Life Science Informatics Publications

Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences

Journal Home page http://www.rjlbpcs.com/

RJLBPCS

ISSN 2454-6348

Original Review Article **DOI: 10.26479/2025.1105.01**

SYNTHETIC STRATEGIC PROTOCOLS AND THERAPEUTIC APPLICATIONS OF PYRAZOLO [3,4-B] PYRIDINES

Amulya Sinha[1*], Arzoo Siddiqui[1], Vaibhav Tripathi[1], Girish Singh[1], Amit Yadav[1], Nikhat Fatima[1], Rudraksh Srivastava[2], Vivek Bhadauria[1]

1. Green Laboratory, Department of Chemistry, Ewing Christian College, University of Allahabad, Prayagraj, Uttar Pradesh, India-211003.

2. EOR and CO_2 Utilization and Storage Lab, Department of Petroleum & Geo-Engineering, Rajiv Gandh Institute of Petroleum Technology Jais, Amethi, Uttar Pradesh-229304, India.

ABSTRACT: A category of heterocyclic scaffolds referred to as pyrazolo[3,4-b] pyridines have two appropriate tautomeric variants: the 1H and 2H isomeric forms. By employing a one-pot method, a reaction involving three constituents comprising 3-amino-5-methyl pyrazole, distinct aromatic or heteroaromatic aldehydes, along with peculiar active methylene molecules with or without involving catalyst results in an array of scaffold analogues exhibiting outstanding yields in a highly effective along with environmentally friendly solvent reaction medium. A wide spectrum of functional group tolerance is appropriate with this conversion. Excellent vasodilators, hypotensive, hypoglycemic, anti-inflammatory, analgesic, as well as antipyretic attributes are few of the several pharmacological applications of this kind. The chemists are keen to develop simple and universal pathways to generate these molecules with remarkable yields.

Keywords: green synthesis, anti-inflammatory, analgesic, anticancer, antipyretic agent.

Article History: Received: August 28, 2025; Revised: Sept 10, 2025; Accepted: Sept 20, 2025.

Corresponding Author: Amulya Sinha* Research Scholar.

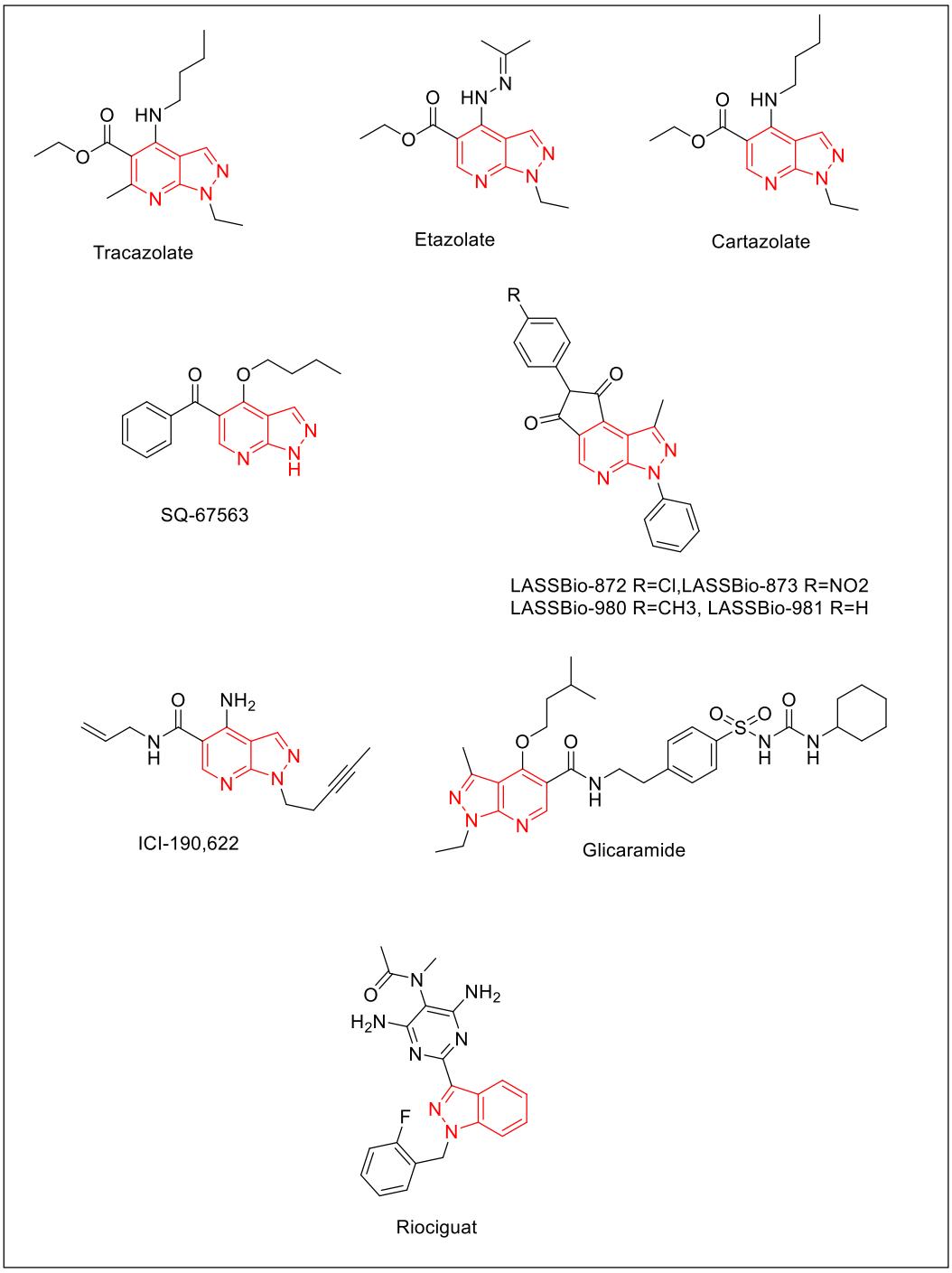
Green Laboratory, Department of Chemistry, Ewing Christian College, University of Allahabad, Prayagraj, India -211003. Email Address: amulya.sinha28@gmail.com

1. INTRODUCTION

Recently, the utilization of ecologically innocuous reagents and reaction conditions based on green chemistry principles is among the most fascinating advancements in synthesizing broadly utilized

organic molecules. Multicomponent domino reactions (MDRs),[1-3] specifically the ones carried out in green hydrated media, have proved to be n enhancing utilitarian instrument to generate chemically as well as biologically significant molecules owing to its convergency, atom economy, and several feasible features with respect to green chemistry.[4,5] A chief pilot in synthetic protocols is the advancement of potent and also eco-friendly synthesis procedures. Since there has been a growing need to synthesize innumerable eco-friendly compounds, ultrasound-promoted chemistry has evolved in the form of a subject which pervades almost every facets of synthetic chemistry.[6] The main objective of this enterprise is to augment the adequate utilization of secured raw substances in order to minimize toxicity. Ultrasonic wave procedure is incorporated in the synthesizing several organic chemicals for a long time.[7] The existence of ultrasound has depicted to increase the reaction rate by multifold as compared to the rate in the absence of ultrasound. In comparison to their silent equivalents (considered without employing ultrasound), reactions have been noticed to take place under mild circumstances and with inexpensive, little active chemicals functioning as catalysts in ultrasonic conditions.[8, 9] One among the most significant objectives in the organic discipline is the control of specificity. The challenge of uniqueness is crucial for multicomponent reactions[10] that incorporate the synchronous molecular interaction of three or more parts because there is a significant chance that different parallel mechanistic pathways will produce different outcomes.[11,12] However, the differentiation of synthetic conversions can be controlled by a number of characteristics, including temperature, pressure, solvent, catalyst category, kinetic or thermodynamic influence, along with various elements.[13,14] Among the most significant class of heterocyclic scaffolds, derivatives of pyrazole have been associated to an array of pharmacological and medicinal uses.[15–22] Pyrazoles have additionally been utilized extensively in pesticides.[23] Nitrogen-fused heterocycles are an essential category of organic molecules with an array of beneficial attributes.[24–27] In fact, there are innumerable data on the synthesis and bioactivities of nitrogen-constituting heterocyclic scaffolds, with pyrazole and pyridine analogues constituting the most significant group of these compounds. In particular, fused pyridine systems, notably pyrazolo pyridine derivates, have demonstrated an extensive range of biological features. These heterocycles, for instance possess antiallergic, antiherpetic, fungicidal, and herbicidal attributes in addition to functioning as HIV reverse transcriptase inhibiting agents, strong cyclin-dependent kinase1 (CDK1) antagonists, protein kinase inhibitors, CCR1 antagonists, blockers of cGMP degradation, and dopamine D3 receptor blockers. [28 - 35] An array of medicinal products, incorporating pyrazole and pyrazolo pyridine framework, comprise Celebrex, rimonabant, cartazolate, as well as etazolate (**Figure 1**). [36–38] Numerous heterocyclic compounds with an extensive variety of biological applications constitute the pyrazolo[3,4-b] pyridine scaffold in the form of a vital molecular constituent.[39 - 41] Heterocyclic compound synthesis has fascinated medicinal chemists primarily owing to its substantial medicinal value and structural array.

For experimental drug design, numerous kinds of heterocyclic analogues with nitrogen atoms create flexible frameworks. [42] Numerous naturally existing molecules and significant prescription drugs comprise pyridine as their parent ring system. A broad spectrum of pharmaceutical effects, encompassing antibacterial,[43] antimycobacterial,[44] antimalarial,[45] antitumor,[46] cytotoxic, anti-diabetic,[47] anti-arrhythmic,[48] and antidepressant attributes,[49] are exhibited by pyridine analogues. Since this ring system is considered to be a crucial core framework in several pharmacological compounds, the pyrazole nucleus has garnered a lot of interest. Numerous combinations of modified molecules have been discovered to have a broad array of biological traits, including antibacterial,[50] antiviral,[51] antileishmanial,[52] anti-inflammatory, [53] and anticancer [54] effects. Schiff's bases, also known as imines or azomethines, depict a broad array of medicinal impacts, notably antibacterial,[55] anticancer,[56] antioxidant,[57] and anticonvulsant [58] capabilities. The target moiety triggers vasodilation and promotes soluble guanylate cyclase (sGC). A strong blocker of glycogen synthase kinase-3 (GSK-3) has been detected as 6-aryl pyrazolo[3,4-b] pyridine II. The 5-HT6 receptor antagonist, Cryopentapyrazole [1,5-a] pyrimidine (III) has a Ki < 1 nM,7 compound IV (Zaleplon) is a medication that is recognized to treat sleep disorders, and cyclopentane ring fused pyrazolo[1,5-a] pyrimidine V. The compound with the greatest inclination for the 5-HT6 receptor (Ki ¼ 88 pM) is pyrazolo[3,4-b] pyrimidine V. With regard to the significance of pyrazole fused heterocycles, innovative techniques for synthesizing these targets have been devised. [59 - 62] A distinguished class of compounds, pyrazolo[3,4-b] pyridines exhibit an assortment of biological along with pharmaceutical characteristics. It has been established that they exhibit antimalarial,[63] cyclin-dependent kinase inhibition,[64-68] GSK 3 inhibition,[69] antiproliferative,[70] antileishmanial,[71] cardiovascular,[72,73] as well as antiviral[74-76] characteristics. Owing to their varied impacts in various sectors, research into compounds that comprise 1H-Pyrazolo[3,4-b]pyridines is enhancing.[77-79] The 4-amino-5-carboxylates of pyrazolo[3,4-b] pyridines comprise ethyl 1-ethyl-4-(2-(propan-2-ylidene)hydrazinyl)-1Hpyrazolo[3,4-b]pyridine-5-carboxylate (Etazolate), an anxiolytic medicament has additionally been recognized owing to its neuroprotective properties. [80] Several drugs derived from this scaffolding material, especially etazolate, trasazolate, LASSBio-872, LASSBio-873, LASSBio-981, and LASSBio-982, have been employed for the treatment of anxiety-concerned illnesses that are linked to GABA-induced neuroinhibition (**Figure 1**).



2.

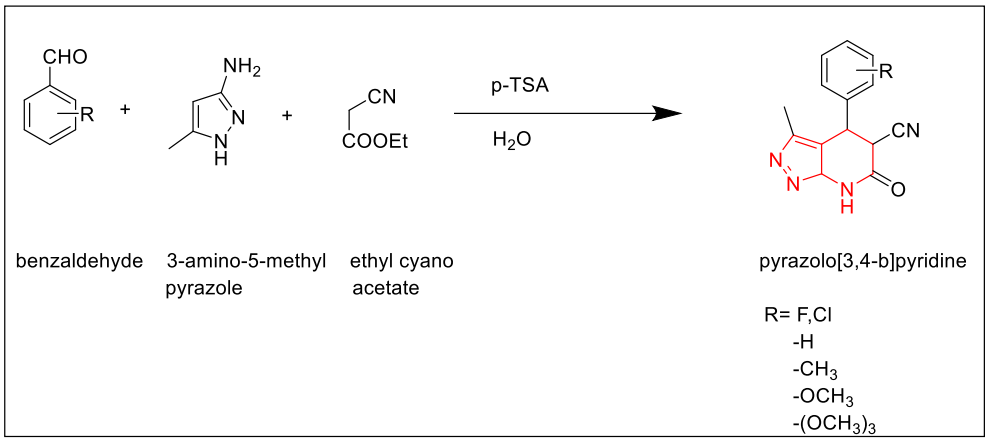
Figure 1 : Neurologically active drugs derived from pyrazolo[3,4-b] pyridines

Synthetic Strategies:

1. **3-methyl-6-oxo-4-phenyl-4,5,6,7-tetrahydro-2Hpyrazolo[3,4-b]pyridine-5-carbonitrile analogues**

A heavy-walled, flask resembling pears with an unconventional tapered exterior joint was loaded with an equimolar mixture (10 mmol) each of suitable aromatic aldehyde, ethyl cyanoacetate, 3-amino-5-methylpyrazole, and 10 mol% p-TSA in aqueous medium (20 ml). [81,82] The reaction mixture was ultrasonicated with respect to designated amount of time at 50% processor power along

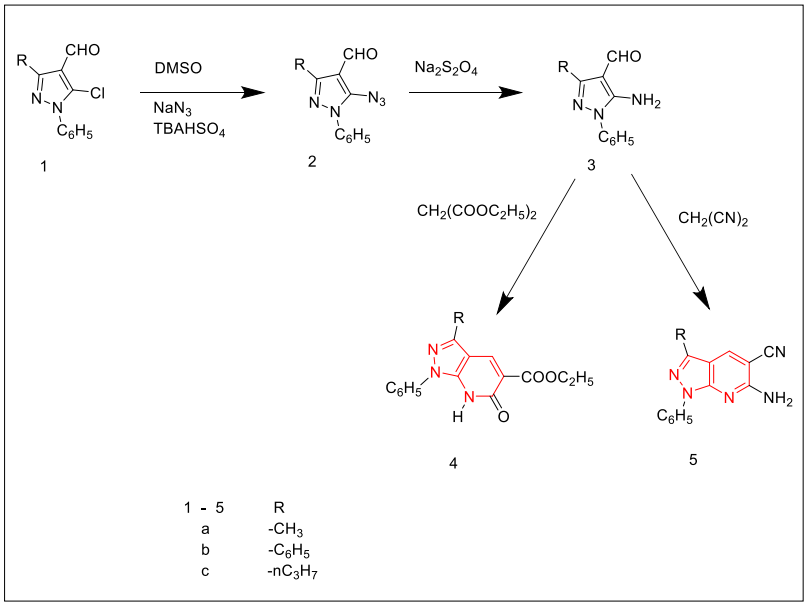
with a 4 s pulse mode until a solid crude material segregated, and the reaction container was joined to a 12 mm tip diameter probe [83] as demonstrated in **Scheme 1**.



Scheme 1

The new synthetic strategy involving annulating a pyridine ring with prepared pyrazole ring so as to manufacture moieties 4 as well as 5. [84–86] Diethyl malonate and also malononitrile, two potent methylene compounds, are generated by carrying out condensation of 3-(alkyl/aryl)-5-amino-l-phenyl-1H-pyrazole-4-carboxalehydes (3) (**Scheme 2**). [87–90]

The essential components for producing numerous physiologically active heterocyclic moieties are o-amino aldehyde derivatives. The following is the preparation of the necessary intermediate 3-(alkyVaryl)- 5-amino-1-phenyl-lH-pyrazole-4-carboxaldehydes (3):

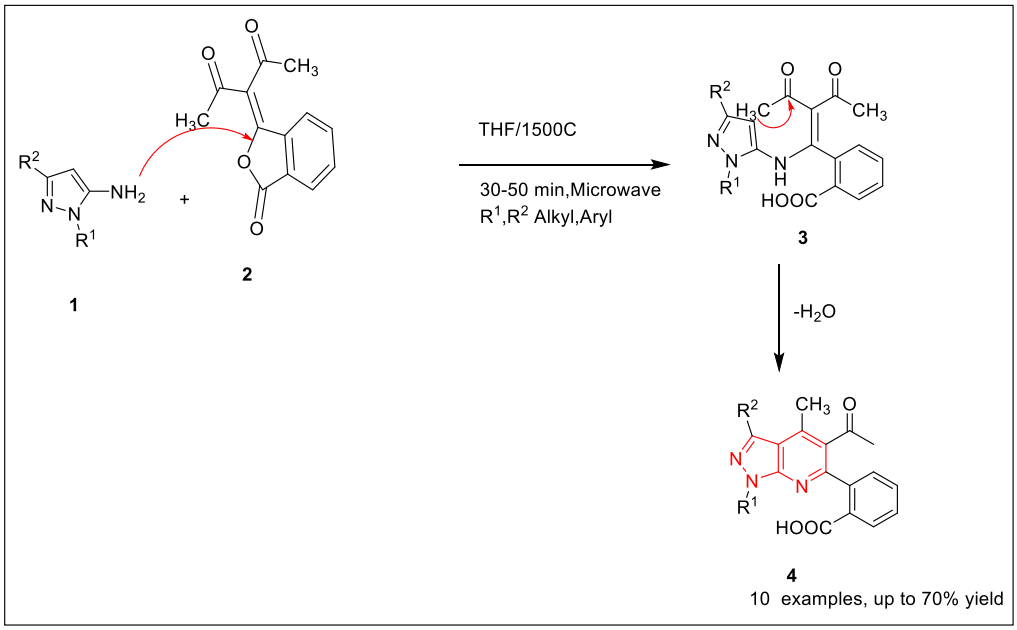


Scheme 2

Microwave assisted synthesis

1. Preparation of 2-(5-Acetyl-1,3,4-triR-1H-pyrazolo[3,4-b] pyridin-6-yl)-benzoic Acids

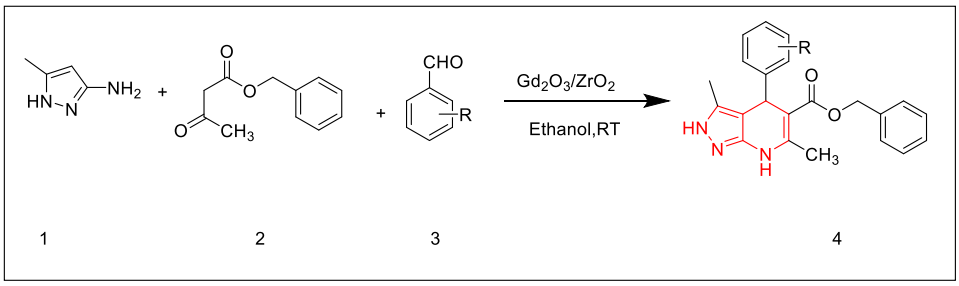
The microwave-facilitated synthesis carried out among N-substituted 5-aminopyrazoles 1 as well as 3-(3-oxo-2-benzofuran-1(3H)-ylidene) pentane-2,4-dione (2) resulted in an innovative array of entirely modified pyrazolo[3,4-b] pyridines [91] 4 following a regioselective fashion. [92, 93]



Scheme 3

2. Catalytic Synthesis of Dihydro-pyrazolo[3,4-*d*] pyridines

Employing a multicomponent one-pot condensation mechanistic procedure in an ethanolic media at the ambient temperature (RT), gadolinium oxide loaded zirconia (Gd_2O_3/ZrO_2) is incorporated as an efficient and viable catalyst for synthesizing unique dihydropyrazolo[3,4-b] pyridine analogues (**Scheme 4**). [94-97]

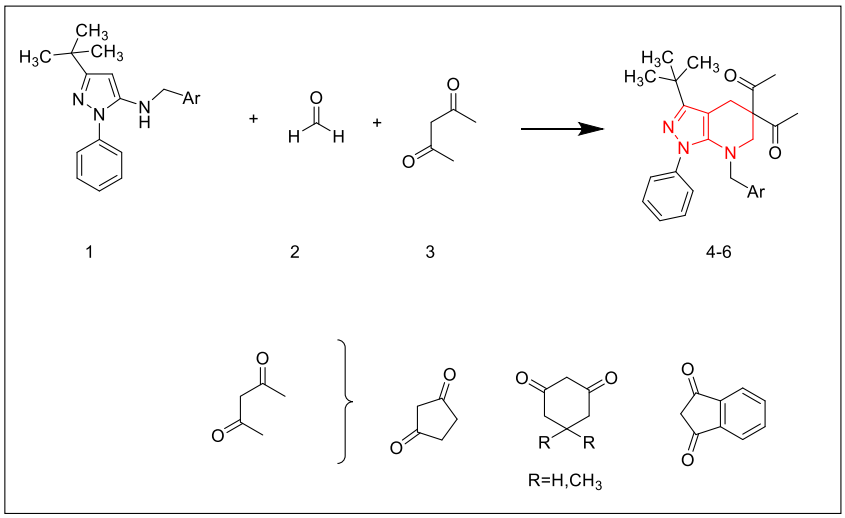


Scheme 4

Condensation Reaction

Pyrazolo[3,4-b] pyridines pirocycloalkanediones

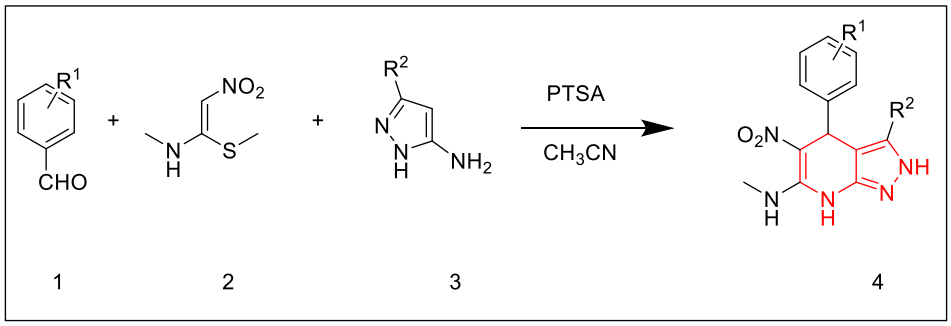
A convenient and straightforward procedure for synthesizing pyrazolopyridine-5-spirocyclodiketones [98, 99, 100, 101] derivatives 4–6 through one pot condensation of derivatives of 5-aminopyrazoles 1, cyclic b-diketones 3, formaldehyde (2 as paraformaldehyde) (**Scheme 5**).[102]



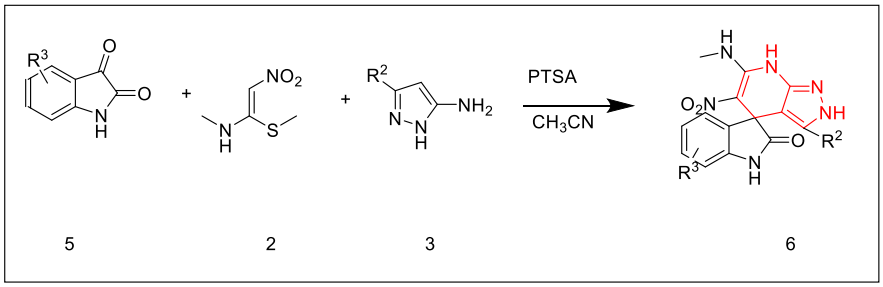
Scheme 5

6. pyrazolo[3,4-b] pyridine scaffolds 4, 6, 8, as well as 9

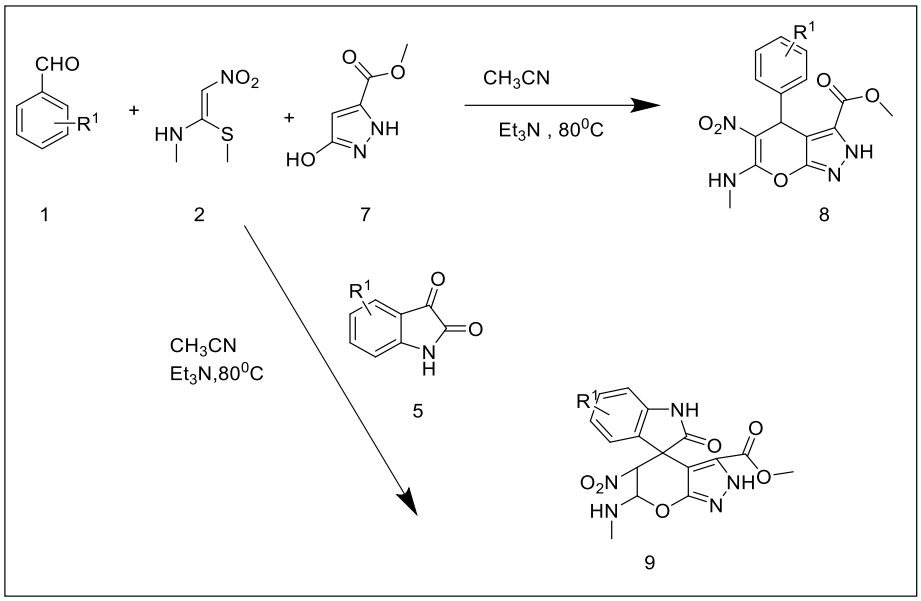
An equimolar mixture comprising 1mmol each of 3-aminopyrazole 3 or methyl 3-hydroxy-1H-pyrazole5-carboxylate 7 , N-methyl-1-(methylthio)-2-nitroethen-1-amine 2, aromatic aldehydes 1 or isatins 5 along with PTSA H_2O or Et_3N (0.3 mmol), was added in a container under 80℃ for few hours (analyzed using Thin Layer Chromatography). When the stirring was discontinued, the obtained mixture underwent cooling to ambient temperature so that the products may separate from the solvent by precipitation. Molecules 4, 6, 8, and 9 have been separated and then recrystallization carried out employing ethanol and dimethylformamide. [103–107]



Scheme 6



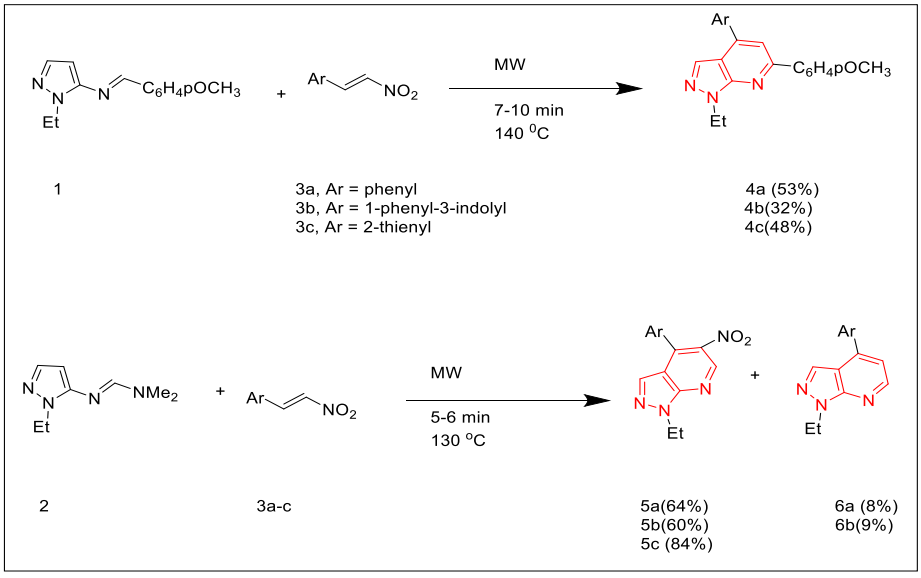
Scheme 7



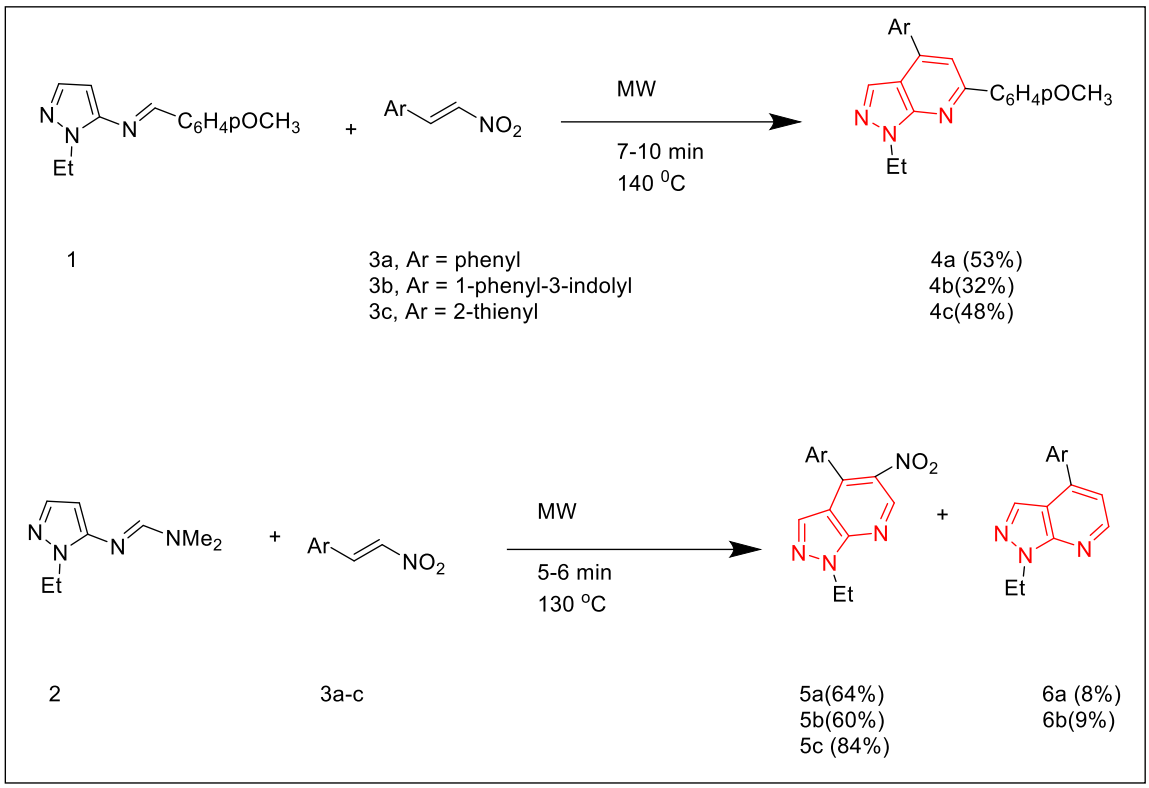
Scheme 8

Cyclization Reactions

Typically, the target compounds are generated employing cyclization processes that begin with various heterocyclic reagents. [108–112] During first instance, the target moieties were procured involving [412] cycloaddition of a 1,2,4-triazepine along with dimethyl acetylenedicarboxylate (DMAD) and consequent 1,3-sigmatropic rearrangement.[113] With respect to second instance, the target moieties were fabricated involving 1,3-dipolar cycloaddition among cyclic ketene N,O-acetals and diphenylnitrilimine. [114] A novel, intriguing, as well as adaptable method was described for creating the desired compound by utilizing MW radiation for performing a Diels–Alder cycloaddition in between pyrazolyl imines as well as aromatic nitroalkenes. [115] This is the first instance of a 2-azadiene [412] cycloaddition containing a pyrazole framework (**Scheme 9**).[116-118]



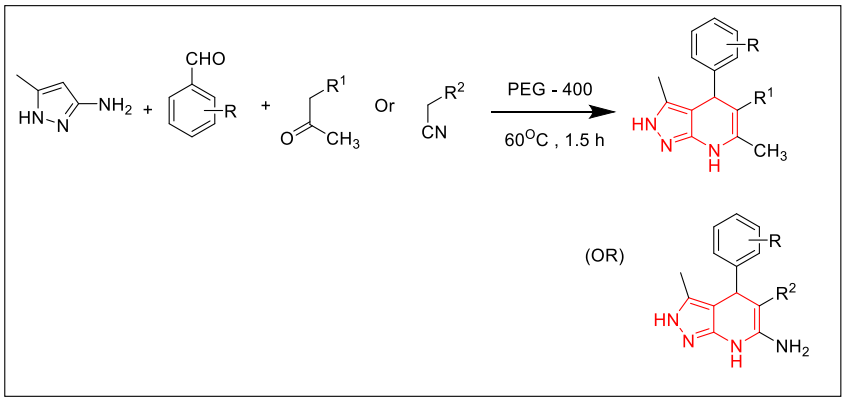
Scheme 9



Scheme 10

9. Preparation of 4,7-dihydro-2H-pyrazolo[3,4-b] pyridines

A mixture of 1 mmol each of 1H-pyrazol-3-amino-5-methyl 1 was combined with a stirred amalgamation of PEG-400 (6 mL) with selected aldehydes 2 and various active methylene compounds 3. The reaction underwent magnetic stirring at 60 °C for 1.5 hours duration. TLC was employed for analyzing the reaction. The solid crude substance was filtered after termination of the process and drenched with extra water. After recrystallizing the obtained crude product from ethanol, the desired pure products were obtained.[119–124]

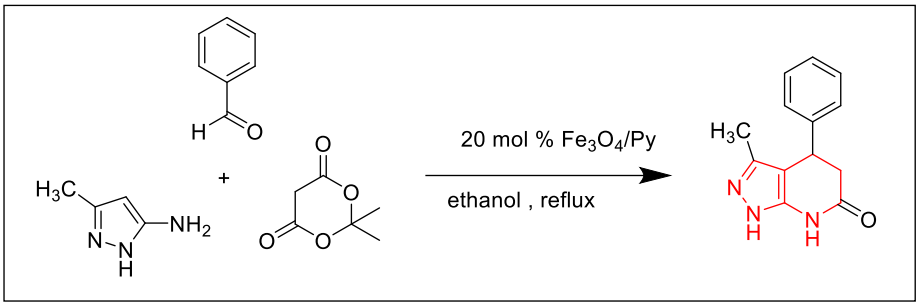


Scheme 11

10. Preparation of 3-methyl-4-aryl-2,4,5,7- tetrahydropyrazolo[3,4-b] pyridin-6-ones

In a round-bottomed flask, mixture constituting Fe_3O_4/Py (40 milligram; approx. 20 mol%) and ethyl alcohol (3 ml) was incorporated with equimolar quantity comprising aldehydes, Meldrum's acid, and 5-methylpyrazol-3-amine. At reflux temperature, the subsequent mixture was rapidly

agitated until the termination of process, as evaluated employing Thin Layer Chromatography (n-hexane–acetone, 4:1). Ten milliliters of heated ethanol were added once the reaction was finished, and an external magnet was used to extract the catalyst. By recrystallizing the crude product from ethanol, pure products were obtained as depicted in **Scheme 12**.



Scheme 12

Biomedical Applications of target compound

As a scaffolding substance for the synthesis of small molecules seeking medicinal qualities to cure various ailments, the target compound has been employed significantly. With respect to its diverse range of biological actions, including its potential to block glycogen synthase kinase-3 (GSK-3) and A1 adenosine receptors, the target compound is a privileged structural framework that has undergone intensive evaluation in medical research (Figure 1). In recent times, arylated pyrazolo[3,4-b] pyridine exhibits the role of a neuroprotector in MPP+-induced neurodegeneration (**Figure 2**), a Raf inhibitor to inhibit positive allosteric modulators (PAMs) and a fibroblast growth factor inhibitor (FGF-R and FGFR3) specifically for bladder cancer management.

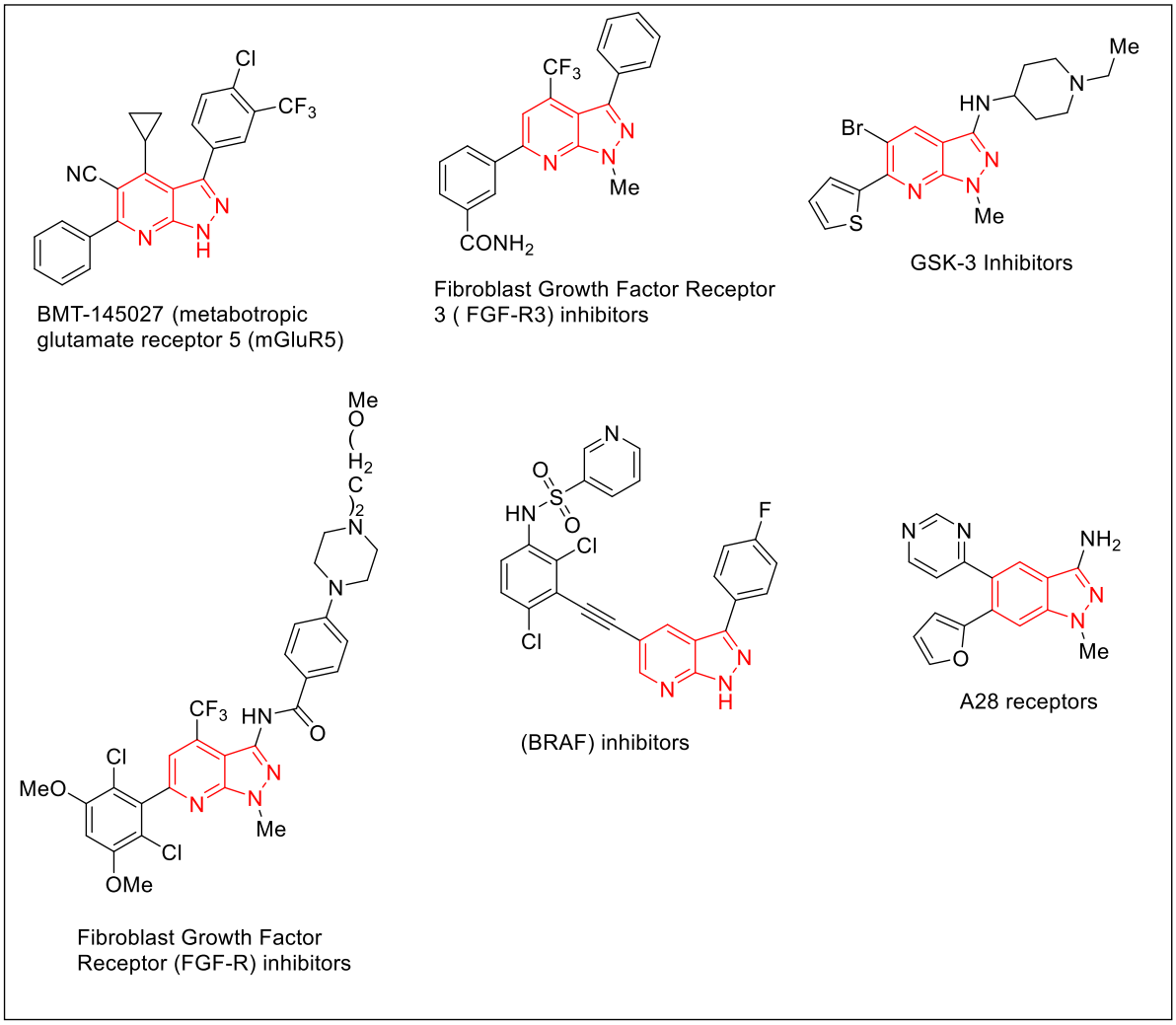


Figure 2: Therapeutic applications of 1H-pyrazolo[3,4-b] pyridines

1. As anti-Alzheimer's agent: 2-(piperazin-1-yl)-N-(1H-pyrazolo[3,4-b] pyridin-3-yl) acetamides have been recognized in the form of a novel category of efficient and unique blockers of amyloid b assemblage and acetylcholinesterase (AChE). The ultimate objective of this investigation is to formulate strong neuroprotective medicinal products to treat Alzheimer's disease employing pyrazolopyridine as well as analyze their biological impact. Therefore, additional efforts have been made to look for other scaffolds and molecules with multi-targeting potential in the current work.[125-127]

2. As TNF-a and IL-6 inhibitors: 4-substituted 1H-pyrazolo[3,4-b] pyridine derivatives (1, SQ-67563: IC50 0.11 lM) have been discovered by Misra et al. to constitute a novel family of cdk2 inhibitors.[128] An efficient and specific cyclin-dependent kinase and cellular anti-proliferative blocker (IC50 0.7 nM) to manage CDK1/cyclin B was discovered by Lin and others in modified moiety's equivalents 2. [129] Witherington and his fellow researchers identified 6-heteroaryl-pyrazolo[3,4-b]pyridine 3 as a blocker of glycogen synthase kinase-3 (GSK-3) with an IC50 of 0.8 nM.[130] The anti-microbial (4, Escherichia coli: IC50 22 lM; Candida albicans: IC50 18 lM),[130,131]

anti-chagasic (5, Trypanosoma cruzi: IC50 1.9 lg/mL),[132] as well as anti-leishmanial (6, Leishmania amazonensis: IC50 0.12 lM)[133] traits of pyrazolo[3,4-b]pyridines are described. Additionally, Y-25510 (7), an analogue of pyrazolo[3,4-b] pyridine, exhibits increase in the in vivo production of IL-la and IL-6 in mice and to stimulate the generation of IL-1a and IL-6 at the level of mRNA expression found in cultured human monocytes.[134,135] Compound 8 exhibited strong in vivo TNF-a suppression (97% reduction of LPS-induced TNF-a discharge in mice at 20 mg/kg po.) and strong p38a MAP kinase inhibitory action (IC50 0.7 nM). [136] By inhibiting TNF-a and PDE-IV, pyrazolo[3,4-b] pyridines 9 [IC50 15.7 nM (TNF-a), >1 lM (PDEIV)] and 10 [IC50 27 nM (TNF-a), >1 lM (PDE-IV)] are said to have anti-inflammatory properties. [137] Similarly, there are reports of biologically active pyrazolo[1,5-a] pyrimidines, isoxazolo[5,4-b] pyridine 13 (TACE inhibitor), and 11 (non-steroidal anti-inflammatory medication)[138] and 12 (COX-2 inhibitor)[139] (**Figure 3**).

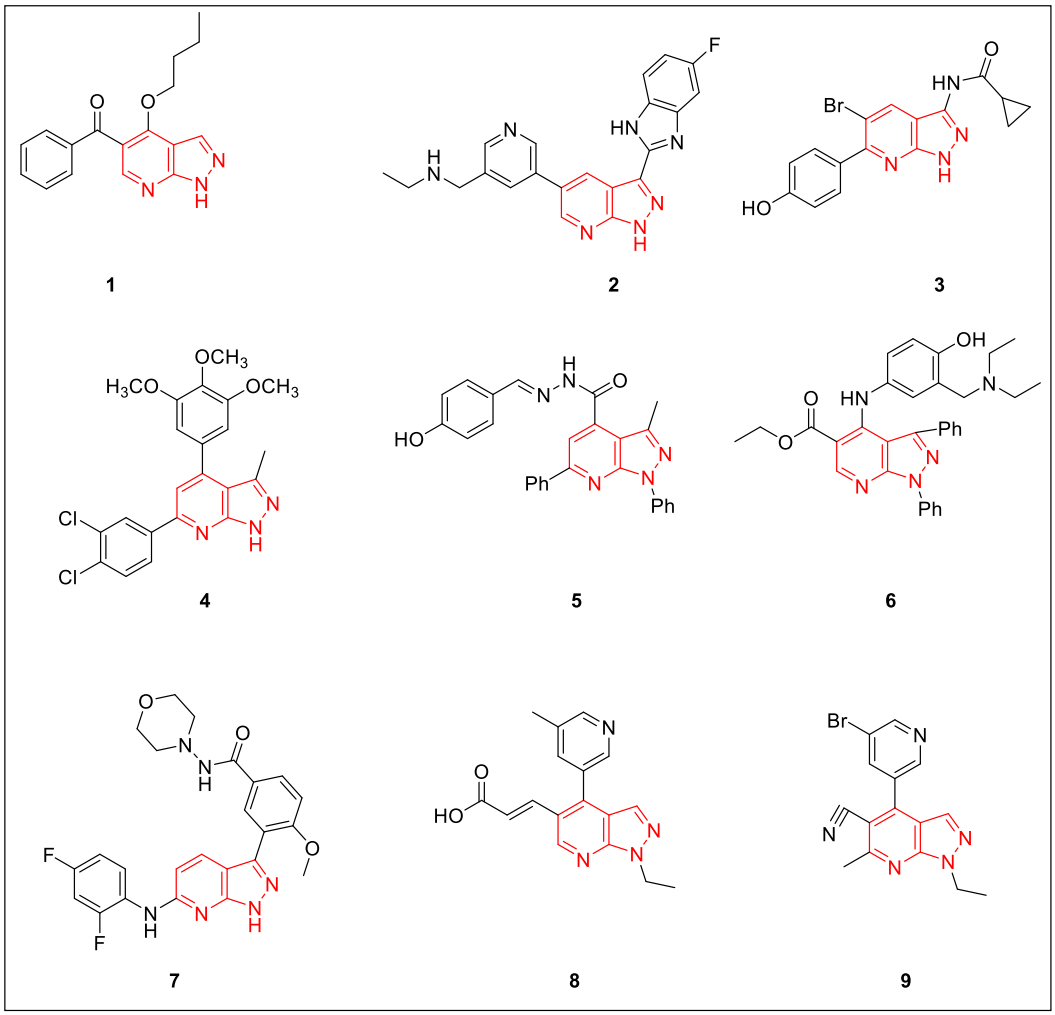


Figure 3 : Some biologically active pyrazolo[3,4-b] pyridines

Antimicrobial and Anti-cancer agents

A, B, C, D, E, and F constitute the pyrazolo[3,4-b]pyridines that demonstrate the potential to possess excellent DNA-binding affinity and potential anticancer properties(**Figure 4**).Pyrazolo[3,4-

b]pyridines C, D, and E were further depicted to adhere to DNA through intercalation(**Figure 5**).[140-142] In addition, by targeting DNA, pyrazolo[3,4-b]pyridines G, H, I, and J exhibited intriguing and extended-spectrum antibacterial characteristics. By targeting DNA, pyrazolo[3,4-b] pyridines K, L, M, N, and O were also recognized in the form of remarkable antibacterial as well as anticancer agents (**Figure 6**).[143] The DNA-binding affinity of the novel molecules was evaluated with the goal to analyze its action mode. In order to confirm the novel analogs' aptitude for binding DNA, molecular docking was also investigated.

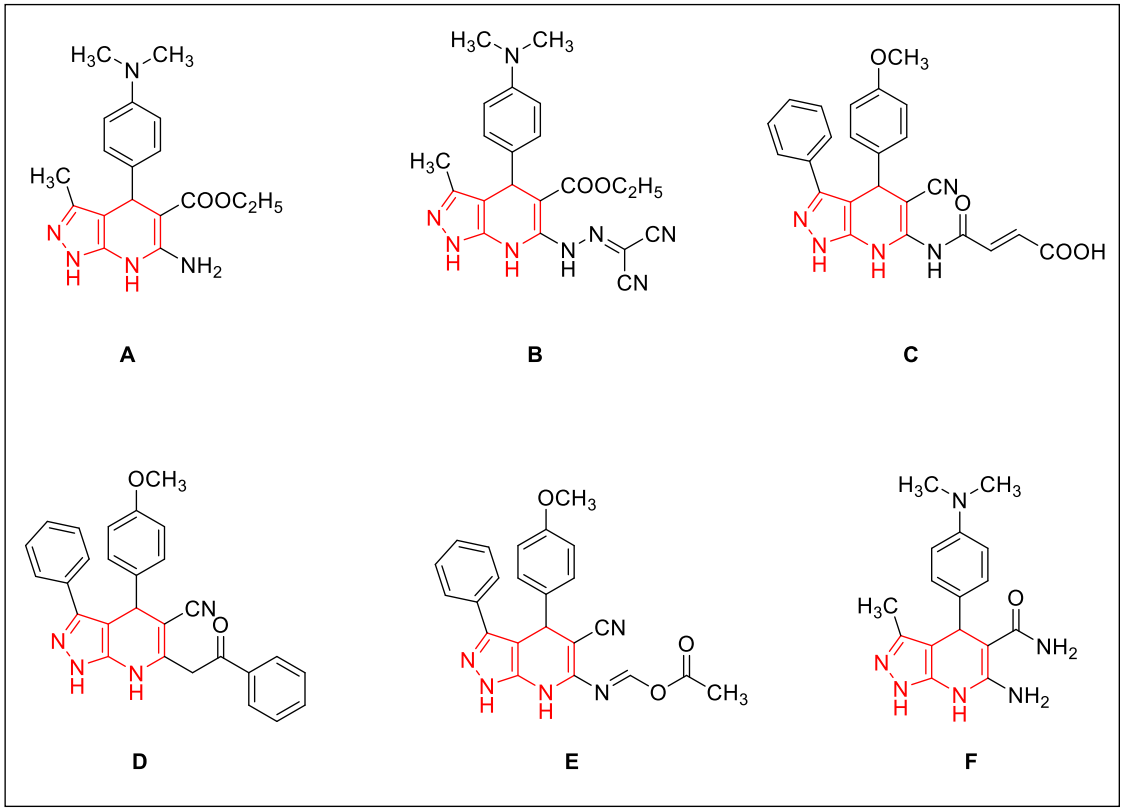


Figure 4: Pyrazolopyridines possessing anticancer efficacy and DNA-binding affinity.

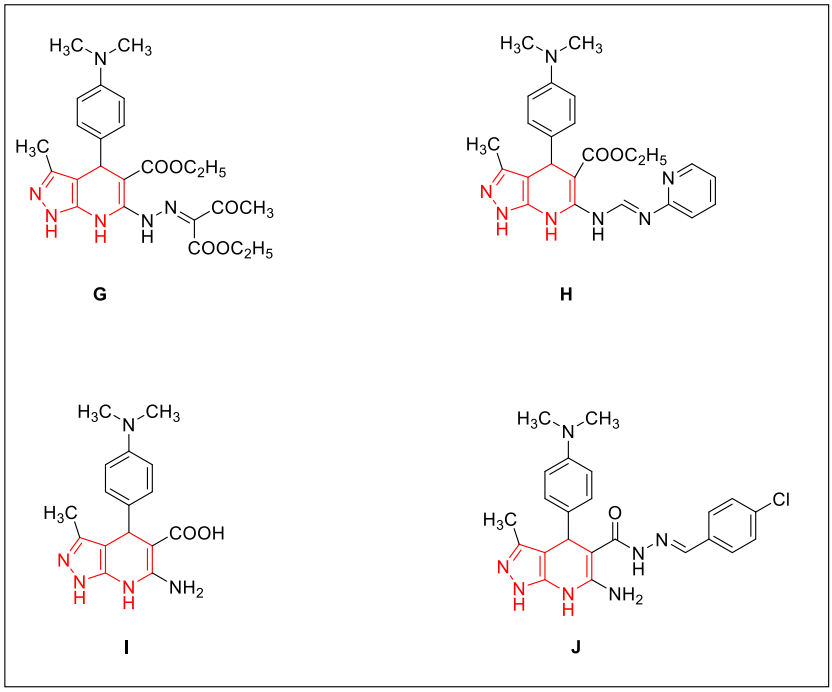


Figure 5: Pyrazolopyridines exhibiting antimicrobial efficacy and DNA-binding affinity.

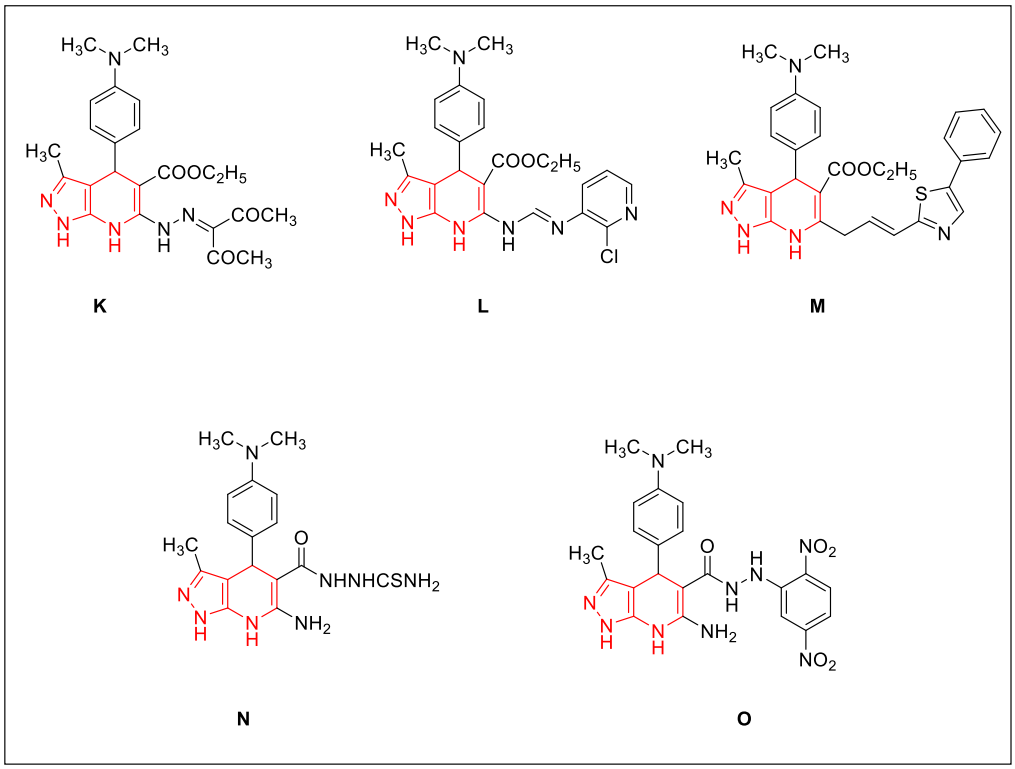


Figure 6: Pyrazolopyridines depicting antimicrobial and anticancer efficacies as well as DNA-binding affinity.

Anti-bacterial activity

The antibacterial attribute was analyzed employing agar well diffusion process. Using nutrient agar medium, the molecules have been evaluated against Klebsiella pneumonia and Escherichia coli as gram-negative bacterial strain (involving Gentamicin as reference drug, 120 mg susceptibility disc, Oxford-England) and Staphylococcus aureus and Streptococcus mutans as gram-positive bacterial

strain (employing Ampicillin as standard, 10 mg susceptibility disc, Oxford-England). Incorporating DMSO as a solvent, the compounds were analyzed against bacterial strains at a dosage of 15 mg/mL; the negative control wells contained just DMSO.[144]

Antifungal activity

Employing sabouraud dextrose agar medium and Nystatin as the baseline medication, the antifungal potential of the investigated compounds against Candida albicans and Aspergillus nigar was determined incorporating the agar well diffusion method. The procedure similar to the antibacterial property was implemented to assess the antifungal activity, with the exception that 100 ml of each tested solution of the evaluated molecules was added to each well, and the plates were then incubated at 25℃ for 48 hours.

Antitumor activity

Through a holding business for biological entities and vaccines (VACSERA), located in Cairo, Egypt, ATCC provided the epidermoid carcinoma (larynx) Hep2. 5-A common anticancer medication, fluorouracil, was employed as a benchmark. The MTT assay was used to test the produced compounds' anti-tumor properties in vitro against the Hep-G2 human liver cancer cell line and the HCT 116 human cell line. Measured and compared to the control was the proportion of undamaged cells. The compounds' anti-cancer properties were contrasted with doxorubicin's cytotoxicity. [145-148] Cartazolate, etazolate, and tracazolate are examples of anxiolytic medications that are pyrazolo[3,4-b] pyridine-embedded heterocycles. They are also found in a glycogen synthase kinase 3 (GSK-3) inhibitor that effectively treats Alzheimer's disease and the cardiovascular therapeutic drug BAY 41-2272.[149-153]

Figure 7: Bio-active compounds

2. CONCLUSION

The primary attributes of above methods are their short reaction time, substantial yields, an extensive selection of compatible substrates, and favorable functional group tolerance. Additionally, these techniques combat low yields, high temperatures externally, and the production of undesirable byproducts. With respect to domains of combinatorial chemistry, diversity-oriented synthetic procedures, sonochemistry, green chemistry, and drug exploration, it is anticipated that these techniques will find widespread use.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals or humans were used for the studies that are based on this research.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

ACKNOWLEDGEMENT

I am sincerely indebted to the Chemistry Department, Ewing Christian College, Prayagraj for their assistance and my supervisor Prof. Vivek Bhadauria for his constant support and guidance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Ganem B. Strategies for innovation in multicomponent reaction design. Acc Chem Res. 2009; 42:463-472.
2. Dandia A, Jain AK, Sharma S. Indium triflate catalyzed one-pot multicomponent synthesis of spiro-hexahydropyrimidines explained by multiple covalent bond formation. Tetrahedron Lett. 2012; 53:5270-5274.
3. Singh MS, Chowdhury S. Recent developments in solvent-free multicomponent reactions: a perfect synergy for eco-compatible organic synthesis. RSC Adv. 2012; 2:4547-4592.
4. Li CJ, Chen L. Organic chemistry in water. Chem Soc Rev. 2006; 35:68-82.
5. Li CJ. Organic reactions in aqueous media with a focus on carbon–carbon bond formations: a decade update. Chem Rev. 2005; 105:3095-3166.
6. Cintas P, Luche JL. Green chemistry: the sonochemical approach. Green Chem. 1999; 1:115-125.
7. Baig NRR, Varma RS. Alternative energy input: mechanochemical, microwave and ultrasound-assisted organic synthesis. Chem Soc Rev. 2012; 41:1559-1584.
8. Jarag KJ, Pinjari DV, Pandit AB, Shankarling GS. Synthesis of chalcone (3-(4-fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one): advantage of sonochemical method over conventional method. Ultrason Sonochem. 2011; 18:617-623.
9. Suslick KS. Ultrasound: its chemical, physical, and biological effects. VCH, New York. 1988; p. 243.
10. Singh BS, Lobo HR, Pinjari DV, Jarag KJ, Pandit AB, Shankarling GS. Ultrasound and deep eutectic solvent (DES): a novel blend of techniques for rapid and energy efficient synthesis of oxazoles. Ultrason Sonochem. 2013; 20:633-639.

11. Li JT, Yin Y, Sun MX. Ultrasound promoted efficient method for the cleavage of 3-aryl-2,3-epoxyl-1-phenyl-1-propanone with indole. Ultrason Sonochem. 2010; 17:359-362.
12. Li JT, Wang SX, Chen GF, Li TS. Some applications of ultrasound irradiation in organic synthesis. Curr Org Synth. 2005; 2:415-436.
13. Mamaghani M, Dastmard S. An efficient ultrasound-promoted synthesis of the Baylis-Hillman adducts catalyzed by imidazole and L-proline. Ultrason Sonochem. 2009; 16:445-447.
14. Saleh TS, El-Rahman NMA. Ultrasound promoted synthesis of substituted pyrazoles and isoxazoles containing sulphone moiety. Ultrason Sonochem. 2009; 16:237-242.
15. Cella R, Stefani HA. Ultrasound in heterocycles chemistry. Tetrahedron. 2009; 65:2619-2641.
16. Ganem B. Strategies for innovation in multicomponent reaction design. Acc Chem Res. 2009; 42:463-472.
17. Padwa A. Domino reactions of rhodium(II) carbenoids for alkaloid synthesis. Chem Soc Rev. 2009; 38:3072-3081.
18. Ban L, Basso A, Giardini L, Riva R, Rocca V, Guanti G. Long-range diastereoselectivity in an Ugi reaction: stereocontrolled and diversity-oriented synthesis of tetrahydrobenzoxazepines. Eur J Org Chem. 2013; 2013:5064-5075.
19. Dömling A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. Chem Rev. 2006; 106:17-89.
20. D'Souza DM, Müller TJJ. Multi-component syntheses of heterocycles by transition-metal catalysis. Chem Soc Rev. 2007; 36:1095-1108.
21. Singh MS, Chowdhury S. Recent developments in solvent-free multicomponent reactions: a perfect synergy for eco-compatible organic synthesis. RSC Adv. 2012; 2:4547-4592.
22. Tejedor D, Garcia-Tellado F. Chemo-differentiating ABB′ multicomponent reactions. Privileged building blocks. Chem Soc Rev. 2007; 36:484-491.
23. Polshettiwar V, Varma RS. Aqueous microwave chemistry: a clean and green synthetic tool for rapid drug discovery. Chem Soc Rev. 2008; 37:1546-1557.
24. Li CJ, Chen L. Organic chemistry in water. Chem Soc Rev. 2006; 35:68-82.
25. Li CJ. Organic reactions in aqueous media with a focus on carbon–carbon bond formations: a decade update. Chem Rev. 2005; 105:3095-3166.
26. Shore G, Yoo WJ, Li CJ, Organ M. Propargyl amine synthesis catalyzed by gold and copper thin films by using microwave-assisted continuous-flow organic synthesis (MACOS). Chem Eur J. 2010; 16:126-133.
27. Stauffer SR, Huang YR, Aron ZD, Coletta CJ, Sun J, Katzenellenbogen BS, Katzenellenbogen JA. Triarylpyrazoles with basic side chains. Bioorg Med Chem. 2001; 9:151-161.
28. Gökhan-Kelekçi N, Yabanoglu S, Küpeli E, Salgın U, Özgen O, Uçar G, et al. A new therapeutic approach in Alzheimer disease: some novel pyrazole derivatives as dual MAO-B inhibitors and

anti-inflammatory analgesics. Bioorg Med Chem. 2007; 15:5775-5786.

29. Balbi A, Anzaldi M, Mazzei M, Miele M, Bertolotto M, Ottonello L, et al. Synthesis and biological evaluation of novel heterocyclic ionone-like derivatives as anti-inflammatory agents. Bioorg Med Chem. 2006; 14:5152-5160.
30. Sahu SK, Banerjee M, Samantray A, Behera C, Azam MA. Synthesis, analgesic, anti-inflammatory and antimicrobial activities of some novel pyrazoline derivatives. Trop J Pharm Res. 2008; 7:961-968.
31. Rajasekaran A, Thampi PP, Ramasamy S. Synthesis and biological evaluation of some 3,5-diaryl-4,5-dihydro-1H-pyrazole derivatives as analgesic and anti-inflammatory agents. Indian J Pharm Sci. 2008; 70:572-576.
32. Kidwai M, Saxena S, Khan MKR, Thukral SS. Synthesis of novel pyrazoline derivatives as potential antimicrobial agents. Bioorg Med Chem Lett. 2005; 15:4295-4298.
33. Narayana B, Vijayaraj KK, Suchetha KN, Ashalatha BV, Kumari NS. Synthesis of some new pyrazoline derivatives and evaluation of their antimicrobial activities. Eur J Med Chem. 2008; 43:1173-1181.
34. Amir M, Kumar S. Synthesis and pharmacological evaluation of pyrazoline derivatives as new anti-inflammatory and analgesic agents. Bioorg Med Chem Lett. 2007; 17:4721-4724.
35. Amir M, Shikha K. Synthesis and anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of some new 2-[(2,6-dichloroanilino)phenyl]acetic acid derivatives. Eur J Med Chem. 2004; 39:535-545.
36. Amir M, Kumar S, Khan SA. Synthesis and anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of some new 1,3,5-trisubstituted pyrazolines. Bioorg Med Chem Lett. 2008; 18:918-922.
37. Amir M, Kumar H, Javed SA, Khan SA. Synthesis and anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of some new 2-[(2,6-dichloroanilino)phenyl]acetic acid derivatives. Eur J Med Chem. 2007; 42:861-868.
38. Amir M, Kumar H, Khan SA. Synthesis and pharmacological evaluation of pyrazoline derivatives as new anti-inflammatory and analgesic agents. Bioorg Med Chem Lett. 2008; 18:918-922.
39. Sahu SK, Behera C, Azam MA. Synthesis, analgesic and anti-inflammatory activities of some pyrazoline derivatives. Eur J Med Chem. 2009; 44:1155-1160.
40. Siddiqui AA, Ali R, Mishra R, Alam O, Ahsan W, Pandeya SN. Synthesis, characterization and biological evaluation of some pyrazoline derivatives as anti-inflammatory agents. Eur J Med Chem. 2010; 45:264-269.
41. Sahu SK, Banerjee M, Samantray A, Behera C, Azam MA. Synthesis and antimicrobial activity of some new pyrazoline derivatives. Med Chem Res. 2010; 19:45-53.

42. Kumar A, Sharma S, Sharma A, Verma R, Singh R. Design, synthesis and biological evaluation of novel pyrazoline derivatives as anti-inflammatory agents. Eur J Med Chem. 2011; 46:3145-3151.
43. Sharma D, Kumar S, Narasimhan B, Ramasamy K, Mani V. Synthesis and evaluation of some novel pyrazoline derivatives as anti-inflammatory agents. Bioorg Med Chem Lett. 2012; 22:6848-6852.
44. Patel NB, Patel KD, Patel J. Synthesis and biological evaluation of pyrazoline derivatives as anti-inflammatory agents. Eur J Med Chem. 2012; 55:240-248.
45. Kumar S, Sharma A, Kumar D. Design, synthesis and evaluation of new pyrazoline derivatives as potential anti-inflammatory agents. Bioorg Med Chem Lett. 2013; 23:201-206.
46. Narayana B, Ashalatha BV, Vijayaraj KK, Kumari NS. Synthesis of some new pyrazoline derivatives and their antimicrobial activities. Eur J Med Chem. 2007; 42:1235-1242.
47. Verma A, Saraf SK. 4-Thiazolidinones: a biologically active scaffold. Eur J Med Chem. 2008; 43:897-905.
48. Amir M, Javed SA, Kumar H, Khan SA. Synthesis of some new pyrazoline derivatives and evaluation of their anti-inflammatory, analgesic and ulcerogenic activities. Eur J Med Chem. 2008; 43:2056-2066.
49. Shukla P, Misra S, Shukla R. Synthesis and antimicrobial activity of some pyrazoline derivatives. Indian J Chem. 2006; 45B:2532-2536.
50. Srivastava S, Yadav R, Jain R. Synthesis and biological evaluation of some new pyrazoline derivatives. Eur J Med Chem. 2010; 45:1512-1518.
51. Sharma S, Kumar D, Singh G, Kumar A. Design, synthesis and evaluation of some novel pyrazoline derivatives as anti-inflammatory and analgesic agents. Eur J Med Chem. 2010; 45:2650-2655.
52. Khan SA, Kumar S, Amir M. Synthesis and biological evaluation of some new pyrazoline derivatives as anti-inflammatory and analgesic agents. Eur J Med Chem. 2008; 43:846-852.
53. Yadav R, Srivastava S, Jain R. Synthesis and antimicrobial activity of some pyrazoline derivatives. Med Chem Res. 2011; 20:1134-1139.
54. Sharma A, Kumar S, Sharma D. Synthesis, characterization and biological evaluation of some new pyrazoline derivatives. Eur J Med Chem. 2011; 46:436-442.
55. Alam O, Rizvi S, Verma A, Siddiqui N, Ahsan W. Pyrazolines: a versatile scaffold for anticancer agents. Eur J Med Chem. 2012; 54:615-626.
56. Narasimhan B, Belsare D, Pharande D, Mourya V, Dhake A. Synthesis and antimicrobial activity of some novel pyrazoline derivatives. Eur J Med Chem. 2004; 39:827-834.
57. Dawood KM, El-Sayed WA, Rageb EA, Ellithey M, Awad HM. Synthesis and anti-inflammatory activity of some pyrazoline derivatives. Eur J Med Chem. 2006; 41:554-561.

58. Desai NC, Joshi VV, Rajpara KM, Vaghani HV. Synthesis and antimicrobial evaluation of some new pyrazoline derivatives. Eur J Med Chem. 2013; 62:653-659.
59. Desai NC, Rajpara KM, Joshi VV, Vaghani HV. Synthesis and biological evaluation of some novel pyrazoline derivatives as anti-inflammatory agents. Eur J Med Chem. 2013; 65:178-184.
60. Dawood KM, Rageb EA, El-Sayed WA, Ellithey M, Awad HM. Synthesis of some novel pyrazoline derivatives and their biological evaluation. Eur J Med Chem. 2010; 45:387-392.
61. halifa ME, El-Hag Ali GA, El-Maghraby MA, El-Sayed WA. Synthesis and biological evaluation of some novel pyrazolo[3,4-b]pyridine derivatives. Eur J Med Chem. 2012; 47:582-590.
62. Amer FA, Hassan NA, Ragab FA, El-Sayed WA. Synthesis, antimicrobial and anti-inflammatory evaluation of new pyrazolo[3,4-b]pyridine derivatives. Eur J Med Chem. 2013; 63:645-653.
63. El-Helby AA, Ragab FA, El-Emam AA. Design, synthesis and antimicrobial activity of some pyrazolo[3,4-b]pyridine derivatives. Bioorg Med Chem. 2012; 20:2254-2261.
64. Ragab FA, Amer FA, El-Sayed WA. Synthesis and antitumor evaluation of new pyrazolo[3,4-b]pyridine derivatives. Eur J Med Chem. 2013; 62:614-623.
65. Abd El-Samii ZA, Radwan MA, El-Bendary ER, El-Gamal KM. Synthesis and evaluation of new pyrazolo[3,4-b]pyridine derivatives as anti-inflammatory agents. Eur J Med Chem. 2011; 46:6053-6060.
66. Hassan NA, Amer FA, Ragab FA, El-Helby AA. Design and synthesis of new pyrazolo[3,4-b]pyridine derivatives as antimicrobial and anti-inflammatory agents. Eur J Med Chem. 2013; 70:1-9.
67. El-Sayed WA, El-Maghraby MA, El-Helby AA. Pyrazolo[3,4-b]pyridine derivatives: synthesis and biological evaluation as anticancer agents. Eur J Med Chem. 2012; 55:144-152.
68. Abd El-Samii ZA, Radwan MA, El-Bendary ER, El-Gamal KM. Synthesis and anticancer activity of some pyrazolo[3,4-b]pyridine derivatives. Eur J Med Chem. 2011; 46:6061-6067.
69. Ragab FA, Amer FA, El-Sayed WA. Synthesis and antimicrobial activity of new pyrazolo[3,4-b]pyridine derivatives. Bioorg Med Chem. 2013; 21:5580-5589.
70. Amer FA, Ragab FA, El-Helby AA. Synthesis of some novel pyrazolo[3,4-b]pyridine derivatives and their antimicrobial evaluation. Eur J Med Chem. 2012; 57:164-172.
71. El-Emam AA, Ragab FA, El-Helby AA. Pyrazolo[3,4-b]pyridine derivatives: synthesis, anticancer and antimicrobial activities. Bioorg Med Chem. 2013; 21:5753-5764.
72. El-Helby AA, Amer FA, Ragab FA. Synthesis and anti-inflammatory evaluation of new pyrazolo[3,4-b]pyridine derivatives. Eur J Med Chem. 2013; 64:140-149.
73. Ragab FA, El-Helby AA, El-Emam AA. Synthesis, antimicrobial and anticancer evaluation of some novel pyrazolo[3,4-b]pyridine derivatives. Eur J Med Chem. 2012; 55:67-75.

74. Abd El-Samii ZA, Radwan MA, El-Bendary ER. Design, synthesis and evaluation of new pyrazolo[3,4-b]pyridine derivatives as anti-inflammatory and analgesic agents. Eur J Med Chem. 2012; 56:218-227.
75. Bate C, Williams A. Pyrazole protects neurons against amyloid-β-induced synapse damage. J Biol Chem. 2011; 286:26888-26896.
76. Kalgutkar AS, Crews BC, Rowlinson SW, Garner C, Seibert K, Marnett LJ. Aspirin-like molecules that covalently inactivate cyclooxygenase-2. Science. 1998; 280:1268-1270.
77. Grundt P, Hubner H, Gmeiner P. Structure–activity relationships of dopamine D3 receptor ligands: pyrazolo[1,5-a]pyridines as potent antagonists. J Med Chem. 2005; 48:2074-2080.
78. Marco JL, Carreiras MC. Recent developments in the design of multitarget-directed ligands for Alzheimer's disease. Curr Top Med Chem. 2006; 6:2057-2075.
79. Ferreira SB, Lima DJ, Monteiro JL, Pilo-Veloso D, de Souza MV. Synthesis and anti-inflammatory activity of new pyrazolo[3,4-b]pyridine derivatives. Eur J Med Chem. 2008; 43:167-173.
80. Singh A, Yadav A, Singh A, Srivastava S. Green synthesis and corrosion inhibition activity of pyrazolo[3,4-b]pyridine derivatives. J Mol Liq. 2019; 294:111662.
81. Khurana JM, Magoo D. Recent advances in the synthesis of pyrazolo[3,4-b]pyridines via multicomponent reactions. Org Biomol Chem. 2019; 17:8561-8578.
82. Sugasawa S, Kakemi K, Yamada H, Hayashi T. Syntheses of heterocyclic compounds. CXII. Pyrazolo[3,4-b]pyridine derivatives. Chem Pharm Bull. 1961; 9:381-386.
83. Sugasawa S, Kakemi K, Hayashi T. Studies on the synthesis of pyrazolo[3,4-b]pyridine derivatives. Chem Pharm Bull. 1963; 11:1064-1068.
84. Ishida R, Goto G. Synthesis of pyrazolo[3,4-b]pyridine derivatives. Yakugaku Zasshi. 1967; 87:839-843.
85. Kakemi K, Hayashi T, Sugasawa S. Syntheses of pyrazolo[3,4-b]pyridine derivatives and their properties. Chem Pharm Bull. 1962; 10:141-147.
86. Yamada H, Kakemi K, Sugasawa S. Studies on pyrazolo[3,4-b]pyridine derivatives. Yakugaku Zasshi. 1964; 84:942-946.
87. Okabe T, Nagata W. Studies on pyrazolo[3,4-b]pyridine derivatives. Chem Pharm Bull. 1965; 13:375-381.
88. Yamada H, Hayashi T, Kakemi K. Pyrazolo[3,4-b]pyridine derivatives: syntheses and biological evaluation. Chem Pharm Bull. 1966; 14:350-356.
89. Dömling A, Huang Y. Recent advances in the chemistry of isocyanide-based multicomponent reactions. Acc Chem Res. 2012; 45:1462-1473.
90. Hulme C, Gore V. Multicomponent reactions: emerging chemistry in drug discovery. Curr Med Chem. 2003; 10:51-80.

91. Orru RVA, de Greef M. Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. Synthesis. 2003; 10:1471-1499.
92. Zhu J. Recent developments in the isocyanide-based multicomponent synthesis of heterocycles. Eur J Org Chem. 2003; 2003:1133-1144.
93. Dömling A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. Chem Rev. 2006; 106:17-89.
94. Ugi I, Dömling A, Hörl W. Multicomponent reactions in organic chemistry. Endeavour. 1994; 18:115-122.
95. Ugi I. Recent progress in the chemistry of multicomponent reactions. Pure Appl Chem. 2001; 73:187-191.
96. Ugi I, Dömling A. The α-aminoalkylation of isocyanides and its importance in multicomponent reactions. Angew Chem Int Ed Engl. 1998; 37:316-332.
97. Zhu J, Bienaymé H. Multicomponent Reactions. Weinheim: Wiley-VCH; 2005.
98. Slobbe P, Ruijter E, Orru RVA. Recent applications of multicomponent reactions in medicinal chemistry. Med Chem Commun. 2012; 3:1189-1218.
99. Akritopoulou-Zanze I. Applications of multicomponent reactions in lead generation and library design. Curr Opin Chem Biol. 2008; 12:324-331.
100. Orru RVA, Ruijter E. Synthesis of heterocycles via multicomponent reactions. In: Katritzky AR, Ramsden CA, Scriven EFV, Taylor RJK, editors. Comprehensive Heterocyclic Chemistry III. Oxford: Elsevier; 2008. p. 1-55.
101. Herrera RP, Marqués-López E, editors. Multicomponent Reactions: Concepts and Applications for Design and Synthesis. Weinheim: Wiley-VCH; 2015.
102. Cioc RC, Ruijter E, Orru RVA. Multicomponent reactions: advanced tools for sustainable organic synthesis. Green Chem. 2014; 16:2958-2975.
103. Dömling A, Wang W, Wang K. Chemistry and biology of multicomponent reactions. Chem Rev. 2012; 112:3083-3135.
104. Banfi L, Riva R. Multicomponent reactions in the synthesis of heterocycles. In: O'Connor CJ, Taylor RJK, editors. Progress in Heterocyclic Chemistry. Vol 18. Oxford: Elsevier; 2006. p. 1-63.
105. Hulme C. Applications of multicomponent reactions in drug discovery and chemical biology. Curr Opin Drug Discov Devel. 2003; 6:774-783.
106. Toure BB, Hall DG. Natural product synthesis using multicomponent reaction strategies. Chem Rev. 2009; 109:4439-4486.
107. El Kaïm L, Grimaud L. Multicomponent access to heterocycles: the case of isocyanide-based reactions. Tetrahedron. 2009; 65:2153-2171.
108. Dömling A, Ugi I. Multicomponent reactions with isocyanides. Angew Chem Int Ed. 2000;

39:3168-3210.

109. Ugi I, Meyr R, Fetzer U, Steinbrückner C. Versuche mit Isonitrilen. Angew Chem. 1959; 71:386-388.
110. Ugi I. The α-addition of imines to isocyanides, a novel and convenient reaction for the preparation of α-amino carboxamides. Angew Chem Int Ed Engl. 1962; 1:8-21.
111. Ugi I. Multicomponent reactions of isocyanides in organic chemistry. Angew Chem Int Ed Engl. 1982; 21:810-819.
112. Hulme C, Chappeta S. The Ugi reaction in drug discovery and development. Methods Mol Biol. 2015; 1233:145-158.
113. Dömling A. Recent applications of multicomponent reactions in medicinal chemistry. Curr Opin Chem Biol. 2002; 6:306-313.
114. Blacklock TJ, Sohar P. Applications of the Ugi reaction in drug discovery. Curr Opin Drug Discov Devel. 2004; 7:777-784.
115. Elders N, van der Born D, Hendrickx LJ, Timmer BJ, Krause A, Janssen E, et al. Isocyanide-based multicomponent reactions for the synthesis of druglike molecules. Chem Soc Rev. 2009; 38:199-209.
116. Marcaccini S, Torroba T. The Ugi four-component condensation reaction and its applications. Nat Protoc. 2007; 2:632-639.
117. Kappe CO. Recent advances in the Biginelli dihydropyrimidine synthesis. New tricks from an old dog. Acc Chem Res. 2000; 33:879-888.
118. Atwal KS, Swanson BN, Unger SE, Floyd DM, Moreland S, Hedberg A, et al. Dihydropyrimidine calcium channel blockers. J Med Chem. 1991; 34:806-811.
119. Grover GJ, Dzwonczyk S, McMullen DM, Normadin D, Sleph PG, Moreland S, et al. Pharmacological profile of dihydropyrimidines as calcium channel modulators. J Cardiovasc Pharmacol. 1995; 26:289-294.
120. Rovnyak GC, Atwal KS, Hedberg A, Kimball SD, Moreland S, Gougoutas JZ, et al. Dihydropyrimidines as novel calcium channel blockers with enhanced efficacy. J Med Chem. 1992; 35:3254-3263.
121. Dolomanov OV, Bourhis LJ, Gildea RJ, Howard JAK, Puschmann H. OLEX2: a complete structure solution, refinement and analysis program. J Appl Crystallogr. 2009; 42:339-341.
122. Sheldrick GM. SHELXT – Integrated space-group and crystal-structure determination. Acta Crystallogr C. 2015; 71:3-8.
123. Misra RN, Rawlins DB, Xiao H, Shan W, Bursuker I, Kellar KA, et al. 1H-Pyrazolo[3,4-b]pyridine inhibitors of cyclin-dependent kinases. Bioorg Med Chem Lett. 2003; 13:1133-1136.
124. Lin R, Connolly PJ, Lu Y, Chiu G, Li S, Yu Y, et al. Bioorg Med Chem Lett. 2007; 17:4297-4301.

125. Patterson C. The World Alzheimer Report 2018: The State of the Art of Dementia Research: New Frontiers. London: Alzheimer's Disease International (ADI); 2018.
126. Hiremathad A, Keri RS, Esteves AR, Cardoso SM, Chaves S, Santos MA. Novel Tacrine-Hydrxyphenylbenzimidazole hybrids as potential multitarget drug candidates for Alzheimer's disease. Eur J Med Chem. 2018; 148:255-267.
127. Jesus M, Gasque O, Marco-Contelles J. Alzheimer's disease, the "One-Molecule, one-target" paradigm, and the multitarget directed ligand approach. ACS Chem Neurosci. 2018; 9:401-403.
128. Witherington J, Bordas V, Gaiba A, Garton NS, Naylor A, Rawlings AD, et al. 6-Aryl-pyrazolo[3,4-b]pyridines: potent inhibitors of glycogen synthase kinase-3 (GSK-3). Bioorg Med Chem Lett. 2003; 13:3055-3057.
129. Goda FE, Abdel-Aziz AM, Attef OA. Bioorg Med Chem. 2004; 12:1845-1852.
130. Foks H, Pancechowska-Ksepko D, Kvdzia A, Zwolska Z, Janowiec M, Augustynowicz-Kopec E. II Farmaco. 2005; 60:513-519.
131. Dias LRS, Santos MB, de Albuquerque S, Castro HC, de Souza AMT, Freitas ACC, et al. Bioorg Med Chem. 2007; 15:211-220.
132. De Mello H, Echevarria AM, Bernardino AM, Canto-Cavalheiro M, Leon LL. Antileishmanial pyrazolopyridine derivatives: synthesis and structure-activity relationship analysis. J Med Chem. 2004; 47:5427-5432.
133. Kusuhara H, Komatsu H, Hisadome M, Ikeda Y. Int J Immunopharmacol. 1996; 18:719-726.
134. Hisadome M, Fukuda T, Matsuyuki H, Ikeda Y, Nomoto K. Int J Immunopharmacol. 1996; 18:379-386.
135. Revesz L, Blum E, Padova FED, Buhl T, Feifel R, Gram H, et al. Bioorg Med Chem Lett. 2006; 16:262-267.
136. Abe Y, Ohne K, Inoue M, Okumura M. US2006/0004003 A1. Astellas Pharma Inc., Tokyo, Japan; 2006.
137. Inoue M, Hashimoto K. JP 1991204877. Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan; 1991.
138. Almansa C, de Arriba AF, Cavalcanti RFL, Gomez LA, Miralles A, Merlos M, García-Rafanell J, Forn J. J Med Chem. 2001; 44:350-356.
139. Zask A, Gu Y, Albright JD, Hogan M, Levin JI, Chen JM, et al. Bioorg Med Chem Lett. 2003; 13:1487-1491.
140. Eissa IH, El-Naggar AM, El-Hashash MA. Design, synthesis, molecular modeling and biological evaluation of novel 1H-pyrazolo[3,4-b]pyridine derivatives as potential anticancer agents. Bioorg Chem. 2016; 67:43-56.
141. El-Gohary NS, Shaaban MI. Design, synthesis, antimicrobial, antiquorum-sensing and antitumor evaluation of new series of pyrazolopyridine derivatives. Eur J Med Chem. 2018;

157:729-742.

142. El-Gohary NS, Shaaban MI. New pyrazolopyridine analogs: synthesis, antimicrobial, antiquorum-sensing and antitumor screening. Eur J Med Chem. 2018; 152:126-136.
143. Hamza A, El-Sayed HA, Assy MG, Ouf NH, Farhan ME. Synthesis and antimicrobial activity of some new triazine, 1,3-oxazine, fused pyridine and pyrimidine derivatives. World Appl Sci J. 2018; 36:637-645.
144. Jian XE, Yang F, Jiang CS, You WW, Zhao PL. Synthesis and biological evaluation of novel pyrazolo[3,4-b]pyridines as cis-restricted combretastatin A-4 analogues. Bioorg Med Chem Lett. 2020; 30:127025.
145. Abdel-Mohsen SA, El-Emary TI. New pyrazolo[3,4-b]pyridines: synthesis and antimicrobial activity. Der Pharma Chem. 2018; 10(4):44-51.
146. Samar C, Ismail A, Helmi T, Khiari J, Bassem J. Substituted pyrazolo[3,4-b]pyridin-3-ones and pyrazolo[3,4-b]pyridine-5-carbaldehyde, new one-pot synthesis strategy amelioration using vinamidinium salts, antibacterial and antifungal activities promising environmental protection. J Bacteriol Parasitol. 2017; 8:1-8.
147. Barghash RF, Eldehna WM, Kovalová M, Vojáčková V, Kryštof V, Abdel-Aziz HA. One-pot three-component synthesis of novel pyrazolo[3,4-b]pyridines as potent antileukemic agents. Eur J Med Chem. 2022; 227:113952.
148. Zhai M, Liu S, Gao M, Wang L, Sun J, Du J, et al. 3,5-Diaryl-1H-pyrazolo[3,4-b]pyridines as potent tubulin polymerization inhibitors: rational design, synthesis and biological evaluation. Eur J Med Chem. 2019; 168:426-435.
149. Nam Y, Hwang D, Kim N, Seo HS, Selim KB, Sim T. Identification of 1H-pyrazolo[3,4-b]pyridine derivatives as potent ALK-L1196M inhibitors. J Enzym Inhib Med Chem. 2019; 34:1426-1438.
150. Kihara T, Yuan J, Watabe T, Kitajima K, Kimura N, Ohkouchi M, et al. Pimitespib is effective on cecal GIST in a mouse model of familial GISTs with KIT-Asp820Tyr mutation through KIT signaling inhibition. Exp Mol Pathol. 2021; 123:104692.
151. Huang Y, Li Y, Dong G, Zhang W, Liu N, Sheng C. Identification of pyrazolopyridine derivatives as novel spleen tyrosine kinase inhibitors. Arch Pharm. 2018; 351:1800083.
152. Markham A, Duggan S. Vericiguat: first approval. Drugs. 2021; 81:721-726.
153. Ravula S, Bobbala RR, Kolli B. Synthesis of novel isoxazole functionalized pyrazolo[3,4-b]pyridine derivatives; their anticancer activity. J Heterocycl Chem. 2020; 57:2535.