ejpmr, 2015,2(4), 750-756

SJIF Impact Factor 2.026

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

SYNTHESIS AND MICROBIAL EVALUATION OF SOME NEWER 6-(3-(1, 2-DIHYDRO-6-PHENYL-2-THIOXOPYRIMIDIN-4-YL) PHENYL AMINO) PYRIDAZIN-3(2H)-ONE VIA A NOVEL CHALCONE SERIES.

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Article Received on 25/06/2015 **Article Revised on 16/07/2015** **Article Accepted on 07/07/2015**

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ABSTRACT

Several substituted pyridazone derivative of acetophenone are condensed with aromatic aldehydes, and resulting chalcones are used for the synthesis of diaryl thiopyrimidines. Organic compounds containing pyrimidines, thiopyrimidines as a core unit are known to exhibit various biological activities and pharmaceutical activities. So, all newly synthesized compounds were screened for their antimicrobial activity. Most of the compounds showed significant antibacterial and antifungal activities.

KEY WORDS: Pyridazone, pyrimidines, thiopyrimidines, Antifungal, Antibacterial.

INTRODUCTION

Organic compounds containing pyrimidines as a core unit are known to exhibit various biological and pharmaceutical activities.[1a, b, c] Over the past decades, many procedures have been reported for the preparation of pyrimidines and thiopyrimidines;[2a,b,c,d] however, after a detailed literature survey, we found that there were no any publications devoted to synthesis of pyridazolone derivatives containing pyrimidines and thiopyrimidines. Pyrimidines have a long and distinguished history extending from the days of their discovery as an important constituent of nucleic acids to their current use in the chemotherapy of AIDS. During the last two decades, several pyrimidines derivatives have been developed as chemotherapeutic agents and have found wide clinical applications. Many pyrimidines and related heterocyclic compounds are found to possess a wide important pharmacophore and privileged structure in

medicinal chemistry. Pyrimidines and thiopyrimidines shows pharmacological activities like antihypertensive,[3] analgesic[4] tuberculosis[5] neuroleptic[6] and antimicrobial activity.[7] On the other side pyrimidines and its derivatives have been received much attention due to their interesting pharmacological Properties.[8-13] Some pyrimidines derivative also studied for their leishmanial chemotherapeutic properties.[14] These interesting microbial properties of thiopyrimidines have been prompted the synthesis of some new series of compounds of this class.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The purities of the compounds were checked on silica-gel-coated Al plates. IR spectra were recorded in KBr on a Perkin Elmer Spectrum BX series FT-IR spectrometer. ^{1}HNMR spectra were recorded on Bruker DRX 300 MHz NMR spectrometer using TMS as internal standard and mass spectra on a Jeol D-300 spectrometer.

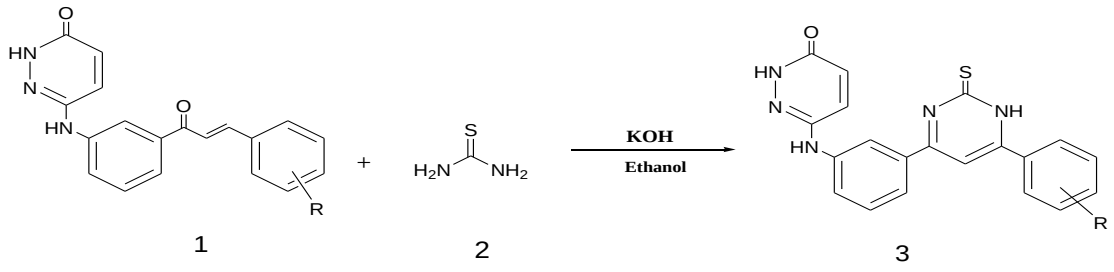
We synthesized novel chalcones using conventional method in the literature.[15, 16] and that novel chalcones used in this research work.

General Procedures: Pyridazin-3(2H)-one (3a-3l)

A mixture of Chalcone (6-(3-((E)-4-Nitro phenyl)but-3-enoyl)phenylamino)pyridazin-3(2H)-one) (0.01mol) and thiourea (0.01mol.) was dissolved in ethanol (20mL) and potassium hydroxide (1g) in water (5mL) and contents were refluxed for 7.5 hrs. Completion of the reaction was monitored by thin layer chromatography (TLC). The crude product obtained was purified by silica gel column chromatography with ethyl acetate/n-hexane (1:1) as eluent (**Scheme-1**).

All other 2-mercaptopyrimidines were synthesised similarly.

Scheme I



Spectral Data Analysis

1 6-(3-(1,2-dihydro-6-(3,4-dimethoxyphenyl)-2-thioxopyrimidin-4-yl)phenylamino) pyridazin-3(2H)-one(3b): **Molecular Formula**; **$C_{22}H_{18}N_5O_3S$**; Yield; 69**%,** m. p.; **173-175^{0}C**; **FT-IR** (KBr): 1610 cm^{-1} (Ar. C=C Str.), 3100-3350 cm^{-1} (Broad peaks for 3 N-H Str.), 1648 cm^{-1} , (C=O), 1500 cm^{-1} (C-N str.); **^{1}H NMR** (DMSO-d_6) (δ ppm) 3.7 (s 6H), 2.4 (s, 1H), 5.8 (s, 1H, Ar-H), 4.3 (s, 1H), δ 7. 3 (s, 1H, Ar-H), 6.65-6.80 (m, 5H, Ar-H), 6.7-7.8 (m, 3H, Ar-H), **Mass**; (m/z), Calculated; **433**; Found **433**(M^+).

2 6-(3-(1,2-dihydro-6-(,4-chlorophenyl)-2-thioxopyrimidin-4-yl)phenylamino) pyridazin-3(2H)-one(7g): **Molecular Formula=$C_{20}H_{14}ClN_5OS$**; Yield= **69%,** m. p. = **172^{0}C**; **FT-IR** (KBr): 1600 cm^{-1} (Ar. C=C Str.), 3000-3250 cm^{-1} (Broad peaks for 3 N-H Str.), 1673.1 cm^{-1} , (C=O), 1458 cm^{-1} (C-N str.); **^{1}H NMR** (DMSO-d_6) (δppm) 1.3 (s, 1H), 2.2 (s, 1H), 2.6 (s, 1H), 2.00 (d, 1H), 2.7 (d, 1H), δ 7. 3 (s, 1H, Ar-H), 7.6-7.70 (m, 4, Ar-H), δ7.4-7.5 (m, 4H, Ar-H), **Mass**; (m/z), Calculated **407. 05** ; Found **407.05**(M^+).

3 6-(3-(1,2-dihydro-6-(4-methoxyphenyl)-2-thioxopyrimidin-4-yl)phenyl amino) pyridazin-3(2H)-one (7i.): Molecular Formula; **$C_{21}H_{17}N_5O_2S$**, Yield; 75**%,** m. p.; **163^{0}C**; **FT-IR**(KBr): 3250 cm^{-1}(Ar C=C Str.), 3101- 3221 cm^{-1}, (Broad peaks for 2 N-H Str.), 1806 cm^{-1} (C=O), 1680 cm^{-1} (C=O); **^{1}H NMR** (DMSO-d_6): (δ ppm); 3.9 (s, 3H) , 5.1 (s, 1H), 7.1 (s,1H), 6.5 (s, 1H), 6.72-7.6 (d, 4H, Ar-H), 6.4-6.5(m, 4H, Ar-H), 7.00-7.30 (m, 2H, Ar-H); 6.4 (s, 1H), **Mass; (m/z)** , Calculated **403.** Found **402.5** (M^+).

4 6-(3-(1,2-dihydro-6-(3,4,5-trimethoxyphenyl)-2-thioxopyrimidin-4-yl) phenylamino) pyridazin-3(2H)-one (3k.): **Molecular Formula**; **$C_{23}H_{21}N_5O_4S$**, Yield; **61%,** m. p.; **173^{0}C**; **FT-IR**(KBr): 3240 cm^{-1}(Ar C=C Str.), 3001- 3121 cm^{-1}, (Broad peaks for 2 N-H Str.), 1800 cm^{-1} (C=O), 1655 cm^{-1} (C=O); **^{1}H NMR** (DMSO-d_6): (δ ppm); 3.9 (s, 9H,), 5.1 (s, 1H), 2.1 (s,1H), 6.5 (s, 2H), 7.6 (d, 2H, Ar-H), 6.4-6.5(m, 3H, Ar-H), 7.00-7.30 (s, 1H, Ar-H); 6.4 (s, 1H), **Mass; (m/z)** , Calculated **463.5** Found **466.3** (M^+)

Antimicrobial Activity

All of the novel synthesized compounds were screened for their antimicrobial activity against the Gram –ve bacteria *Escherichia coli* (ATCC 8739) and Gram +ve bacteria *Staphylococcus aureus (ATCC6538*), in addition to their antifungal activity against *Aspergillus Niger* (ATCC16404) *Candida albicans* (ATCC10231) using ager diffusion methd[17, 18] at a concentration 20mg/mL. DMSO used as a solvent. Compound **3a, 3c & 3i** shows highly

efficient antibacterial activity against *S. aureus* (*ATCC* 6538) more than Penicillin standard. Compound **3g, 3h, 3i & 3l** shows antifungal activities more than reference fungal. Many synthesized compounds was also found to be efficient equivalent to standard, e. g. Penicillin, Grysofulvin.

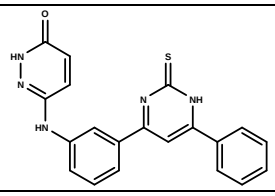
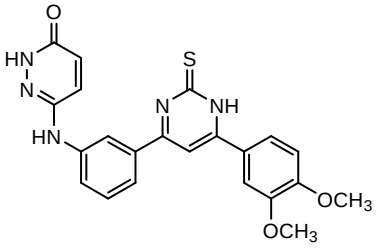
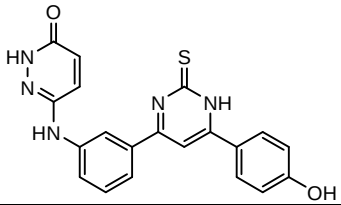
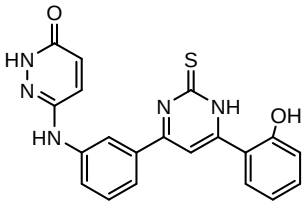
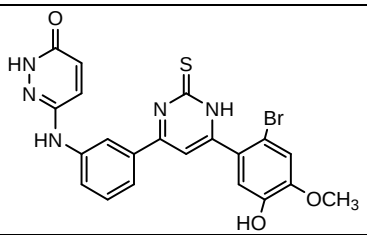
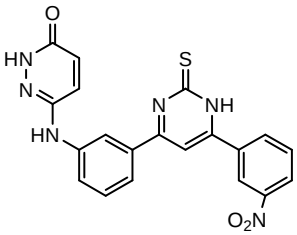
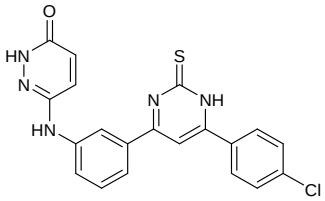
Table-2: Antimicrobial activity of Thiopyrimidine Derivatives

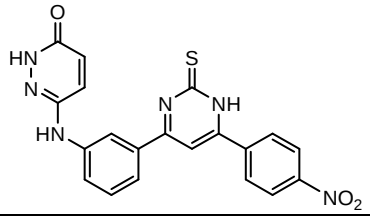
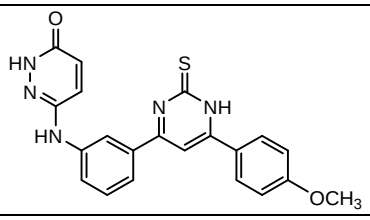
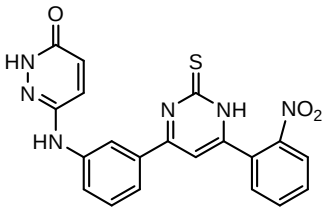
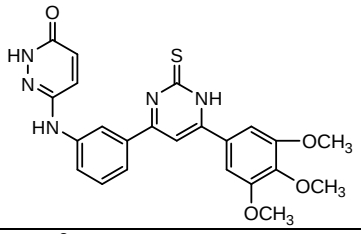
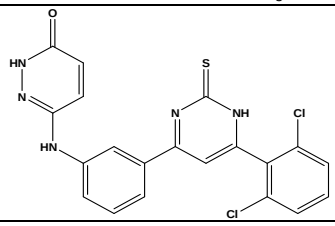
Entry	R	Antibacterial Activity		Antifungal Activity.	
		E. Coli **(ATCC 8739)**	***S. aureus*** ***(ATCC6538)***	**A. Niger (ATCC16404)**	**C. Albicans (ATCC10231)**
3a	-H	**11mm**	**10mm**	-ve	10mm
3b	3,4-OCH_3	7mm	8mm	-ve	8mm
3c	4-OH	**12mm**	**10mm**	-ve	-ve
3d	2-OH	8mm	-ve	-ve	**11mm**
3e	3,4,5-Br,OCH_3,OH	10mm	6mm	-ve	9mm
3f	3-NO_2	9mm	7mm	10mm	10mm
3g	4-Cl	8mm	9mm	**11mm**	8mm
3h	4-NO_2	**11mm**	7mm	**12mm**	9mm
3i	4-OCH_3	**11.5mm**	9mm	-ve	**11mm**
3j	2-NO_2	10mm	9mm	-ve	**13**
3k	3, 4, 5-OCH_3	-ve	**11mm**	8.5mm	**10.5mm**
3l	3,4-OH	10.5mm	**10mm**	8.5mm	**12mm**
	Penicillin	**10.5mm**	**8.5mm**	-	-
	Grysofulvin	-	-	**10.5mm**	**10mm**

RESULTS AND DISCUSSION

Many synthetic methods of pyrimidine have been reported from urea, thiourea and Guanidine with chalcones. But synthesis of pyrimidines from urea gives very low yield as compared to thiourea and Guanidine. In the present work, we describe the synthesis of thiopyrimidines which have biological important in chemistry by using 6-(3-((*E*)-3-phenylacryloyl)phenyl amino) pyridazin-3(*2H*)-one to give 6-(-3-(-2marcapto-6-phenylpyrimidin-4yl)pyridazin-3(*2H*)-one.(3a-l) by conventional method. The product obtained in 60 to 78 % yield within around seven hours by refluxing. Best result in terms of yield and reaction time was obtained with small amount of alkali (Aqueous KOH). The structures of the compounds were established on the basis of spectroscopic data and elemental analysis. (**Table 1)**

1. Table-4 Physical data of Substituted Thiopyrimidines

Entry	R	Structure of Compound	Yield[a] (%)	Time (Hrs)	M.P. (°C)
3a	-H		65	7.5 hrs	187-189
3b	3,4-OCH_3		69	8 hrs	173-175
3c	4-OH		59	7.5 hrs	189-191
3d	2-OH		70	7.5 hrs	165-7
3e	3,4,5-Br,OCH_3,OH		58	7.5 hrs	172-174
3f	3-NO_2		78	8 hrs	168-170
3g	4-Cl		72	7.5 hrs	193-195

3h	4-NO_2		50	8 hrs	156-158
3i	4-OCH_3		75	7.5 hrs	160-162
3j	2-NO_2		56	7.5 hrs	190-192
3k	3, 4, 5-OCH_3		71	8 hrs	178
3l	3,4-OH		57	7.5 hrs	168-170

CONCLUSION

Pyrimidines occupy a distinct and unique place in our life. This hetero cyclic moiety has great biological and medicinal significance. A large array of pyrimidine drugs possesses a variety of medicinal properties. 2- Marcapto pyrimidines have been shown more importance properties in the field of synthetic organic chemistry. The method used in the synthesis of newer pyrimidines was found good because all products obtained have moderate to good percentage yield. Many of newer pyrimidines shown antimicrobial activities. The advantage of this synthesis was good to moderate yield by using small amount of alkali.

ACKNOWLEDGEMENT

The authors are thankful to the Management of Konkan Education Society, Principal Dr. S. S. Gurav, The Head of Department Dr. D. V. Bhagat for providing necessary facilities.

REFERENCES

1. (a) Kappe,C. O. Tetrahedron 1993; 49: 6937, and references cited therein. (b) Sharma, A. K.; Jayakumar, S.; Hundal, M. S.; Mahajan, P. M. J. Chem. Soc., Perkin Trans. 2002; 1: 774. (c) Sasaki, S.; Cho, N.; nara, Y.; Harada, M.; Endo, S.; Suzuki, N.; Furuya, S.; Funjino, M. J. Med. Chem. 2003; 46: 113.
2. For selected examples, see: (a) Khosropour, A. R.; Baltork, I. M.; Ghorbankhani, H. Catal. Commun. 2006; 7: 713. (b) Gholap, A. R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. Green Chem. 2004; 6: 147. (c) Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Raj, K. S.; Prasad, A. R. J. Chem. Soc., Perkin Trans., 2001; 1: 1939. (d) Heravi, M. M.; Ranjbar, L.; Derikvand, F.; Alimadadi, B. Mol. Diversity 2008; 191: and references cited therein.
3. A. EI- ZK Abd-Samii; pharmazie. 1996; 51: 540-543.
4. K. K. Vijaya Raj; B. V. narayan; N Ashalatha; suchita Kumari, J. Pharmacol Toxicol, 2006; 1(6): 559-565.
5. M. G.Moustafa; H.I. Zeinab; A.A. Soad, Hetero. Chem., 2004; 1: 5762.
6. R. Filler. Chem Technol., 1974; 4: 752-757.
7. M. A. Amin; M. M. Iamil; Ei-Helby,G. A. Addel; A. H. Bauomy; E. I.-Morsy, Ahmad; Alexandria, J. Pharm.Sci., 2003; 17: 1-11.
8. I Bouabdallah; L.A. M'barek; A. Zyad; A Ramadan; I Zidane; A. Melhaoui. *Nat. Prod. Res*., 2006; 20: 1024–1030.
9. L.P. Davis; D.J. Brown; S.C. Chow; GAR Johnston. *Neuro. Sci. Lett.*, 1983; 41: 189.
10. L. P. Davis; D.J. Brown; J.H. Sekrit; S.C. Chow; GAR Johnston. *Sci*., 1984; 34: 2177.
11. N. P. Peet; N.L. Lentz; S. Sunder; M.W. Dudley; AML Ogden. *J. Med. Chem*., 1992; 35: 3263-3269.
12. M.Z. Rizk; A. Z. Abdel-Hamid; L.H. Feddah. *Egypt. J. Pharm. Sci*., 1993; 34: 57-65.
13. D. P. Jiang; B.A. Hesson; D. L. Dusak; D.G. Jexter; E.H. Kang. *J. Med. Chem*., 1990; 33: 1721-1728.
14. Ducki, S.; Hadfield, J. A.; Lawerence, N. J.; Zhang, X. *Planta Med.* 1996; 62: 185.
15. Gupta, R; Gupta, A. K.; Paul S.; Kachroo, P. L.; *Indian J. Chem*. 1995; 34B: 61.
16. Shrikrishna D. Tupare, Satish A. Dake, Santosh V. Nalage, Sidhanath Bhosale, Rajendra P. Pawar, *International Journal of Organic Chemistry*, 2012; 2: 371-376.
17. Grayer, R. J.; Harborne, J. B. *Phytochemistry*, 1994; *37:* 19-42.
18. Irob, O. N.; Moo-Young, M.; Anderson, W. A. *Int. J. Pharm*. 1996; *34:* 87-90.