EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 5
174-179
Year: 2024

SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL EVALUATION OF SOME 2-MERCAPTO- 4-SUBSTITUTED PHENYL, 6-(5-BROMO,2-HYDROXY PHENYL) PYRIMIDINES

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Article Received on 11/03/2024 **Article Revised on 01/04/2024** **Article Accepted on 21/04/2024**

ABSTRACT
In the present work a new series of 2-Mercapto-4-substituted phenyl,6-(5-bromo,2-hydroxy phenyl) Pyrimidines(6a-d) derivatives were synthesized from substituted propan-1,3-diones i.e.(β-diketones) (4a-d). The substituted β-diketones (4a-d) react with thiourea in DMF solvent and refluxed it at 75^0C to obtained product. The newly synthesized compounds are characterized by H^1NMR, IR, Mass spectra and elemental analysis. These newly synthesized compounds were also screened for their in -vitro antibacterial, antifungal, anti-oxidant and anti-inflammatory activities.

KEYWORDS: Propan-1,3-diones, Thiourea, 2-Mercapto Pyrimidines, Antibacterial, Antifungal, Anti-oxidant and Anti-inflammatory activities.

INTRODUCTION
In nature heterocyclic compounds are abundant such as alkaloids, vitamins, amino acids, antibiotics, hormones, hemoglobin containing heterocyclic atoms are important for the synthesis of novel drugs. More numbers of synthetic heterocyclic compounds like pyrrole, pyrrolidine, furan, thiophene, piperidine, pyridine, pyrimidines and thiazole show significant pharmacological activity. Among these compounds pyrimidines are of very much important in medicinal field. Nitrogen containing heterocyclic ring play an important role in Medicinal chemistry, Biochemistry and pharmacological studies. Pyrimidine is a six-member heterocyclic compound which contains two nitrogen atoms at positions 1 and 3. Pyrimidine derivatives are known to be biologically active compounds. Pyrimidine and its derivatives exhibited several therapeutic applications.[1] which include antimicrobial,[2] anticancer,[3] anti-inflammatory,[4] anti-malarial,[5] anti-diabetic,[6] anti-HIV,[7] anthelmintic,[8] CNS depressants,[9] Cardiac agents,[10] antioxidant,[11,12] antitubercular.[13,14] The synthesis of 2-mercapto pyrimidine is attracting research work because it involves both S and N atoms in their structures.[15,16] In a view of analytical applications of 2- mercapto pyrimidines, it is interest to know the physiochemical properties such as stability of the complexes with metal ions.[17] The 2-mercapto pyrimidine is a significant class of pyrimidine, exists in tautomeric equilibria with thione forms. In a view of biological applications of substituted pyrimidines, it is interest to study the synthesis, characterization and their biological biological activity. Considerable research work was done in the past, synthesis of propan-1,3-diones (β-diketones)(4a-d) with their antibacterial activity and antifungal activity.[18] Now in the present research work some novel 2-Mercapto- 4-substituted phenyl, 6-(5-bromo, 2-hydroxy phenyl) Pyrimidines(6a-d) compounds have been synthesized from propan-1,3-diones (β-diketones). The structural characterization, antibacterial activity, antifungal activity, antioxidant activity and anti-inflammatory activities of synthesized compounds have been investigated.

MATERIALS AND METHODS
All the chemicals and solvents were of good research grade, highest purity and commercially available. The IR spectra was recorded by using Shimadzu IR affinity-1FTIR spectrophotometer, H1NMR spectra were recorded on Bruker advance II 400 MHz spectrometer, Mass spectra were recorded on ESI and Melting point were determined by open capillary tube method which are uncorrected. All the synthesized compounds (6a-d) were purified by recrystallization method and purity was checked by TLC and elemental analysis.

General procedure for the Synthesis of 2-Mercapto-4-substituted phenyl, 6-(5-bromo,2-hydroxy phenyl) Pyrimidines (6a-d)

The synthesis involves the following steps.

Synthesis of 4-bromo phenyl acetate

Take 4-bromo phenol (0.05M) fused with acetic anhydride (5ml) and sodium acetate. The mixture was refluxed for 1hr. then cooled for 15 min. and poured in ice water. Acetate layer was separate out by separating funnel. The product was obtained 4-bromo phenyl acetate (1).

Synthesis of 5-bromo, 2-hydroxy acetophenone (2)

Take aluminum chloride (120 g) in kjeldal flask and add compound (1) (40 ml) drop wise. Heat the reaction mixture in oil bath for 60 min at 120^0C. It was cooled and add in to acidified ice crushed water to get crude product of 5-bromo,2-hydroxy acetophenone (2).

Synthesis of 2-substituted benzoyloxy 5-bromo acetophenone (3a-d)

A mixture of compound (2) (0.05M) and substituted benzoic acid (0.05M) were dissolved in dry pyridine at 00 C. Then add $POCl_3$ dropwise with constant stirring bellow 10^0C. The reaction mixture was allowed to stand for overnight at room temperature. Then it was poured in ice cold 10% HCl. Then the product was wash by 10% $NaHCO_3$ and water. Recrystallized the product by ethanol to obtained a series of 2- substituted benzoyloxy 5-bromo acetophenone (3a-d).

Synthesis of substituted propane 1,3-diones (4a-d)

Take compound (3a-d) (0.05M) was dissolved in dry pyridine. The reaction mixture was heated up to 60^0C with pulverized KOH slowly with constant stirring. After 5-6 hr. the reaction mixture was acidified by dil. HCl in ice cold water. The crude product was filtered, washed it with $NaHCO_3$ (10%) and water. Recrystallized the product from ethanol-acetic acid mixture to get substituted propane 1,3-diones (4a-d).

Synthesis of 2-Mercapto- 4-substituted phenyl, 6-(5-bromo,2-hydroxy phenyl) Pyrimidines (6a-d)

A mixture of compound Propan-1,3-dione (β-diketones) (4a-d) (0.02 M) and thiourea (0.02 M) dissolved in DMF solvent. It was refluxed on water bath at 75^0C for 1hr. The reaction mixture was cooled at room temperature and pour in ice cold water. The product was obtained and recrystallized it by aq. alcohol to obtained a series of 2-Mercapto-4-substituted phenyl, 6-(5-bromo, 2-hydroxy phenyl) Pyrimidines (6a-d).

The general reaction **scheme-I** for the synthesis of final product.

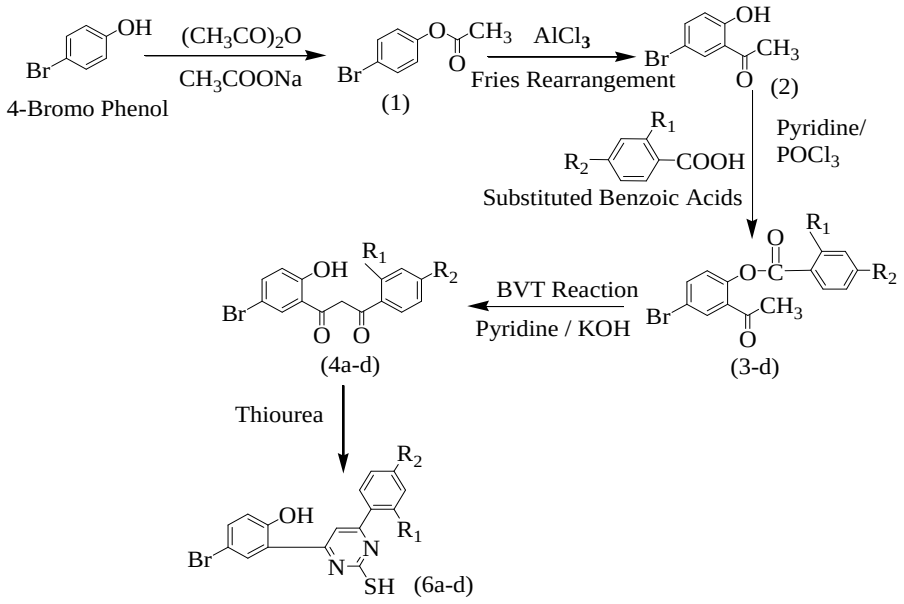

Table 1: Physical data of 2-Mercapto- 4-substituted phenyl, 6-(5 -bromo,2-hydroxy phenyl) Pyrimidines (6a-d).

Code	Compound Name	M.F./M.W.	-R_1	-R_2	Rf value	M.P.(^{0}C)	Yield(%)
6a	2-mercapto-4-(4-methyl phenyl)-6-(5-bromo, 2-hydroxy phenyl) Pyrimidine	$C_{17}H_{13}BrN_2OS$ / (373.27)	-H	-CH_3	0.71	154 -156	74
6b	2-mercapto-4-(4-nitro phenyl)-6-(5-bromo,2-hydroxy phenyl) Pyrimidine	$C_{16}H_{10}BrN_3O_3S$ / (404.24)	-H	-NO_2	0.65	276 -278	81
6c	2-mercapto-4-(2-chloro phenyl)-6-(5-bromo,2-hydroxy phenyl) Pyrimidine	$C_{16}H_{10}BrClN_2OS$ / (393.69)	-Cl	-H	0.62	214 -217	66
6d	2-mercapto-4-(4-chloro phenyl)-6-(5-bromo,2-hydroxy phenyl) Pyrimidine	$C_{16}H_{10}BrClN_2OS$ / (393.69)	-H	-Cl	0.68	254 -256	70

Spectroscopic Characterization

(6a)2-mercapto-4-(4-methyl,phenyl)-6-(5-bromo,2-hydroxy-phenyl) pyrimidine: Solid,Yellow,IR(cm-^{1}): 3389 (Ar-OH),3067(Ar-C-H),2924(ArCH_3), 1632 (C=N), 1444(C=C),649(C-Br), 1283 (C-O).^{1}H-NMR (δppm): 7.0-8.1(m,8H of Ar-H), 2.40 (s,3H of -CH_3), 2.50 (s,1H of -S-H),3.34(S,1H of Ar-OH). MASS (m/z, %): 372(M+). C, H, N, S, O%: Calculated (Found) C: 54.70 (48.24), H:3.67(3.15),N:7.50 (7.32), S:8.59 (8.41), O:4.29 (4.17).

(6b) 2-mercapto -4-(4-nitro phenyl)-6-(5-bromo,2-hydroxy-phenyl) Pyrimidine: Solid,Yellow,IR(cm-^{1}):3364 (Ar-OH), 3100(Ar-C-H),1611(C=N), 1440 (C=C), 630(C-Br), 1115(C-O),1350 (-NO_2).^{1}H-NMR (δ ppm): 7.3-8.3(m,8H of Ar-H),3.38(s,1H of Ar-OH), 2.50 (s,1H of-S-H). MASS (m/z, %):403(M+). C, H, N, S, O% Calculated (Found): C:47.54 (47.19),H:2.49 (2.23), N:10.39(10.26),S:7.93(7.68) O:11.87 (11.59).

(6c) 2-mercapto-4-(2-chloro phenyl)-6-(5-bromo,2-hydroxy-phenyl) pyrimidine: Solid,Yellow,IR(cm^{1}):3077(Ar-OH),2927 (Ar-C-H),1639(C=N), 1459 (C=C),525(C-Br),1271(C-O),755(C-Cl). ^{1}H-NMR (δ ppm):7.31-8.63(m, 8H of Ar-H), 3.38 (s,1H of Ar-OH),2.50 (s,1H of -S-H). MASS(m/z%) :392 (M+).C, H, N, S,O%Calculated (Found): C:48.81(48.54), H:2.56(2.42), N:7.12(7.08), S:8.14(8.09),O:4.06 (4.01).

(6d) 2-mercapto-4-(4-chloro phenyl)-6-(5-bromo,2-hydroxy-phenyl) pyrimidine: Solid,Yellow,IR(cm-^{1}): 3278(Ar-OH),2925(Ar-C-H),1630 (C=N),1442 (C=C), 524 (C-Br),1281(C-O),641 (C-Cl).^{1}H-NMR (δ ppm): 6.90 -8.8 (m,8H of Ar-H),3.34 (s,1H of Ar-OH),2.51 (s,1H of -S-H).MASS (m/z, %):392(M+). C,H,N,S,O% Calculated(Found): C:48.81(48.64), H:2.56(2.48), N:7.12 (7.10), S:8.14(8.09),O:4.06 (4.01).

ANTIBACTERIAL ACTIVITY

Antibacterial screening of newly synthesized 2-Mercapto-4-substituted phenyl, 6-(5-bromo,2-hydroxy phenyl) Pyrimidines (6a-d) was carried out against *staphylococcus aureus (gram +ve)*, *Salmonella typhus* (*gram–ve*) bacteria by disc diffusion method.[19] and compared with standard Ofloxacin (2 µg). Muller Hinton Agar was used as basal medium for test of bacteria. The compounds tested at concentration of 50 µg/ml, 100 µg/ml and 250 µg/ml for bacterial growth in DMSO solvent it was added to the wells made on culture medium. After 24 hrs. of incubation at 37^{0}C for antibacterial activity record the zone of inhibition.

Table 2: Antibacterial activity against2-Mercapto- 4-substituted phenyl,6-(5-bromo, 2-hydroxy-phenyl) Pyrimidines (6a-d).

Compound code	Zone of inhibition in mm							
	Salmonella typhi (gram -tive)				*Staphylococcus aureus(gram +tive)*			
	Concentrations µgm/ml				Concentrations µgm/ml			
	50	100	250	Ofloxacin 2 mcg	50	100	250	Ofloxacin 2 mcg
6a	NI	NI	NI	NI	NI	NI	NI	NI
6b	NI	NI	NI	NI	NI	NI	**11**	NI
6c	NI	NI	NI	NI	NI	NI	NI	NI
6d	NI	NI	NI	NI	NI	NI	NI	NI
Moderate active = 7-12, NI = No Inhibition								

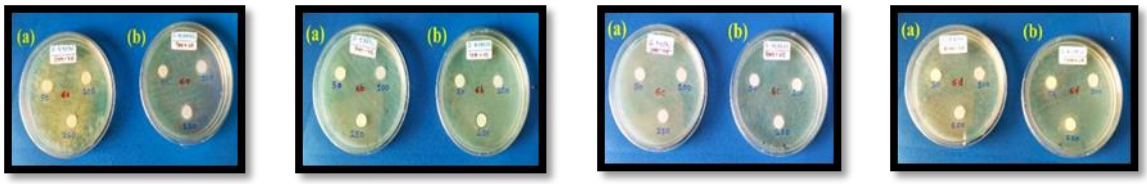

Figure 1: Zone of inhibition of compound 6c and 6d against *Salmonella typhi* and *Staphylococcus aureus.*

ANTIFUNGAL ACTIVITY

Antifungal screening of newly synthesized 2-Mercapto-4-substituted phenyl, 6-(5-bromo,2-hydroxy phenyl) Pyrimidines (6a-d) was carried out against *Candida albicans and Aspergillus niger* fungus by disc diffusion method [20] and compared with standard Fluconazole 25 µgm. Muller Hinton Agar was used as basal medium for test of fungi. The compounds tested at concentration of 50 µg/ml, 100 µg/ml and 250 µg/ml for fungal growth in DMSO solvent it was added to the wells made on culture medium. After 24 hrs. of incubation at room temperature for antifungal activity record the zone of inhibition.

Table 3: Antifungal activity against 2-Mercapto-4-substituted phenyl,6-(5-bromo,2-hydroxy phenyl) Pyrimidines (6a-d).

Compound code	Zone of inhibition in mm							
	Candida albicans				*Aspergillus niger*			
	Concentrations µgm/ml				Concentrations µgm/ml			
	50	100	250	Fluconazole 25 µgm	50	100	250	Fluconazole 25 µgm
6a	NI	NI	NI	NI	NI	NI	NI	NI
6b	NI	NI	NI	NI	**07**	NI	NI	NI
6c	NI	NI	NI	NI	NI	**10**	**11**	NI
6d	NI	NI	NI	NI	**11**	**12**	**14**	NI
Highly active = 13-24, Moderate active = 7-12, NI = No Inhibition								

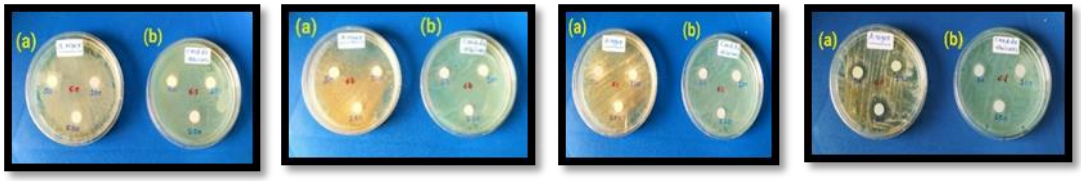

Figure 2: Zone of inhibition of product 6a-d against *Candida albicans and Aspergillus niger*

ANTI-INFLAMMATORY ACTIVITY

Reference drug Ibuprofen was added 10 mg in to10 ml of distilled water. Serial dilution from above stock solution takes 0.1ml, 0.2ml, 0.3ml and prepare 10 ppm, 20 ppm and 30 ppm and also it was performed for sample 2-Mercapto- 4-substituted phenyl, 6-(5-bromo,2-hydroxy phenyl) Pyrimidines (6a-d) extract. The reaction mixture was prepared using 2.8 ml of phosphate-buffered saline (pH 6.4) and 0.2 ml of egg albumin then take 2 ml of sample extract(6a-d) from each different concentration were mixed with reaction mixtures. A similar procedure was used for reference ibuprofen drug solution. The absorbance of these solutions was determined by using spectrophotometer at a wavelength of 660 nm. The % denaturation of the protein (% inhibition) was determined.[21]

Table 4: Anti-inflammatory activity of synthesized 2-Mercapto- 4-substituted phenyl, 6-(5-bromo,2-hydroxy phenyl) Pyrimidines (6a-d).

Sr. No.	Compound Code	% Inhibition		
		Concentration of compound in ppm		
		10 ppm	20 ppm	30 ppm
1	6a	49.77	55.90	65.83
2	6b	73.56	75.49	83.22
3	6c	51.04	52.70	58.05
4	6d	32.33	61.86	84.76
5	Ibuprofen	87.36	88.90	90.23

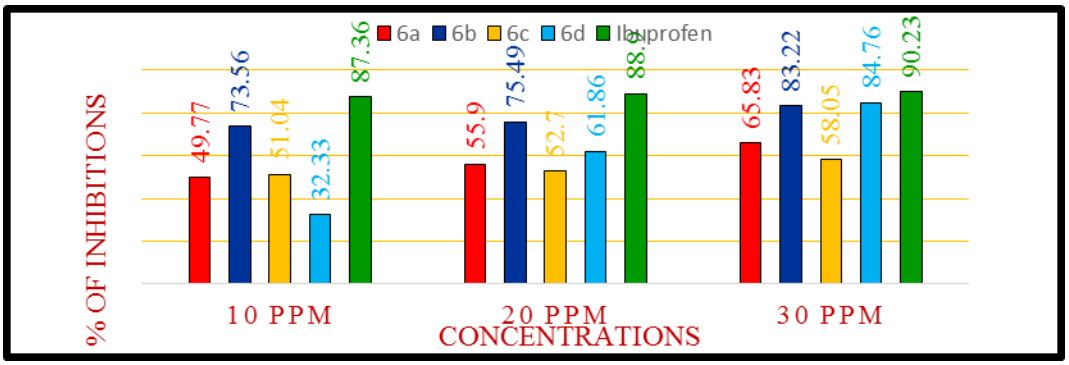

Figure 3: Showing % inhibition in Anti-inflammatory analysis.

ANTI-OXIDANT ACTIVITY

Stock solution of DPPH (2, 2-diphenyl-1-picrylhydrazyl) was prepared by dissolving 1.083 mg in 10 ml of ethanol. Stock solution of sample 2-Mercapto- 4-substituted phenyl, 6-(5-bromo,2-hydroxy phenyl) Pyrimidines(6a-d).100 µg/ml was prepared by dissolving 1 ml of sample in 10 ml of ethanol. From this stock solution, further dilutions were prepared of concentrations 10,20,30,40 and 50 µg/ml using ethanol. Similarly, stock solution of standard ascorbic acid was

prepared by dissolving 10 mg ascorbic acid in 10 ml ethanol. From this stock solution further dilutions of concentrations 1, 2, 3, 4, and 5µg/ml were prepared. Absorbance of blank (5 ml ethanol + 1 ml DPPH solution) as a positive control was recorded using colorimeter at 517 nm. Similarly, the absorbance of sample and comparative standard ascorbic acid was taken at 517 nm and recorded.[22]

Table 5: Anti-oxidant activity of synthesized 2-Mercapto- 4-substituted phenyl, 6-(5-bromo,2-hydroxy phenyl) Pyrimidines (6a-d).

Sr. No.	Compound Code	% Scavenging Activity				
		Concentration of compound in µg/ml				
		10 µg/ml	20 µg/ml	30 µg/ml	40 µg/ml	50 µg/ml
1	6a	34.87	35.53	51.10	52.20	57.24
2	6b	41.45	45.18	56.58	60.53	62.50
3	6c	45.84	56.15	62.07	62.29	67.32
4	6d	37.50	41.23	51.32	52.42	54.61
5	Ascorbic acid (Standard)	80.26	91.22	95.61	96.27	97.80

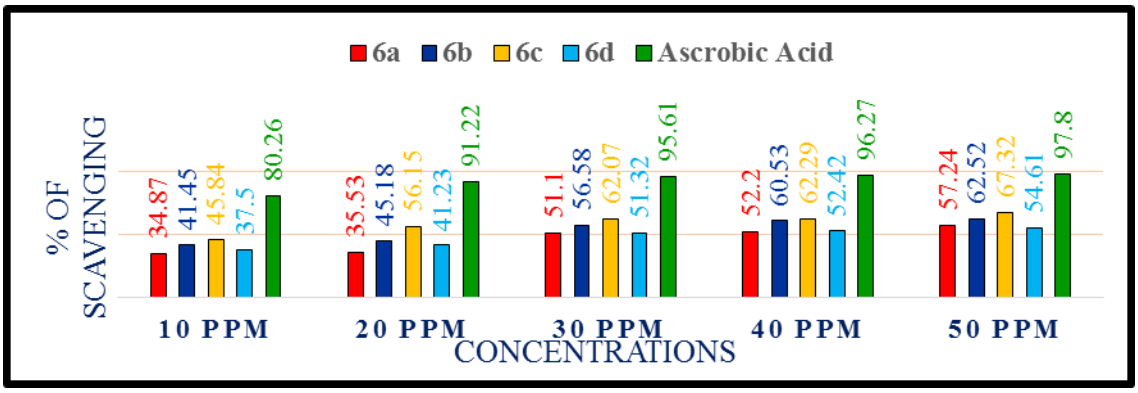

Figure 4: Showing % scavenging in Anti-oxidant analysis.

RESULTS AND DISCUSSION

The elemental analysis, H^1 NMR, Mass and IR spectral data were elucidated the proposed structures. The antibacterial activity of the compounds 6a-d performs against *Salmonella typhi* (gram -tive) and *Staphylococcus aureus* (gram +tive) bacteria at 50 µg/ml,100 µg/ml and 250 µg/ml concentrations and record the zone of inhibition with compare to standard Ofloxacin. In antifungal analysis, the compounds 6a-d shows activity against *Candida albicans* and *Aspergillus niger* at 50 µg/ml,100 µg/ml and 250 µg/ml concentrations by using standard Fluconazole. Anti-inflammatory activity of synthesized (6a-d) compounds determine % Inhibition at 10 ppm, 20 ppm and 30 ppm concentrations using standard drug Ibuprofen. Anti-oxidant activity of synthesized (6a-d) compounds determined % Scavenging at 10 µg/ml,20 µg/ml,30 µg/ml,40 µg/ml and 50 µg/ml concentration by using standard Ascorbic acid.

CONCLUSION

In the present work newly synthesized 2-Mercapto- 4-substituted phenyl, 6-(5-bromo, 2-hydroxy phenyl) Pyrimidines (6a-d) involves different steps to get good yield. The structure of synthesized compound was elucidated on the basis of ^{1}H-NMR, IR and Mass spectral data. In antibacterial activity only 6b compound shows moderate activity against Staphylococcus aureus at concentration 250 µgm.Antifungal activity compound 6b, 6c and 6d showed good activity against Aspergillus niger at concentration 50 µgm,100 µgm and 250 µgm. Antioxidant activity as indicated by absorbance at 517 nm of compounds 6a-d) increased with increasing concentration. Higher value of absorbance of the reaction mixture indicated greater reducing power. The reducing power was found to be in order of 6a>6c>6b>6d.Also compounds 6a-d exhibited significant anti-inflammatory activity by using albumin denaturation technique at 30 ppm concentration.

ACKNOWLEDGEMENTS

The author is thankful to the Principal, Vidyabharati Mahavidyalaya, Amravati for providing the laboratory facilities, encouragement. Also thankful to Director, SAIF Panjab University, Chandigarh for providing NMR, IR and Mass spectra analysis, Prof.Dr. Sharda Deore, Government Pharmacy College, Amravati for Pharmacological activity and Dr.S.R. Gulhane Microbiology Diagnostic Lab, Amravati for biocidal activity.

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