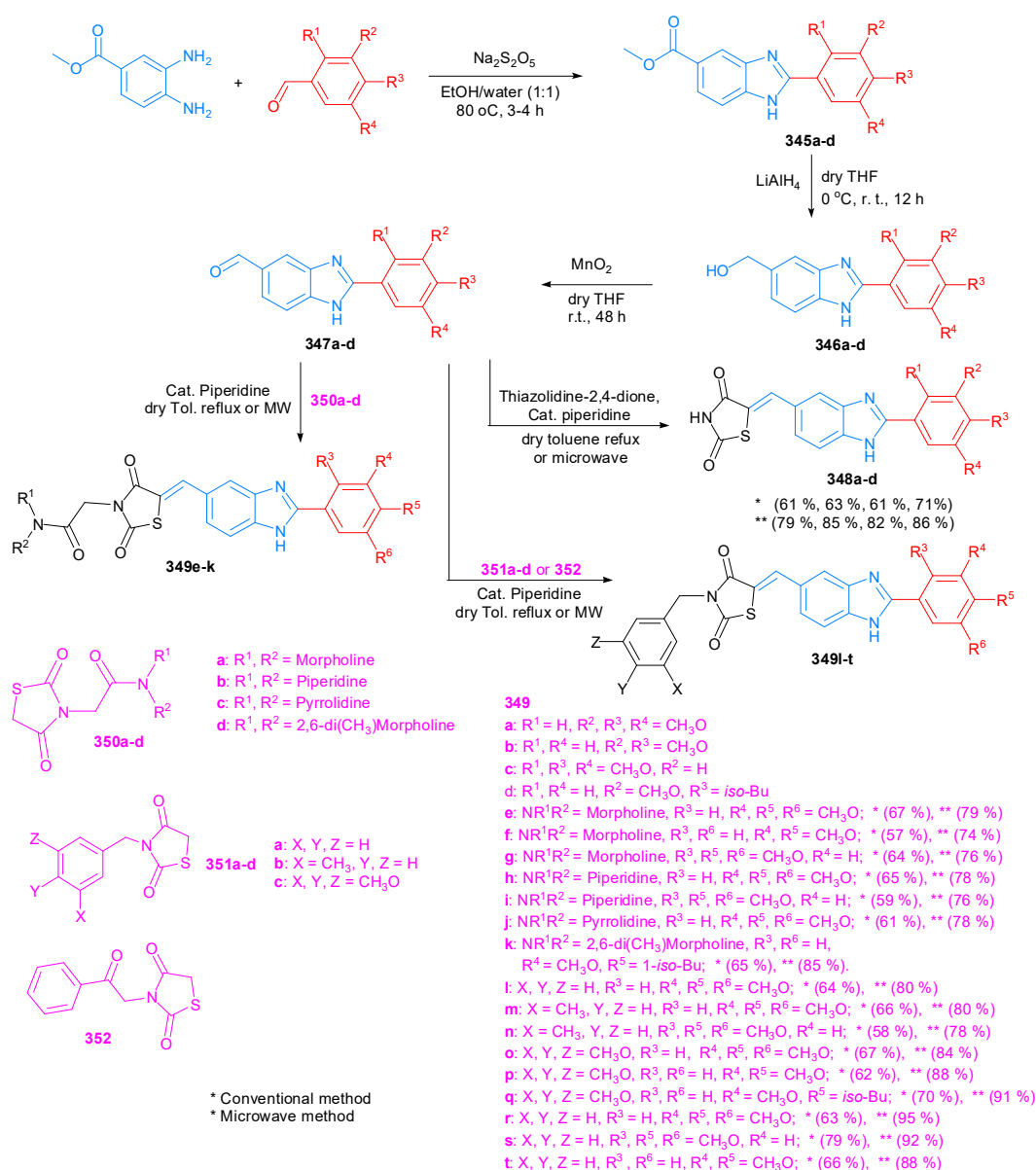
Scheme S-70. Benzimidazole-biphenyl-pyrazolo-ethanones **332** synthesized from Benzoimidazol-acetic hydrazide with chalcones **331**.



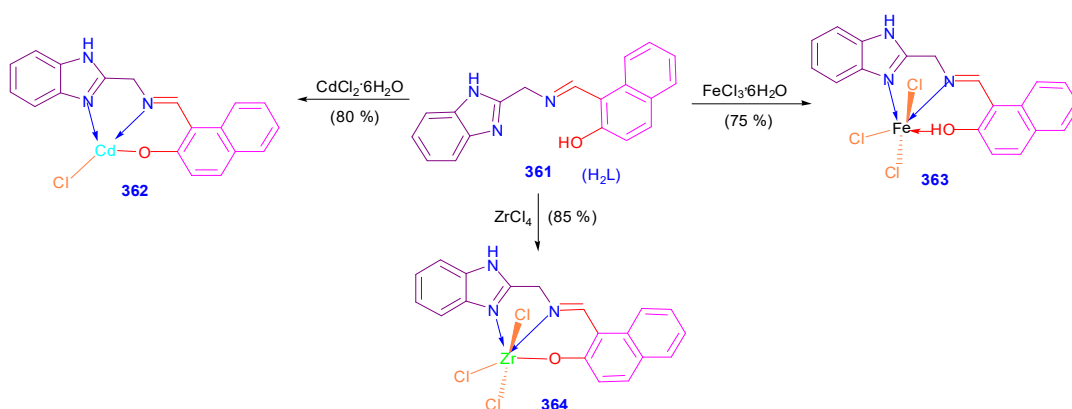
Scheme S-71. Synthesis of variety thiazole and thiazinane benzimidazole derivatives **334-341** starting from 5-chloro and carboxy-1*H*-benzoimidazol-2-yl-acetonitrile.



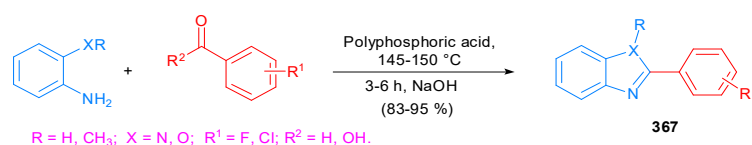
Scheme S-72. Synthesis of 2-[5-(3,4-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-3-pyrazolyl]-1*H*-benzimidazoles **344**, which were found to be the most active for anticancer activity.



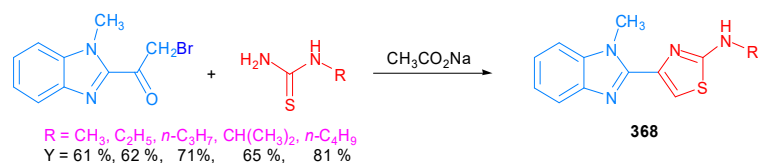
Scheme S-73. Multistep synthesis of 5-methylenebenzimidazole-3-substituted thiazolidine-2,4-diones **349-352**.



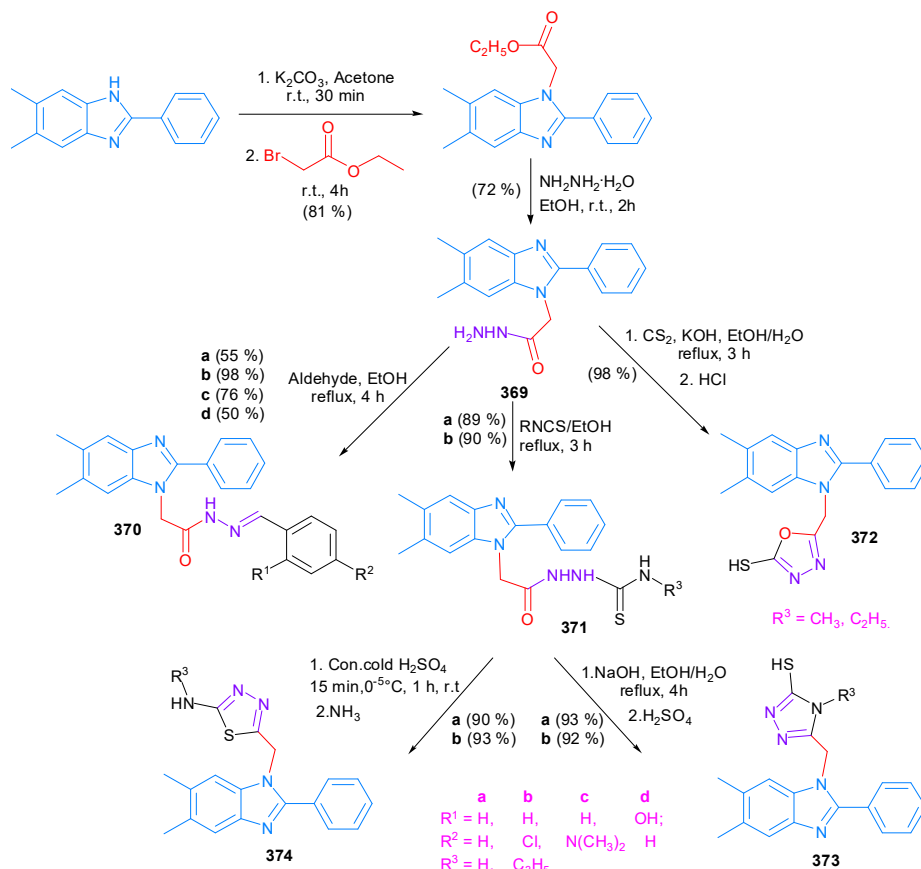
Scheme S-74. Chemical structure of Zr (IV), Cd(II) and Fe (III) benzimidazole complexes **362-364**.



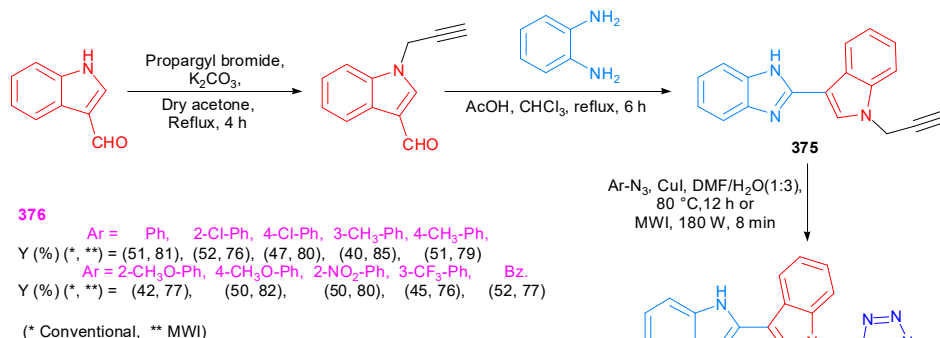
Scheme S-75. Polyphosphoric acid catalysed synthesis of 2-substituted benzimidazoles and benzoxazoles **367**.



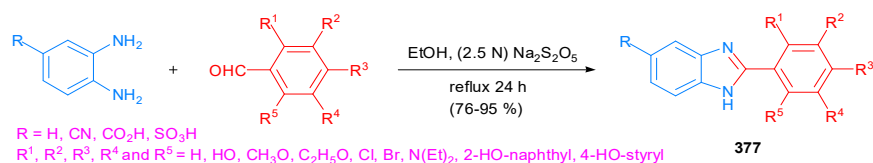
Scheme S-76. Synthesis of alkyl-[4-(1-methyl-1H-benzoimidazol-2-yl)-thiazol-2-yl]-amine **368** from Alkyl-thiourea and 2-bromo-1-(1-methyl-1H-benzoimidazol-2-yl)-ethanone.



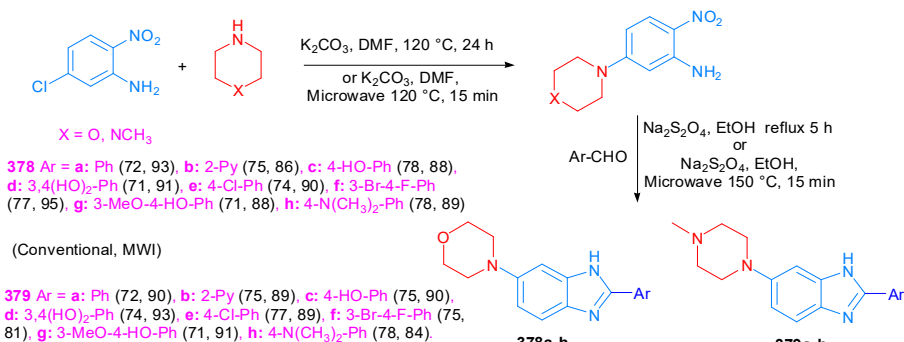
Scheme S-77. Synthesis of [1,2,4] triazole-3-thiol benzimidazoles **373** and [5-(5,6-Dimethyl-2-phenylbenzoimidazol-1-ylmethyl)-[1,3,4] thiadiazol-2-yl] alkylamine **374** respectively.



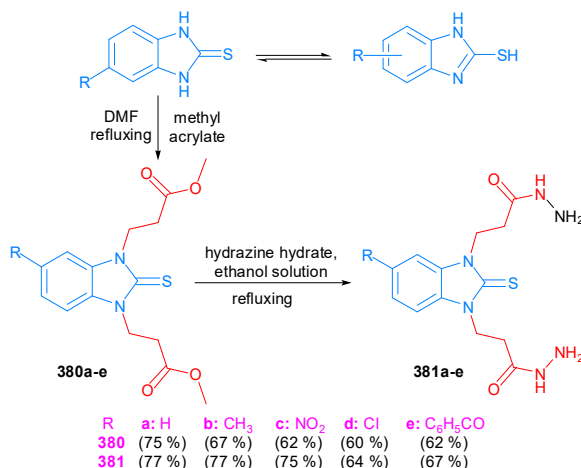
Scheme S-78. Cu(I) catalysed Click Chemistry reaction, that led the 2-[1-(1-aryl-1H-[1,2,3] triazol-4-ylmethyl)-1H-indol-3-yl]-1H-benzoimidazole moieties **376**.



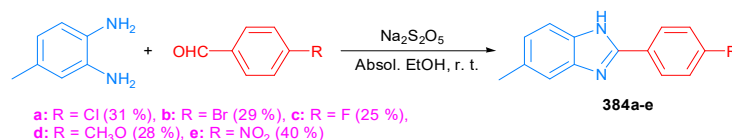
Scheme S-79. A facile synthesis of three series of arylbenzimidazole derivatives **377**.



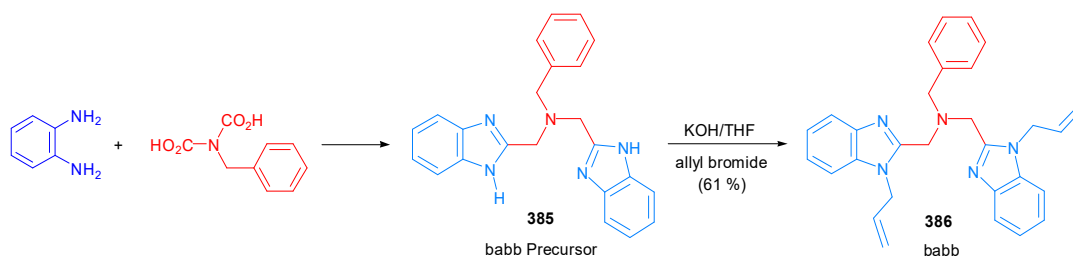
Scheme S-80. Microwave assisted synthesis of 6-morpholin-4-yl and 6-(4-methyl-piperazin-1-yl)-2-aryl-1H-benzimidazoles **378a-h** and **379a-h**.



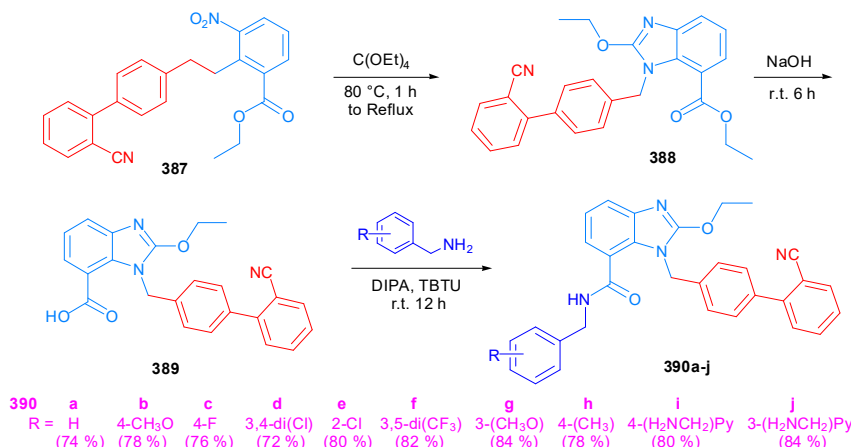
Scheme S-81: Synthetic approach of 5-substituted-1,3-dihydrobenzimidazole-2-thione **380a-e** bearing two propanoic hydrazide **381a-e**.



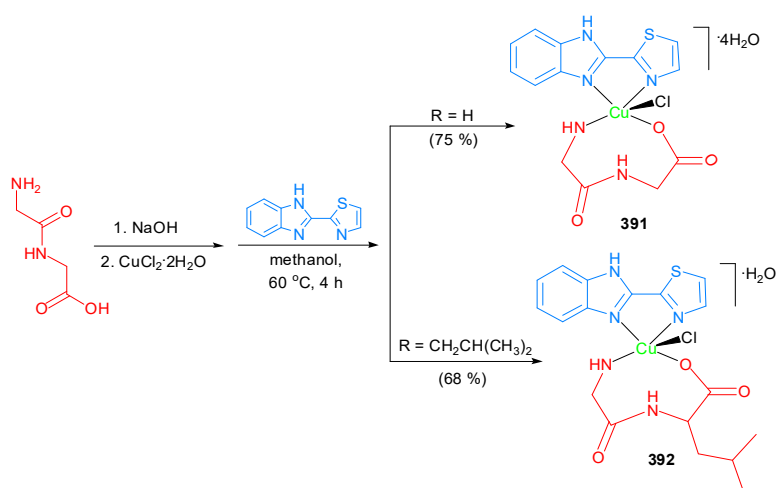
Scheme S-82. Synthesis of 2-(4-substituted phenyl)-5-methyl-1H-benzimidazoles **384a-e**.



Scheme S-83. Benzylamine linked with two allyl benzimidazoles **386** used as ligand in the preparation of Ni complexes.



Scheme S-84. Synthesis of benzimidazole carboxamide derivatives as potent antioxidant agent **390a-j**.



Scheme S-85. Two new complexes, 2-(4'-thiazolyl)benzimidazole based Cu(II)-dipeptide complexes, $[\text{Cu}(\text{Gly-Gly})(\text{TBZ})(\text{Cl})] \cdot 4\text{H}_2\text{O}$ **391** and $[\text{Cu}(\text{Gly-LLeu})(\text{TBZ})(\text{Cl})] \cdot \text{H}_2\text{O}$ **392** synthesized as antioxidant agents