SUNTEXT REVIEWS

SunText Review of Pharmaceutical Sciences
ISSN: 2766-5232

Open Access
Research Article
Volume 4:1

Synthesis, Characterization and Biological Activity of 4-[2-Hydroxy-5-(Aryl-Diazenyl) Phenyl]-6-(Aryl) Pyrimidine Derivatives

Bhosale MT[1,*], Dighe PR[1] and Deshmukh AS[2]

[1]*Department of Pharmaceutical Chemistry, S.M.B.T. College of Pharmacy, India*
[2]*Department of Pharmaceutics, Indrayani Vidya Mandir's, Krishnarao Bhegade Institute of Pharmaceutical Education and Research, India*

[*]**Corresponding author:** Bhosale MT, S.M.B.T College of Pharmacy, Nandi Hills, Dhamangaon, Tal- Igatpuri, Dist-Nashik, India; E-mail: madhavibhosale2001@gmail.com

Received date: 20 November 2023; **Accepted date:** 30 November 2023; **Published date:** 06 December 2023

Citation: Bhosale MT, Dighe PR, Deshmukh AS (2023). Synthesis, Characterization and Biological Activity of 4-[2-Hydroxy-5-(Aryl-Diazenyl) Phenyl]-6-(Aryl) Pyrimidine Derivatives. SunText Rev Pharm Sci 4(1): 122.

DOI: https://doi.org/10.51737/2766-5232.2023.022

Abstract

In an effort to create novel heterocyclic compounds and investigate their biological potential, new chalcone and pyrimidine derivative series 4-(2-hydroxy-5-(aryl- diazenyl)phenyl)-6-(aryl) pyrimidin derivatives were synthesized by using various aromatic amines and 4-hydroxybenzaldehyde. The newly synthesized compounds and their structures were confirmed using IR spectroscopic technique. The in vitro antibacterial properties of the recently synthesized pyrimidine derivatives were examined. Several recently synthesized compounds were found to exhibit promising action against certain bacterial stains. According to research on antibacterial action, pyrimidine derivatives with nitro groups in their chemical structure have higher activity.

Keywords: Heterocyclic compounds; Chalcones; Pyrimidine; Anti-bacterial activity

Introduction

Pyrimidines are the heterocyclic aromatic compounds contain two nitrogen atoms at positions 1 and 3 of the six membered ring. Heterocycles containing pyrimidine moiety are very useful because they consist of an important class of natural and non-natural products, many of which exhibit useful biological activities and clinical applications. Pyrimidine is essential to numerous biological activities [1]. The ring system is seen in derivatives of nucleic acids. Primary components include vitamins (Vit B1), Alkaloids (Heteromines, Crambescins, Manzacidins, Variolins, Bleomycin), Toxins, Co-enzymes, Uric acid, and Purines [2-4]. Pyrimidines consists of important group of antibacterial drugs, which have made a great impact on the field of antibacterial chemotherapy predominantly from last few years. Pyrimidine nucleus act as chemotherapeutic agents and exhibit anticancer activities [5]. The nucleosides Cytosine, Thymine, and Uracil, Thiamine (vitamin B1), and Alloxan are among the many compounds and derivatives in nature that contain the pyrimidine ring system as substituted and ring fused compounds [6]. Numerous synthetic substances, including barbiturates and the HIV medication Zidovudine, also consist of pyrimidine moieties [7]. The presence of pyrimidine base in Thymine, Cytosine, and Uracil, which are the essential building blocks of nucleic acids DNA and RNA, is one important reason for their broad therapeutic applications [8]. Because of their tremendous practical value and broad range of biological functions, fused pyrimidines are still attracting a lot of study [9]. Pyrimidines and their derivatives are regarded as crucial elements in pharmaceuticals and agricultural chemicals. There is a lot of evidence that several pyrimidine derivatives have anti-mycobacterial [10], anti-tumour [11], anti-viral [12], anti-cancer [13], anti-inflammatory [14], cytotoxic [15], anti-microbial [16], anti-fungal and anti-oxidant [17] properties. Because these compounds exhibit a wide spectrum of pharmacological effects, our goal was to develop novel series of pyrimidine derivatives. Consequently, we outline the synthesis of several pyrimidine derivatives in this work.

Scheme

General procedure for the synthesis (1a-b)

The para-chloro aniline and the substituted derivatives of benzaldehyde (Aromatic amines (0.01moL) were added in conc. HCl (5 mL) and the mixture is then boiled for 10 minutes. The

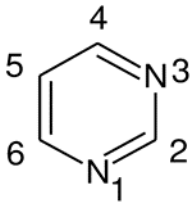
resulting solution was allowed to cool to 0–5∘C in ice bath. This solution was mixed with a dropwise addition of a cold, aqueous sodium nitrite (NaNO2) (0.01 moL, 10 mL) solution. Next, a vigorous stir was given to the reaction mixture. To obtain diazonium chloride solution, the reaction mixture's temperature has to be kept between 0 and 5 °C for at least an hour. The resultant diazonium solution was then gradually added to an alkaline suspension (10 mL, 0.01 moL) of 4-hydroxybenzaldehyde in water while stirring continuously to maintain a temperature range of 0–5∘C. The reaction mixture's pH was kept between 8 and 10 by concurrently adding 10% aqueous sodium hydroxide (NaOH) solution. The resulting reaction mixture was kept as it is for overnight. The obtained solid precipitate was filtered using Whatman filter paper and recrystallized using ethanol [18].

General procedure for the synthesis of chalcones (2a-f)

Ethanol (30 mL) was combined with compound (1a-b) and substituted aromatic ketones. The mixture was then thoroughly mixed at room temperature. 10 mL of a 20% aqueous NaOH solution was gradually added to this combination. For a minimum of 12 hours, the reaction mixture was swirled over the magnetic stirrer. The reaction mixture was then kept for overnight. It was then poured into beaker containing crushed ice. After neutralizing the excess alkali in the reaction mixture, a diluted hydrochloric acid solution was added dropwise to the reaction mixture, slightly acidifying it. The man filter paper was used to filter the chalcone derivative after it precipitated out. Using ethanol, the crude chalcone product was recrystallized [19].

General procedure for the synthesis (3a-f)

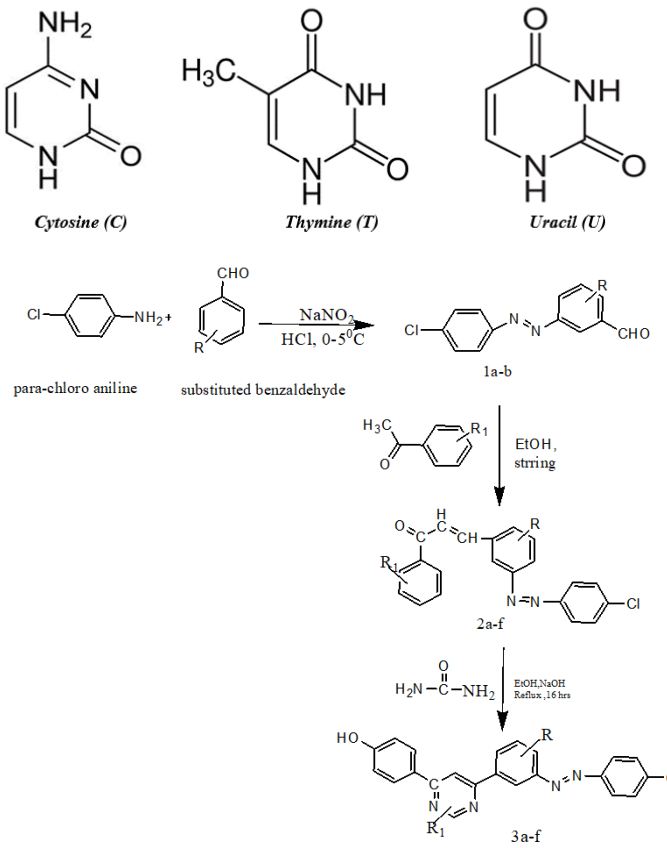
In 30 mL of ethanol, a solution of 2a-f (0.01moL) and urea (0.01moL) was made. Ten milliliters of a 20% aqueous NaOH solution were added to this mixture. After that, the mixture was refluxed for at least 16 hours on a water bath. After the mixture had reached room temperature, it was transferred into the beaker with the crushed ice. Pyrimidine derivatives precipitate out their solid byproduct. Whatman filter paper was used to filter the resultant solid, and ethanol was used to recrystallize it [18].



The structures and IUPAC names of synthesized compounds are as shown below in (Table 1).

IR Spectral Characterization

Comp. 3a (Str.) - 3252.1817 cm-1 OH, 3051.4695 cm-1 Sp2CH, 814.87 cm-1C-Cl, 1088.82 cm-1 C-N, 1636.92 cm-1 C=N, 1583,1488.53 cm-1 Ar C=C



Comp. 3b (Str.) – 3659.97 cm-1 O-H, 3137.48 cm-1 Sp2 CH, 2850.75 cm-1 Sp3 CH, 809.27 cm-1 C-Cl, 1087.81 cm-1 C-N, 1684.71 cm-1 C=N, 1588.43, 1487 cm-1 Ar C=C

Comp. 3c (Str.) – 3631.30 cm-1 O-H, 3040.53 cm-1 Sp2CH, 810.25 cm-1 C-Cl, 1088.44 cm-1 C-N, 1584.80 cm-1 , 1487 cm-1 Ar C=C, 607.87 cm-1 C-Br

Comp. 3d (Str.) –3390.87 cm-1 O-H, 3076.95 cm-1 Sp2CH, 2825.27 cm-1 Sp3CH, 822.48 cm-1 C-Cl, 1267.36 cm-1 C-N, 1632.43 cm-1, 1434.64cm-1 Ar C=C

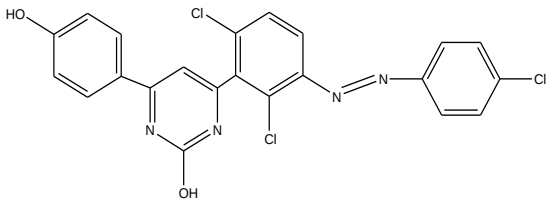
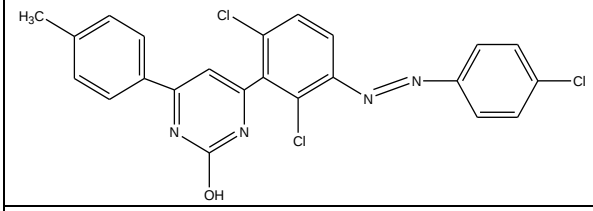
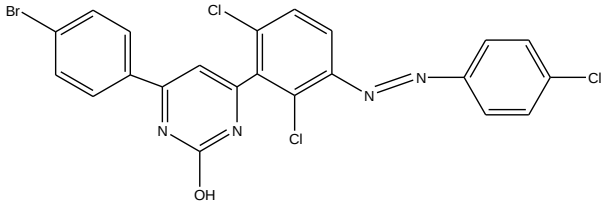
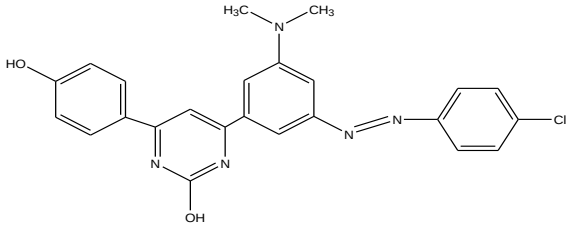
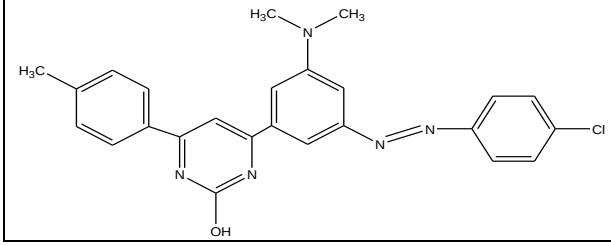
Comp. 3e (Str.) –3647.23 cm-1 O-H, 3051.46 cm-1 Sp2CH, 2901.73cm-1 Sp3CH, 814.70 cm-1 C-Cl, 1090.97 cm-1 C-N, 1694.27 cm-1 C=N, 1583.26 cm-1,1529.26cm-1 Ar C=C

Antimicrobial Activity

The newly synthesized compounds were tested using the well diffusion method against a panel of several gram-positive and gram-negative bacterial strains to determine their antibacterial activity. Bacterial strains used for the screening were S. aureus (gram Positive) and E. coli (gram Negative). For the study, stock solutions of conventional drugs or pyrimidine derivatives in dimethyl sulfoxide (DMSO) at a concentration of 100 μg/mL were

created. In this work, agar medium and sanitized petri plates were used. Zone of inhibition measurements on nutrient agar plates were used to assess the antibacterial activity of several substances. After thoroughly mixing the nutrient agar medium, it was autoclaved for at least 15 minutes at 120°C and 15 pounds of pressure. The bacterial cultures were introduced to 10 mL of sterilized agar media. Bacterial suspensions were employed for additional testing following a 36-hour incubation period. Petri plates were filled with this material, which was then left to set.

Table 1: *IUPAC name of synthesized compounds.*

Compounds	IUPAC Name
3a 	4-[2,6-Dichloro-3-(4-chloro-phenylazo)-phenyl]-6-(4-hydroxy-phenyl)-pyrimidin-2-ol
3b 	4-[2,6-Dichloro-3-(4-chloro-phenylazo)-phenyl]-6-p-tolyl-pyrimidin-2-ol
3c 	4-(4-Bromo-phenyl)-6-[2,6-dichloro-3-(4-chloro-phenylazo)-phenyl]-pyrimidin-2-ol
3d 	4-[3-(4-Chloro-phenylazo)-5-dimethylamino-phenyl]-6-(4-hydroxy-phenyl)-pyrimidin-2-ol
3e 	4-[3-(4-Chloro-phenylazo)-5-dimethylamino-phenyl]-6-p-tolyl-pyrimidin-2-ol

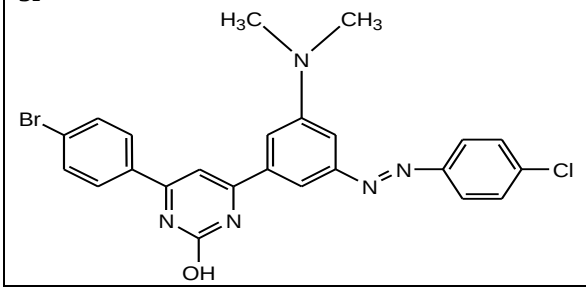
3f 	4-(4-bromo-phenyl)-6-[3-(4-chloro-phrnylazo)-5-dimethylamino-phenyl]-pyrimidin-2-ol

Table 2: *Physical data of synthetic compounds.*

Comp. Code	Molecular formula	Mole. Wt.	R	R_1	Melting Point (°C)	% yield	Rf value
3a	$C_{22}H_{13}Cl_3N_4O_2$	471.72	2,6 dichloro	p-OH	246-248	78	0.92
3b	$C_{24}H_{19}Cl_3N_4O$	485.79	p-dimethylamino	p-CH_3	250-253	75.5	0.78
3c	$C_{23}H_{16}BrCl_3N_4O$	550.66	2,6 dichloro	p-Br	256-258	80.3	0.85
3d	$C_{24}H_{20}ClN_5O_2$	445.90	p-dimethylamino	p-OH	260-262	83.0	0.77
3e	$C_{25}H_{22}ClN_5O$	443.93	2,6 dichloro	p-CH_3	253-256	88	0.78
3f	$C_{24}H_{19}BrClN_5O$	508.80	p-dimethylamino	p-Br	255-258	66	0.56

Table 3: *Antimicrobial activity of synthesised pyrimidine derivatives.*

Compound	Average zone of inhibition in mm	
	S. aureus	***E. coli***
3a	22	-
3b	20	21
3c	-	18
3d	20	19
3e	25	24
3f	21	20
Ciprofloxacin	30	31

A 5 mm cork borer was used to drill two wells. 0.1 mL of test sample and standards were placed in this well. For a whole day, every nutrient agar plate was incubated at 37°C in order to evaluate the effects of microorganisms. We observed petri plates for a distinct zone of inhibition on the plates. The zones of inhibition for these substances were then measured in diameter. The biological activities were tested for the compounds against microorganisms and average value has been reported here [20,21]. The results of antimicrobial activity of the test compounds have been collected in (Table 2,3).

Results and Discussion

A new series of chalcones (2a-f), and pyrimidines derivatives (3a–f), were synthesized as depicted in Scheme. The first stage was the equimolar reaction of aromatic amines with 4-hydroxybenzaldehyde to produce various azo-aldehydes (1a-b). The typical process used in this work to synthesize chalcones (2a–f) is reacting equimolar amounts of different substituted azo-aldehydes with p-hydroxyacetophenone, p-methylacetophenone, and p-bromoacetophenone in an ethanolic alkaline medium. The process of refluxing freshly synthesized substituted chalcones and urea in ethanol in the presence of an aqueous NaOH solution yielded pyrimidine derivatives (3a–f). The reaction mixture was then cooled in crushed ice. The newly created chemicals were described using infrared spectroscopy. The in vitro antibacterial efficacy of the recently synthesized pyrimidines and chalcones against both gram-positive and gram-negative bacteria was assessed. A conventional medication called ciprofloxacin was utilized to compare with newly created substances. The pyrimidine compound (3a-f) showed a variable range zone of inhibition,

according to the values survey. The majority of the substances have demonstrated well to moderate biological activity against the strains of bacteria. Compounds 3e have shown excellent activity against both gram positive and gram-negative bacterial strains as compared with the standard drug Ciprofloxacin.

Conclusion

A series of chalcones, and pyrimidines derivatives were synthesized. All the newly synthesized compounds were characterized spectroscopically using analytical techniques i.e., IR. Anti-bacterial studies reveal that compounds 3e have shown the highest activity among all newly synthesized compounds when compared with standard drug.

Acknowledgement

Authors are thankful to Principal and management of SMBT COP and IVM's KBIPER for providing necessary facilities to carry out this research work.

References

1. Ravi Kumar K, Sumanjali KNSS, Chandana MP, Srilatha N, Koteswara Rao P. Synthesis, characterization and anti-microbial activity of novel pyramidine derivatives. J Drug Deliv Ther. 2021; 11: 98-102.
2. Bhat AR. Biological activity of pyrimidine derivativies : a review. Org Med Chem. 2017; 1-4.
3. Sulistyowaty MI, Nofianti KA, Budiati T. Synthesis and brine shrimp bioassay of chalcone and its two Methoxy derivatives. Int J Pharmamceutical Chem Res. 2013; 2: 719-724.
4. Bhoi MN, Patel KD, Rajani SD. Microwave assisted synthesis, biological characterization and docking studies of pyrimidine derivatives. Curr Microw Chem. 2016; 3: 186-178.
5. Ali N, Elkanzi A. Synthesis and biological activities of some pyrimidine derivatives : a review. Orient J Chem. 2020; 36: 1001-1015.
6. Sahoo BM, Rajeswari M, Jnyanaranjan P, Binayani S. Green expedient synthesis of pyrimidine derivatives via chalcones and evaluation of their anthelmintic activity. Indian J Pharm Educ Res. 2017; 51: 701-706.
7. Sharma V, Chitranshi N, Agarwal AK. Significance and biological importance of pyrimidine in the microbial world. Int J Med Chem. 2014: 1-31.
8. Mohamed MS, Awad SM, Ahmed NM. Synthesis and antimicrobial activities of new indolyl -pyrimidine derivatives. J Appl Pharm Sci. 2011; 1: 76-80.
9. Wardakhan WW, Hamed FI, Samir EM. Synthesis and cytotoxic activity of novel tetrahydobenzo[b]thiophenee-derived heterocycle. Eur Chem Bull. 2016; 5: 82-87.
10. Ishak CY, Metwally NH, Wahbi HI. In-vitro Antimicrobial and antifungal activity of pyrimidine and pyrazolo- [1, -a] pyrimidine. Int J Pharm Phytopharm Res. 2013; 2: 407-411.
11. Abdo NYM. Synthesis and antitumor evaluation of novel dihydropyrimidine, thiazolo [3,2- a] pyrimidine and pyrano [2,3-d] pyrimidine derivatives. Anal Chim Acta. 2015; 62: 168-180.
12. Zone NS, Birhanu T. Survey and antimicrobial activity study of ethnomedicinal plants in selected districts of north Shewa zone, Oromia, Ethiopia. Infect Drug Resist. 2021; 5511-5520.
13. Kantankar A, Rao YJ, Mallikarjun G, Hemasri Y. Rational design, synthesis, biological evaluation and molecular docking studies of chromone-pyrimidine derivatives as potent anti-cancer agents. J Mol Struct. 2021; 1239: 130502.
14. Basha NJ, Goudgaon NM. A comprehensive review on pyrimidine analogs-versatile scaffold with medicinal and biological potential. J Mol Struct. 2021; 1246: 131168.
15. Apu AS, West E, Road M, City JI. Assesment of cytotoxic activity of two medicinal plants using brine shrimp (Artemai salina) as an experimental tool. Int J Pharm Sci Res. 2013; 4: 1125-1130.
16. Nascimento GGF, Locatelli J, Freitas PC, Silva GL, Piracicaba UM De. Antibacterial activity of plant extract and phytochemicals on antibiotic- resistant bacteria. Brazilian J Microbiol. 2000; 31: 247-256.
17. Adhikari A, Kalluraya B, Sujith KV, Chandra G, Mahmood R. Synthesis, characterization and biological evaluation of dihydropyrimidine derivatives. Saudi Pharm J. 2012; 20: 75-79.
18. Pandhurnekar CP, Meshram EM, Chopde HN, Batra RJ. Synthesis, characterization, and biological activity of derivatives. Org Chem Int. 2013; 11-21.
19. Gb R, Sn L, Ma B. Synthesis, characterisation and antimicrobial activity of some pyrimidine derivatives from chalcones. Recent Trends Math Phys Chem Libr. 2020; 37-47.
20. Deshmukh AS, Dighe PR, Shelke SJ. Estimation of antibacterial activity of crude extracts of the vetia peruviana. Int J Microbiol Curr Res. 2019; 1: 23-25.
21. Fayed AA, El-farargy AF, Yousif NM, Gad FA, Kalmouch AA, Fayed AA. Synthesis, anti-microbial evaluation and cytotoxicity bioassay of some synthesized novel pyridazine derivatives comparison to standard drugs. Der Pharma Chem. 2015; 7: 316-322.