Synthesis of 3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one Derivatives by one pot, three Component Reaction and their Antimicrobial Activity

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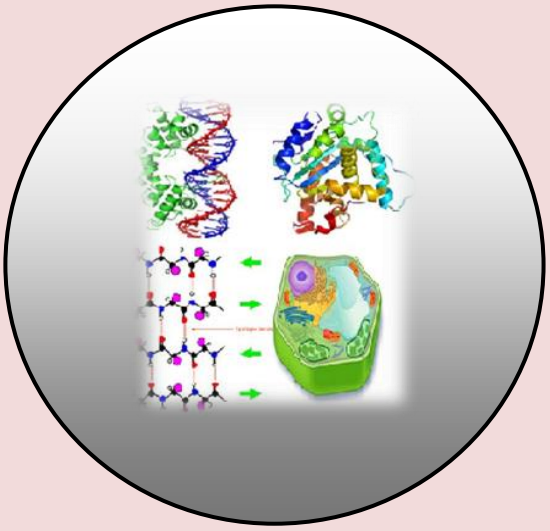

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RESEARCH PAPER

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Synthesis of 3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one Derivatives by one pot, three Component Reaction and their Antimicrobial Activity

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ABSTRACT

A series of novel urea analogs of 3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one derivatives of biological interest were designed and synthesized by biginelli reaction, and their structures were characterized by various spectroscopic methods such as UV, IR, ^{1}H, $^{13}CNMR$ and mass spectral analysis. This protocol has a simple work-up process and shows advantages of broad substrate scope. Their antimicrobial activity against a panel of various bacterial strains (Staphylococcus aureus, Bacillus subtilis and Pseudomonas aeruginosa) was evaluated, and the result suggested that all the compounds showed lesser activities against reference drug (Ampicillin). These compounds with different substituents, namely 4a-h displayed very desperate in vitro antimicrobial activity.
Keywords: Antibacterial Drug, Absorption and Screening.

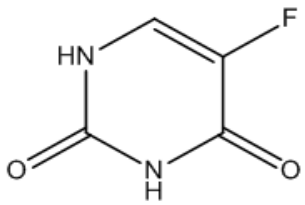
INTRODUCTION

There are several pyrimidines which have been procured from the nucleic acid hydrolyses such as uracil, thymine and cytosine. All the cells contain nucleic acids as an essential constituent and it has been discovered that all living matters contain cytosine which is present in both types of nucleic acids i.e. ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) while uracil and thymine are present only in RNA and DNA respectively (Agarwal 2006). Besides this, vitamin B1, barbituric acid (2, 4, 6-trihydroxy pyrimidine) and its several derivatives e.g. Veranal, which are used as hypnotics, also possess pyrimidine ring (Jain et al. 2008). Exhausted literature review reveals that there are a diverse number of compounds, having pyrimidine nucleus, which exhibit a broad range of biological activities. These heterocyclic nuclei have attracted a large number of chemist and developed their interest in synthesis of compounds having nitrogen in their heterocyclic ring. There are large number of compounds that possess heterocyclic moiety show a wide range of pharmacological activity like, 5-flourouracil shows anticancer activity; Idoxuridine and Triflouridine show antiviral activity; Zidovudine and Stavudine posess anti-HIV activity; Trimethoprim, Sulphamethiazine, Sulphadiazine exhibit antibacterial activity; Minoxidil and Prazosin serve as antihypertensive drug; Phenobarbitone used as sedative-hypotic and anticonvulsant; Propylthiouracil, Thinozylamine show antithyroid and H_{1}- antihistaminics

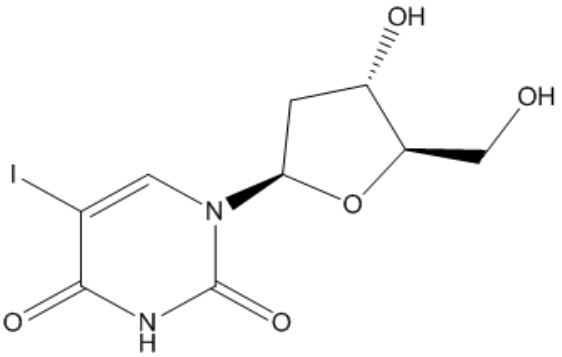
activitives respectively; Fervennuline used as antibiotics (Gavilan et al. 2008), anticancer (Ahmed et al. 2009, Mohamed et al. 2007, Amr et al. 2006), and antitumor drug (Gangjee et al. 2010, Ajam et al. 2008, Amin et al. 2009, Kraljevic et al. 2010). Heterocyclic moieties containing nitrogen represent a class of molecules of great importance in organic chemistry and play an important role in our daily life. These structures are found in many natural products and, are responsible for the activity of compounds. These types of compounds are playing important role in medicinal chemistry. A detailed study of literature suggested the prominent biological properties and wide range applications of nitrogen heterocycles (Verma et al. 2017). The chemistry of pyrimidines is a promising field for the study of their biological and pharmacological uses.

Many antimicrobial products are being used in the world market, but successful treatment of bacterial infections is becoming the difficult task as resistance to current agents becomes more widespread. So many new classes of antimicrobial agents are being provided to the market in recent years; there is still an urgent need for the devolvement of effective agents that offer fruitful treatment against pathogen. Pyrimidinone nucleus possesses broad range of pharmacological properties such as calcium channels blockers, antioxidant, anticancer, and anti-inflammatory activity. These properties of pyrimidinone attracted the attention of synthetic chemists. Furthermore, there are a number of marine natural products containing dihydropyrimidine-5-carboxylate core that are potent HIVgp-120-CD4. There are many biologically important heterocyclic derivatives of ureas which have been reported in the literature. For example, N-2,4-pyrimidine-N–N0-phenyl/alkyl ureas had been reported as TNF-a inhibitor(Brugel et al. 2006, Maier et al. 2006), pyrido-quinazolone analogs exhibit antifungal, antibacterial, and anticancer activities (Tiwari et al. 2006).

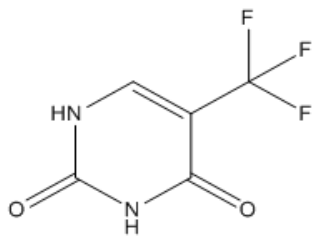
From the literature survey it had been found that these types of compounds (title compounds) were synthesized by multicomponent biginelli type condensations of cycloalkanones (except cycloheptanone), urea or thiourea and aldehydes (Zhu et al. 2005). However, to the best of our knowledge, there has been no report on synthesis and evaluation of biological activities of 3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one derivatives. Thus, in order to design and develop new potential biologically active compounds, synthesis of 3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one derivatives 4a-4h and evaluation of their antimicrobial activities have been done.



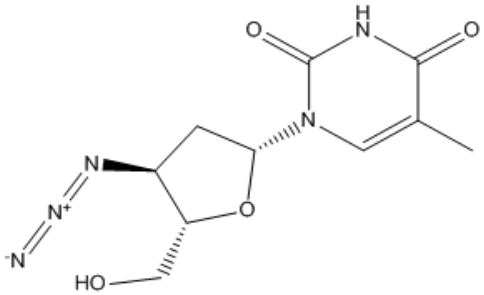
5-flourouracil



5-Iodo-2'-deoxyuridine (Idoxuridine)



5-Trifluoromethyl-2,4(1H,3H)-pyrimidinedione (Triflouridine)



Zidovudine

Pyrimidone scaffold containing Drugs

Experimental Section

MATERIALS AND METHODS

All chemicals were purchased from Alfa Aesar and Sigma–Aldrich. Perkin–Elmer FTIR spectrophotometer and Bruker 300 MHz instrument were used for recording Infrared (IR) spectrum and ^{1}H and ^{13}CNMR spectra respectively. The DART-MS of compound was recorded on a JEOL AccuTOF JMS-T100LC mass spectrometer having a DART source. UV spectrum was recorded on UV–visible Double-Beam Spectrophotometer (systronic-2203) instrument. DMSO-d_6 was used as solvent. Melting point was determined in a melting point apparatus and is uncorrected.

General procedure for the synthesis of compounds (4a-4h)

0.01mol of cycloheptanone (1), 0.006mol of substituted benzaldehyde (2a-2h) and 0.015mol of urea (3) were dissolved in 10 ml of ethanol. To this mixture was added 4-5 drops of conc. HCl. The reaction mixture was refluxed for 8-10 h on a water bath and the completion of reaction was monitored on TLC and the reaction mixture was left overnight. The solid thus formed was collected, washed with luke warm water and recrystallized with ethanol (Zhu et al. 2005).

4-(4-chlorophenyl)-3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one (4a): White colored powder , yield: ~52%; m.p.:220˚C; Rf value: 0.704 (70% Hexane: Ethyl Acetate); IR (KBr) v_{max}: 3424-3243 (N-H stretching), 3091 (=C-H stretching), 1696 (C=O stretching); The ^{1}HNMR (300 MHz, in $CDCl_3$): δ = 1.17-2.309 (m, 10H), 6.7 (s, NH), 9.91 (s, NH), 7.436-7.775(m, 4H), 7.436 (s, 1H); ^{13}CNMR ($CDCl_3$): δ = 25.58, 27.82, 30.04, 31.42, 43.57, 128.83, 130.83, 134.18, 134.46, 134.59, 141.43, 204.85; MS, m/z: 277.1099.

4-(4-nitrophenyl)-3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one (4b): Yellow colored powder , yield: ~48%; m.p.: 190˚C; Rf value: 0.69 (70% Hexane: Ethyl Acetate); IR (KBr) v_{max}: 3440-3261 (N-H stretching); 3086 (=C-H stretching); 1705 (C=O stretching); The ^{1}HNMR (300 MHz, in $CDCl_3$): δ = 1.12-1.92 (m, 10H), 6.6 (s, NH), 9.88 (s, NH), 8.1-8.5(m, 4H), 7.38 (s, 1H); ^{13}CNMR ($CDCl_3$): δ = 24.80, 27.45, 30.01, 31.25, 42.95, 128.1, 128.90, 133.69, 134.86,135.02, 141.20, 203.56; MS, m/z: 287.13.

4-phenyl-3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one (4c): White colored powder, yield: ~55%; m.p: 200˚C; Rf value: 0.71 (70% Hexane: Ethyl Acetate); IR (KBr) v_{max}: 3421-3241 (N-H stretching), 3088 (=C-H stretching), 1685 (C=O stretching); The ^{1}HNMR (300 MHz, in $CDCl_3$): δ = 1.05-1.88 (m, 10H), 6.2 (s, NH), 9.72 (s, NH), 7.7-7.92 (m, 5H), 7.28 (s, 1H); ^{13}CNMR ($CDCl_3$): δ = 24.98, 27.02, 29.27, 31.32, 42.79, 127.9, 128.86, 133.75, 134.04, 134.21, 140.57, 203.98; MS, m/z: 242.74.

4-(2-chlorophenyl)-3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one (4d): White colored powder, yield: ~50%; m.p.: 150; Rf value: 0.73 (70% Hexane: Ethyl Acetate); IR (KBr) v_{max}: 3424-3244 (N-H stretching), 3095 (=C-H stretching), 1698 (C=O stretching); The ^{1}HNMR (300 MHz, in $CDCl_3$): δ = 1.09-2.31 (m, 10H), 6.8 (s, NH), 9.92 (s, NH), 7.41-7.75(m, 4H), 7.41 (s,1H); ^{13}CNMR ($CDCl_3$): δ = 25.52, 27.84, 30.10, 31.60, 43.50, 128.80, 130.86, 134.05, 134.55, 134.60, 141.31, 204.67; MS, m/z: 277.1099.

4-(4-hydroxyphenyl)-3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one (4e): brown colored powder, yield: ~60%; m.p: 185˚C; Rf value: 0.70 (70% Hexane: Ethyl Acetate); IR (KBr) v_{max}: 3647 (OH stretching), 3415-3242 (N-H stretching), 3086 (=C-H stretching), 1694 (C=O stretching); The ^{1}HNMR (300 MHz, in $CDCl_3$): δ = 1.15-2.4 (m, 10H), 5.9 (s,OH), 6.8 (s, NH), 9.88 (s, NH), 7.42-7.78(m, 4H), 7.39 (s, 1H); ^{13}CNMR ($CDCl_3$): δ = 25.75, 27.71, 30.33, 31.58, 44.02, 128.70, 129.9, 134.15, 134.08, 134.91, 140.83, 204.75; MS, m/z: 258.32.

4-(2-hydroxyphenyl)-3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one (4f): Brown colored powder, yield: ~58%; m.p: 195˚C; Rf value: 0.71 (70% Hexane: Ethyl Acetate); IR (KBr) v_{max}: 3667 (OH stretching), 3415-3242 (N-H stretching), 3086 (=C-H stretching), 1694 (C=O stretching);

The ^{1}HNMR (300 MHz, in $CDCl_3$): δ = 1.1-2.2 (m, 10H), 6.8 (s, OH), 6.82 (s, NH), 9.86 (s, NH), 7.0-7.8 (m, 4H), 7.40 (s, 1H); ^{13}CNMR ($CDCl_3$): δ = 25.15, 27.79, 30.38, 31.66, 44.22, 128.83, 128.88, 134.08, 134.11, 134.87, 140.71, 204.69; MS, m/z: 258.32.

4-(4-hydroxy-3-methoxyphenyl)-3,4,6,7,8,9-hexahydro-1h-cyclohepta-pyrimidin-2(5H)-one (4g): Dark brown colored powder, yield: ~62%; m.p: 160˚C; Rf value: 0.65 (70% Hexane: Ethyl Acetate); IR (KBr) v_{max}: 3656 (OH stretching), 3422-3258 (N-H stretching), 3094 (=C-H stretching), 1703 (C=O stretching); The ^{1}HNMR (300 MHz, in $CDCl_3$): δ = 1.2-2.02 (m, 10H), 3.85 (s, 3H), 6.1 (s, OH), 7.1 (s, NH), 10.0 (s, NH), 7.48-7.86 (m, 3H), 7.447 (s, 1H); ^{13}CNMR ($CDCl_3$): δ = 25.86, 28.27, 30.98, 32.54, 45.32, 56.06, 129.02, 129.05, 134.88, 134.25, 135.08, 141.13, 204.82; MS, m/z: 288.15.

4-(4-flurophenyl)-3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one (4h): White colored powder, yield: ~53%; m.p: 212°C; Rf value: 0.72 (70% Hexane: Ethyl Acetate); IR (KBr) v_{max}: 3424-3245 (N-H stretching), 3092 (=C-H stretching), 1696 (C=O stretching); The ^{1}HNMR (300 MHz, in $CDCl_3$): δ = 0.82-2.2 (m, 10H), 6.8 (s, NH), 9.97 (s, NH), 7.4-7.78 (m, 4H), 7.39 (s, 1H); ^{13}CNMR ($CDCl_3$): δ = 25.50, 27.86, 29.95, 30.85, 43.59, 128.86, 130.88, 134.23, 134.43, 133.80, 140.98, 204.75; MS, m/z: 260.13.

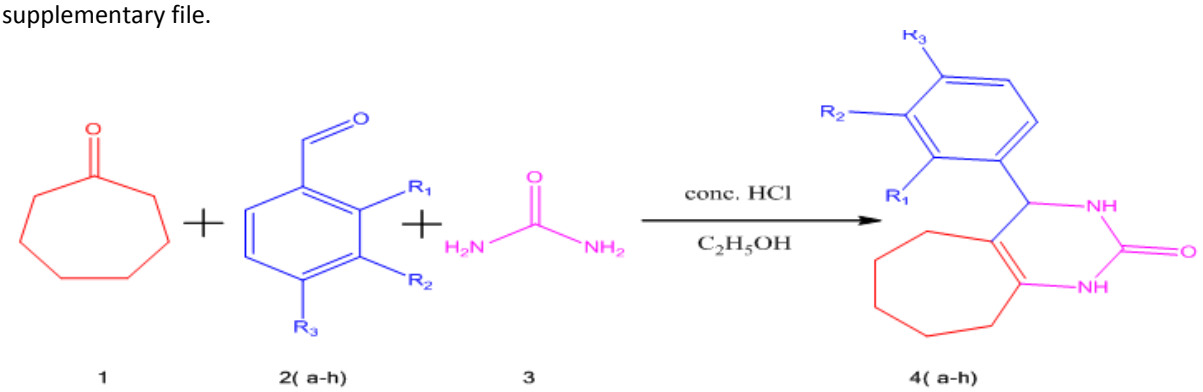
Atom in molecule (AIM approach)

The strength of hydrogen bond can be characterized by topological parameters. The interactions may be classified as per Rozas *et al.* (Rozas et al. 2000) as: (i) strong H-bonds are $\nabla^2\rho_{(BCP)} < 0$ and $H_{BCP} < 0$ (ii) Medium H-bonds are $\nabla^2\rho_{(BCP)} > 0$ and $H_{BCP} < 0$ and (iii) Weak H-bonds are $\nabla^2 \rho_{(BCP)} > 0$ and $H_{BCP} > 0$. Molecular graph of the compound (4a) at B3LYP/6- 31G (d, p) level using AIM program is presented in Figure 3. Figure 3 shows that there no hydrogen bonding in the molecule 4a.

RESULTS AND DISCUSSION

Chemistry

The chemical route involved in the synthesis of 4a–h is illustrated in Scheme 1 and Figure 1 shows the possible reaction route for this reaction. A key intermediate 1-[(2-oxocycloheptyl) phenylmethyl] urea was synthesized by reaction of substituted benzaldehyde(2a) and urea(3) followed by addition of cycloheptanone (1). Further this intermediate underwent cyclization with elimination of water to produce the final product (4a-4h). This process devoid of any purification by chromatographic methods and analytically pure products were obtained by simple washing of product with luke warm water followed by recrystallization with ethanol. The reaction was carried out under mild condition and products were characterized by various spectroscopic methods. From literature it is well known IR spectrum of primary amide group (urea) shows a double band in the region 3140-3500cm^{-1}, this band is replaced by a single band in the same region which appeared due to the N-H stretching of secondary amide group of product 4a. ^{1}HNMR of product 4a shows two singlet at δ 9.91 ppm and 6.7 ppm (-NH-, proton), and signal due to aldehydic proton at δ 10 ppm disappear in product 4a but signal due to aromatic protons of aromatic aldehyde present in spectrum. Carbon of carbonyl group of cycloheptanone and aromatic aldehyde shows signal at δ 214 ppm and 200 ppm respectively. ^{13}CNMR spectrum of product 4a shows a signal at δ 204 ppm which appeared due to carbon of -NH-CO-NH- . The UV spectrum of compound 4a shows a λ_{max} peak at 220 nm, also in agreement with the proposed structure and, solvent used for obtaining UV spectrum was DMSO. UV-visible, IR, mass, ^{1}H and ^{13}C spectrum of compound 4a was given in supplementary file.



Scheme 1. Synthetic routes for synthesis of pyrimidine derivatives.

Comp	R1	R2	R3	Comp	R1	R2	R3
4a	H	H	Cl	**4e**	H	H	OH
4b	H	H	NO2	**4f**	OH	H	H
4c	H	H	H	**4g**	H	OCH3	OH
4d	Cl	H	H	**4h**	H	H	F

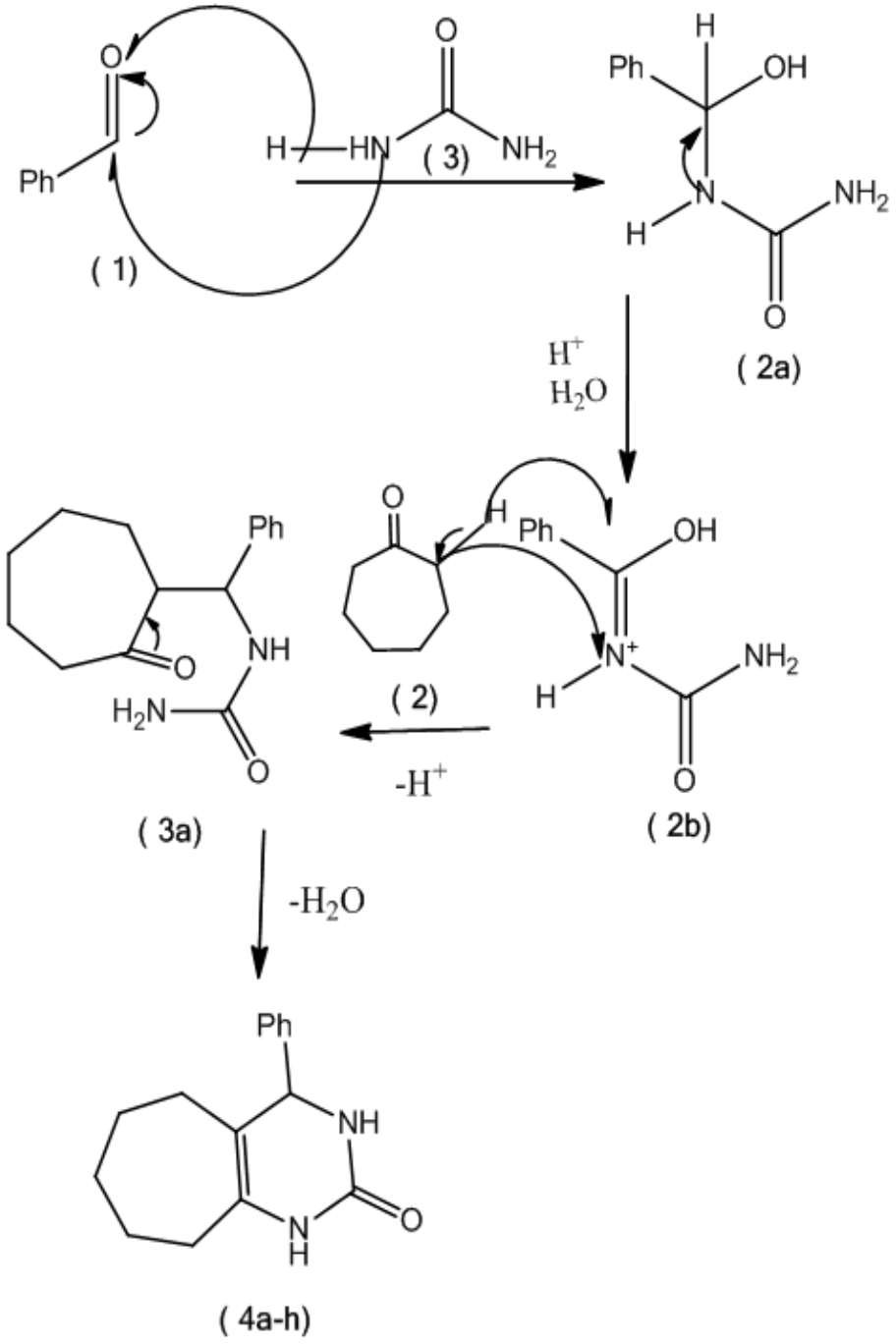


Figure 1. Plausible reaction Mechanism for the formation of Compounds 4(a-h).

Biological assay

These newly synthesized series (compounds 4a-4h) were evaluated for in vitro antibacterial activity against two gram-positive bacterial strains (*Bacillus subtilis and Staphylococcus aureus*) and a gram-negative bacterial strain (*Pseudomonas aeruginosa*) using agar-well diffusion method (Bauer et al. 1966) and a comparative antibacterial activity plot of compounds 4a-h with standard drug ampicillin and bacterial strain were given in Figure 2a and Figure 2b.

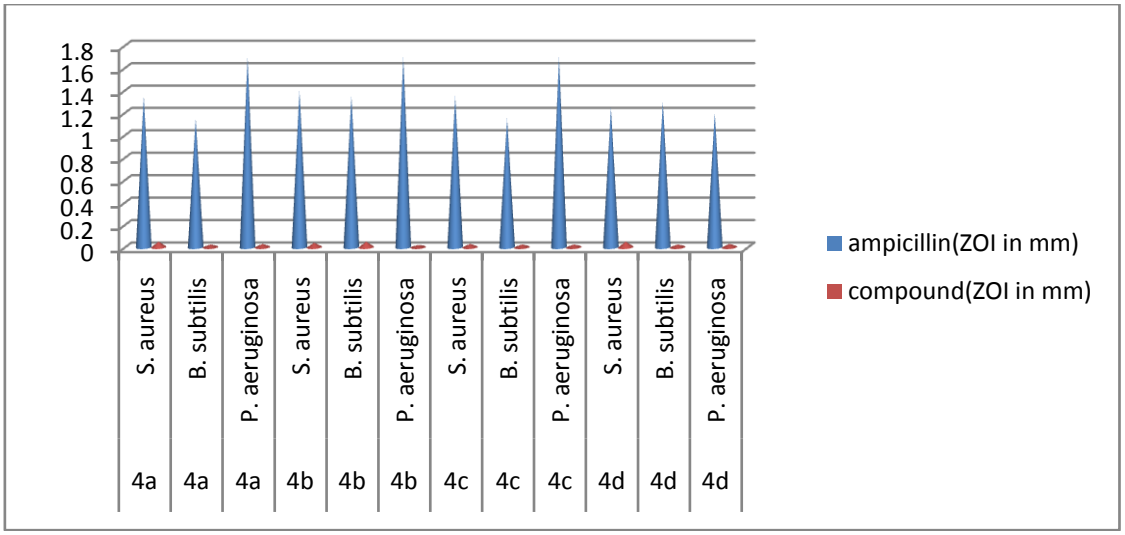


Figure 2a. Activity plot of 4a-d showing comparative antibacterial activity with ampicillin and pathogens.

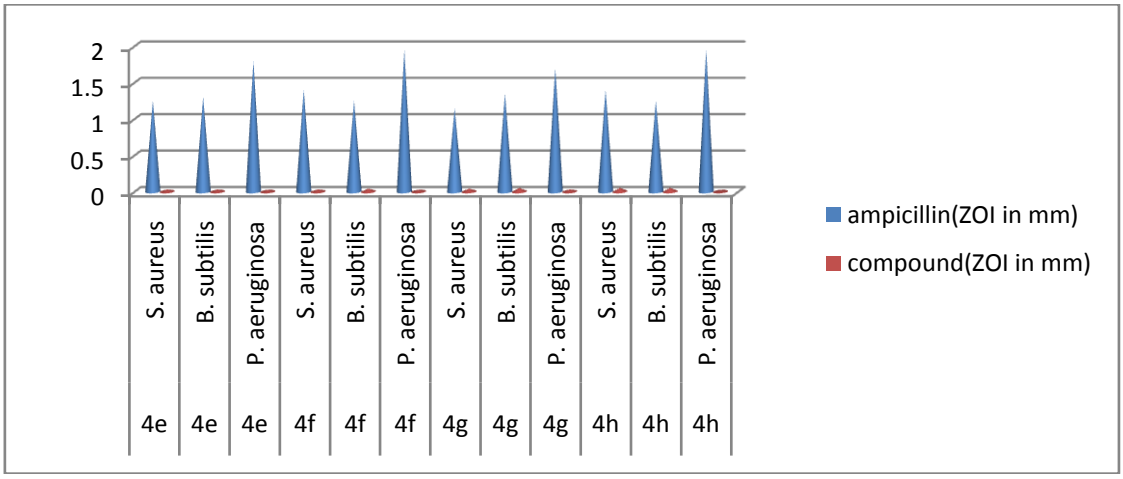


Figure 2b. Activity plot of 4e-h showing comparative antibacterial activity with ampicillin and pathogens.

Table 1. Antibacterial activity of synthesized compound 4a-4h against diverse strains (diameter of zone of inhibition).

compound	Bacterial Strains	Zone of Inhibition [ZOI (in mm)]		compound	Bacterial Strains	Zone of Inhibition [ZOI (in mm)]	
		Ampicillin	compound			Ampicillin	compound
4a	*S. aureus*	1.35	0.05	4e	*S. aureus*	1.25	0.03
	B. subtilis	1.15	0.025		*B. subtilis*	1.3	0.03
	P. aeruginosa	1.7	0.03		*P. aeruginosa*	1.8	0.025
4b	*S. aureus*	1.4	0.04	4f	*S. aureus*	1.4	0.03
	B. subtilis	1.35	0.05		*B. subtilis*	1.25	0.04
	P. aeruginosa	1.7	0.02		*P. aeruginosa*	1.95	0.025
4c	*S. aureus*	1.35	0.03	4g	*S. aureus*	1.15	0.04
	B. subtilis	1.15	0.025		*B. subtilis*	1.35	0.05
	P. aeruginosa	1.7	0.025		*P. aeruginosa*	1.7	0.03
4d	*S. aureus*	1.25	0.05	4h	*S. aureus*	1.4	0.05
	B. subtilis	1.3	0.025		*B. subtilis*	1.25	0.05
	P. aeruginosa	1.2	0.03		*P. aeruginosa*	1.95	0.015

Agar well diffusion method

In this method solidification of the nutrient agar medium was done in sterile petriplates and spreading was carried out for bacterial pathogens (*Bacillus subtilis, Pseudomonas aeruginosa and Staphylococcus aureus*). Standard method was applied to prepare wells and each well of nutrient agar medium was loaded with 100 µl of antibiotics with bacterial lawn. All these plates were kept for overnight in an incubator at 37˚C Antibiotic sensitivity was considered by taking the average zone of inhibition (in mm).

Biological result

The result of antimicrobial activity was summarized in table 1, measuring the zone of inhibition in mm. The antibacterial activity was compared with standard drug ampicillin.

This series of compounds (4a-4h) did not show the expected activity. All the compounds (4a-4h) were found inactive against *Staphylococcus aureus, Bacillus subtilis* and *Pseudomonas aeruginosa.*

CONCLUSION

The study reports the successful synthesis of some new 3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one(4a-h) derivatives. The final synthesized compounds were characterized by their spectral data (IR, ^{1}H-NMR, ^{13}C-NMR, Mass). Both the synthesis and antimicrobial activity (against *Staphylococcus aureus, Bacillus subtilis* and *Pseudomonas aeruginosa*) of the final compounds 4a-h were done for the first time to the best of our knowledge. None of the newly synthesized compounds, 4a-h could inhibit any of the bacterial strains investigated. Though several pyrimidines compounds are reported to show many pharmacological activities but these particular compounds did not show any antibacterial activity. Therefore a more extensive study is needed to obtain newer biologically active derivatives of 3,4,6,7,8,9-hexahydro-1H-cyclohepta-pyrimidin-2(5H)-one. This result put forth an idea that more different types of active pharmacophores should be incorporated into the synthesized molecules so as to enhance their activity.

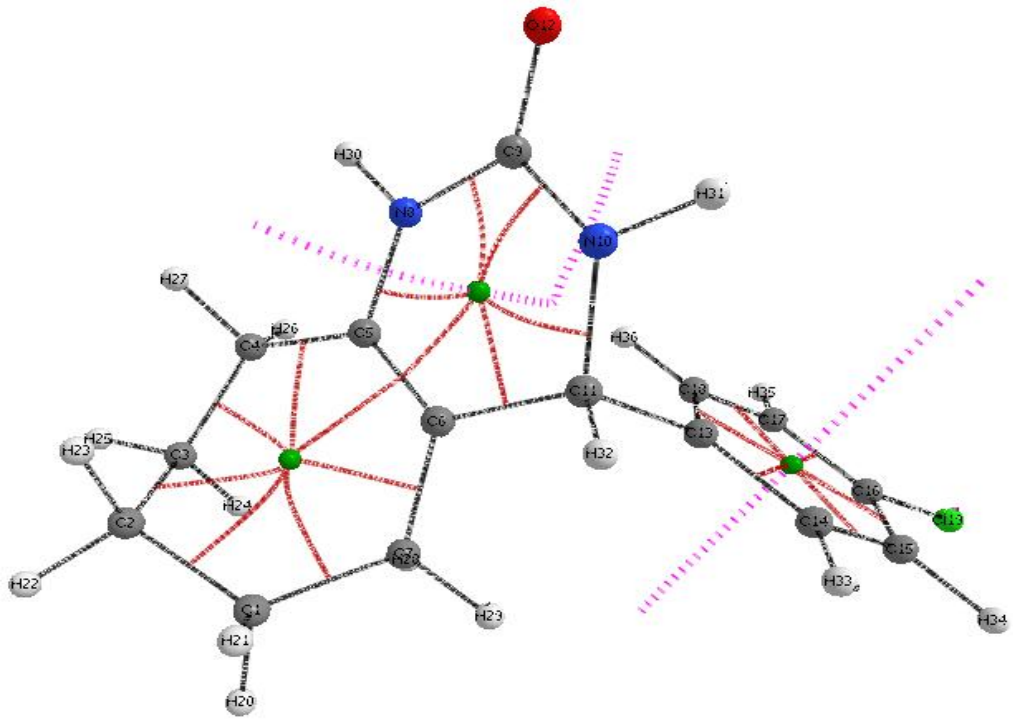


Figure 3. Molecular graph of the compound (4a) using AIM program at B3LYP/6- 31G (d,p) level ring critical points (small green sphere), bond critical paths (black lines), ring critical point to bond critical paths (red lines) and ring critical point attractor path (purple lines).

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Supporting Information Summary

The experimental UV, IR, Mass, ^{1}H and ^{13}C spectra are provided as supplementary information.

Conflict of Interest

The authors declare no conflict of interest.

REFERENCES

Agarwal, O.P. (2006). Organic chemistry, Reaction and Reagent, 735.

Ahmed, O.M. and Mohamad, M.A. (2009). Synthesis and anti-tumor activities of some new pyridines and pyrazolo [1, 5- a] pyrimidine. *Eur. Med. Chem.* 44, 3519-3523.

Ajam, M.A., Kumar, B.P.R. and Suresh, B. (2008). Synthesized pyrido [2, 3-d] pyrimidines. *Ind. J. Pharm. Sci.* 672-677.

Amin, K.M., El-Zahar, M.I., Anwar, M.M., Kamel, M.M. and Mohamed, M.H. (2009). Synthesis and anticancer activity of novel tetralin-6-ylpyridine and tetralin-6-ylpyrimidine derivative. *Acta Poloniae Pharmaceutical and Drug Res*. 66, 279 -291.

Amr, A.G.E., Mohamed, A.M., Mohamed, S.F., Hafez, N.A.A. and Hammam, A.G. (2006). Anticancer activities of some newly synthesized pyridine, pyrane, and pyrimidine derivatives. *Bioorg. Med. Chem.* 14, 5481–5488.

Bauer, A.W., Kirby, W.M.M., Sherris, J.C. and Turck, M. (1966). Antibiotic Susceptibility Testing by a Standardized Single Disk Method. *American Journal of Clinical Pathology*. 45, 493–496.

Brugel, T.A., Maier, J.A., Clark, M.P., Sabat, M., Golebiowski, A., Bookland, R.G., Laufersweiler, M.J., Laughlin, S.K., Van Rens, J.C., Biswanath, D., Hsieh, L.C., Mekel, M.J. and Janusz, M.J. (2006). Development of N-2,4-pyrimidine-N-phenyl-N0-phenyl ureas as inhibitors of tumor necrosis factor alpha (TNF-a) synthesis. *Bioorg Med Chem Lett.* 16, 3510–3513.

Gangjee, A., Kurup, S., Ihnat, M.A., Thorpe, J.E. and Shenoy, S.S. (2010). Synthesis and biological activity of N^4-phenylsubstituted-6-(2,4-dichloro phenylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamines as vascular endothelial growth factor receptor-2 inhibitors and antiangiogenic and antitumor agents. *Bioorg. Med. Chem.* 18, 3575–3587.

Gavilan, M.D., Gomez-Vidal, J.A. and Serrano, F.R. (2008). Synthesis, characterization and biological screening of some novel sulphur bridged pyrazole, thiazole, coumarin and pyrimidine derivatives. *Bio. Med. Chem. Lett.* 18, 1457-1460.

Jain, M.K. and Sharnevsas, S.C. (2008). Organic chemistry, III edition, 997-999.

Kraljevic, T.G., Krištafor, S., Šuman, L., Kralj, M., Ametamey, S.M., Cetina, M. and Malic, S.R. (2010). 5,6-disubstituted pyrimidine derivative were synthesized. *Bioorg. Med. Chem.* 18, 2704–2712.

Maier, J.A., Brugel, T.A., Clark, M.P., Sabat, M., Golebiowski, A., Bookland, R.G., Laufersweiler, M.J., Laughlin, S.K., Van Rens, J.C., Biswanath, D., Hsieh, L.C., Brown, K.K., Juergens, K., Walter, R.L. and Janusz, M.J. (2006). Development of N-2,4-pyrimidine-N-phenyl-N0-alkyl ureas as orally active inhibitors of tumor necrosis factor alpha (TNF-a) synthesis. *Bioorg Med Chem Lett*, 16, 3514–3518.

Mohamed, N.R., El-Saidi, M.M.T., Alia, Y.M. and Elnagdi, M.H. (2007). Utility of 6-amino-2- thiouracil as a precursor for the synthesis of bioactive pyrimidine derivatives., *Bioorg. Med. Chem.* 15, 6227–6235.

Tiwari, A.K., Mishra, A.K., Bajpai, A., Mishra, P., Sharma, R.K., Pandey, V.K. and Singh, V.K. (2006). Synthesis and pharmacological study of novel pyrido-quinazolone analogues as anti-fungal, antibacterial, and anticancer agents. *Bioorg Med Chem Lett*, 16, 4581–4585.

Verma, A.K., Bishnoi, A., Fatma, S. and Parveen, H. (2017). An Easy Synthetic Access to Spiro Derivatives Containing Pyrido [1,2-a]pyrimidine and Quinoline Scaffolds and Their Antimicrobial Activity. Chemistry Select. 2, 4006–4009; DOI: 1002/slct.201700228

Zhu, Y., Huang, S. and Pan, Y. (2005). Highly chemoselective multicomponent biginelli-type condensations of cycloalkanones, urea or thiourea and aldehydes. *Eur. J. Org. Chem.* 2354–2367.

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