A Sustainable Eco-Friendly One-Pot Multicomponent Synthesis via Mechanochemical Reaction Using Lemon Juice

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Abstract
Green and sustainable chemistry have become very important in modern organic synthesis, especially in reactions that use solvent-free conditions, multicomponent reactions, grinding techniques, and natural catalysts and also in order to grant all chemical reactions the status of safe and eco-friendly reactions. In this research, according to the above point of view the sulfathiazole diazonium salt (1) was prepared and react with malononitrile in the presence of sodium acetate to yield aryl hydrazone propane dinitrile (2), which was then reacted with hydrazine in acidic media to obtain the building unit 2,5-diamino pyrazole (3). Subsequently, we used the one-pot threecomponent reactions among compound (3), aromatic aldehydes and malononitrile, using lemon juice as acid through free-solvent grinding technique. The 2-amino pyridine carbonitrile derivatives (4-7) were obtained in good yield using water as recrystallizing agent. Actually these compounds were illustrated via FT-IR and ^{1}H-NMR spectroscopy and also by theoretical biological study using the Molecular Docking program.

Keywords: Green chemistry, sustainable chemistry, amino pyridine carbonitrile, 2,5-diamino pyrazole, multicomponent reactions, grinding technique

Introduction

Multicomponent reactions (MCRs) are unusual strategies in organic chemistry due to their high efficiency in synthesizing complex molecules by combining three or more reactants in a one-pot step within a single reaction vessel (Clark and Macquarrie, 2002; Zhu, J. et al., 2015;Poliakoff et al., 2002).These reactions are characterized by saving time and energy compared to traditional methods that involve several steps. (Graziano et al., 2023; Neto et al., 2021), This makes them highly valuable in the preparation of organic compounds, especially heterocyclics , with diverse biological and pharmaceutical applications. (Eckert, 2012; Gulati et al., 2021; Tandi et al., 2025). Furthermore, the one-pot synthesis process makes tracking the reaction process easier and reduces separation and purification processes. (Anastas and Warner,1998; Lancaster, 2010), In accordance with the fundamentals of modern green chemistry (Azli et al., 2025; Journal of Chemical Education, 2026).

Recently, an interesting of developing eco-friendly synthesis methods that are sparing the use of solvents and harmful chemicals (Ardila-Fierro & Hernández, 2021; Howard et al., 2018**)**. Among these methods, mechanochemistry, which relies on grinding and is often carried out under solvent-free conditions, has emerged (James et al., 2012; Gomollón-Bel, 2019). The grinding technique offers several advantages, including ease of implementation, reducing the reaction time, increased molecular collision efficiency, and reduced the energy consumption and use of toxic organic solvents (Hernández & Juaristi, 2012; Stolle, 2015). This makes it a sustainable technique and also suitable for modern applications in organic synthesis (Ardila-Fierro & Hernández, 2021; Boldyreva, 2013; Colacino & Štrukil, 2020; Friščić et al., 2020).

Another important aspect of green chemistry is the use of natural biocatalysts instead of harsh or expensive conventional catalysts (Siddiqui et al., 2020). Lemon juice is a promising natural catalyst due to its citric acid and other organic acids, which possess good catalytic properties in many organic reactions (Pal & Dey, 2016; Suri et al., 2021). Furthermore, lemon juice is inexpensive, readily available, non-toxic, and biodegradable, making it an environmentally friendly alternative to traditional chemical catalysts (Patil et al., 2013; Sangshetti et al., 2019).

Water recrystallization is an important and environmentally friendly method for purifying organic compounds. Water is considered one of the best green solvents due to its low toxicity, non-flammability, and low cost compared to traditional organic solvents (Capello et al., 2007). This method relies on the different solubility of the compound in hot and cold water, allowing for the production of pure crystals with good yields and high purification efficiency (Dicks & Batey, 2016; Jones, 2014). Using water also reduces the health risks and environmental pollution associated with volatile and toxic organic solvents, making water recrystallization compatible with the principles of green chemistry and environmental sustainability (Anastas & Eghbali, 2010; Clarke et al., 2018). Furthermore, this method is easy to apply, safe, and minimizes chemical waste, enhancing its importance in modern applications of organic synthesis and chemical compound purification (Bala et al., 2022; Dicks & Batey, 2019).

Therefore, the scope of this research is to develop an efficient green synthesis method based on the one-pot multi-component reaction under grinding conditions, using lemon juice as a natural catalyst. This method is designed to prepare heterocyclic compounds represented by 2-amino pyridine dicarbonitrile derivatives (4-7) efficiently under simple and eco-friendly reaction conditions.

EXPERIMENTAL

Melting points (M.P.) were measured on Electrothermal Stuart SMP 10. melting point apparatus. Infrared (FT-IR) spectra were recorded as (KBr) disk using a Bruker, FT-IR spectrophotometer (Pye Unicom sp 2000). Nuclear Magnetic Resonance Spectrometer (H^1-NMR): Measurement of the nuclear magnetic resonance spectrum using a **Bruker Bio Spin Gmbll Spectrophotometer 400MHz Turkey**, using DMSO-d_6 as a solvent and TMS as an internal reference. Spectral regions were expressed in (ppm). The measurements were performed at Gaze Osman Paşa University, Turkey. Thin layer chromatography (TLC) was carried out on silica gel (120 mesh) with 13% gypsum coated plates (2x10) cm, activated for one hour at (110-120°C) before use and the plates were developed with iodine vapor. And the assigned structure of the prepared compounds was corroborated by available physical and spectral methods.

-Synthesis Methods of 4-((3,5-diamino-1H-pyrazol-4-yl) diazenyl)-N-(thiazol-2yl) benzenesulfonamide (Elgemeie et al., 1988).

In beaker (50ml) a mixture of sulfathiazole (0.01 mole) and HCl concentration (4 ml) was cooled on an ice bath (0-5°C) then treated with aqueous solution of $NaNO_2$ (1gm; 0.01mole/ 10 ml water). The precipitate of diazonium salt (1) was taken and added to an aqueous solution of malononitrile (0.1 mole/50ml water) followed by adding CH_3COONa (12.5 g) and crushed ice with stirring. The precipitate was filtrated to obtain the compound (2),Table (1), which then dissolved in methanol (15 ml) and reacted with hydrazine (0.1mole) via reflux conditions (10 min), cooling and acidified with acetic acid. The solid was filtrated and mixed with water (20 ml) and leave to settle for (24 hours) . The precipitate was collected and recrystallized from ethanol to afford the compound (3), Table (1).

Table (1): The physical properties and spectral data for compounds (1 &2)

Comp. No.	Colour	M.Wt.	M.P.°C	Yield %	R_f Benzen:MeOH	FT-IR (υcm^{-1})			
						NH_2	NH	CN	C=N
2	Orang	232	dec.> 360	90	0.543	—	3221	2219	1603
3	Deep green	364	265-267	98	0.430	3338	3132	—	1627

Synthesis of 4-((5-amino-3-((6-amino-3,5-dicyano-4-arylpyridin-2-yl) amino)-1H-pyrazol-4-yl) diazenyl)-N-(thiazol-2-yl) benzenesulfonamide (4-7)

Method A: Grinding technique (Mahmoud and El-Sewedy 2018)

A ceramic mortar, a mixture of compound (3) , malononitrile and substituted aldehyde in ratio (1:2:1) was acidified by freshly prepared lemon juice (1 ml)then grinded for (20 min.).The progress completion of the reaction were tracked using thin layer chromatography (TLC) in a solvent system (Benzene: MeOH / 8:2). The reaction mixture was then poured into a beaker (50 ml) containing ice water with stirring. The resulting precipitate was then filtered off and washed several times with cold water to remove the acid. The resulting precipitate was dried and recrystallized from water to give compounds (4-7), which showed the physical constants as shown in Table (2).

Method B: Reflux conditions (Mahmoud and El-Sewedy 2018)

Amixture of compound (3) , malononitrile and substituted aldehyde in ratio (1:2:1) was dissolved in diethyl sulfonate (DMSO) (10 ml) in acidic medium of freshly prepared lemon juice (1 ml). The reaction mixture then poured into round bottomed flask (25 ml) equipped with condenser, followed by reflux for (5 hours). Cooling and poured into beaker (50 ml) contained of ice- water. The mixture was stirred and the resulting precipitate was filtered off and washed several times with (30 ml) of cold water to remove the excess acid indicated by litmus paper. The precipitate is dried and recrystallized using ethyl alcohol to give compounds (4-7), which it possessed th same physical properties and spectral data that were prepared in method (A) but with low yield.

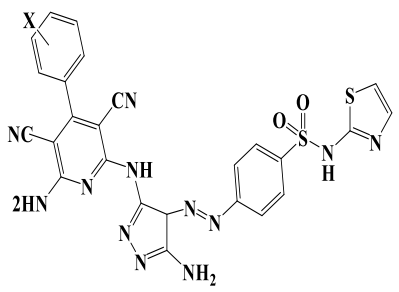


Table (2): Physical properties and spectral data for compounds (4-7)

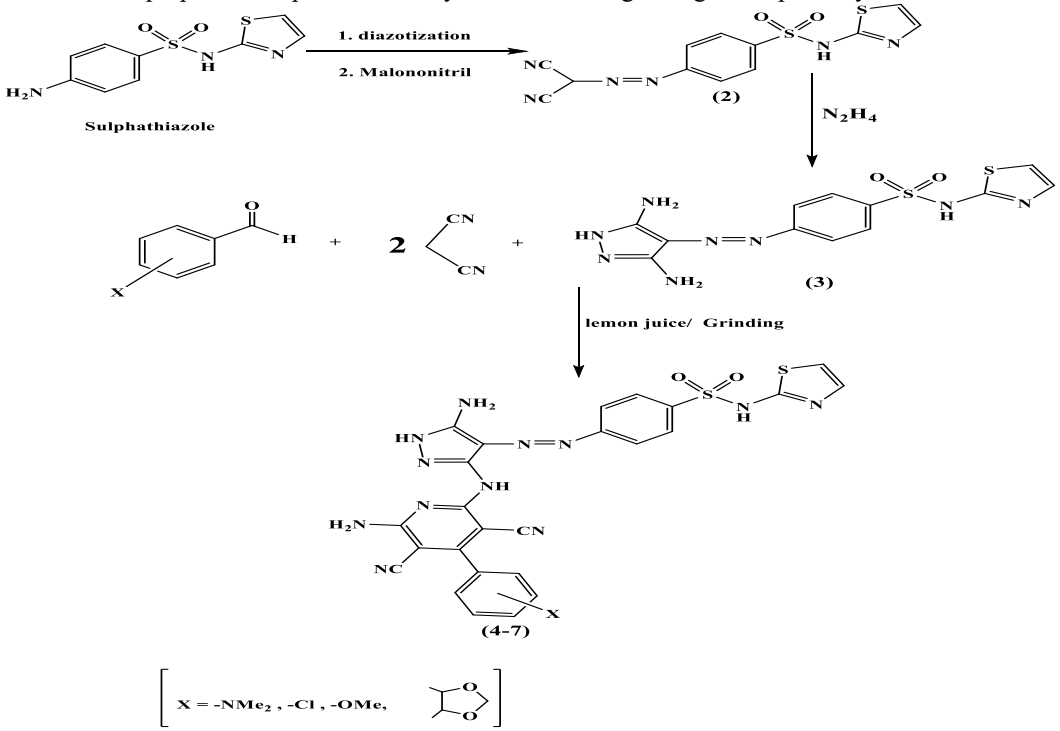
Comp. No.	X	M.P.°C	Yield %	R_f Benzen:MeOH	FT-IR (υcm^{-1})				
					NH_2	NH	CN	C=N	C=C aromatic
4		235-237	81	0.51	3320	3222	2219	1620	1600
5	p-NMe_2	238-239	80	0.57	3443	3301	2213	1599	1586
6	m-OMe	225-227	78	0.56	3327	3200	2220	1615	1589
7	p-CH_3	227-229	85	0.59	3445	3331	2212	1608	1608

Table (3): ^{1}H-NMR spectroscopy for compounds (4-7)

Comp. No.	^{1}H-NMR(δppm)
4	O-CH_2-O (s, 6.15-6.25, 2H); Ar-H & NH2 (m, 7.22-7.24, 3H); Ar-H & Thiazole (m, 7.62-7.66, 4H); Ar-H (d, 8.32, 2H); NH-bridge (s, 8.60-8.61, 1 H); SO_2-NH (s, 11.90, 1H).
5	$N(CH_3)_2$ (s, 2.97-3.02, 6H); Ar-H & NH2 (m, 7.15-7.18, 4H); Ar-H & Thiazole (m, 7.35-7.37, 4H); Ar-H (d, 8.22, 2H); NH-bridge (s, 8.75-8.76, 1H); SO_2-NH (s, 12.73, 1H).
6	OCH_3 (s,3.75-3.81,3H); Ar-H & NH2 (m, 7.27-7.28, 4H); Ar-H & Thiazole (m, 7.51-7.54, 4H); Ar-H (d, 7.90, 2H); NH-bridge (s, 8.49-8.50, 1H); SO_2-NH (s, 12.80, 1H).
7	CH3(s,2.32,3H); Ar-H (m,7.15-7.32,4H); Ar-H & Thiazole & NH2 (m, 7.30, 8H); Ar-H (d, 7.91-7.92, 2H); NH-bridge & NH-pyrazol (s, 8.24-8.26, 2H); SO_2-NH (s, 12.63, 1H).

Results And Discussion

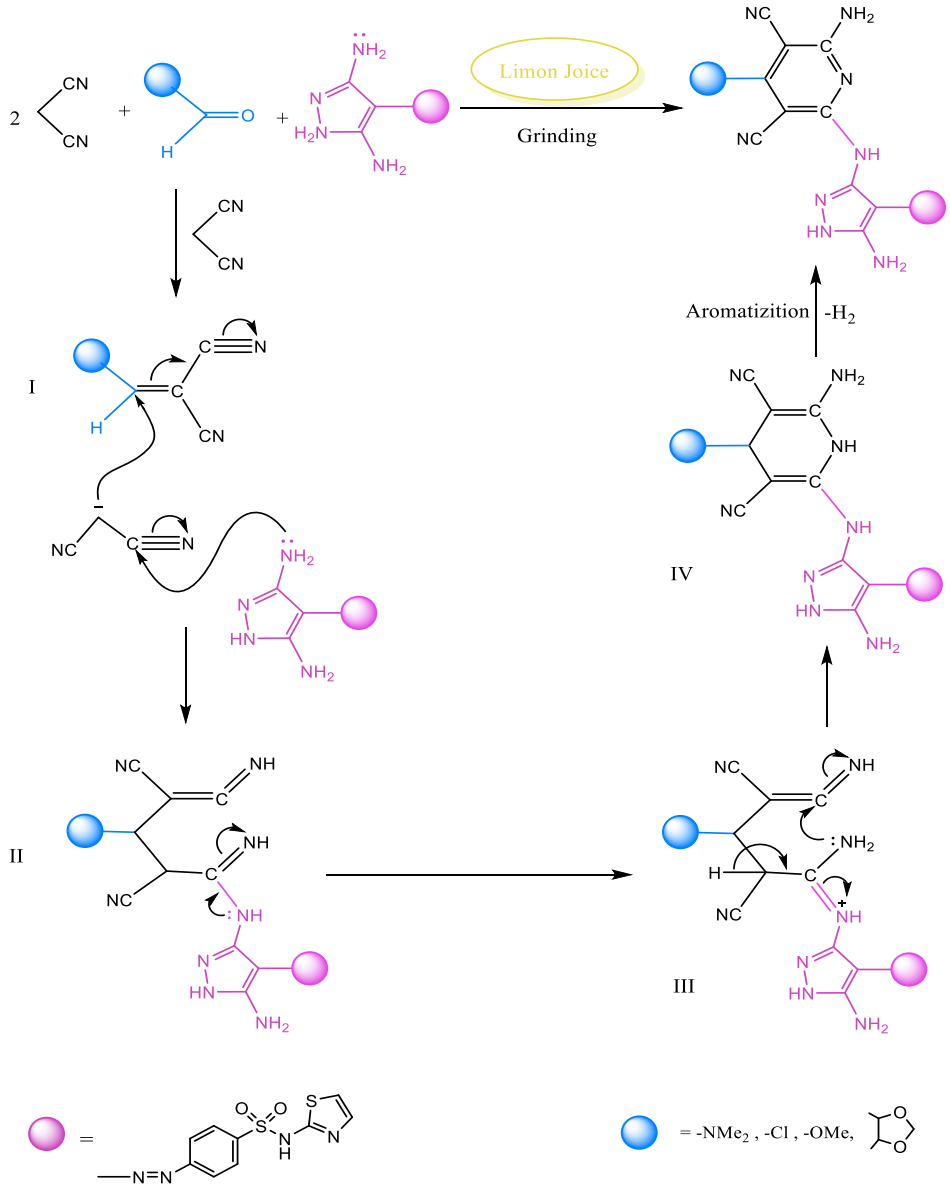
All prepared compounds were synthesized through the general pathway bellow:



Scheme (1): The synthetic pathway for compounds (4-7)

These compounds were prepared via a ternary reaction among compound (3), malononitrile, and substituted aldehyde in ratio (1:2:1) in an acidic medium (lemon juice) via grinding technique for (20 minutes) to give 2-amino pyridine dicarbonitrile derivatives (4-7).Given that the preparation reaction relied on the grinding method, it was necessary to compare the reaction with the well-known traditional preparation methods (reflux conditions) while tracking the completion of the reaction using thin-layer chromatography (TLC). The reaction was observed to be complete after (5) hours, a long time compared to the (20) minutes via grinding method. Furthermore, the percentage of products formed was lower, and their purity was lower. Therefore, the grinding method was adopted because it yields the same

products in the solid phase with high efficiency and purity. It is believed that the reaction mechanism proceeds via a Knoevenagel reaction first between benzaldehyde and one molecule of malononitrile to give the alkene (I), which undergoes successive nucleophilic attack by two malononitrile molecules and amine (3) to give the intermediate compounds (II), (III), and (IV) sequent, culminating in a five-substituted pyridine ring, Scheme (2).



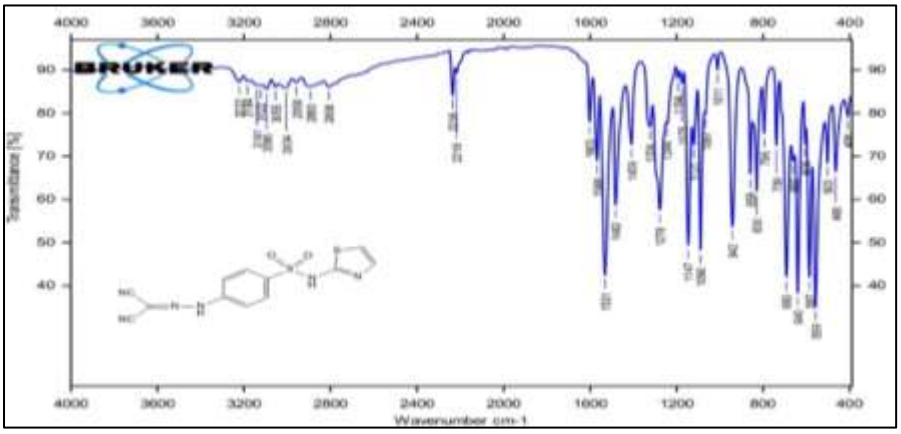
Scheme (2): The mechanism of synthetic compounds (4-7)

These compounds were characterized using (FT-IR) spectroscopy. The positions (3320-3445), (3200-3331), and (2212-2220) showed elastic absorption bands at the sites describing the functional groups: primary amine (NH_2), secondary amine (NH), and cyanide group, respectively. Other elastic absorption bands, listed in Table (2), provide preliminary evidence for the prepared structures.

Whereas, in (^{1}H-NMR) spectroscopy, compounds (4-7) shown chemical shifts towards high blocking, describing the absorption of the NH_2 at (7.15-7.30 ppm), while giving a clear shift of NH-bridge the at the ppm shift of (8.24-8.76) and a characteristic shift of SO_2-NH at the (11.90-12.80) position, as well as the other shifts listed in Table (3) that confirm the correctness of the structural composition of the prepared and selected compounds.

Conclusion

- The grinding technique has been proven its effectiveness in improving the reaction specification (reducing the reaction time, yield enhancement and pure products).
- The using water as recrystallizing solvent was an excellent choice to give pure product as economic and eco-friendly solvent.
- The lemon juice shown higher reactivity as acid catalyst than the mineral acids.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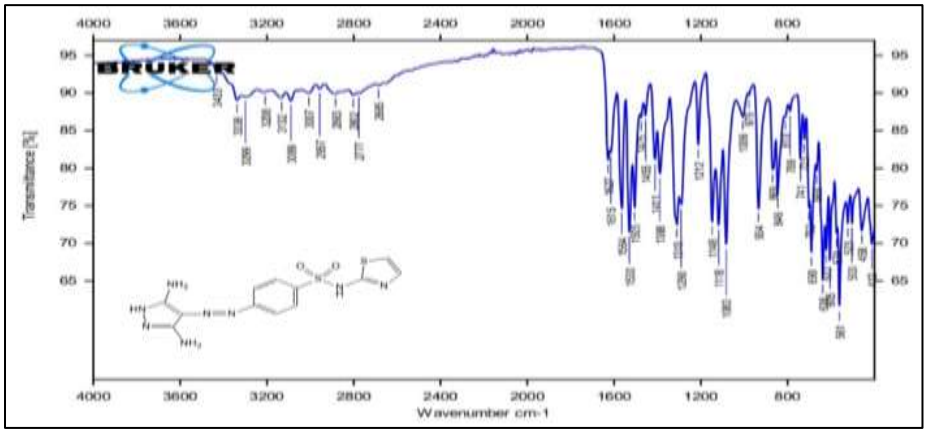
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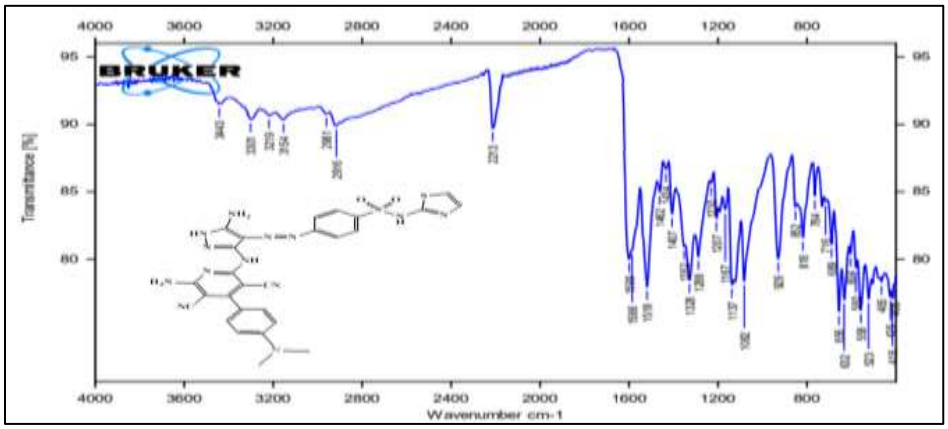
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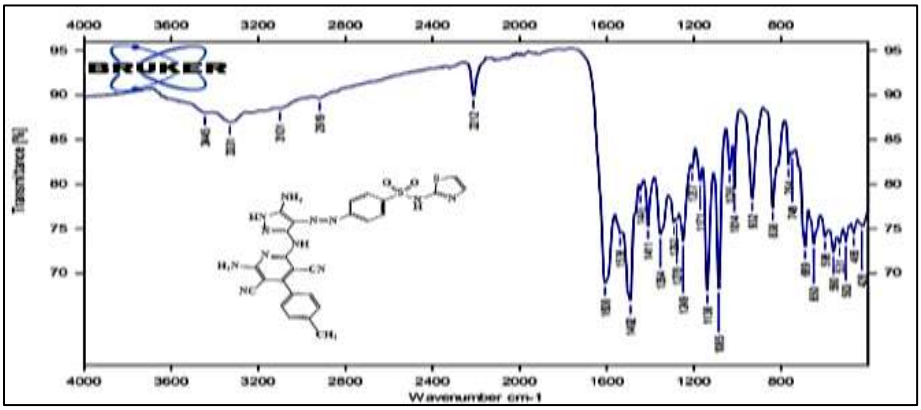
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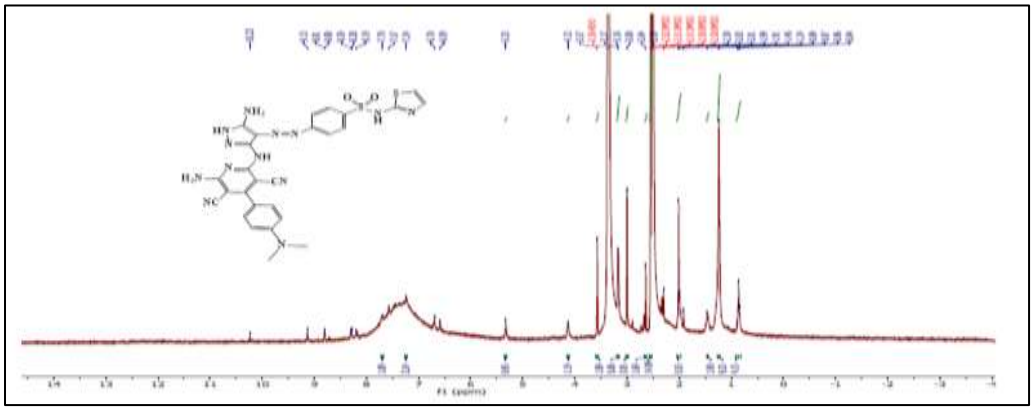

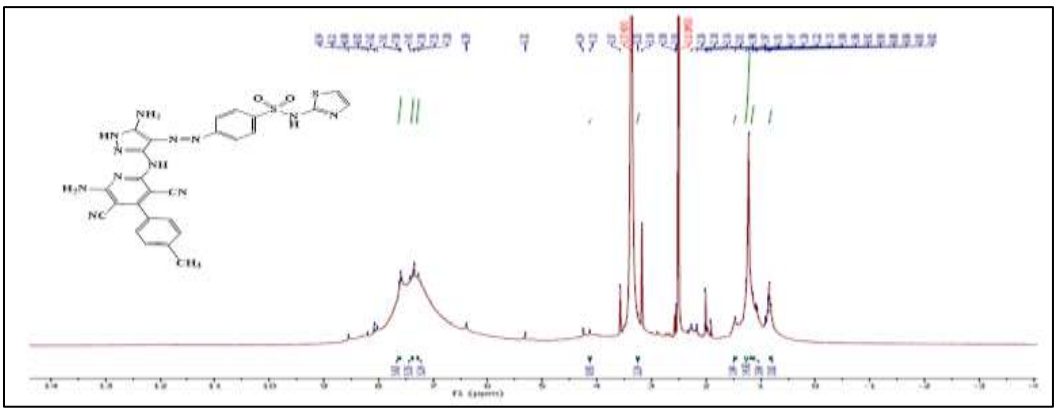

Reference

1. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*. Oxford University Press, 1998.
2. Anastas, P., & Eghbali, N. (2010). Green chemistry: principles and practice. *Chemical Society Reviews*, *39*(1), 301-312.
3. Ardila-Fierro, K. J., & Hernández, J. G. (2021). Sustainability assessment of mechanochemistry: challenges and opportunities for green chemical synthesis. *Chemical Science*, *12*(43), 14324-14336.
4. Ardila-Fierro, K. J., & Hernández, J. G. (2021). Sustainability assessment of mechanochemistry: challenges and opportunities for green chemical synthesis. *Chemical Science*, *12*(43), 14324-14336.
5. Azli, N. A. M., Ghani, F. S. A., Hassan, N. P., & Abdullah, N. (2025). Recent Review of One-Pot Synthesis of Heterocyclic Compounds Utilizing Green Catalysts. *Malaysian Journal of Chemistry*, *27*(1), 283–295.
6. Bala, M., Sharma, V., & Pratap, R. (2022). Water: The most clean and sustainable solvent for organic transformations and purification processes. *Journal of Molecular Liquids*, *360*, 119431.
7. Boldyreva, E. V. (2013). Mechanochemistry of organic solids: past, present and future. *Chemical Society Reviews*, *42*(18), 7719-7738.
8. Capello, C., Fischer, U., & Hungerbühler, K. (2007). What is a green solvent? A comprehensive framework for the environmental assessment of solvents. Green Chemistry, 9(6), 527-534.
9. Clark, J. H.; Macquarrie, D. J. *Handbook of Green Chemistry and Technology*. Blackwell Science Ltd., 2002.
10. Clarke, C. J., Tu, W. C., Levers, O., Bröhl, A., & Hallett, J. P. (2018). Green and sustainable solvents in chemical processes. *Chemical Reviews*, *118*(2), 747-800.
11. Colacino, E., & Štrukil, V. (Eds.). (2020). *Mechanochemistry and Emerging Technologies for Sustainable Chemical Manufacturing*. Royal Society of Chemistry.
12. Dicks, A. P., & Batey, R. A. (2016). *Green Organic Chemistry in Lecture and Laboratory*. CRC Press.
13. Dicks, A. P., & Batey, R. A. (2019). *Green Organic Chemistry in Lecture and Laboratory* (2nd ed.). CRC Press.
14. Eckert, H. (2012). Diversity Oriented Syntheses of Conventional Heterocycles by Smart Multi Component Reactions (MCRs) of the Last Decade. *Molecules*, *17*(1), 1074-1102.
15. Elgemeie H. G., El-Fahham H. A., Mekheimer R. Novel synthesis of condensed pyridin-2(1H)-thione derivatives from arylidenecyanothioacetamides and cycloalkanones. Sulfur Lett. 1988; 8:187–198.
16. Friščić, T., Mottillo, C., & Politakos, N. (2020). Mechanochemistry for sustainable organic synthesis and pharmaceutical manufacturing. *Green Chemistry*, *22*(3), 560-575.
17. Gomollón-Bel, F. (2019). Ten Chemical Innovations That Will Change Our World: IUPAC 2019. *Chemistry International*, *41*(2), 12-17.
18. Graziano, G., Stefanachi, A., Contino, M., Prieto-Díaz, R., Ligresti, A., Kumar, P., Scilimati, A., Sotelo, E., & Leonetti, F. (2023). Multicomponent Reaction-Assisted Drug Discovery: A Time- and Cost-Effective Green Approach

Speeding Up Identification and Optimization of Anticancer Drugs. *International Journal of Molecular Sciences*, *24*(7), 6581.

19. Gulati, S., John, S. E., & Shankaraiah, N. (2021). Microwave-assisted multicomponent reactions in heterocyclic chemistry and mechanistic aspects. *Beilstein Journal of Organic Chemistry*, *17*, 819-865.
20. Hernández, J. G., & Juaristi, E. (2012). Green synthesis of bioactive heterocycles and their precursors under solvent-free conditions or in sustainable media via mechanochemistry. *Chemical Communications*, *48*(89), 10933-10942.
21. Howard, J., Cao, Q., & Browne, D. L. (2018). Mechanochemistry as an emerging tool for molecular synthesis: a user's guide. *Chemical Science*, *9*(12), 3080-3094.
22. James, S. L., Adams, C. J., Bolm, C., Braga, D., Collier, P., Friščić, T., Grepioni, F., Harris, K. D. M., Hywel, G., Jones, W., Krebs, A., Mack, J., Maini, L., Orpen, A. G., Parkin, I. P., Shearouse, W. C., Steed, J. W., & Waddell, D. C. (2012). Mechanochemistry: opportunities for new and cleaner synthesis. *Chemical Society Reviews*, *41*(1), 413-447.
23. Jones, A. G. (2014). *Crystallization Process Systems*. Butterworth-Heinemann.
24. Jissel Cabrera-Franco; Hayley Rivas; Raymond Cruz; Zhicheng Jin;Jianmei Cui. (2026).
25. Small Changes, Big Impact: Integrating Green Chemistry into the Organic Chemistry Laboratory through Optimized Experimental Methods. *Journal of Chemical Education (ACS)*, *103*(5), 1410-1418.
26. Lancaster, M. Green Chemistry: An Introductory Text Royal Society of Chemistry, 2010.Mahmoud, Naglaa F. H., and Ahmed El-Sewedy. (2018). 'Multicomponent Reactions, Solvent-Free Synthesis of 2-Amino-4-aryl-6-substituted Pyridine-3,5-dicarbonitrile Derivatives, and Corrosion Inhibitors Evaluation', Journal of Chemistry, 2018: 7958739.
27. Neto, B. A. D., Rocha, R. O., & Rodrigues, M. O. (2021). Catalytic Approaches to Multicomponent Reactions: A Critical Review and Perspectives on the Roles of Catalysis. *Molecules*, *27*(1), 132.
28. Pal, R., & Dey, T. (2016). Lemon juice as a natural catalyst: A green protocol for the synthesis of bioactive heterocycles. *Green Chemistry Letters and Reviews*, *9*(4), 183-199.
29. Patil, S. S., Magar, D. D., & Patil, S. A. (2013). Lemon juice: An efficient natural catalyst for the synthesis of organic compounds under solvent-free conditions. *Chinese Chemical Letters*, *24*(3), 231-234.
30. Poliakoff, M.; Fitzpatrick, J. M.; Farren, T. R.; Anastas, P. T. “Green Chemistry: Science and Politics of Change.” *Science*, 2002, 297, 807–810.
31. Sangshetti, J. N., Kokare, N. D., & Shinde, D. B. (2019). Natural fruit juices as green and sustainable catalysts in organic synthesis: A review. *Journal of Chemical Sciences*, *131*(8), 73-95.
32. Siddiqui, I. R., Singh, P. K., & Rahaman, M. (2020). Bio-based catalysts in organic synthesis: A sustainable step towards green chemistry. *Journal of Cleaner Production*, *264*, 121544.
33. Simon, M.-O.; Li, C.-J. “Green Chemistry Oriented Organic Synthesis in Water.” *Chemical Society Reviews*, 2012, 41, 1415–1427. DOI: 10.1039/C1CS15222J.
34. Stolle, A. (2015). *Ball Milling in Organic Synthesis: A Green and Sustainable Approach*. Royal Society of Chemistry.
35. Suri, S., Chandra, S., & Rawat, D. S. (2021). Lemon juice (Citrus limon): An excellent organic catalyst for the synthesis of diverse organic scaffolds. *Synthetic Communications*, *51*(14), 2115-2140.
36. Tandi, M., Sharma, V., Gopal, B., & Sundriyal, S. (2025). Multicomponent reactions (MCRs) yielding medicinally relevant rings: a recent update and chemical space analysis of the scaffolds. *RSC Advances*, *15*, 1447-1489.
37. Zhu, J., Wang, Q., & Wang, M. X. (Eds.). (2015). *Multicomponent Reactions in Organic Synthesis*. John Wiley & Sons.