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Research Article

SYNTHESIS, CHARACTERIZATION AND IN VITRO ANTIMICROBIAL EVALUATION OF NOVEL 2-MERCAPTO-4,6-DISUBSTITUTED PHENYL PYRIMIDINE DERIVATIVES

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ABSTRACT

Objective: Synthesis and antimicrobial evaluation of a novel 2-mercapto-4,6-disubstituted phenyl pyrimidine derivatives.

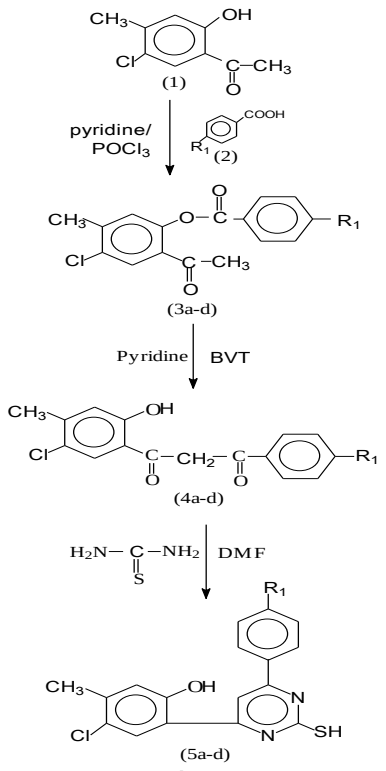
Methods: A series of novel 2-mercapto-4,6-disubstituted phenyl pyrimidine derivatives(5a-d) were synthesized by refluxing 1-(2'hydroxy aryl)-3-(substituted aryl) prop-1,3-dione(4a-d) with thiourea in DMF solvent and obtained in good yield. 1-(2'-hydroxy aryl)-3-(substituted aryl) prop-1,3-dione(4a-d) were obtained by BVT rearrangement in pyridine medium from corresponding 2-benzoyloxy acetophenone (3a-d). The newly synthesized compounds are characterized by IR, H^1NMR mass spectral studies and elemental analysis. These compounds were also screened for their In-vitro antibacterial and antifungal activities.

Results and conclusion: Preliminary results reveal that some of the synthesized compounds are showing promising antibacterial and antifungal activity.

Keywords: 2-mercapto-4,6-disubstituted pyrimidines, prop-1,3-dione, thiourea, antibacterial, antifungal activity.

INTRODUCTION

Recent decades have witnessed an exponential growth in the applications of heterocyclic compounds containing nitrogen, oxygen and sulphur due to their wide range of pharmacological activities. Pyrimidine based heterocyclic compounds are of interest as potential bioactive molecules and exhibit analgesic, (1)antihypertensive(2), antipyretic(3), antiviral(4) and anti-inflammatory(5) activities. These are also associated with nucleic acid, antibiotic, antimalarial, anticancer drugs(6).Many of the pyrimidine derivatives are reported to possess potential CNS depressant properties(7).



R1 -Cl, -OCH3

Fig. 1: Experimental scheme for the synthesis of 2-mercapto-4,6-disubstituted phenyl pyrimidines (5a-d)

There are few reports concerning with pyrimidine ring containing mercapto groups (8).The mercapto derivatives have been shown to exhibit cytotoxic activity (9) and various derivatives of mercapto fused with pyrimidine ring were synthesized and evaluated for antibacterial, antifungal activities in our laboratory (10, 11).hence it was thought of interest to synthesize new derivatives of mercapto pyrimidines by simple method and investigate them for biological and pharmacological activities.

From the above facts it was contemplated to synthesize a novel series of 2-mercapto-4,6-disubstituted phenyl pyrimidines. The final synthesized compounds were screened for their in-vitro antibacterial,antifungal activities.

The key starting materials 2-benzoyloxy acetophenone (3a-d) were prepared by condensation of 5-chloro-2-hydroxy-4-methyl acetophenone (1) in pyridine medium using appropriate aromatic acids(3-OCH_3 benzoic acid/4-OCH_3 benzoic acid/Para chloro benzoic acid/2,4-dichloro benzoic acid)(2)in presence of $POCl_3$.1-(2'-hydroxy aryl)-3-(substituted aryl) prop-1,3-dione(4a-d) were obtained by BVT(12) of corresponding 2-benzoyloxy acetophenone as per known procedures. A mixture of diketone and thiourea in DMF solvent was refluxed to yield the title compounds 2-mercapto-4,6-disubstituted phenyl pyrimidines(5a-d).The synthetic strategies adopted to obtain the target compounds are depicted as **Scheme-01.**

MATERIAL AND METHODS

The IR spectrum is recorded by using Alpha Bruker IR spectrometer using a thin film on KBr pellets and frequencies are expressed in cm^{-1}.The H^1NMR spectra were recorded on bruker advance ii 400 MHz NMR spectrometer. All spectra were obtained in CDCl3 and DMSO d_6 as a solvent. Chemical shifts values are reported as values in ppm relative to TMS as internal standard. Mass spectra were recorded on ESI. Melting point were determined by open capillary method and are uncorrected. All the synthesized compounds were purified by recrystallization. Elemental analysis was also performed. Purity of the compound was checked by TLC.

Synthesis

A mixture of diketone (0.01 mole) and thiourea (0.01 mole) in DMF(50 ml) solvent was refluxed on water bath at 75-90 ^{0}C for 1hr and mixture was cooled and pour in ice cold aqueous solution. The solid separated was washed with water and crystallized from aq. alcohol to give mercapto pyrimidines. The progress of the reaction was monitored by TLC (benzene: chloroform 8:2).The physical data is as follows.

Spectral data for all the compounds

1) 2-mercapto-4-(3-OCH3 phenyl)-6-(2' hydroxy-4' methyl-5' chloro phenyl) pyrimidine:

M.wt:-358.5gm, M.P:-142 ^{0}C, yellow solid coloured compound.

H^{1}Nmr:-400 MHz ($CDCl_3$): 10.37(s, 1H, SH), 6.68-8.07(m, 7H, Ar-H)

IR(cm^{-1}):3526(Ar-OH),3026(CH),1577(C=N),1427(C=C),1265(-OCH3),773(C-Cl),2559(S-H).

Mass :359 (M^+)

2) 2-mercpto-4-(4-OCH3 phenyl)-6-(2' hydroxyl -4' methyl-5' chloro phenyl) pyrimidine:

M.wt:- 358.5gm,M.P:-150 ^{0}C,yellow solid coloured compound.

H^{1}NMR:-400 MHz ($CDCl_3$):12.4(s,1H,SH),6.8-7.4(m,7H,Ar-H)

IR(cm^{-1}):3448(Ar-OH), 2983(CH),1605(C=N),1428(C=C),1263(-OCH3),772(C-Cl),2554(S-H).

Mass :359 (M^+)

3) 2-mercpto-4-(4-chloro phenyl)-6-(2' hydroxyl -4' methyl-5' chloro phenyl) pyrimidine:

M.wt:- 363 gm, M.P:-179 ^{0}C, white solid coloured compound.

H^{1}NMR:-400 MHz ($CDCl_3$):11.9 (s,1H,SH),6.15-8.4 (m,7H,Ar-H)

IR(cm^{-1}):3448(Ar-OH), 2982(CH),1612(C=N),1424(C=C),761(C-Cl),2557(S-H).

Mass :364 (M^+)

4)2-mercapto-4-(2,4-dichloro phenyl)-6-(2' hydroxyl-4'methyl-5' chloro phenyl) pyrimidine:

M.wt:- 397.5 gm, M.P:-152 ^{0}C, white solid coloured compound.

H^{1}NMR:-400 MHz ($CDCl_3$):11.9 (s,1H,SH),7.4-8.2 (m,7H,Ar-H)

IR(cm^{-1}):3431(Ar-OH), 2962(CH),1624(C=N),1408(C=C),771(C-Cl),2544(S-H).

Mass: 398 (M^+)

Antimicrobial activity

The in-vitro anti microbial screening of newly synthesized 2-mercapto-4,6-disubstituted pyrimidine was carried out against gram +ve organisms (staphylococcus aureus), Gram –ve organisms(Salmonella typhus, pseudomonas aeruginosa and E.coli) and fungi(Candida albicans and aspergillus niger) by disc diffusion method(13) and compared with that of the standard drugs Oxacillin and Fluconazole respectively.MIC of each drug was defined as the lowest concentration of an antimicrobial that will inhibit the visible growth of micro organism after incubation time. Muller Hinton Agar was used as basal medium for test of bacteria and fungi respectively. The compounds tested at a concentration of 50ug/ml for bacterial 500ug/ml for fungal growth in DMF solution was added to the wells made on culture medium. After 24hr of incubation at 25^{0}C for antibacterial activity and 48hrs at 30^{0}C for antifungal activity, the zone of inhibition was compared with the standard drug Oxacillin (sensitivity at 13mm or more) and Fluconozole (sensitivity at 11mm or more).The antibacterial activity results revealed that compounds showed significant activity against gram +ve organisms. The compound 5a, 5b, 5c, 5d showed good activity against E. coli and most of the compounds displayed significant activity against S. aureus. However the compounds showed only moderate activity against the gram –ve organisms when compared to the standard drug.

In the antifungal activity, compounds showed moderate to weak activity against A. niger. The compounds 5a, 5b, 5c, 5d showed significant activity against C. albicans when compared to the standard drug.

RESULTS AND DISCUSSION

A novel series of 2-mercapto-4,6-disubstituted phenyl pyrimidine (5a-d) derivatives have been synthesized and screened for their in-vitro antibacterial and antifungal activities. The physical data of the final synthesized compounds are as follows:-

Table 1: Physical data of 2-mercapto-4,6-disubstituted phenyl pyrimidine derivatives (5a-d)

Compound	Ar-COOH	M.W.	M.P(^{0}C)	Elemental Analysis			Yield (%)
				C (%)	H (%)	N (%)	
5a.	3-OCH_3	358.5 gm	142-144^{0}C	60.3	4.18	7.82	53
5b.	4-OCH_3	358.5 gm	148-150^{0}C	60.3	4.18	7.82	76
5c.	4-Cl	363 gm	177-179^{0}C	56.19	3.30	7.79	65
5d.	2,4-Cl	397.5 gm	152-155^{0}C	51.3	2.76	7.04	75

M.W: Molecular Weight; **M.P**: Melting point in ^{0}C

Table 2: Antimicrobial activity of 2-mercapto-4,6-disubstituted phenyl pyrimidine (5a-d) by disc diffusion method

S. No.	Tested compounds	Bacterial(zone of inhibition in mm) at 50µg/ml				Fungal(zone of inhibition in mm) at 500µg/ml	
		E.coli	P.aeruginosa	S.typhi	S.aureus	A.niger	C. albicans
1.	5a	11 mm	_	12 mm	18 mm	_	18 mm
2.	5b	13 mm	12 mm	14 mm	16 mm	15 mm	16 mm
3.	5c	15 mm	11 mm	13 mm	17 mm	16 mm	12 mm
4.	5d	14 mm	12 mm	13 mm	19 mm	_	10 mm

Oxacillin sensitivity -13mm or more, **Fluconazole** sensitivity -12mm or more.

'–' No inhibition

The structures of the newly synthesized compounds were established on the basis of spectral data and elemental analysis. The compounds were purified by recrystallization from appropriate solvents. The completion of the reaction is monitored by TLC.

The antimicrobial activity of the compounds showed good activity against the gram +ve organism most of the synthesized compounds showed significant activity against staphylococcus aureus.

The compounds also displayed good activity against fungal organism C. albicans.

CONCLUSIONS

From the above results it can be concluded that the compound having electron releasing group (C_6H_5) exhibit more activity. Further introduction of chlorine atom and hydroxyl group in benzene ring increases anti-microbial activity of compounds. Among the compounds (5a-d) disubstituted halogens (5d) are more active than mono substituted halogens (5c) against antimicrobial activity and the rest compound (5a, 5b) show moderate activity.

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REFERENCES

1. Anshu chaudhary, pramod Kumar Sharma, prabhakar verma, Nitin Kumar, Rupesh dudhe.Microwave assisted synthesis of novel pyrimidine derivatives and investigation of their analgesic and ulcerogenic activity. Medicinal chemistry research 2012; 21(11):3629-45.
2. Sekiya T, Hiranuma H, Hata S, Mizogami S, Hanazuka M, Yamada S. Synthesis and hypertensive activity of 4-amino-2-(4-cinnamoylpiperazino)-6,7-dimethoxyquinazoline derivatives. J.Med chem.1983 26(3):411-6.
3. Makino H, Kuzuna S, Naka T, Saijo T, Maki Y. Anti-inflammatory, analgesic, and antipyretic activities of methyl 7-butyl-4, 5, 6, 7-tetrahydro-3-methylamino-4, 6-dioxo-5-propyl-2H-pyrazol o [3, 4-d] pyrimidine-2-carboxylate (AA-2379), a novel non-acidic agent. Agents Actions. 1988 Dec; 25(3-4):385-93.
4. Ajitha.M, Rajnarayana K. Synthesis and evaluation of new-3-substituted – [3, 4-dihydropyrimidinones-Indolin-2-ones for cytotoxic activity. Int J pharmacy and pharmaceutical Sciences. 2011;3(4):89-93.
5. M Amir, SA Javed, Harish Kumar Pyrimidine as anti-inflammatory agent: A review 2007; 69(3): 337-343.
6. V.N.Ingle, S.T.Kharche and U.G.Upadhyay. Synthesis of some new 4-0-(-β-D-glucopyranosyloxy)-4,6–diaryl –tetra hydro pyrimidine -2-thianes and their biological activities. Indian journal of chemistry. 2004, pp 2027-2031.
7. Abdellatif M. Salaheldin and Ligia M.Rodrigues. Synthesis of some novel pyrazolo [3, 4-d] pyrimidine derivatives. Arikvoc 2007; 16: 92-100.
8. M.P.V.Boarland and J. F. W. McOmie. Pyrimidine part III.The ultra-violet adsorption spectra of some polysubstituted pyrimidines**.** J. Chem. Soc.**,** 1952, 3722-3728
9. Xanthopoulou MN, Hadjikakou SK, Hadjiliadis N, Schumann M, Jurkschat K, Michaelides A, Skoulika S, Bakas T, Binolis J, Karkabounas S, Charalabopoulos K.Synthesis,structural characterization and in vitro cytoxicity of organotin (IV) derivatives of heterocyclic thioamides,2-mercaptobenzothiazole,5-chloro-2-mercaptobenzothiazole,3-methyl-2-mercaptobenzothiazole and 2-mercaptonicotinic acid. J Inorg Biochem. 2003 Aug 1; 96(2-3):425-34.
10. MN Kumaraswamy, DA Prathima Mathias, C Chandrashekhar, VP Vaidya. Synthesis and pharmacological evaluation of 2-mercapto-4-substituted-naphtho [2, 1-b] furo [3, 2-d] pyrimidines, Indian journal of pharmaceutical sciences. 2006 ; 68 (6): 731-736
11. Gertrude B. Elion, Elizabeth Burgi, George H. Hitchings. Studies on Condensed Pyrimidine Systems.IX. The Synthesis of some 6-Substituted Purines J. Am. Chem. Soc., 1952, 74 (2): 411–414
12. George A. Kraus, Brian S. Fulton, Soon Hyung Wood. Aliphatic acyl transfer in the Baker-Venkataraman reaction J. Org. Chem., 1984, 49 (17): 3212–3214
13. Murray P.R, Baron E.J, Pfaller M.A, Tenover F.C, Yolken R, American Society for Microbiology, Washington DC, 1995, 1342-1349.