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Green and efficient protocol for synthesis a new series of fused pyrimidine derivatives incorporating thioamide moiety

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***Abstract*---**In the recent decades, heterocyclic compounds six membered ring occupied a great deals of attention due to its wide and varied applications in medical, pharmaceutical, agricultural and industrial fields. Herein in this work fused pyrimidine as active type of the mentioning above have been successfully prepared by using supreme green chemistry techniques represented by solid phase one-pot muticomponent reaction (Biginille reaction) and microwave irradiation via mixing equimolar of thioamide (phenyl thiourea)-dimedone and substituted Benzaldehyde in presence of (2% mole) of boric acid and few drops of glacial acetic acid as selective acid catalyst at power (700 watt) for (1 min) to afford 7,7, dimethyl-1-phenyl-4-aryl-3,4,6,7,8–5H-quinazolin-2-thione-5-one (1-7) as pure products with high persentage.

***Keywords*---**one-pot multicomponent, macrowave irradiation, thioamide, fused pyrimidines.

1 Introduction

Multicomponent reaction became an efficient powerful tool for the construction of complex molecules especially when the reaction accelerated by another type of green chemistry technique represented by microwave irradiation and also because they are formed in one-pot condensation reaction without isolating of intermediate with simple reaction, both energy and raw matured are saved and reducing the reaction time. (Ghasemzadeh, Eshkevari, Tavakoli & Zamani, 2020; Cedric et al., 2019; Benjamin, Rotstein, Serge, Vishal & anderi 2014; Jiang, Rajale, Wever, Tu & Li 2010). Due to the all above mentioning supreme properties, in this work we used these green chemistry two techniques to achieve

a new series of fused pyrimidines as active example of six membered heterocyclic compounds which received a great deals of attention in the recent decades because they occupied a prominent place in medical field as anti-cancer (Nishimura et al., 2022), anti-hypertensive (Tahmasbi, Koukabi & Armand., 2022), anti-malaria (Rogerio & Graebin., 2018), anti-tubercular (Venkatesh, Bodke, Manjunatha & Kumar., 2021), anti-HIV (Filho et al., 2012), anti-oxidant reagent (Sanli et al., 2020), anti-inflammatory (Zarenzhad, Farjam & Iraqi., 2021) and anti-epileptic (Suresh., 2012). As well as, the unit building thioamide due to its practical synthetic applicability, it known today as biological active compound (Patel, Parmar, Patel, Dadhania & Suresh., 2021), either plant protection agent or drugs (Kanevskaya, Bondartsova & Fedotova., 2020), as additives to the lubricating oils and greases (Liu et al., 2021) and as interesting ligands in coordination chemistry (Pääkkonen, Jääskeläiene, Kosheroy & Hirva., 2022). Therefore , in this work fused pyrimidines represented by compounds 7,7, dimethyl-1-phenyl-4-aryl-3,4,6,7,8–5H-quinazolin-2-thione-5-one (1-7) were performed successfully through Biginelli reaction as a type of one-pot three component reaction among thioamide, dimidone and substituted benzaldehyde accelerated by microwave irradiation using (700 watt) for (1 min) in presence of (2% mole) Boric acid and few drops of glacial acetic acid as selective acid catalyst.

2 Materials and Methods

Method A (Shaymaa & Maysa'a, 2017): Equimolar (0.001 mole) of thioamide, dimedone and substituted benzaldehyde were dissolved in (20 ml) abs. ethanol in presence of (2% mole) boric acid and (2 drops) glacial acetic acid as active acid catalyst followed by reflux for (4 hrs.) with using of thin layer chromatography to follow the reaction process. cooling then poured in ice- water with stirring followed by filtration of the solid product and watching thoroughly with cold water many times to remove the excess of acids , drying then recrystallized from water (Table 1)

Method B (Mohanta, Pati & Behera, 2020): Equimolar (0.001 mole) of thioamide , dimidone and substituted benzaldehyde were mixed and irradiated under microwave oven at power (700 watt) for (1 min) in presence of (2 % mole)boric acid and (2 drops) glacial acetic acid. Cooling followed by adding (10ml) of acetone to separate the boric acid then filtration and reduce the filtrate volume to a half by evaporation followed by adding of ice-water with stirring to afford the solid product which then filtrated off, dry followed by recrystallized form water.

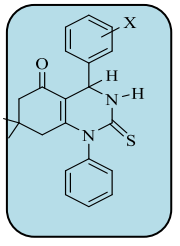
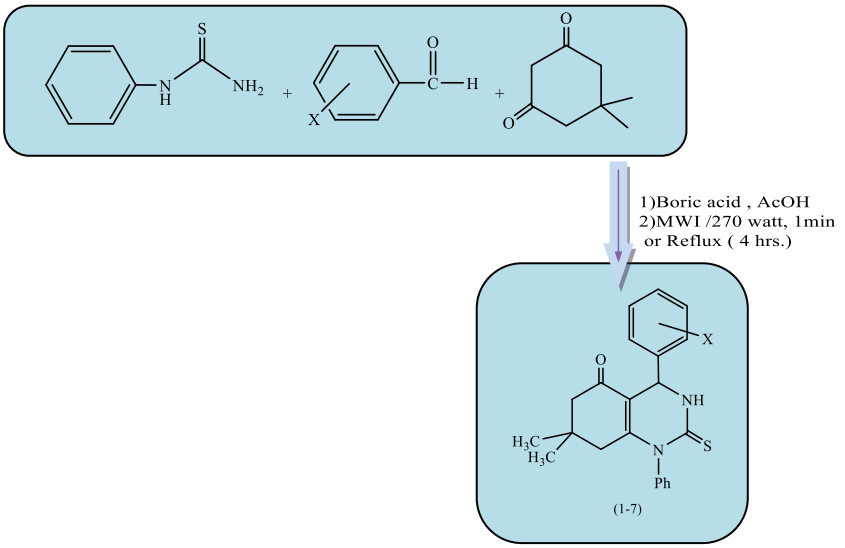


Table 1

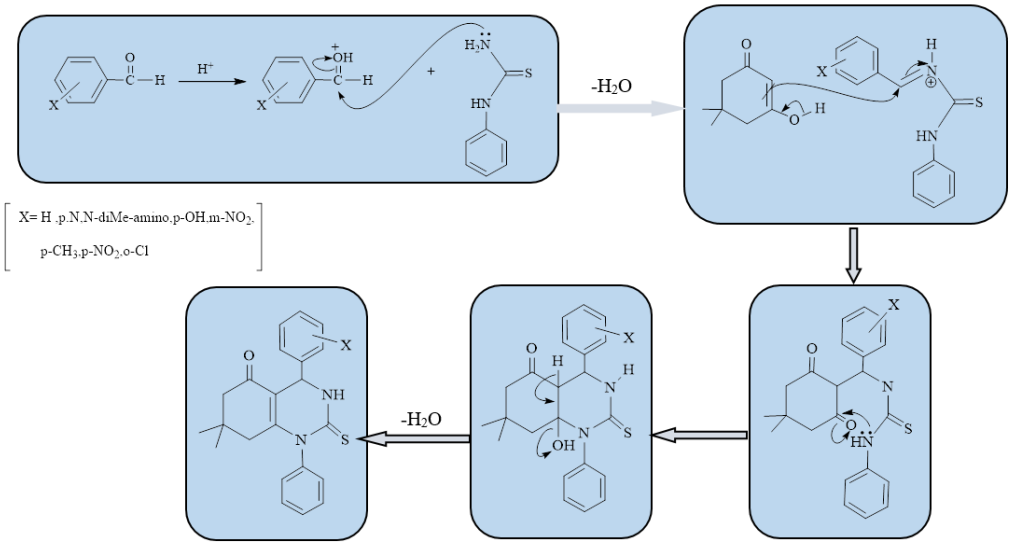
Comp. No.	X	M.P (°C)	Yield (%)	Molecular Formula	Color	T.L.C Benzen: Methanol 8:2
1	H	49-51	70	$C_{22}H_{22}N_2OS$	Yellow	0.720
2	p-N,N- diMe-amino	43-45	98	$C_{24}H_{27}N_3OS$	Brown dark	0.654
3	p-OH	64-67	81	$C_{22}H_{22}N_2O_2S$	Brown	0.666
4	m-NO_2	60-63	98	$C_{22}H_{21}N_3O_3S$	Yallow	0.640
5	p-Me	49-52	81	$C_{23}H_{24}N_2OS$	Green	0.720
6	p-NO_2	70-73	75	$C_{22}H_{21}N_3O_3S$	Brown	0.674
7	o-Cl	53-55	80	$C_{22}H_{21}ClN_2OS$	Brown	0.638

3 Results and Discussions

Fused pyrimidine-2-thion were prepared according the following Equation :



Multicomponent reaction are an efficient reactions in the synthetic pathway of heterocyclic compound especially when these compounds prepared in solid phase and as well as using the water as suitable solvent to treat all prepared compounds as an efficient substitute for laboratory organic solvents . Basically these two green chemistry techniques reducing the reaction time simple, efficient and yield enhancement . Actually, fused pyrimidine-2-thio (1-7) were prepared stepwise through the following mechanism (Mohammed, Moustafa, Ahmed, EL-Syed & Mohamed., 2022)



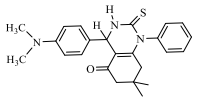
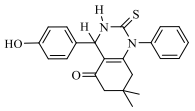
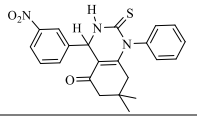
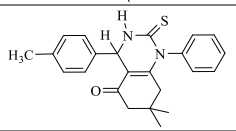
All these compounds shown in U.V. spectroscopy absorption bonds at λ_{max} (nm): (328-244) and (313-228) due to the ($n \rightarrow \pi^*$) and ($\pi \rightarrow \pi^*$), whereas, in FT-IR spectroscopy they shown (C=S) absorption bond at (υ cm^{-1}) (1616-1487) at it is high level due to the fused hetro cyclic system, (C=O) absorption bond at (1699-1645) and (c=c)absorption bond at (1665-1591) in addition to the other functional absorption bonds listed in Table(2).

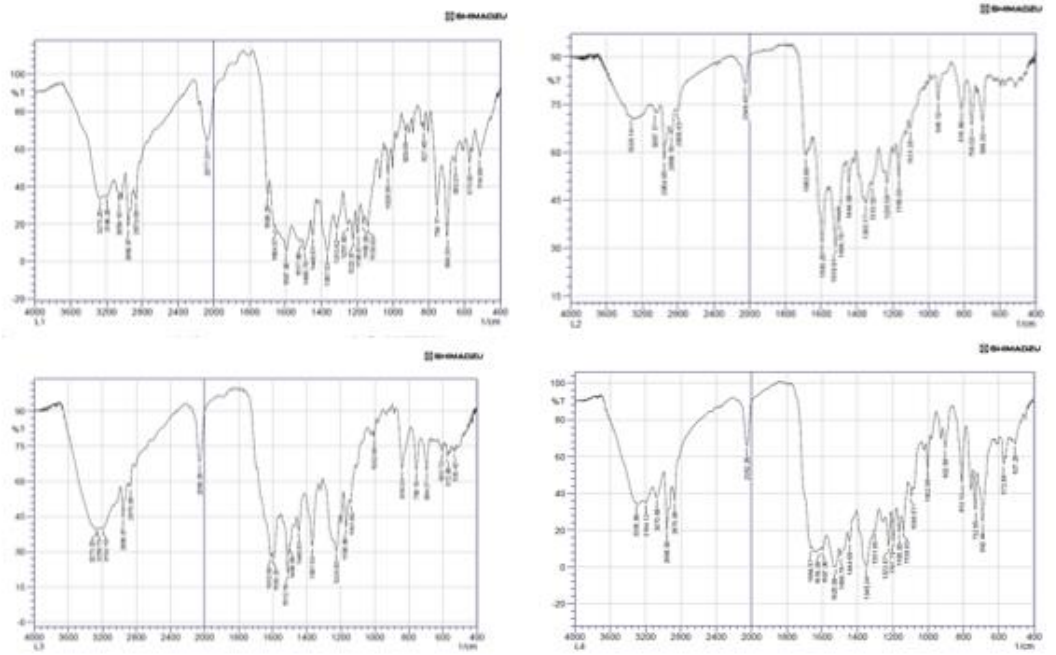
Table 2

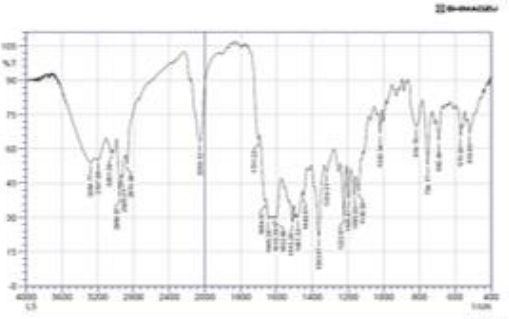
Comp. No.	FT-IR.V cm^{-1}								
	NH	=C-H	CH_3		C=O	C=C	C=S	others	U.V MeOH or EtOH λ_{max} nm
			asym.	sym.					
1	3273	3059	2957	2870	1699	1665	1597	---	244,231
2	3329	3057	2955	2868	1684	1593	1519	---	244,228
3	3260	3058	2957	2870	1685	1610	1593	OH 3273	275,244
4	3306	3071	2959	2870	1665	1618	1597	NO_2 asym1525 sym1348	293,244
5	3285	3052	2957	2870	1665	1645	1616	---	244,235
6	3362	3073	2957	2870	1665	1597	1517	NO_2 asym1225 sym1197	304,244
7	3343	3063	2957	2870	1645	1591	1487	C-Cl 752	328,313

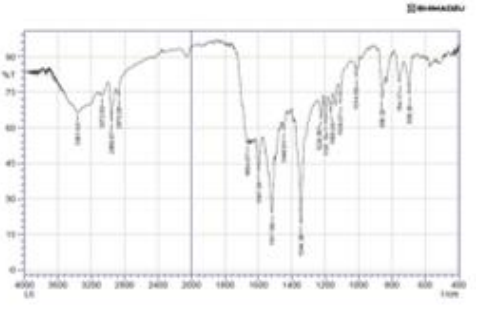
while in ^{1}H-NMR – spectroscopy, the compound (2-5) gave significant peaks at (δ ppm) (9.45-9.80) refer to the pyrimidine amino group as singlet peak in addition to the other characteristic peaks listed in (table 3) which came in agreement with the suggested structure.

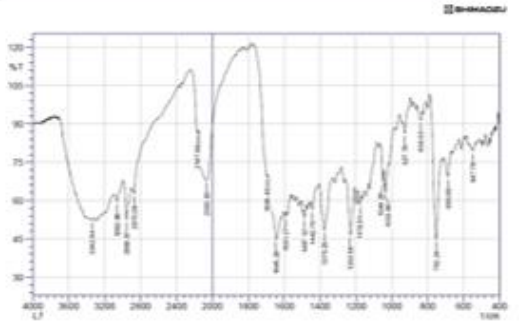
Table 3

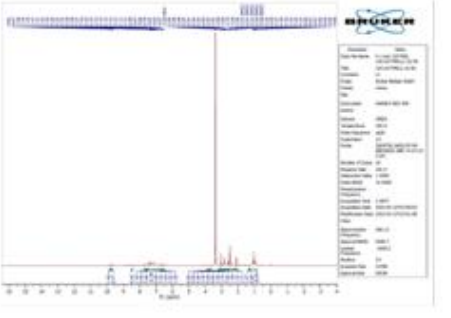
Comp. No	Structure	^{1}H-NMR, DMSO-d6, δ(ppm)
2		CH_2(s,1.05 ,2H) , CH_2(s,2.02,2H); $2CH_3$(s,2.54 ,6H);N,N-$2CH_3$(s,3.05,6H), CH(s,6.56 ,1H) aromatic (m,6.57-7.70,5H);p-N,N-di-Me amino phenyl (AB system)(d-d,7.47-7.68,4H); NH(s,9.8 ,1H)
3		CH_2(s,0.84 ,2H) , CH_2(s,1.15,2H); $2CH_3$(s,2.09 ,6H); CH(s,6.49,1H); aromatic (m,6.52-7.57,5H); NH(s,9.71,1H);OH(s,9.78,1H) ; p-OH phenyl (AB system)(d-d,7.58-7.78,4H);
4		CH_2(s,0.90 ,2H);CH_2(s,1.09,2H); $2CH_3$(s,2.1,6H) ; CH(s,4.64,1H); aromatic (m,7.0-8.31,9H); NH(s,9.8 ,1H)
5		CH_2(s,0.89 ,2H) , CH_2(s,1.07,2H); $2CH_3$(s,4.64 ,6H); CH_3-phenyl(s,4.75,3H);CH(s,6.51,1H); aromatic (m,6.96-7.80,9H); NH(s,9.45,1H)

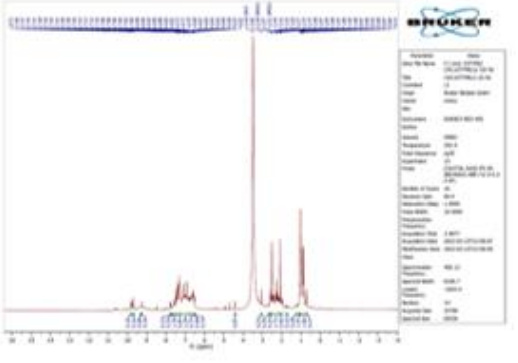


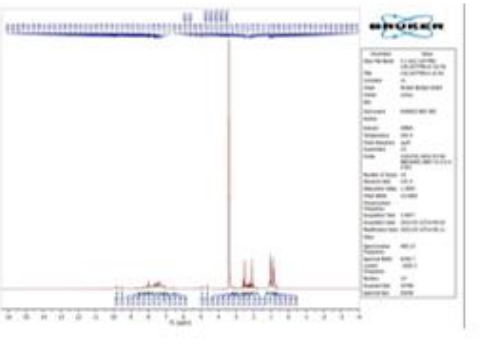


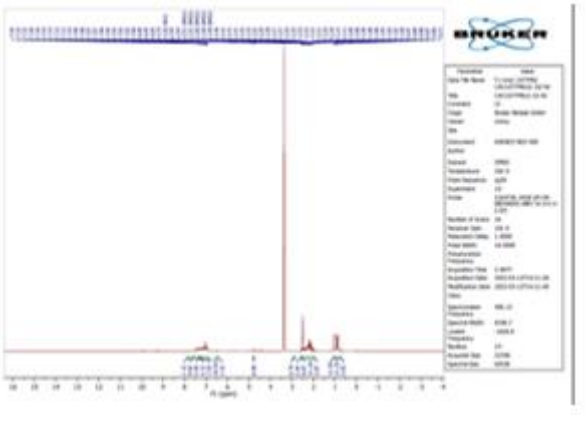












4 Conclusion

In this work the using of solid phase one-pet multicomponent reaction and microwave irradiation techniques were very useful due to the reducing the reaction time with yield enhancement as well as gave pure products with simple work up. Actually, we used small amounts of starting material, therefore this synthetic pathway is very economic and safe. As well as thin layer chromatography has an effective and simple role to determining the reaction time and measuring the purity of the prepared compounds.

References

Benjamin H. Rotstein, Serge Zaretsky, Vishal Rai, and anderi K. Yudin .(2014) Small Heterocycles In Multicomponent Reactions *Chem Rev 114,8323-8358*

Cedric S. Graebin[1,*] , Felipe V. Ribeiro[1] , Kamilla R. Rogerio[2] and Arthur E. Kummerle[1,*] .(2019) Multicomponent reaction for the synthesis bioactive compounds :A review *Current Organic Synthesis 16,855-899*

Filho , A.,W.N., Ricardo; Brauer, C.N.Martin; A.T.Palm-Forster,Mieder ; N. Deolireiroc, Ronaldo;Wessjohann.A.,Luger (2012). Patented catalysts for the synthesis and biological applications of dihydropyrimidinones: reacent advances of the biginelli reaction,*Source*: *Recent Patentson Catalysis*, Vol.,No. 1,pp. 51-73 (23).

Ghasemzadeh M. A. Eshkevari B.M. Tavakoli .M and Zamani F. (2020) Metal-organic frameworks :advanced tools for multicomponent reaction . *Green Chem.22,7265,7300*

Jiang B. , Rajale T. , Wever W. , Tu S. , and Li G. (2010) Multicomponent Reaction for the Synthesis of Helerocycles *Chem Asian 5,2318-2335*

Kanevskaya, I. V., Bondartsova, A. S. Fedotova, O. V. (2020). Biginelli synthesis of regioisomeric 5, 6-dihydro-4H-benzo [4, 5] imidazo [1, 2-a] pyranopyrimidin-4-ones. *Russian Journal of Organic Chemistry*, 56, 1753-1757.

Liu, C., Huang, W., Zhang, J., Rao, Z., Gu, Y. and Jerome, F. (2021). Formal dehyde in multicomponent reactions. *Green Chem.*, 23, 1447-1465.

Mohammed S.M.Moustafa A.H.,Ahmed ,N.EL-Syed,H.A.,Mohamed A.S.A.(2022),Nano-K_2CO_3-Catalyzed Biginelli-Type reaction: Regioselective synthesis, DFT study and Antimicrobial Activity of 4-aryl-6-methyl-5-phenyl-3,4-dihydropyrimidine-2(1H)-thiones. Russian Journal of Organic Chemistry , Vol.58, No.1,pp.136-143.

Mohanta., P. P., Pati, H. N. and Behera, A. K. (2020). The construction of flourophoric thiazolo- [2,3-b] quinazolinone derivatives: a multicomponent domino synthetic approach. *Royal Society of Chemistry*, 10, 15354-15359.

Nishimura, Y., Kikuchy, H., Kubo, T., Arai, R., Toguchi., Y, Boyuan sunaga, K, S, cho, H. (2022) synthesis of 4, 4-disubstituted 3, 4 dihydro pyrimidin-2(1h)-ones and thiones, the corresponding products of biginelli reaction using ketone, and their anti proliferative effect on hl-60cells. *Chem-Pharma*, 70,111-119.

Pääkkonen .I , Jääskeläiene .S , Kosheroy .I , O , Hirva .P . (2022) The effect of halogens in the coordination of 2-pyridinethioamide to gold centers .*Polyhedron volume 226,116114 .*

Patel, U., Parmar, B. Patel, P., Dadhania, A. and Suresh. E. (2021). The synthesis and characterization of Zn (II)/ cd (II) based MOFS by amixed ligand strategy:

AZn (II) mof as a dual functional material for reversible dye adsorption and as a heterogeneous catalyst for the biginelli reaction. *(Research Article) mater. Chem. Front* ,5, 304-314.

Rogerio, K. R.,Graebin. C. S, et al .(2018). Synthesis and molecular modeling studies of pyrimidinones and pyrrolo [3, 4,-d]- pyrimidinodiones as new antiplasmodial compounds original article. *Mem. Inst. Oswaldo cruz* 113(8).

Sanli, Y., Tan, Zhao., Y, Wei., Y, Wong., D, Chen., R, and Tao., L. (2020). Anti-cancer polymers via the biginelli reaction. *Journal ACsMacro Letters Manuseript* ID mz 004963. R1.

Shaymaa K., Younis and Maysa'a, K. Shaker. (2017). Synthesis of some new fused pyrimidine compounds. *Raf. J. Sci.*, Vol. 26, No. 1, pp. 92-99.

Suresh, S, T. (2012). Past present and future of the biginelli reaction: a critical perspective. *Journal of Organic Chemistry*, p 66-133.

Tahmasbi, M., Koukabi, N. and Armand pour, O. (2022). Sono and nano: A perfect synergy foreco compatible biginelli reaction heterocyclic, *Communications* ,Vol. 28,1.

Venkatesh, T., Bodke, Y. D., Manjunatha, B. and Kumar S. R. (2021). Synthesis, antitubercular activity and molecular docking study of substituted [1, 3] dioxino [4, 5-d] pyrimidine derivatives via facile CAN catalyzed biginelli reaction .*Journal of Medicinal Chemistry* ,Vol. 40, pages 1037-1049.

Zarenzhad, E.M Farjam, M., Iraqi, A. (2021). Synthesis and biological activity of pyrimidines-containing hybrids : Focusing on pharmacological application . *Journal of Molecular Structure*, Vol. 1230, 129833.