Formation and Uses of Imidazo[1,2-a]pyrimidines and Related Compounds: A Review Comprising Years 2000-2021

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Abstract: This work covers the selected synthetic papers of imidazo[1,2-a]pyrimidine and its derivatives between the years 2000 and 2021. Synthesis of the heterocyclic moiety, application of this scaffold to biological activities, and secondary applications like corrosion inhibition are provided. The authors hope that readers will find the treatise useful.

Keywords: Imidazo[1,2-a]pyrimidine, syntheses, biological applications, uses.


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INTRODUCTION

This review article has been designed in a way that the grand category, sub-categories, and examples are provided, starting from the least recent article to the most recent one.

SYNTHETIC WORKS ASSOCIATED WITH BIOLOGICAL ACTIVITY

Known Molecules

There are known drug candidates in the market with imidazopyrimidine skeleton. Here are some examples for them (See Figure 1):
Figure 1: Some known examples of imidazopyrimidines in use.

GABA<sub>A</sub> Ligands that are Functionally Selective
Jensen and coworkers reported that γ-Aminobutyric acid (GABA) is the major inhibiting neurotransmitter in the central nervous system. Imidazo[1,2-a]pyrimidines are GABA<sub>A</sub> receptor benzodiazepine binding site ligands. They can show functional selectivity for the α3 subtype over the α1 one (1) (See Figure 2).
Figure 2: Preparation of pyridylphenylimidazo[1,2-a]pyrimidines as GABA receptor benzodiazepine binding ligands.

Synthesis and Biological Activities of Some Imidazopyrimidines
An Armenian research group has studied the synthesis and biological activities of 4-substituted 6,7-dihydro-7,7-dimethyl-5-oxo-9H-pyrano-[4',3':4,5]-thieno [3,2-e]imidazo [1,2-a] pyrimidines and their hydrochlorides and their anticonvulsant and tranquilizer properties (2) (See Figure 3).
**Figure 3**: Synthesis of pyranothienoimidazo[1,2-a]pyrimidine compound.

**Antiinflammatory Response of Imidazopyrimidine Derivatives**
Vidal and co-authors (2001) prepared six imidazo[1,2-a]pyrimidine (IP) derivatives and tested on leukocyte functions in vitro and inflammatory response was also tested, this response is induced by zymosan in the mouse air pouch. The authors reported that imidazo[1,2-a]pyrimidines possess antiinflammatory potential (3) (See Figure 4).

**Figure 4**: Imidazopyrimidine derivatives for researching the antiinflammatory activity.

**Synthesis of GABA Agonists**
A group from Merck, Inc with Blackaby as the first author has reported the preparation of GABA-selective agonists through a series of synthetic steps (4) (See Figure 5).
Preparation of GABA<sub>A</sub> Agonists Against Anxiety

Jennings et al. showed that imidazo[1,2-a]pyrimidines and triazines could function as GABA<sub>A</sub> agonists for the treatment of anxiety. The group has prepared seven compounds and investigated their affinity and efficacy at α1 and α3 subtype GABA<sub>A</sub> receptors, by varying the terminal pyridine ring. The route to synthesize the molecules has been shown in the figure below (5) (See Figure 6).

Figure 5: Preparation of tributyl Sn-C bond and reaction with aryl halide; eight instances were reported.

Figure 6: Preparation of 3-aryl-substituted imidazopyrimidine derivative.
Compounds Showing Anti-inflammatory Property and COX-2 selectivity

A Chinese research group (Zhou et al.) has investigated the synthesis and anti-inflammatory activity of imidazo[1,2-a]pyrimidine derivatives positioned adjacent with two aryl groups were designed and synthesized in order to improve their anti-inflammatory activities. The synthesized compounds presented anti-inflammatory activities with some COX-2 selectivity (6) (See Figure 7).

Preparation of New Antimicrobial Agents

New antimicrobial agents, containing imidazo[1,2-a]pyrimidine skeletons, have been synthesized by Al-Tel and Al-Qawasmeh in 2010. The antimicrobial activities were tested with Gram-positive and negative bacteria. Some of the test compounds were efficient in the inhibition of Gram-positive and negative strains. According to the results, the substituents on phenyl rings are the determining factor of biological activity. The antibacterial activity is dramatically lowered if the molar refractivity is increased (7)(See Figure 8).

Dual KSP and Aurora-A Kinase Inhibitors

Geng and coworkers reported that four series of dihydropyrazolo[3,4-b]pyridines and benzo[4,5]imidazo[1,2-a]pyrimidines were designed and synthesized as being KSP and Aurora-A kinase inhibitors, at the same time. This was achieved by adding some Aurora-A kinase inhibitory fragments into the KSP inhibitor body and it was named as CPUYL064. Two enzyme inhibition assays and a cytotoxicity assay in vitro were conducted with 19 target compounds. The results indicated that some target compounds could inhibit both enzymes and several compounds were significantly inhibitive against HCT116 cell line. Although they were moderate KSP and Aurora-A kinase inhibitors, two compounds displayed a remarkable cytotoxic activity in the micromolar range, especially against the HCT116 and HepG2 cell lines. Cancer treatment with dual-function inhibitors seems to be possible (8) (See Figure 3).
**Figure 8:** Synthesis of new antimicrobial agents containing imidazopyrimidine moiety.

**Figure 9:** Preparation of dual-function inhibitors. R\(^1\) is furyl. R\(^2\) is 4-methoxy, 4-nitro, 4-trifluoromethyl, 3-chloro-4-fluoro, and 4-fluoro.
Compounds Inhibiting Wnt/b-catenin signaling pathway
In the regulation of embryonic development and tumorigenesis, Wnt/b-catenin signaling possesses an important role. When it is deregulated, severe cases like cancer occur and Wnt signaling helps establish a good platform for the pharmacology-related targeting of cancer. A series of imidazopyrimidines were prepared by Cosimelli and coworkers, and they discovered that some compounds were able to inhibit the signaling pathway of Wnt/b-catenin with the help of a luciferase reporter assay. Also, cell proliferation was found in selected cancer lines and APC or b-catenin gene was mutated. The most successful compounds in the series could downregulate the expression of Wnt target genes (9) (See Figures 10 and 11).

\[
\begin{align*}
&\text{OMe} & & \text{Br} & & \text{O} & & \text{N} \leftarrow \text{EtOH} \rightarrow \text{heat} \\
&\text{OMe} & & \text{MeO} & & \text{N} & & \text{H} \\
&\text{OMe} & & \text{MeO} & & \text{N} & & \text{H} \\
&\text{OMe} & & \text{MeO} & & \text{N} & & \text{H}
\end{align*}
\]

Figure 10: Preparation of mono- and di-benzyl-substituted imidazopyrimidine compounds.

\[
\begin{align*}
&\text{OMe} & & \text{N} & & \text{NH} \leftarrow \text{CHCl}_3, \text{DMAP} \rightarrow \text{60 °C, 2h} \\
&\text{OMe} & & \text{N} & & \text{NH} \\
&\text{OMe} & & \text{N} & & \text{NH}
\end{align*}
\]

Figure 11: Benzylation of the 5-hydroxy group.

Synthesis of Some Mannich Bases Incorporating Imidazopyrimidine Core
Aeluri and co-workers prepared Mannich bases containing imidazo[1,2-a]pyrimidine skeleton. Imidazo[1,2-a]pyrimidine skeleton was prepared with a one-pot, three-component reaction, in which 2-aminopyrimidine, a secondary amine or piperazine, and excess formaldehyde in methanol were used. The products were tested in vitro against three human cancer cell lines. Antiproliferative activity was found for most of the compounds. Three of them showed effective inhibition, with GI 50 values similar to the standard drug used (10) (See Figure 12).
Synthesis of Tricyclic Dihydropyrimidines
Some tricyclic dihydropyrimidines were synthesized by Kaur et al. using a procedure which endows a one-pot, three-component Traube-Schwarz reaction, along with Zn(ClO$_4$)$_2$.6H$_2$O as the catalytic entity. All the purified compounds were screened for their _in vitro_ anticancer activity, against three cancer cell lines, namely prostate cancer cells (PC3), lung cancer cells (NCI-H1299), and colon cancer cells (HCT116). The authors investigated _in vitro_ DNA-intercalation ability with UV-Vis spectrophotometry, and found that the compound was inserted into the DNA base pairs and interacted strongly with the DNA double helix (11) (See Figure 13).

Antigiardial Response of Imidazopyrimidines
Velázquez-Olvera and co-workers investigated _in vitro_ of the antigiardial response of a group of imidazopyrimidine compounds against _Giardia lamblia_ WB’s trophozoites and albendazole was employed as the reference drug. The synergism of albendazole with the most active imidazopyrimidine compound was also studied. The most potent compound had 3-hydroxymethyl-4-fluorophenyl substituents on the skeleton, and the parent compound to compare had p-tolyl substituent only. As a conclusion, researchers found that 2-aryl-3-hydroxymethyl substituents created a good synergism against the reference (12) (See Figure 14).

Synthesis and Biological Activity of Biphenyl-Containing Imidazopyrimidines
Al-Lami and coworkers reported the four-step synthesis of fourteen compounds. In the first step, 2-aminopyrimidine and biphenyl phenacyl bromide were reacted to give the imidazopyrimidine skeleton. In the second step, Vilsmeier-Haack reaction was employed to introduce an aldehyde group at the 3-position. The aldehydes formed were reacted with various aromatic amines to form...
Schiff's bases in the third reaction. Sodium borohydride was used to reduce the Schiff's bases to 3-aminomethyl-2-biphenylimidazo[1,2-a]pyrimidines. Different bacteria were tested for antimicrobial effect of some of the synthesized compounds (13) (See Figure 15).

![Four step synthesis of fourteen compounds for antimicrobial assay.](image)

Figure 15: Four step synthesis of fourteen compounds for antimicrobial assay.

**PDE10A enzyme inhibitors**
Moszczyński-Pętkowski and coworkers synthesized new substances containing imidazo[1,2-a]pyrimidine skeleton for possible interaction with PDE10A. Some compounds displayed a very high activity and also presented a good metabolic stability (14) (See Figure 16).
Antitumor Activity along with Antimicrobial and Antioxidant Effect of some Imidazopyrimidine Derivatives

Farag and coworkers investigated the potential utility of imidazo[1,2-a]pyrimidine derivatives. Many compounds synthesized in this study showed a very good in vitro antitumor activity against MCF-7 cell line. Their antimicrobial and antioxidant activities were also found to be high. Some computational studies like DFT and SAR were also reported (15) (See Figures 17).
Homopiperazine-Containing Imidazopyrimidine Derivatives

Homopiperazine-containing new imidazo[1,2-a]pyrimidine derivatives (3 in total) were prepared and screened by Mantipally and coworkers, in terms of in vitro cytotoxicity against HeLa and A549 by MTT technique (16) (See Figure 18).

**Figure 17:** Synthesis of benzimidazopyrimidines from nitriles and aminobenzimidazoles.

**Figure 18:** Preparation of imidazopyrimidine from aminimidazole and substitution of the chloro group with homopiperazine and further functionalization of the homopiperazine side group.
**Dihydropyrimidine as Monastrol Analogs**

Tawfik and co-workers prepared twenty-one 3,4-dihydropyrimidine compounds, as monastrol analogs, having 1,3-benzodioxole moieties at position 4 and also having different substituents at positions 2, 3 and 5. These compounds were screened towards 60 cancer cell lines under NCI (USA) protocol. The researchers also reported the assay of levels of active caspase-3 and caspase-9. They also studied molecular docking of some compounds to illustrate the interaction between inhibitors and the kinesin spindle protein allosteric binding site (17) (See Figure 19).

![Figure 19: Synthesis of imidazopyrimidine derivatives as monastrol analogs.](image1)

**Synthesis and Antimicrobial Activity of Quinoline-Containing Imidazopyrimidines**

Quaternary salts from a quinoline compound were prepared by Elenich and coworkers, then imidazo[1,2-a]pyrimidine derivatives, along with other heterocycles, were produced with the use of dinucleophilic reagents. A great deal of the synthesized compounds showed antimicrobial activity (18) (See Figure 20).

![Figure 20: Imidazopyrimidine compounds for antimicrobial activity.](image2)

**Fluoromethylated Imidazopyrimidines**

Jismy and coworkers synthesized fluoromethylated derivatives of imidazo[1,2-a]pyrimidines and benzimidazo[1,2-a]pyrimidines with a Michael addition/intramolecular cyclization. In this reaction, 2-aminoimidazole derivatives were reacted with 4,4,4-trifluorobut-2-ynoate under C-O bond activation. The formed compounds are examples of C-C, C-N, and C-S bond-forming synthons. Some derivatives possessed micromolar IC50 values against monoamine oxidase B and butyrylcholinesterase and as known well, these two enzymes are important targets considered by neurodegenerative disorders (19) (See Figure 21).
Stabilizing Effect for KRAS 24
Pancreatic, pulmonary, and colorectal cancers involve an oncogene named KRAS, so it constitutes an important target for the treatment of these cancers. A group of molecules were found by D’Aria and coworkers to perform a stabilizing effect on the NMR structure of 22-mer KRAS 24. Finally, compound 19 was found to be the best candidate and it may be considered that this compound is possibly a prototype of a new class of drugs which could be used for the treatment of tumors which express mutations of KRAS and which resist current therapies (20) (See Figure 22).

Ten Year Review of Therapeutic Potentials of Pyrimidines
Zhuang and coworkers described the 10-year review of therapeutic potentials of pyrimidine-based compounds and their antimicrobial activities (21) (See Figure 23).
HIV-1 Integrase Inhibitors
As known well, anti-human immunodeficiency virus 1 (anti-HIV-1) drugs make it a target for HIV-1 integrase (IN) enzyme. The researchers with Zadeh as the first author modified the structure of N-arylindole β-diketoacids (favorite inhibitors of IN) with 4-oxo-4,10-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylic acid derivatives for the development of new anti-HIV-1 drugs (22) (See Figure 24).

Attempts to Use Imidazo[1,2-a]pyrimidines in Photodynamic Therapy
Some imidazo[1,2-a]pyrimidines were found by Lima and coworkers to generate singlet oxygen and thus, they could serve as intracellular photosensitizers. Photodynamic therapy of these compounds indicated that they absorbed and emitted within 400-500 nm, they showed low cytotoxicity when not in use (in the dark), they are taken inside cells efficiently, they fluoresce inside cells, they generate singlet oxygen with irradiation of the system, and cancer cells are killed in two hours and at a low concentration (23) (See Figure 25).

PURELY SYNTHETIC WORKS
Vilsmeier Formylation of Imidazo[1,2-a]pyrimidines
Vilsmeier reaction is largely employed to add formyl groups to a molecule. In this reaction, phosphorus oxytrichloride and N,N-dimethylformamide are used. A Latvian group with Saldabol was the first author has used this methodology to add formyl (-CH=O) groups to imidazo[1,2-a]pyrimidine at the 3 position. When the formylating reagent is taken as double, the side furyl group was also formylated (24) (See Figure 26).

Synthesis of 2-carbamoyl-3-arylimidazo[1,2-a]pyrimidines
Majcen-Le Marechal and coworkers have reported a series of 3-aryl-substituted imidazo[1,2-a]pyrimidine-2-carboxamide structures (25) (See Figure 27).

Synthesis of Dihydroimidazopyrimidine
Kochergin and coworkers used 2,3-dihydroimidazo[1,2-a]pyrimidine in the synthesis where 2-aminopyrimidine was used by two different routes. The first route involved reacting 2-aminopyrimidine with ethylene halohydrin (bromo or chloro) and further reacting with thionyl chloride, while the other method involved 1,2-dibromoethane reacting with 2-aminopyrimidine and when the intermediary product was treated with sodium hydroxide and then with hydrobromic acid, dihydroimidazopyrimidine was obtained (26) (See Figure 28).
Figure 25: Synthesis of a tricyclic hetero compound for photodynamic therapy applications.

Figure 26: Formylation of 2-furyl-containing imidazopyrimidines.

Figure 27: A series of 3-aryl-substituted imidazopyrimidine-2-carboxamides.
Fusion to the imidazopyrimidine core
A double annelation reaction by Chowdhury and colleagues yielded a variety of tri- and tetracyclic heterocycles in a one-pot reaction (27) (See Figure 29).

Antipyrine-containing imidazopyrimidine heterocycle
Abu-Elmaati described the syntheses of many heterocycles, in which he reported an imidazo[1,2-a]pyrimidine that contains an antipyrine substituent (28) (See Figure 30).

One-pot synthesis of imidazo[1,2-a]pyrimidines
Late professor Alan Roy Katritzky is a legend in heterocyclic chemistry, and he has reported the one-pot synthesis of imidazo[1,2-a]pyrimidines. He and his colleagues used 2-aminopyrimidine and 1,2-bis(morpholinyl)-1,2-dibromoethane, with which two intermediates, namely A and B occurred with the sequential removal of benzotriazolyl (denoted as Bt here) moieties, then a rearrangement in the ring gives two imidazopyrimidine derivatives (29) (See Figure 31).

Figure 28: Synthesis of 2,3-dihydroimidazo[1,2-a]pyrimidine with two different routes.

Figure 29: Tricyclic and tetracyclic imidazopyrimidine derivatives in one-pot reactions.
**Figure 30**: Synthesis of pyrazole-containing imidazopyrimidines.

**Figure 31**: Syntheses of two imidazopyrimidines with the use of dibromo-dimorpholinylethane. Two compounds were reported.

**Figure 32**: Synthesis of imidazopyrimidines on solid support.

Heterocycle formation on a solid support
El Kazzouli and his coworkers reported the formation of imidazo[1,2-a]pyrimidine by employing a solid-phase support (30) (See Figure 32).

**Formylation on Monosaccharides**

Bari et al. reported another formylation reaction applied on monosaccharides and the heterocycle was obtained with 2-aminobenzimidazole (31) (See Figure 33).

![Diagram](image)

**Figure 33**: Imidazopyrimidine obtained with monosaccharides.

**Imidazo[1,2-a]pyrimidin-5-ones**

According to the publication by Sączewski et al., imidazolin-2-oxime ethers react with alkenes and imidazo[1,2-a]pyrimidin-5-ones. In addition, a retro-ene reaction takes place when ethyl prop-2-ynoate and 2,3-dihydroimidazo[1,2-a]pyrimidin-5(1H)-one is obtained (32) (See Figure 34).

**Fluorescent Probes for the Localization and Function of Peripheral Benzodiazepine Receptor (PBR)**

PBR is mainly found in the mitochondria, and its overexpression is encountered, for example, in glioma, breast cancer, Alzheimer’s disease, and activated microglia. Among the handful of compounds synthesized by Laquintana and coworkers, an imidazopyridine-7-nitrofurazan conjugate showed the best result and could be considered as a new useful fluorescent probe for the visualization of activated microglia and PBR (33) (See Figure 35).

**Reaction of an Imidazole and a Pyran to Give Imidazopyrimidine Derivatives**

A new method was proposed by El Otmani and their co-workers used 4-hydroxy-6-methylpyran-2-one and 2-amino-4,5-dicyanoimidazole with an alcohol (methanol, ethanol, n-propanol, and n-butanol) to obtain dicyanoimidazopyrimidine acetic acid derivatives and their corresponding esters of the alcohol used (34) (See Figure 36).
Formation of Imidazopyrimidines via a Nucleophilic Attack on Styrenes

A new stereoselective nucleophilic attack on styrenes was described by Muzalevskiy and colleagues. First, the styrene is reacted with sodium methoxide and potassium tert-butoxide, then brominated to yield the trifluoromethyl ketones. These compounds were found to be good starting materials having a trifluoromethyl moiety. Imidazopyrimidine compounds were reported to be obtained in medium yields (35) (See Figure 37).

Hydrazinolysis of Imidazopyrimidines

Ermolat’ev and co-workers reported the microwave-assisted hydrazinolysis of imidazopyrimidines to yield mono- and di-substituted imidazoles. This protocol is advantageous due to the absence of the use of strong acids and is better than the classical reaction in which α-haloketones react with N-acetylguanidine (36) (See Figure 38).

Synthesis of Benzylimidazopyrimidines

Bakherad devised an efficient synthesis of 2-benzylimidazo[1,2-a]pyrimidines in water, incorporating Sonogashira coupling with various aryl iodides, and without copper co-catalyst, in the presence of K$_2$CO$_3$ as the base. (37) (See Figure 39).
Figure 35: Synthesis of fluorescent probes for peripheral benzodiazepine receptor.

Figure 36: Formation of 7-methyl-2,3-dicyanoimidazo[1,2-a]pyrimidine-5-acetic acid and its ester.
**Figure 37:** Use of styrene derivatives to yield imidazopyrimidines.

**Figure 38:** Hydrazinolysis of imidazopyrimidines.
**Catalytic Chalcogenation of Imidazopyrimidines**

Li and coworkers reported a very potent and environmentally friendly catalytic chalcogenation of imidazopyrimidine compounds with dichalcogenides. They used copper(I) iodide as catalyst and the reaction was conducted under air. Smooth reactions were observed and the yields were moderate to excellent and no other additive was required (38) (See Figure 40).

**Synthesis of 4-Amino-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-6-carbonitrile Derivatives**

Hu and coworkers developed a fast and green method for the preparation of 4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-6-carbonitrile derivatives. The reaction is characterized by its one-pot condensation of 2-aminobenzimidazole, several aldehydes, and malononitrile and the catalyst employed was ammonium acetate in ethanol. The catalyst is very cheap and is readily available, and the workup is environmentally friendly (39) (See Figure 41).

**Figure 39:** Sonogashira-powered cyclization of 2-aryl substituted imidazopyrimidines.

**Figure 40:** Chalcogenation at the 3-position by using diphenyldisulfide and copper iodide.

**Figure 41:** Three-component reaction of aminobenzimidazole, an aldehyde, and malononitrile in ammonium acetate medium. $R^1$ is phenyl, 4-methylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-hydroxyphenyl, 4-cyanophenyl, and 4-pyridyl.
Synthesis of Some Imidazopyrimidines and Catalytic Hydrogenation of them

Some new derivatives of imidazo[1,2-a]pyrimidine have been studied by Borisov et al in 2013, and catalytic hydrogenation methods were developed for them. For the first time, partial reduction of the imidazole ring on imidazo[1,2-a]pyrimidine hydrogenation was reported (40) (See Figure 42).

![Chemical reactions and structures](image)

**Figure 42:** Formation of some imidazopyrimidine heterocycles and partial hydrogenation of some of them.

Synthesis of New Benzimidazole Derivatives

Novel benzimidazole derivatives were synthesized by Mehranpour and Zahiri with the reaction between 2-substituted 1,3-bis(dimethylamino)-trimethinium salts and 2-aminobenzimidazole in the presence of acetic acid or triethylamine in acetonitrile as solvent (41) (See Figure 43).
Figure 43: Formation of imidazopyrimidines via dimethylaminomethinium salts.
Thermal Cyclization of Thioxopyrimidines

Burbuliene et al. reported the reaction of methyl (2-methylsulfanyl-6-phenyl-4-thioxopyrimidin-3(4H)-yl)acetate with hydrazine hydrate, at room temperature, in 1-butanol as solvent to yield the hydrazide. They committed the same reaction at reflux temperature by employing different solvents like methanol, acetonitrile, n-butanol or dimethylformamide and they found that 1-amino-7-phenyl-5-thioxo-1,5-dihydroimidazo[1,2-a]pyrimidin-2(3H)-one with a thermal cyclization pattern (42) (See Figure 44).

Figure 44: Synthesis of imidazopyrimidines with thermal cyclization of thioxopyrimidines.

Review about C-H Arylation

Aziz and Piguel, in their mini-review published in 2017, studied C-H arylations of heterocycles, in which imidazo[1,2-a]pyrimidines played a major role. Some examples were provided (43). (See Figures 45-54).

Figure 45: Arylation of imidazopyrimidine at 3-position.
Figure 46: Arylation at 3-position.

Figure 47: Arylation at 3-position while there is another group at 2-position.

Figure 48: Heteroannulation at 3- and 5-positions.

Figure 49: Development of a new strategy over the problematic, previous one.
Figure 50: Dimroth rearrangement and subsequent C-H arylation of an imidazopyrimidine.

Figure 51: Arylation and subsequent hydrazinolysis of an imidazopyrimidine.

Figure 52: C-H (het)arylation and subsequent hydrazinolysis.
Formation of Some Bridgehead Heterocycles

Reacting 2-aminopyrimidine and acetyl acetone, Bhagat and Telvekar reported the formation of Imidazo[1,2-a]pyrimidines at around 70% reaction yield (44) (See Figure 55).

Use of Copper Oxide Nanoparticles in the Formation of Imidazopyrimidines

Rawat and Rawat studied the copper oxide nanoparticles-catalyzed reaction employed 2-aminobenzimidazole, several aldehydes, and several terminal alkynes to give imidazo[1,2-a]pyrimidines. The reaction did not employ solvents, and 6-endodig cyclization occurs. Of the 20 compounds, 2,4-bis(4-methoxyphenyl)-substituted compound was found to sense zinc ion in a fluorescent manner.
WHO’s maximum allowable zinc concentration in drinking water is much higher than the detection limit of this sensor (45) (See Figure 56).

\[
\text{Hierarchically porous sphere-like copper(II) oxide nanoparticles (HS-CuO)}
\]

\[
\text{Neat, 100 °C}
\]

**Figure 56:** A three-component reaction catalyzed by HS-CuO to yield imidazopyrimidines.

**C-H Bond Chalcogenation of Imidazopyrimidines**

Bettanin and coworkers studied the C-H chalcogenation of N-heteroaryl compounds with ammonium iodide as the catalyst, in a minimal amount of dimethylsulfoxide, water, and acetic acid (2.5 M, 2.5 M, 1 M, respectively) and no metallic catalyst was used. This approach was also very efficient in the C-H bond chalcogenation of other 5-membered N-heteroaryl compounds (46) (See Figure 57).

\[
\text{NH}_4\text{I (10 mol%)}
\]

\[
\text{DMSO/H}_2\text{O (2.5:2.5 equiv.)}
\]

\[
\text{AcOH (1 equiv.), 110 °C}
\]

\[
X = S (6 h), \text{Se (14 h)}
\]

**Figure 57:** C-H chalcogenation of imidazopyrimidines.

**Chromen-2-one-Containing Imidazopyrimidine Derivatives**

Yagodinets et al. Reported the reactions of 4-(4-bromoacetylphenyl)-3-hydroxy-2H-chromen-2-one with suitable heterocycles yielded quaternary salts, and the reactions of the same bromo derivative with pyrimidin-2-amine provided corresponding imidazo[1,2-a]pyrimidine derivatives (47) (See Figure 58).

**IBX/NIS-Induced Intramolecular Oxidative Annulation without Metallic Catalyst**

Imidazo-heterocycles were synthesized by Makra and coworkers, without a metallic catalyst, with an IBX/NIS-induced intramolecular oxidative annulation of Mannich substrates. The reaction includes iodination, NH-oxidation, formation of intramolecular C-N bonds, and retro-Claisen-Schmidt reaction with high reaction yields. A sequential one-pot reaction process has also been reported (48) (See Figure 59 and 60).
**Figure 59:** A three-component one-pot reaction involving the formation of an imidazopyrimidine.

**Figure 60:** IBX- and NIS-mediated reaction yielding imidazopyrimidine derivatives.

**A Review About Pyrimidine-Containing Five-Membered Heterocycles**

Pyrimidine-containing five membered heterocyclic ring systems were reviewed for the last two decades by Maji in 2019 (49). (See Figures 61-65).

**Figure 61:** Formation of imidazopyrimidines via an iminoalkene.
**Figure 62:** Using fluoro or difluoropyridine, the authors obtained imidazopyrimidines at room temperature.

**Figure 63:** Three-component syntheses in which magnetite was used as a catalyst.

**Figure 64:** Three-component synthesis of a benzimidazopyrimidine ketone.
**Improved Synthesis of 18F-GTP1**

In the past, 18F-GTP1’s synthesis was hard and yields were low, chromatographic separations were inefficient, and product quality was variable. This synthesis was referred to as the first-generation. White and coworkers devised a more successful, second-generation synthesis, which could be extended to the kilogram scale. Lithium aluminum deuteride caused the placement of geminal deuterium atoms on the structure, then an efficient amide-forming reaction led to the key acrylamide coupling partner compound. Tricyclic imidazo[1,2-a]pyrimidine compound was introduced with a highly successful annulation reaction. Unlike the first-generation synthesis, no chromatographic separations were required and the final step involved a successful and reproducible tosylation step (50) (See Figure 66).

**Dichalcogenation of Imidazopyrimidines**

Obah Kosso and coworkers treated imidazo[1,2-a]pyrimidine and similar heterocycles with dichalcogenation at C6 position and the oxidizing medium was iodine coupled with dimethylsulfoxide and the starting compound were diarylchalcogenides. This strategy was efficient, and the regioselectivity and yields were excellent (51) (See Figure 67).

**Halogenation of Imidazole-Derived Heterocycles**

Neto and coworkers reported trihaloisocyanuric acid as a practical and eco-friendly reagent for regioselectively halogenation of imidazole-derived heterocycles (52) (See Figures 68 and 69).

**Review of Imidazopyrimidines for Direct C-H Bond Functionalization**

Patel and coworkers prepared a review article in which direct C-H bond functionalization of imidazopyrimidines and other related compounds (53) (See Figures 70-77).
**Figure 66**: Improved synthesis of an imidazopyrimidine derivative.

A total of 40 examples for both

**Figure 67**: Dichalcogenation of imidazopyrimidine at 3-position and 6-position.
Figure 68: Use of trihaloisocyanuric acid with a heteroaromatic compound for imidazole-derived heterocycles.

Figure 69: Synthesized imidazopyrimidine bases.

Figure 70: C-H bond functionalization of an imidazopyrimidine derivative.

Figure 71: Substitution of 3-H with a hydrocarbon chain.

Figure 72: Functionalization of 3-H with an aminothiazole derivative.
Functionalization of 3-H position with a photochemical route employing an iridium complex.

Electrolysis of an imidazopyrimidine derivative, yielding a 3,3′-dimer.

Addition of an aminoheterocycle at 3 position with tert-butylhydroperoxide.

Addition of an aldehyde group to the 3-position.

Functionalization of imidazopyrimidine 3-position with a sulfonimidoyl group.

Formation of Benzoimidazotriazolopyrimidines
Fedotov and coworkers described a new synthetic methodology to benzo[4,5]imidazo[1,2-a][1,2,3]triazolo[4,5-e]pyrimidines. The synthesis included the condensation of 3-(arylazo)benzo[4,5]imidazo[1,2-a]pyrimidine-4-amines from aminobenzimidazoles and 3-oxo-2-phenylazopropionitrile and, with copper(II) acetate as catalyst, the mentioned compounds formed with oxidative cyclization with around 75% yield. The compounds showed good quantum yields, maximal absorption within 380-400 nm, and maximal emission within 470-500 nm (54) (See Figure 51).
ONE-POT, MULTICOMPONENT SYNTHETIC METHODS

Multicomponent Reaction Approach
A one-pot approach to substituted imidazo[1,2-a]pyrimidines is described by Kiselyov and Smith, with a convenient protocol. The reaction is general with nitrile, aldehyde, and aminoheterocycle components. The reaction yields are around 70% and isolation is easy (55) (See Figure 79).

A Multicomponent Reaction with Isonitriles
2-Aminopyrimidine, aldehydes, and isonitriles undergo a multicomponent reaction to yield imidazopyrimidines. A Russian research group, with Parchinsky as the first author, published a paper in which they showed the very possibility of the formation of several isomeric compounds (56) (See Figure 80).

One-pot multicomponent synthesis of 3-amino-2-arylimidazo[1,2-a]pyrimidine derivatives
Adib and co-workers used 2-aminopyrimidine, a benzaldehyde (substituted or not), and imidazolin-2,4,5-trione in a one-pot, solvent-free and multicomponent reaction to obtain imidazopyrimidine derivatives (57) (See Figure 81).

Figure 78: Synthesis of a benzoimidazotriazolopyrimidine compound.

Figure 79: Structures of the formed compounds.

Figure 80: A multi-component reaction to give imidazopyrimidine derivatives.
Synthesis of aryl-benzo[4,5]imidazo[1,2-a]pyrimidine amines
Reddy et al. grafted tetraethylene glycol-bridged 1-vinylimidazolium mesylate onto the surface of cross-linked polyethylene glycol methacrylate. This structure served as an excellent catalyst for the synthesis of N-methyl-2-nitro-aryl-benzo[4,5]imidazo[1,2-a]pyrimidine amines in a multi-component reaction employing 1H-benzo[d]imidazol-2-amine and (E)-N-methyl-1-(methylthio)-2-nitroethenamine and several aldehydes under solvent-free conditions. The catalyst can be reused and its catalytic activity can maintain its superiority after seven cycles. The whole protocol is green, no waste side products, no solvent involved, and no column chromatography is needed (58) (See Figure 82).

Synthesis of Benzoimidazopyrimidine Derivatives with NiFe$_2$O$_4$, as the Catalytic Entity
Hamidinasab and coworkers prepared a modified NiFe$_2$O$_4$ nanoparticle for use in the multicomponent synthesis of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives under green conditions. The reaction provided high reaction yields, reaction times were shorter, purification was simple, and reaction conditions were mild by environmental means (59) (See Figure 83).
Silica Sulfuric Acid as the Catalytic Entity

Basyouni and coworkers devised a simple and efficient, and eco-friendly synthetic method for synthesizing benzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile derivatives with excellent yields. They prepared the final compounds with a multicomponent reaction among 2-aminobenzimidazole, several aldehydes, malononitrile or ethyl cyanoacetate as active nitriles, and silica sulfuric acid/ethylene glycol as the catalytic system. The significant aspects of this synthetic methodology are very short reaction times in terms of minutes, high yields, and cost-effectiveness (60) (See Figure 84).

Fe$_3$O$_4$@C-SO$_3$H Nanoparticles as the Catalytic Entity

In order to synthesize a separable magnetic Fe$_3$O$_4$@C-SO$_3$H nanoparticle (MNP) with high catalytic activity in organic transformation, three environmental-benign and low-cost sulfonic acid functionalized magnetic nanoparticles (Fe$_3$O$_4$@C-SO$_3$H) were successfully synthesized by Damghani et al. Benzo[4, 5] imidazo[1,2-a]-pyrimidine derivatives were synthesized under solvent-free conditions in excellent yields (61) (See Figure 85 and 86).
Use of Starch-Functionalized Magnetite Nanoparticles as the Catalytic Entity

One-pot, multicomponent synthesis of imidazopyrimidine compounds was realized in an efficient and environmentally friendly fashion by Verma et al. The components were aromatic aldehydes, active methylene compounds, and 2-aminobenzimidazole and ultrasonic irradiation was employed. Starch-functionalized magnetite nanoparticles were used as the catalytic entity in the reaction. The developed reaction system used mild reaction conditions, isolation was easy, atom economy was high, products were obtained in good to excellent reaction yields, no column chromatography was involved, and the catalyst was magnetically separable and reusable. (62) (See Figure 87).

Figure 87: An aldehyde, an active methylene compound, and benzimidazole react to give a benzimidazo[1.2-a]pyrimidine compound at room temperature, with silica-functionalized magnetite particles as the catalytic entity. 21 compounds were reported.

Synthesis of Imidazopyrimidine-Based Pyrans

Imidazo[1,2-a]pyrimidine-2-carbaldehyde, malononitrile, acids in which C-H activation is possible and sodium carbonate as base were reacted by Güngör in a one-pot fashion to yield new imidazo[1,2-a]pyrimidine-based pyrans at room temperature and similar to other compounds, a multicomponent reaction scheme was adopted. Mild reaction conditions, the absence of the need for column chromatographic separations, and the medium to good reaction yields are the main advantages for this multicomponent reaction (63) (Figure 88).

Figure 88: New imidazopyrimidine-based pyran compounds.

Heteroannulation of Imidazopyrimidines

Akbari and coworkers prepared a nanomaterial heterogeneous catalyst and used this in the
heteroannulation of imidazopyrimidines with a multicomponent reaction among 2-aminobenzimidazole, compounds having acidic C-H entities, and several aromatic aldehydes. The protocol was green and catalyst loading was low, yields were high to quantitative, reaction times were short, and the catalyst could be recycled at least four runs (64). (See Figure 89).

Dihydrobenzoimidazopyrimidine Synthesis with ZnFe$_2$O$_4$ as the Catalytic Entity

2-Amino-4-substituted 1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitriles were synthesized with a multicomponent reaction among benzimidazole, aldehydes, and malononitrile under ultrasonic irradiation and heterogeneous ZnFe$_2$O$_4$ as the nanocatalyst. The synthetic methodology is especially remarkable in that the reaction time is short, handling is easy, simple, efficient, and the reaction yield is high and the catalyst is recoverable (65) (See Figure 90).

Figure 89: Three-component synthesis of heteroannulated imidazopyrimidines.

Figure 90: 2-Amino-4-substituted 1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile compounds.

Magnetite@Titanium Dioxide@Ionic Liquid Zeolitic Imidazolate Framework as the Catalytic Entity

One-pot synthesis of benzoimidazopyrimidine compounds was utilized with a magnetite@titanium dioxide@ionic liquid-zeolitic imidazolate framework, which showed high catalytic activities. The three-component reaction (various aldehydes, 2-aminobenzimidazole, and ethyl acetoacetate) was conducted at room temperature. Similarly to other magnetic catalysts, the nanocatalyst was easily recovered with a magnet and the catalytic behavior of it remained the same for six catalytic runs. The advantages were that yields were excellent, procedures were simple, reaction times were short, workup was simple, and reaction conditions were mild (66) (See Figures 100 and 101).
Anamika and coworkers prepared a ferrocene-dithiocarbamate zinc(II) complex to serve as a heterogeneous bifunctional catalyst in the three-component synthesis of imidazopyrimidines (67) (See Figure 93).

Güngör prepared ten imidazo[1,2-a]pyrimidines with imidazole substituents in which imidazo[1,2-a]pyrimidine-2-carbaldehyde, benzil, a selection of primary amines, and ammonium acetate with p-toluenesulfonic acid as catalyst were reacted in a one-pot and multicomponent reaction, under microwave irradiation. The reaction yields are medium to good, carrying many different substituents on the skeleton and the reaction conditions are optimum. The solvent utilized was ethanol, which can be considered as a green solvent. (68) (See Figures 94 and 95).

**Figure 94:** Three-component reaction yields a main product and a by-product.

**Figure 95:** A second reaction used a two-component reaction, then the third molecule gets in.

**MISCELLANEOUS USES**

**Proton Sensitive Organic Fluorescent Dyes**

Aydıner and Seferoglu devised a series of proton sensitive functional organic fluorescent dyes based on coumarin and imidazo[1,2-a]pyrimidine. They reported the synthetic effort, photophysics in different solvents, and protonation study with trifluoroacetic acid as the titrant. 7-dialkylaminocoumarin-based compounds had the best fluorescent performance, and the compound having morpholine moiety was considered for its potential of colorimetric and luminescent pH sensor compound (69) (See Figures 96 and 97).

**Figure 96:** Formation of coumarin-based imidazopyrimidines with morpholine group.
Use of Selenoester Derivatives in the Treatment of Mercury(II) Chloride

In situ-generated sodium selenocarboxylates reacted with 2-(chloromethyl)imidazo[1,2-a]pyrimidine in water and ethanol. Phenyl/4-tolyl selenoesters of imidazo[1,2-a]pyrimidine were obtained in water and 4-chlorophenyl/2-thienyl selenoesters of the same heterocyclic system were only obtained in ethanol. A model compound was used for studying the behavior of selenoesters with mercury(II) chloride. Reaction with HgCl₂ yielded a bis(imidazopyrimidinyl)selenide, bis(imidazopyrimidinyl)diselenide and the HgCl₂ compound. The selenoester derivatives could be considered in the treatment of mercury(II) chloride-induced toxicity (70) (See Figure 98-100).

Figure 97: Incorporation of an aromatic group at the 6-position with Suzuki coupling. Six compounds were reported.

Figure 98: Formation of chloromethylimidazo[1,2-a]pyrimidine scaffold.

Figure 99: Synthesis of the selenoacetate derivative of imidazopyrimidine.

Figure 100: Three separate experiments for the synthesis of mercury(II) selenide.
Heterocycles Having Long Fatty Chains
El-Sayed and coworkers reported condensed and non-condensed heterocycles having long fatty chains in the hope of obtaining surface active biological compounds. 2-Cyano-3-(dimethylamino)-N-octadecylacrylamide was the starting compound to obtain several pyrimidine, pyran, and similar heterocycles. Propylene oxide helped these compounds transform into nonionic surface active compounds. The high solubility of these compounds allowed them to be used in easy absorption. The authors report that they reduce the surface tension of liquids, and they have high wetting and emulsification property (71) (See Figure 101).

![Figure 101: An enaminonitrile compound reacts with 2-aminobenzimidazole, with the elimination of dimethylamine, forms the long-chained benzimidazolopyrimidine compound.](image)

CORROSION INHIBITION

Corrosion Inhibition of C38 Steel in 1 M HCl
2-(m-Methoxyphenyl)imidazo[1,2-a]pyrimidine was tested along with another compound, in the corrosion inhibition study by Ghazoui et al. According to potentiodynamic polarization studies, it was found that the inhibitors employed behaved as mixed-type. The inhibitors were found to be adsorbed on the steel surface according to Langmuir isotherm. Corrosion rate decreased with the use of these two inhibitive compounds, and when the concentrations increased, the effect was remarkable. Inhibitory concentration of the compound was 1 millimolar and EI% was 95.7% (72) (See Figure 102).

![Figure 102: 2-(3-methoxyphenyl)imidazo[1,2-a]pyrimidine, used as a corrosion inhibitor.](image)

Inhibitive Effect of 2-phenylimidazo[1,2-a]pyrimidine-3-carbaldehyde
In hydrochloric acid solution, corrosive inhibition of the synthesized compound, 2-phenylimidazo[1,2-a]pyrimidine-3-carbaldehyde, was tested on carbon steel. It is an expected consequence that increasing concentration of the inhibitor will lead to a decreased rate of corrosion. A mixed-type inhibition was discovered with the polarization studies. Langmuir's isotherm model was used to describe the adsorption behavior of the inhibitory entity. B3LYP/6-31+G(d,p) level of DFT was used to explain the inhibitive effects of the synthesized compound. Molecular dynamics simulation showed that the molecule could adsorb on alpha-iron(III) oxide (111) surface in hydrochloric acid through the oxygen and nitrogen atoms and pi-electrons. Experimental and theoretical results are quite harmonious with each other (73) (See Figure 103).

![Figure 103: 2-Phenylimidazo[1,2-a]pyrimidine-3-carbaldehyde.](image)
Anodic Dissolution of Copper in Sodium Chloride Medium

The mechanism of anodic dissolution of copper in sodium chloride medium has not been discovered until now. 4-Amino-3-(phenyldiazenyl)benzo[4,5]imidazo[1,2-a]pyrimidin-2(1H)-one was tested for its efficiency as a corrosion inhibitor for copper, in sodium chloride solution at a concentration of 3.5% by weight. Aerated NaCl solution simulates a marine environment and adding the inhibitor or not adding it serves as a solution to uncovering the mechanistic part. According to potentiodynamic polarization (PDP), the inhibitor is effective at a low concentration in the 3.5% NaCl solution. The inhibition efficiency was about 93% owing to adsorption and to electrochemical investigation. Electrochemical impedance spectroscopy (EIS) showed that the inhibitor acted with both diffusive and kinetically controlled processes. The adsorptive isotherm model fit with Langmuir's. The inhibitor can be used in marine environments like water coolers, desalination plants, power plants, and oil production. DFT and MD studies supported experimental part and explain more about the mode of adsorption on Cu surface (74) (See Figure 104).

Figure 104: Preparation of the imidazopyrimidin-2(1H)-one compound and subsequent diazotization to obtain a representative corrosion inhibitor.

THEORY-POWERED EXPERIMENTAL STUDIES

Non-planarity of Imidazopyrimidines

2,4-Diphenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine and some other derivatives of it were researched both theoretically and experimentally, in the solvents, namely 1,4-dioxane and dimethylformamide. All of the compounds are non-planar, which is indicative of great electronic and structural properties. One of the compounds are reactive at the highest owing to its lowest E(HOMO), E(LUMO) and DE. The electronic spectra of the compounds were studied in terms of the number of bands. In addition, TD-B3LYP/6-311G (d, p) in gas phase, 1,4-dioxane, and dimethylformamide showed a nice agreement with the spectra recorded (75) (See Figure 105).

Figure 105: Structures synthesized in this study. R³ is hydrogen, fluorine, bromine, methyl, nitro, or methoxy, and R² is hydrogen, fluorine, or methoxy.

Studying the Tautomerism of Six Imidazopyrimide Compounds by IR, NMR, and DFT

A combination of spectral analyses like FTIR and NMR and theoretical calculations were performed for six imidazopyrimidine compounds. The compounds were synthesized with the 1-aryl-4,5-dihydro-1H-imidazol-2-amine hydrobromide and diethyl phenylmalonate, and sodium methoxide was used as a base. Tautomeric transitions in the structures were investigated in the gas, solution, and crystalline states. NMR and FTIR analyses did not help much about identification of the tautomeric forms present in the solution and also in the solid state. X-ray analysis, however, identified that all compounds were present in the keto-keto tautomeric form in the crystalline state. Theoretical studies at DFT/B3LYP/6-311++G(d,p) level was successful to indicate that, in the gas phase and in the solution, two tautomeric forms coexist. Theoretical studies and FTIR-NMR spectra allowed for the calculation of all tautomeric forms and, to a limited extent, the identification is possible (76) (See Figure 106).
Figure 106: Synthesis of a reduced form of an imidazopyrimidine and illustration of existing tautomeric forms. Six compounds with differing R radicals were reported.

Single-Crystal and Theoretical Study of an Imidazopyrimidine and its Thiazole Analog

Dylong and coworkers prepared imidazo[1,2-a]pyrimidin-2-ylacetic acid and its thiazole analog, and structurally characterized with single-crystal X-ray diffraction and computational studies in the form of Hirshfeld surfaces, which helped understand the intermolecular interactions of the crystals. FTIR and Raman spectra of both crystals were obtained and interpretations were made with DFT calculations and potential energy distribution (PED) analyses of computed normal vibrations. When the researchers recrystallized the compounds from deuterium oxide, they observed that the carboxylic OH groups were completely deuteriated (77) (See Figure 107).

Figure 107: Synthesis of imidazopyrimidine ester in low yield and basic/acidic hydrolysis of the compound to obtain a carboxylic acid.

Figure 108: Formation of the benzimidazolopyrimidine and subsequent methylation of the compound.

REFERENCES


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