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One-Pot Multicomponent Synthesis Of Pyrazolo Pyrido Pyrimidine-Diones Empoyed By Agotf

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ABSTRACT:

In order to find high-efficiency and low-toxic antimicrobial drugs and a novel transition metal triflate as catalyst activity was utilized for the first time to acquire a synthesis of nine new 3-methyl-1,4,8,9-tetrahydro-5H-pyrazolo[4,3:5,6]pyrido[2,3-d]pyrimidine-5,7(6H)-diones derivatives via a one-pot five-component reaction of substituted aromatic and hetero aromatic aldehydes, barbituric acid, ethyl acetoacetate, hydrazine hydrate and ammonium acetate in aqueous alcoholic medium under catalytic condition . The obtained derivatives were confirmed by measure of advanced spectroscopic data viz; ^{1}HNMR, ^{13}CNMR and LCMS. The derivatives were also studied by antimicrobial activity against bacterial as well as fungal strains and also estimated the measure inhibition zone. The methodology is expeditious and furnishes varied advantages like shorter reaction time, energy efficiency, eco-sustainability and work under mild condition

KEYWORDS:

Aromatic aldehydes, barbituric acid, ethyl acetoacetate, hydrazine hydrate and ammonium acetate AgOTf, pyrazolo-pyrido-pyrimidine-diones, antimicrobial activity

1. INTRODUCTION:

In modern organic synthesis, the multicomponent reactions (MCRs) are an effective and environmentally friendly procedure for providing a vast range of molecular systems in a single one-pot operation. As a result, an interesting in telescopic reactions has recently progressed. The single one-pot telescoped reaction was involved a sequential chemical reagent addition, avoiding multiple-step transformations in absence of without any workup, minimizing several purification stages , solvent switching having a maximum atom economy, being quick and easy to operate, saving energy, time, and being environmentally friendly. Multicomponent reactions (MCRs) [1–3] significant role play an essential in modern organic and applied chemistry, where in, the desired molecules are prepared from three or more different substrates through reactions in well-known approaches [4].Drug companies may take advantage of multicomponent reactions (MCRs). These reactions can be utilized to synthesize highly functionalized, biologically relevant natural and active molecules, including polycyclic structures.

They deliver considerable advantages over linear-stepwise syntheses and reduction in waste production [4, 5]. With the aim to avoid the formation of toxic materials and byproducts arising from chemical processes, chemists need to cultivate environmentally-friendly strategies [6]. Nowadays, ultrasound has emerged as a dynamic tool in the synthesis of novel heterocycles owing to distinctive and advantageous features such as greater selectivity, low energy utilization, excellent acoustic cavitation, better consumption of raw materials, high yields of products and reduced reaction durations [7]. The method is safe, efficient and involves the use of green solvents such as water and/or EtOH. Hence, ultrasonication has emerged as an innocuous, green technique in organic synthesis and has been proved beyond doubt to be an advanced technique over conventional methods [8].

Despite excessive progress in the telescopic reactions for the synthesis of pyrimidines and fused pyrimidine derivatives and the different limitation are existed. The most of the literature methods are involved harsh reaction conditions, prolong reaction times, and various purification steps, which restrict their practical utility. Besides, it must perform a comprehensive comparison description, the better yield of product, less reaction time, suitable solvent medium, more selectivity, and highest environmental stability. Overcoming these constraints might result in a more efficient, scalable, and environmentally sustainable synthesis of heterocycles.

Among fused N-heteroaromatic substances, those containing pyrazole [1,5-a]pyridine and pyrido [1,2-b] indazole ring systems are medicinally important owing to the three-component coupling of one-pot condensation [1-3], biological activities of pyrazole derivatives [4,5], PI3Kδ Inhibitors [6], antimicrobial activities [7,8], Antioxidant [9], anti-tumor activity [10], PI3K/mTOR Dual Inhibitors [11], EGFR-TK inhibitors [12,13], anticancer [14,15], inflammatory and analgesic 16], antihistaminic (H1)[17], anticonvulsant and antidepressant [18], antifungal [18], antifungal activity[19], diuretic activity[20], antiviral and cytotoxic agents[21]

Recently, several catalytic processes have been developed for the synthesis of pyrimidines and their derivatives by using solid polymer catalysts like Amberlyst-15 [22], PEG-OSO3H [23], Pyrazolyl-pyrimidine porous-organic-polymer [24], Researchers have also used various hazardous metal catalysts like manganese [26], and iron [27] prepare pyrimidine derivatives .

In summary, we have improved a simple but an efficient procedure for the preparation of 3-methyl-1,4,8,9-tetrahydro-5H pyrazolo [4,3:5,6] pyrido[2,3-d] pyrimidine-5,7(6H)-dione and from easily prepared tetrahydropyrido-pyrimidine-2,4-diones by oxidative aromatization using AgOTf as the oxidant as shown in scheme-1 .

2.1. EXPERIMENTAL SECTION:

All the chemical, synthetic grade reagents and solvent were procured from Sigma Aldrich chemicals. The melting points of all synthesized compounds were determined in open capillary tube and are uncorrected. The ^{1}HNMR and ^{13}CNMR spectra ($CDCl_3$) were measured on Brucker (400MHz) spectrometer using TMS as internal and also chemical shift expressed in δ ppm. The molecular weight of the synthesized analogous was estimated by LCMS spectrometer. The purity of all obtained derivatives was identified by thin layer chromatography and iodine was used as visualizing agent.

2.2. GENERAL PROCEDURE FOR THE PREPARATION OF COMPOUNDS (6a–6i):

In a 25 mL conical flask, a mixture of aldehyde (1 mol), hydrazine hydrate (1 mol), ethyl acetoacetate (1 mol), barbituric acid (1 mol), ammonium acetate (1.2mol) and ethanol and water (5 mL) were taken in 50mL of RBF. The enhancement activity substances such as silver triflates (0.5 mol) added in above the reaction.

After completion of the reaction was recognized by thin layer chromatography (eluent:4:6::EtOAc: n-hexane), the prepared reaction was quenched into crushed ice; the formed precipitate was filtered, repeatedly washed with water (3 × 25 mL) and left in the oven at 75°C for 30 min. EtOH was then added to dissolve the solid and the solution was dried over anhydrous Na_2SO_4; the solvent was removed by suction and the impure product thus obtained was further purified by recrystallization using EtOH to get the desired products(6a–6i) at 84–92%yield.

2.2.1.4-(4-Hydroxy-3-methoxyphenyl)-3-methyl-1,4,8,9-tetrahydro-5Hpyrazolo[4′,3′5,6] pyrido [2,3-d] pyrimidine-5,7 (6H)-dione (6a)

Yield: 91%; Pale yellow solid; M.P.:264-2660C : 1H NMR(400 MHz,CDCl3)*δ*ppm: 1.772 (3H,s, CH3), 3.760 (3H, s, OCH3), 3.885 (1H, s, NH), 4.557 (1H, s, CH), 6.850 (1H, d, J = 7.6 Hz, Ar-H), 6.858 (1H, d, J = 7.6 Hz, Ar-H), 7.270 (1H, s, Ar-H), 8.759 (1H, s, NH), 9.128 (1H, s, OH), 9.779 (1H, s, NH), 10.820 (1H, s, NH); 13C NMR (100 MHz, CDCl3) *δ*ppm : 10.86, 30.73, 105.17, 127.17, 128.85 , 130.84, 132.89, 133.28, 138.55, 143.53, 151.81, 160.59, 164.79. Molecular weight (m/z) : 341.75 [M]+.

2.2.2.4-(3,4-Dimethoxyphenyl)-3-methyl-1,4,8,9-tetrahydro-5Hpyrazolo[4,3:5,6]pyrido[2,3-d] pyrimidine-5,7(6H)-dione (6b)

Yield: 90%; Yellow solid; M.P.:254-256^{0}C : ^{1}H NMR(400 MHz,$CDCl_3$)*δ*ppm: 1.854 (3H,s, CH_3), 3.547 (1H, s, NH), 3.689 (3H, s, OCH_3), 3.753 (3H, s, OCH_3), 4.874 (1H, s, CH), 5.891 (1H, s, NH), 6.912 (1H, d, J = 8.0 Hz, Ar-H), 7.214 (1H, s, Ar-H), 7.454 (1H, d, J = 5.8 Hz, Ar-H), 8.584 (1H, s, NH), 11.230 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*ppm: 11.56, 32.78, 54.85, 56.89, 105.87, 110.46 , 114.88, 120.07, 122.66, 128.54, 134.56, 141.78, 146.72, 150.51, 158.89, 162.38. Molecular weight (m/z): 355.17 [M]+.

2.2.3.4-(3,4,5-trimethoxyphenyl)-3-Methyl-1,4,8,9-tetrahydro-5HPyrazolo[4,3:5,6]pyrido [2,3-d] pyrimidine-5,7(6H)-dione (6c)

Yield: 92%; yellow solid; M.P.:258-260^{0}C:^{1}HNMR(400MHz,$CDCl_3$)*δ*ppm : 1.654 (3H,s,CH_3), 3.582 (6H,s, $(OCH_3)_2$), 3.768 (3H, s, OCH_3), 4.814 (1H, s, CH), 6.117 (1H, s, NH), 7.318 (d, J= 8.0Hz, 2H, Ar-H), 8.452 (1H, s, NH), 8.844 (1H, s, NH), 10.957 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*ppm :11.47, 32.48 , 53.82 , 54.86, 103.96, 111.85, 114.50 , 118.87, 122.36, 128.04, 137.46, 140.58, 144.12, 152.81, 157.59, 162.80. Molecular weight (m/z): 385.21 [M]+.

2.2.4.4-(4-Fluorophenyl)-3-methyl-1,4,8,9-tetrahydro-5Hpyrazolo[4,3:5,6]pyrido[2,3-d] pyrimidine-5,7(6H)-dione (6d)

Yield:85%;Paleyellowsolid;M.P:245-2470C:1HNMR(400MHz,CDCl3)*δ*ppm: 1.951(3H,s,CH3), 4.507 (1H,s,CH), 6.221(1H, s, NH), 6.885 (2H, d, J = 8.0 Hz, Ar-H), 7.518 (2H, d, J = 9.4 Hz, Ar-H), 8.884 (1H, s, NH), 9.523 (1H, s, NH), 10.818 (1H, s, NH); 13C NMR (100 MHz, CDCl3) *δ*ppm : 10.77, 31.53, 105.07, 128.54, 128.93, 129.44, 138.05, 152.12, 158.77, 160.07, 161.83, 163.21, 164.71, 166.25. TO Molecular weight (m/z) :314.45 [M+2].

2.2.5.4-(4-Chlorophenyl)-3-methyl-1,4,8,9-tetrahydro-5Hpyrazolo[4,3:5,6]pyrido[2,3-d] pyrimidine-5,7(6H)-dione (6e)

Yield: 85%; Pale yellow solid ; M.P.:241-243^{0}C : ^{1}H NMR(400 MHz,$CDCl_3$)*δ*ppm :1.657 (3H,s, CH_3), 3.771 (1H, s, NH), 4.917 (1H, s, CH) , 6.914 (2H, d, J = 7.6 Hz, 2H, Ar-H), 7.110 (2H, d, J = 4.2 Hz, Ar-H), 7.784 (1H, s, NH), 8.801 (1H, s, NH), 9.874 (1H, s , NH) ; ^{13}C NMR (100 MHz, $CDCl_3$) *δ*ppm : 10.85, 30.53, 124.85 , 128.24 , 128.78, 130.08, 132.76, 134.83, 148.23, 158.88, 160.01. Molecular weight (m/z) : 329.32 [M]+.

2.2.6.4-(2,4-Dichlorophenyl)-3-methyl-1,4,8,9-tetrahydro-5Hpyrazolo[4,3:5,6]pyrido[2,3-d] pyrimidine-5,7 (6H)-dione (6f):

Yield: 86%; Pale yellow solid; M.P - 274-276^{0}C : ^{1}H NMR(400 MHz,$CDCl_3$)δppm: 2.107 (3H,s, CH_3), 3.841 (1H, s, NH), 4.892 (1H, s, CH), 7.129 (1H, d, J = 8.2 Hz, Ar-H), 7.231 (1H, d, J = 8.8 Hz, Ar-H), 7.448 (1H, s, Ar-H), 9.147 (1H, s, NH), 10.047 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δppm : 10.76, 31.52, 103.76, 120.77, 125.77, 128.81, 129.44, 130.19, 132.68, 138.85, 144.73, 153.81, 159.29, 164.79. Molecular weight (m/z) : 363.65 [M]+.

2.2.7.4-(4-Bromophenyl)-3-methyl-1,4,8,9-tetrahydro-5H pyrazolo[4,3:5,6] pyrido[2,3-d] pyrimidine-5,7(6H)-dione (6g)

Yield: 88%; Pale red solid ; M.P .: 268-270^{0}C : ^{1}H NMR(400 MHz,$CDCl_3$) δppm : 2.041 (3H,s, CH_3), 4.775 (1H, s, CH), 6.730 (1H, s, NH), 6.945 (2H, d, J = 10.4Hz, Ar-H), 7.338 (2H, d, J = 8.8 Hz, Ar-H), 8.773 (1H, s, NH), 10.015 (1H, s, NH), 11.236 (1H, s, NH). 13C NMR (100 MHz, CDCl3) δppm: 11.07, 30.25, 103.55, 128.44, 128.81, 129.07, 137.66, 153.02, 157.01, 159.14, 161.08, 163.20, 165.70, 168.25. Molecular weight (m/z) : 374.08 [M+2]

2.2.8. 4-(4-Nitrophenyl)-3-methyl-1,4,8,9-tetrahydro-5H-pyrazolo[4,3:5,6]pyrido[2,3-d]

Pyrimidine-5,7(6H)-dione (6h)

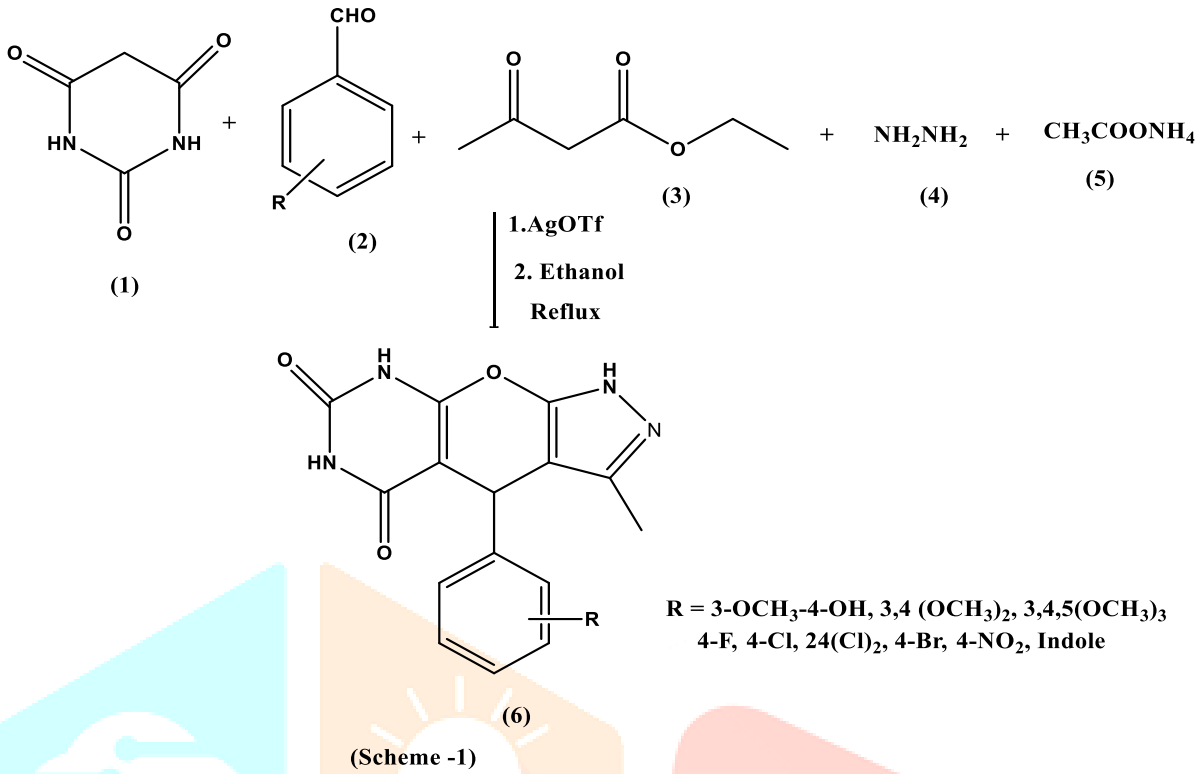
Yield: 87%; yellow solid; M.P.:250-251^{0}C : ^{1}H NMR(400 MHz,$CDCl_3$)δppm : 2.147 (3H,s, CH_3), 3.33 (1H, s, NH), 5.00 (1H, s, CH), 6.37 (2H, d, J = 8 Hz, Ar-H), 7.38 (2H, d, J = 8.4 Hz, Ar-H), 8.73 (1H, s, NH), 10.15 (1H, s, NH), 11.36 (1H, s, NH); 13C NMR (100 MHz, CDCl3) δppm: 11.87, 29.55, 126.52, 128.76, 129.51, 130.76, 132.88, 134.43, 149.70, 159.80, 159.77. Molecular weight (m/z): 340.58 [M]+.

2.2.9. 4-(1H-Indol-2-yl)-3-methyl-1,4,8,9-tetrahydro-5H-pyrazolo [4,3:5,6] pyrido [2,3-d]

Pyrimidine-5,7(6H)-dione (6i)

Yield:90%; Pale yellow solid; M.P.:281-2830C : 1H NMR(400 MHz,CDCl3) δppm : 2.012 (3H,s, CH3) , 3.532 (1H, s, NH), 4.912 (1H, s, CH), 7.045 – 7.241 (2H, m, Ar-H), 7.412 (1H, t, J = 8.0 Hz, Ar-H), 7.713 (1H, t, J = 5.8 Hz, Ar-H), 8. 113 (1H, t, J = 5.2 Hz, Ar-H), 8.714 (1H, s, NH), 9.814 (1H, s, NH), 10.765 (1H, s, NH), 11.471 (1H, s, NH) ; 13C NMR (100 MHz, CDCl3) δppm : 10.95, 31.84 , 52.08 , 55.17, 102.96, 112.07, 113.54 , 120.57 , 122.02, 129.07, 135.82, 142.17, 146.07, 153.33, 158.78, 162.07 : Molecular weight (m/z) : 334.21 [M]+.

3. RESULTS AND DISCUSSION:



(Scheme -1)

4.1. CHEMISTRY:

In this investigation, the most commonly utilized synthetic protocol to prepare the approach of the desired derivatives is given in the "**scheme-1"**. The starting materials one-pot five-component reaction of substituted aromatic and hetero aromatic aldehydes, barbituric acid, ethyl acetoacetate, NH_2NH_2 and CH_3COONH_4 in water under catalytic condition were treated in explored by silver in ethanol as solvent at reflux scaffold titled derivatives such as Pyrazolo pyrido pyrimidine-diones, the reaction condition was controlled and start the reaction by Lew's acid catalyst as "AgOTf "at reflux. The scope and advantages of this catalyst, the accelerated rate of reaction, an excellent scaffold the by this catalyst, very low reaction time and the scope this catalyst commercially available, easy work up and also nontoxic nature.

During this reaction, an optimization of the different catalysts, temperature, solvent as well as loaded catalyst was applied and the result exhibited and given below. There is different transition metal triflate and non-transition metal triflate was applied during this reaction at constant temperature. The entry "4" gave 92%. The entry "1", "2" and entry "3" are most effective catalyst but effect of product very moderate, such as 57%, 62% and 73% respectively. The entry " 4 " is powerful Lew's acid catalyst that is produced excellent yield is "92%".

Table –1: Comparison among the various catalyst synthesis of titled compound (6c):

Entry	Catalyst	Time (h)	Yield (%)
1	Al $(OTf)_3$	6	57
2	Cu $(OTf)_2$	6	62
3	Zn $(OTf)_2$	6	73
4	AgOTf	6	92

The amount of catalyst is very most significant role play during in this reaction; 1mmole amount of the catalyst was utilized in starting, acquired traces amount of product and gradually developing up to 3 mmol amount of the catalyst during the reaction. Hence, maximum amount yield obtained (92%). Further, amount of the catalyst increased up to entry "5" and get no improvement as shown Table-2.

Table-2: Optimization amount of the catalyst (AgOTf) for synthesis of derivatives (6c):

Entry	Catalyst (mol)	Time (h)	Yield (%)
1	0.5	6	traces
2	1.0	6	45
3	2.0	6	65
4	3.0	6	92
5	4.0	6	92

It noticed that following the above catalyst impact during the reaction method, we followed to the evaluated of solvent effects applying a several of solvents, including H_2O, CH_3CN, EtOH, MeOH, and MDC. Our observations are identified that the good reaction conditions are those if without the use of solvents and also the completion of the reaction as well as for the yield of the desired product compared than those obtained in any of the solvents investigated **(Table-3).**

Table-3: The effect of the solvent for synthesis of compound (6c):

Entry	Catalyst (mmol)	Time (h)	Yield (%)
1	H_2O	3	25
2	MeOH	3	48
3	EtOH+H_2O	3	92
4	DMF	3	58
5	MDC	3	66

3.2. BIOLOGICAL ACTIVITY:

The tested samples were evaluated for their ***invitro*** antibacterial and antifungal potent activities of the following micro broth dilution technique. The ***invitro*** antibacterial potent activity was examined against gram (+Ve) bacterial strains such as B. subtilis and S.aureus and gram (-Ve) bacterial strains such as against E.coli and P.aeruginosa. The ***invitro*** antifungal activity was evaluated against the fungal strains such as A.Niger and C.albicans. The standard drugs were referred for this study were "**Ciprofloxacin and Ketonozole**" for antibacterial as well as antifungal screening. Mueller Hinton Broth was used as a nutrient medium for bacteria and Sabouraud dextrose Broth for fungal growth. Inoculums size for test strain was adjusted to 108 CFU/mL by comparing the turbidity. The results were recorded in the form of primary and secondary evaluation. The stock solution (2000 µg/mL) of the compounds under investigation and standard drugs was prepared by successive two fold dilution and these descriptions are evidenced by **table-4.**

Table-4: Antimicrobial activity screening activity synthesized scaffold:

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S. aureus	E. coli	S. typhi	B.substills	A. niger	C. albicans
6a	12	15	14	12	10	11
6b	16	17	17	15	12	11
6c	20	19	18	19	14	14
6d	17	17	15	12	12	13
6e	23	23	24	24	18	18
6f	22	23	23	24	19	19
6g	10	11	12	08	08	08
Ciprofloxacin	27	27	25	25	NA	NA
Ketonozole	NA	NA	NA	NA	22	22
DMSO	---	----	---	---	---	---

We observed that the ***invitro*** anti-bacterial activity of desired compound (6a-6i), mostly electron withdrawing group of compound viz; 6a and 6f showed low active potent while electron donating group of compounds " 6b, 6c, 6f " were showed moderate active potent. The compound "6e and 6f" were showed excellent active potent due to halogen group present in the compound. We also observed the Antifungal Activity of compound (6a-6g) were showed different activity compound "6c" showed good activity and rate of the compound showed low to moderate activity.

4. CONCLUSIONS

In this study, we developed a novel ultrasound-assisted, catalyst-free one-pot five-component synthesis of fourteen new pyrazolo-pyrido-pyrimidine-diones in water as a medium. The significant description of this strategy highlights green solvent usage, readily available starting materials, energy efficiency, absence of catalyst, simple product isolation, avoiding column purification steps, cost-effective, absence of hazardous organic solvents, good to excellent yields, versatility, promoting good reaction rate, minimization of waste and easy to handle. Moreover, the protocol represents a better and more innovative green methodology towards the synthesis of the target compounds. This research effectively employed a telescopic reaction methodology under mild, room-temperature conditions to synthesize pyrimidine and fused pyrimidine derivatives. The streamlined, efficient methodology obviated the necessity of vigorous reaction conditions..

5. AKOWNLDEMENT:

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6. REFERENCES:

1. Bose DS,Fatima L,Mereyala HB. "Green chemistry approaches to the synthesis of 5-Alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones by a three-component coupling of one-pot condensation reaction: comparison of ethanol, water, and solvent-free conditions". J Org Chem. 2003;68(2):587–590. doi:10.1021/jo0205199

2. TabassumS, Govindaraju S, Pasha MA. "Sonochemistry– an innovative opportunity towards a one-pot three-component synthesis of novel pyridyl piperazine derivatives catalyzed by meglumine in water" New J Chem. 2017;41(9):3515–3523. doi:10.1039/C6NJ03919G.

3. Saied Abdullah El-Assiery, Galal Hosni Sayed, Ahmed Fouda," Synthesis of some new annulated pyrazolo-pyrido (or pyrano)pyrimidine, pyrazolo pyridine and pyran pyrazole derivatives", Acta Pharm. 54 (2004) 143–150

4.Muhammad Faisal, Aamer Saeed, Sarwat Hussain, Parsa Dar & Fayaz Ali Larik ." Recent developments in synthetic chemistry and biological activities of pyrazole derivatives", Journal of Chemical Sciences, Volume 131, article number 70, (2019),

5.Tansu Sezer Kaya, Kadir Turhan," The synthesis of biologically active pyrazolo[3,4-b]pyridine and pyrido[2,3-d]pyrimidine derivatives", Bull. Chem. Soc. Ethiop. 2025, 39(6), 1201-1212 DOI: https://dx.doi.org/10.4314/bcse.v39i6.14

6.Mariola Stypik 1,2,et al ," Design, Synthesis, and Development of Pyrazolo[1,5-a]pyrimidine Derivatives as a Novel Series of Selective PI3Kδ Inhibitors: Part II—Benzimidazole Derivatives",Pharmaceuticals (Basel)". 2022 Jul 27;15(8):927. doi: 10.3390/ph15080927

7.Anhar Abdel-Aziem, Marwa Sayed El-Gendy, Abdou Osman Abdelhamid," Synthesis and antimicrobial activities of pyrido[2,3-d]pyrimidine, pyridotriazolopyrimidine, triazolopyrimidine, and pyrido[2,3-d:6,5d']dipyrimidine derivatives", European Journal of Chemistry, Vol. 3 No. 4 (2012): December 2012, https://doi.org/10.5155/eurjchem.3.4.455-460.683

8. Farag A El-Essawy 1,✉, Mohammad Ahmad Odah," Design and Synthesis of Polyheterocyclic Compounds Containing Pyrazolo pyridopyrimidine Nucleus with Antimicrobial Activities," Chemistry Open. 2024 Apr 29;13(6):e202400070. doi: 10.1002/open.202400070

9.Ahmed Ali Fadda et al ,"Synthesis and Antioxidant of Some New Pyrazolo[1,5-a]pyrimidine, Pyrazolo[5,1-b]quinazoline and Imidazo[1,2-b]pyrazole Derivatives Incorporating PhenylsulfonylMoiety", Letters in Applied NanoBioScience,Volume 10, Issue 3, 2021, 2414 – 2428, https://doi.org/10.33263/LIANBS103.24142428

10. Wen-Ge Guo et al , " Design, synthesis and anti-tumor activity studies of novel pyrido[3, 4-d]pyrimidine derivatives", Bioorganic & Medicinal Chemistry Letters,Volume 76, 15 November 2022, 129020, https://doi.org/10.1016/j.bmcl.2022.129020.

11. ‡Sylvain Routier* et al ," Design, Synthesis, and Biological Activity of Pyridopyrimidine Scaffolds as Novel PI_3K/mTOR Dual Inhibitors", Journal of Medicinal Chemistry , Vol 57/Issue 3

12. Aya I. Hassaballah et al ," New pyrazolo[3,4-d]pyrimidine derivatives as EGFR-TK inhibitors: design, green synthesis, potential anti-proliferative activity and P-glycoprotein inhibition" DOI: 10.1039/D3RA05401B (Paper) RSC Adv., 2024, 14, 1995-2015.

13.Mohamed El Hafi et al ," Synthesis of New Pyrazolo[3,4-d]pyrimidine Derivatives: NMR Spectroscopic Characterization, X-Ray, Hirshfeld Surface Analysis, DFT, Molecular Docking, and Antiproliferative Activity Investigations", Journals Molecules Volume 29 Issue 21 10.3390/molecules29215020

14. Nadia Hanafy Metwally, Emad Abdullah Deeb & Ibrahim Walid Hasani," Synthesis, anticancer evaluation, molecular docking and ADME study of novel pyrido[4′,3′:3,4]pyrazolo[1,5-a]pyrimidines as potential tropomyosin receptor kinase A (TrKA) inhibitors", . Metwally et al. BMC Chemistry (2024) 18:68; https://doi.org/10.1186/s13065-024-01166-7

15. Ameen Ali Abu-Hashem a,b,, Othman Hakami a,b,, Nasser Amri ,” Synthesis, anticancer activity and molecular docking of newquinolines, quinazolines and 1,2,4-triazoles with pyrido[2,3-d] pyrimidines”, Heliyon 10 (2024) e26735

16. SondhiSM, et al. “Anticancer, anti-inflammatory and analgesic activity evaluation of heterocyclic compounds synthesized by the reaction of 4-Isothiocyanato-4-methylpentan-2-one with substituted o-Phenylenediamines, o-Diaminopyridine and (Un)Substituted “ Aust J Chem. 2001;54(1):69–74. doi:10.1071/CH00141.

17. Shishoo CJ, Shirsath VS, Rathod IS, Patil MJ, Bhargava SS. “Design, synthesis and antihistaminic (H1) activity of some condensed 2-(substituted) arylaminoethyl-pyrimidine-4-(3H)-ones”. Arzneim Forsch. 2001;51(3):221–231. doi:10.1055/s-0031-1300028.

18.ZhangHJ, WangSB, WenX, LiJZ, QuanZS.” Design, synthesis, and evaluation of the anticonvulsant and antidepressant activities of pyrido[2,3-d] pyrimidine derivatives”. Med Chem Res. 2016;25: 1287–1298. doi:10.1007/s00044-016-1559-1.

19. Hanafy FI. Synthesis and antifungal activity of some new pyrido [2,3-d]pyrimidines. Eur J Chem. 2011;2: 65–69. doi:10.5155/eurjchem.2.1.65-69.303

20. Parish HAJr, Gilliom RD, Purcell WP, Browne RK, Spirk RF, Harold D, et al. “Syntheses and diuretic activity of 1,2-dihydro-2-(3-pyridyl)-3H-pyrido[2,3-d] pyrimidin-4-one and related compounds”. J Med Chem. 1982;25(1):98–102. doi:10.1021/jm00343a022.

21. El-Subbagh H, Abu-Zaid SM, Mahran MA, BadriaFA, Al-Obaid AM.” Synthesis and iological evaluation of certain α,β-unsaturated ketones and their corresponding fused pyridines as antiviral and cytotoxic agents”. J Med Chem. 2000;43(15):2915–2921. doi:10.1021/jm000038m.

22.M.M. Katiya, M.G. Dhonde, J.M. Gajbhiye,Solvent-free synthesis of Thiobarbituric acids using Amberlyst-15 as a green catalyst Curr. Green Chem., 4 (2017), 10.2174/2213346104666170704115006

23. S.G. Patel, P.J. Patel, D.B. Upadhyay, A. Puerta, A. Malik, N.K. Kandukuri, R.K. Sharma, J.M. Padrón, H.M. Patel “Insights into microwave assisted synthesis of spiro-chromeno[2,3-d]pyrimidines using PEG-OSO_3H catalyst: DFT study and their antiproliferative activity”, J. Mol. Struct., 1292 (2023), Article 136174, 10.1016/j.molstruc.2023.136174

24.N. Deibl, R. Kempe “Manganese-catalyzed multicomponent synthesis of pyrimidines from alcohols and Amidines”,Angew. Chemie Int. Ed., 56 (2017), pp. 1663-1666, 10.1002/anie.201611318

25.P. Liu, Y. Yang, Y. Tang, T. Yang, Z. Sang, Z. Liu, T. Zhang, Y. Luo “Design and synthesis of novel pyrimidine derivatives as potent antitubercular agents”, Eur. J. Med. Chem., 163 (2019), pp. 169-182, 10.1016/j.ejmech.2018.11.054

26.R. Mondal, S. Sinha, S. Das, G. Chakraborty, N.D. Paul “Iron catalyzed synthesis of pyrimidines under air”, Adv. Synth. Catal., 362 (2020), pp. 594-600, 10.1002/adsc.201901172