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Synthesis and Antibacterial activity of some 4,5-disubstituted-6-Methyl-1,2,3,4-Tetrahydropyrimidin-2(1*H*)-one derivatives

Divyang H. Shah and Prof. (Dr.) Dhrubo Jyoti Sen
Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat

Abstract
Eight new 4,5-disubstituted-6-methyl-1,2,3,4-tetrahydropyrimidin-2(1*H*)-one derivatives are synthesized by three steps. All synthesized compounds are confirmed by IR, Mass and H^1NMR. Antibacterial activity is carried out by filter disc method. All test compounds are active against the gram negative E.coli and in higher concentration active against the gram positive S.aureus. Compounds 6b and 6e are more potent among synthesized series.

*Corresponding author, Mailing address:
Divyang H. Shah
E-mail: divyang.pharma87@gmail.com

Key words:
Biginelli reaction, Tetrahydropyrimidines, Zone of inhibition, Gram +ve bacteria, Gm –ve bacteria

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Introduction:
The treatment of many infectious diseases are challenging due to resistance to antimicrobial agents. The emergence of resistance among bacteria to a wide variety of structurally unrelated antibacterial agents such as β-lactams, macrolides, tetracyclines and fluoroquinolones as well as selected dyes and disinfectants has become a serious public health concern so makes it necessary to continue the search for new antibacterial agents.

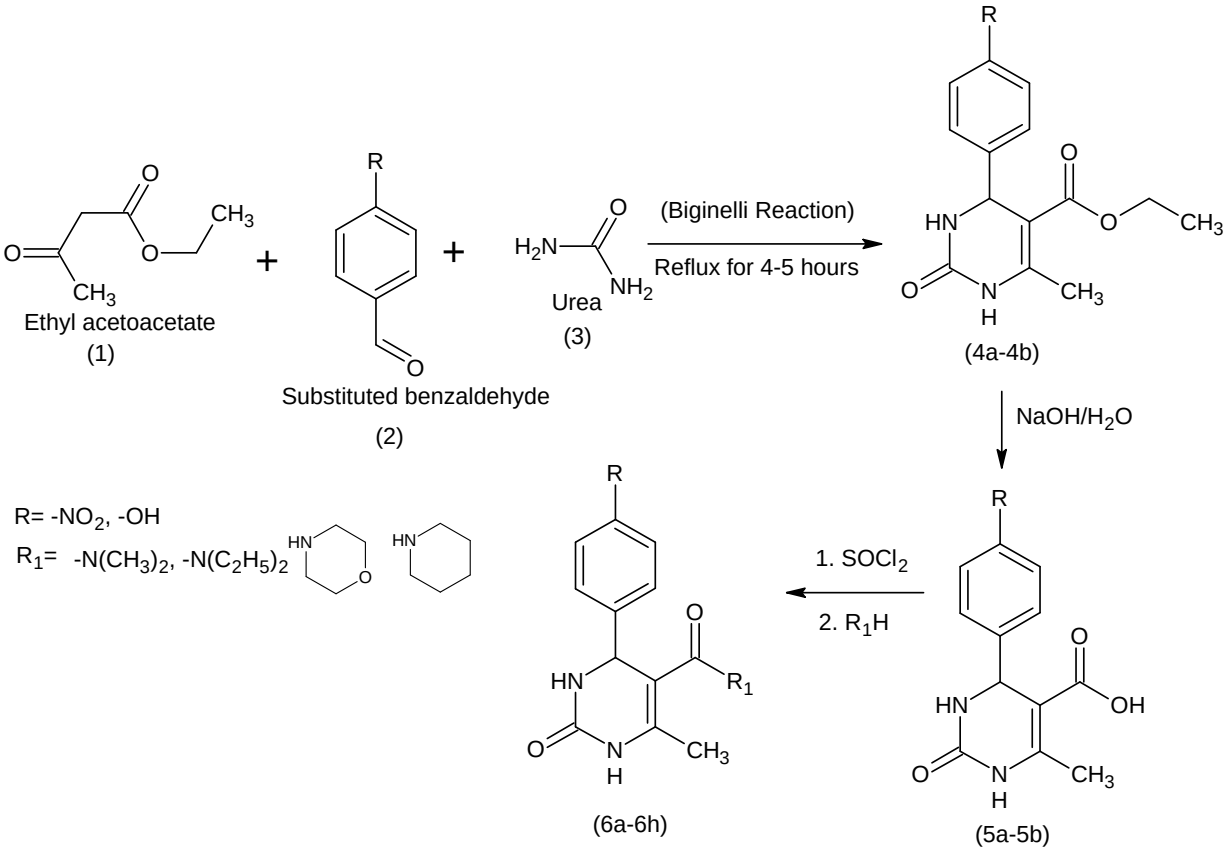
In recent scenario heterocycles plays a major rule in drug synthesis. In that respect pyrimidine plays a significant rule among other heterocycles. From the literature survey, in recent years 4,5-disubstituted-6-methyl-1,2,3,4-tetrahydropyrimidin-2(1*H*)-one have attracted considerable interest because of their therapeutic and pharmacological properties. Several of them have been found to exhibit a wide spectrum of biological effects including antimicrobial, antitumour, antiviral, antihypertensive, calcium channel blocker, alpha-1a adrenergic antagonist,

neuropeptide antagonist. So it was planed to synthesize a novel series of 4,5-disubstituted-6-methyl-1,2,3,4-tetrahydropyrimidin-2(1*H*)-one derivatives and to check their activity as antimicrobial activity.[1-2]

Experimental:

The entire chemicals were supplied by S.D. Fine chem. (Mumbai), Finar chem. Ltd (Ahmedabad) and Loba Chemie. Pvt. Ltd. (Mumbai). Melting points were determined by open tube capillary method and are uncorrected. Purity of compounds was checked by thin layer chromatography (TLC) on silica gel G in solvent system hexane-ethyl acetate (1:2), the spots were located under iodine vapours or UV light. IR spectra of all compounds were recorded on FT-IR 8400S Shimadzu spectrophotometer using KBr. Mass spectra were obtained using 2010EV LCMS Shimadzu instrument.

Scheme of Synthesis:



General Procedure for Ethyl 4-(4-substitutedphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine -5-carboxylate [1-4]

0.1mole (6gm) of urea, 0.1mole, substituted benzaldehyde and 0.1mole (12.6ml) of ethyl acetoacetate were taken and refluxed with 2-3 drops of Conc. HCl and sufficient quantity of ethanol at 70-80°C temperature for 4-5 hrs. It was then allowed to cool and after addition of water, precipitate was obtained, which was filtered and recrystallized from ethanol. **(4a-4b)**

General procedure of 4-(4-substitutedphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylic acid [5]

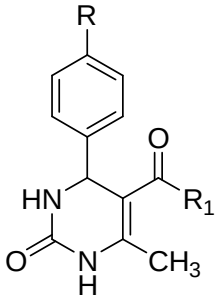
Ethyl-4-(4-substitutedphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01mole) was refluxed with 50 ml of 10% alcoholic NaOH for 1 hr and after cooling the reaction mixture

and acidification with Conc. HCl precipitate of acid was obtained, which was filtered, washed with water and recrystallized from ethanol. **(5a-5b)**

***General Procedure of Preparation of* 4,5-disubstituted-6-methyl-1,2,3,4-tetrahydropyrimidin-2(1*H*)-one derivatives**[5]

4-(4-substitutedphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylic acid (0.01mole) was refluxed with 15ml of thionyl chloride for 30mins. Unreacted thionyl chloride was removed by heating the reaction mixture on water-bath. After cooling the acid chloride product, 3 to 4 times of different amines and ethanol as reaction medium was added. Reaction mixture was stirred for 5 hrs then added cold water to the reaction mixture. Precipitate was obtained, which was filtered and recrystallized from ethanol. **(6a-6h)**

Physical Characteristics of Synthesized Compounds

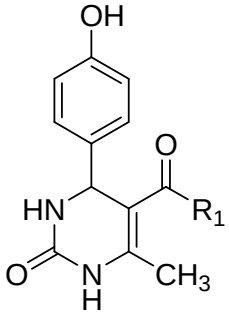


Compound code	R	R_1	Molecular Formula	Molecular Weight (g/mol)	Melting Point (°C)	Yield (%w/w)	R_f Value
4a	OH	$-OC_2H_5$	$C_{14}H_{16}N_2O_4$	276.29	232-234	78.00	0.57
4b	NO_2	$-OC_2H_5$	$C_{14}H_{15}N_3O_5$	305.29	208-211	75.00	0.57
5a	OH	-OH	$C_{12}H_{12}N_2O_4$	248.23	188-192	45.00	0.38
5b	NO_2	-OH	$C_{12}H_{11}N_3O_5$	277.23	162-166	46.00	0.33
6a	OH	$-N(CH_3)_2$	$C_{14}H_{17}N_3O_3$	275.3	204-208	78.00	0.60
6b	OH	$-N(C_2H_5)_2$	$C_{16}H_{21}N_3O_3$	303.36	207-210	72.24	0.58
6c	OH	-(4-morpholinyl)	$C_{16}H_{19}N_3O_4$	317.34	198-202	62.00	0.52
6d	OH	-piperidinyl	$C_{17}H_{21}N_3O_3$	315.37	194-197	64.40	0.56
6e	NO_2	$-N(CH_3)_2$	$C_{14}H_{16}N_4O_4$	304.3	178-180	73.48	0.65
6f	NO_2	$-N(C_2H_5)_2$	$C_{16}H_{20}N_4O_4$	332.35	184-186	65.54	0.62
6g	NO_2	-(4-morpholinyl)	$C_{16}H_{18}N_4O_5$	346.35	180-184	58.00	0.52
6h	NO_2	-piperidinyl	$C_{17}H_{20}N_4O_4$	344.37	176-180	56.00	0.52

Mobile phase: (Hexane: Ethyl acetate 1:2)

Table 1: Physicochemical parameters

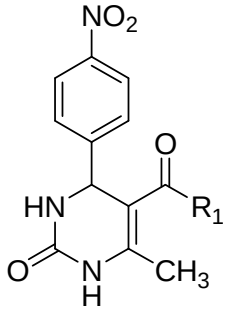
Spectral data of synthesized compounds



Compound Code	R_1	IR (υ, cm^{-1})	Mass (m/z)	NMR (δ, ppm)
4a	$-OC_2H_5$	-OH (3500-3100), -C=O (1718,1699), $-CH_3$ deformation (1450), C-O (1230)	277.0 $[M]^+$	
5a	-OH	OH broad (3400-3250), -NH (3213), -C=O (1710,1677), $-CH_3$ deformation (1450), C-O (1230)	249.0 $[M]^+$	
6a	$-N(CH_3)_2$	-OH (3500-3250), -NH (3213), -C=O (1687,1646) $-CH_3$ deformation (1427), C-N (1234)	276.30 $[M]^+$	
6b	$-N(C_2H_5)_2$	OH (3450-3250), -NH (3213), -C=O (1680, 1646), $-CH_3$ deformation (1488), C-N (1234)	303.9 $[M]^+$	-----
6c	-(4-morpholinyl)	OH (3500-3250), -C=O (1680,1645), $-CH_3$ deformation (1461), C-N (1224)	317.8 $[M]^+$	6.55-7.06 (m, 4**H**, Ar**H**), 6.47-6.49 (d, 2**H**, N**H**), 5.54 (s, 1**H**, O**H**), 5.07 (s, 1**H**, C**H**), 3.85-3.91 (t, 4**H**, CH_2), 3.57-3.60 (t, 4**H**, CH_2), 1.66-1.70 (s, 3**H**, CH_3)
6d	-piperidinyl	-NH(3244), -C=O (1693), $-CH_3$ deformation (1450)	315.7 $[M]^+$	

Table 2: Spectral data of synthesized compounds

Spectral data of synthesized compounds



Compound code	R_1	IR (υ, cm^{-1})	Mass (m/z)	NMR (δ, ppm)
4b	$-OC_2H_5$	-NH (3236), -C=O (1728,1704), $-NO_2$ (1537,1355), $-CH_3$ deformation (1461) , C-O (1218)	305.9 $[M]^+$	
5b	-OH	OH Broad (3250-3510), -NH (3200), -C=O (1725,1643), $-NO_2$ (1533,1346), $-CH_3$ deformation (1486), C-O (1228)	277.8 $[M]^+$	
6e	$-N(CH_3)_2$	-NH (3226,3116), -C=O (1686,1644), $-NO_2$ (1547,1346), $-CH_3$ deformation (1461), C-N (1226)	304.7 $[M]^+$	7.53-8.19(m, 4**H**, Ar**H**), 6.47-6.49 (d, 2**H**, N**H**), 5.07 (s, 1**H**, C**H**), 2.98-2.99(d, 6**H**, CH_3), 1.70 (s, 3**H**, CH_3)
6f	$-N(C_2H_5)_2$	-NH (3116), -C=O (1673,1634), $-NO_2$ (1553,1346), $-CH_3$ deformation (1464), C-N (1226), -NH (3089, 3238)	332.9 $[M]^+$	
6g	-(4-morpholinyl)	-NH (3089, 3238), -C=O (1683,1643), $-NO_2$ (1535,1346), $-CH_3$ deformation (1461), C-N (1218)	346.7 $[M]^+$	
6h	-piperidinyl	-NH (3236, 3255), -C=O (1677, 1643), $-NO_2$ (1527,1346), $-CH_3$ deformation (1427)	344.8 $[M]^+$	

Table 3: Spectral data of synthesized compounds

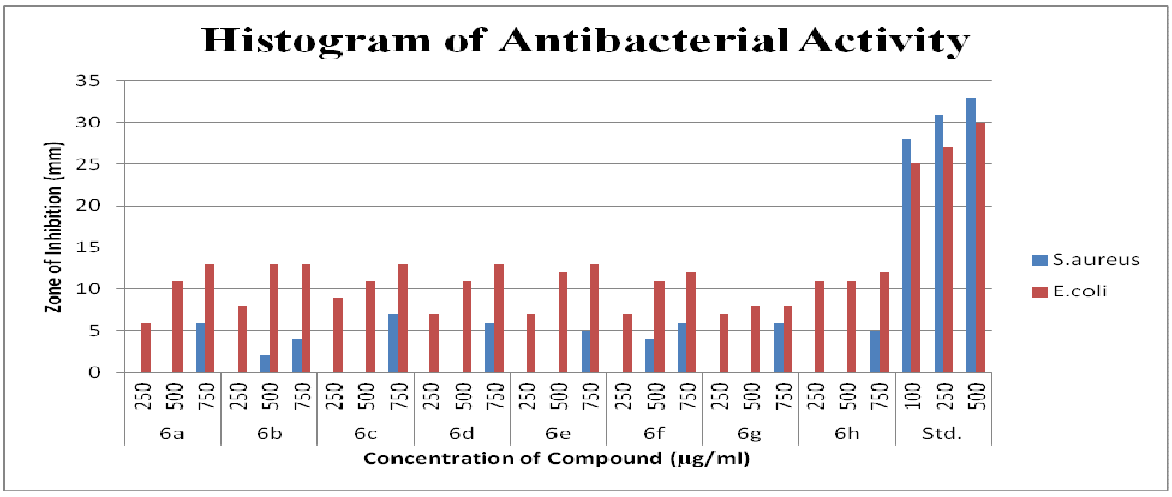
Antibacterial Activity[6,7]

The microbiological assay is based upon a comparison of inhibition of growth of micro-organisms by measured concentrations of test compounds with that produced by known concentration of a standard antibiotic ciprofloxacin using microorganisms *Staphylococcus aureus* (MTCC No. 96) *a*nd *Escherichia coli* (MTCC No. 521).

A filter paper sterilized disk saturated with measured quantity of the sample was placed on plate containing solid bacterial medium (nutrient agar broth) which has been heavily seeded with spore suspension of the tested organisms. After inoculation, the diameter of the clear zone of inhibition surrounding the sample has been taken as measure of inhibitory power of sample against the particular test organisms.

Compound Code	Concentration (µg/ml)	Zone of Inhibition (mm)	
		Gram +ve	Gram -ve
		S.aureus	*E.coli*
6a	250	00	06
	500	00	11
	750	06	13
6b	250	00	08
	500	02	13
	750	04	13
6c	250	00	09
	500	00	11
	750	07	13
6d	250	00	07
	500	00	11
	750	06	13
6e	250	00	07
	500	00	12
	750	05	13
6f	250	00	07
	500	04	11
	750	06	12
6g	250	00	07
	500	00	08
	750	06	08
6h	250	00	11
	500	00	11
	750	05	12
Ciprofloxacin	100	28	25
	250	31	27
	500	33	30
Control		00	00

Table 4: Zone of inhibition



Results and Discussion:

4,5-disubstituted-6-methyl-1,2,3,4-tetrahydropyrimidin-2(1*H*)-one derivatives have been synthesized by 3 steps. Reactions have been monitered by TLC. All synthesized derivatives have been confirmed by IR, Mass and H^1NMR. Antibacterial activity has been carried out by the filter disk method. All compounds showed activity against the gram negative *E.coli* and in higher concentration activity has been found against gram positive *S.aureus*.

References:

1) Lanjewar KR, and Rahatgaonkar AM. Synthesis and Anti-microbial activity of 5-(2-aminothiazol-4-yl)-3,4-dihydro-4-phenyl pyrimidine-2(1H)-one; *Indian Journal of Chemistry*, **2009**, 48B, 1732-1737.
2) Kumar DBA. et al. Microwave assisted facile synthesis of aminopyrimidines bearing benzofuran and investigation of their anti-microbial activity; *Indian Journal of Chemistry*, **2006**, 45B, 1699-1703.
3) Naik TA, and Chikhalia KH. Studies on synthesis of pyrimidine derivatives and their pharmacological evalution, *E. Journal of Chemistry*, **2007**, 4(1), 60-66.
4) Humle R. et al. Cyanamide a convenient building block to synthesis 4-aryl-2-cyanoimino-3,4-dihydro-1H-pyrimidine system via multicomponentreaction, *Tetrahedron* **2008**, 64, 3372-3380.
5) Furniss B. S. et al. Vogel's textbook of practical organic chemistry, An imprint of Addison, Wesley Longman, inc. 5thedition, **1998**, 1166-1168.
6) Pelczar MJ, Chan ES, Pelczar JR, Krieg NR. Microbiology, McGraw-Hill Book company. **1997**, 5, 73-98.
7) Mohamed NR et al. Utility of 6-amino-2-thiouracil as a precursor for the synthesis of bioactive pyrimidine derivatives, *Bioorganic and Medicinal Chem*. **2007**, 15, 6227-6235.