Research Paper

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Synthesis, Characterization and Biological Activity of Some New Biginelli Products

Chemistry

KEYWORDS : Multicomponent reaction, Biginelli, Dihydropyrimidine, Anti-microbial activity.

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ABSTRACT

Dihydropyrimidines (DHPMs) are important due to their excellent pharmacological properties. In the present work, we have synthesized new functionalized DHPMs which includes a three component cyclocondensation reaction of benzoylacetone, benzaldehyde and urea, using catalytic amount of concentrated HCl in ethanol. Structures of the compounds have been confirmed by spectroscopic methods. The newly synthesized DHPMs showed prominent anti-microbial activity against the gram-negative (Escherichia coli and Klebsiell) and gram-positive bacteria (Staphylococcus aureus).

Introduction

Multicomponent reactions (MCRs) are of increasing importance in the organic and medicinal chemistry for various reasons[1] such as their high degree of atom economy, applications in the combinatorial chemistry and diversity-oriented synthesis[2-5]. In MCRs three or more reactants come together in a single reaction vessel to form a new product that contains portion of all the components. Nitrogen heterocycles are abundant in nature and are of great significance in life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics, and alkaloids, as well as pharmaceuticals, herbicides, dyes, and many more compounds[6]. One prominent MCR that produces an interesting class of nitrogen heterocycles is the Biginelli dihydropyrimidine synthesis. In 1983, Italian chemist Pietro Biginelli[7] reported the acid catalyzed cyclocondensation reaction of a β-ketoester (1), aldehyde (2) and urea (3) or thiourea , a procedure known as the Biginelli reaction is receiving increasing attention. The reaction was carried out by simple heating a mixture of three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one- pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidine-2(1*H*)-one (4) Dihydropyrimidines are well known for their diversified biological activities in the field of pharmaceutical research[6]. This fact led to invention of a wide range of synthetic methods for the synthesis of DHPMs and their chemical modifications[10]. In the present work, we wish to report new dihydropyrimidines using Biginelli reaction. These DHPMs derivatives were screened for their anti-microbial property.

Result and Discussion

The dihydropyrimidines were synthesized as per the reported Biginelli reaction (Figure2).

Spectral Characterization:

The structure of DHPMs are confirmed by FT-IR, 1H-NMR and Mass spectroscopy.

5-benzoyl-6-methyl-4-phenyl-3,4dihydropyrimidin-2(1H)-one(KT-01)

According to the general procedure DHPM KT-01 was obtained from benzoylactone, benzaldehyde and urea in 67% yield, mp:210-213. IR (KBr) cm^{-1}: 3297 (N-H str.), 3108 (C-H str.), 1691 (>C=O), 1576, 1457,1427 (ring skeleton), 1330 (CH3). ^{1}H NMR 300 MHz (DMSO-d6, δ ppm) : 1.69 (s, 3H, CH3), 5.39 (s, 1H, CH), 7.20-7.47 (m, 10H, Ar-H), 7.71 (s, 1H, NH), 9.11 (s, 1H, NH). Mass: [m/e (%)], M. Wt.: 293.1 (M^+), 250.1, 167.1.

(6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5yl)(phenyl)methanone (KT-02)

According to the general procedure DHPM KT-02 was obtained from benzoylactone, benzaldehyde and thiourea in 63% yield, mp:220-222. IR (KBr) cm^{-1}: 3282 (N-H str.), 2998 (C-H str.), 1680 (>C=O), 1573, 1468, 1424 (ring skeleton), 1355 (CH3),

1204 (C=S). ^{1}H NMR 300 MHz (DMSO-d6, δ ppm): 1.19 (s, 3H, CH3), 3.73 (s, 3H, OCH3), 4.79 (s, 1H, CH), 6.8-8.02 (m, 9H, Ar-H), 8.43 (s, 1H, NH), 8.60 (s, 1H, NH). Mass: [m/e (%)], M. Wt.: 307, 306, 305.

5-benzoyl-4-(4-chlorophenyl)-6-methyl- 3,4dihydropyrimidin-2(1H)-one(KT-03)

According to the general procedure DHPM KT-03 was obtained from benzoylactone ,p- chlorobenzaldehyde and urea in 70% yield, mp:236-238. IR (KBr) cm^{-1}: 3278 (N-H str.), 2927 (C-H str.), 1718 (>C=O), 1567, 1444, 1420 (ring skeleton), 1355 (CH3). ^{1}H NMR 300 MHz (DMSO-d6, δ ppm): 1.70 (s, 3H, CH3), 5.41 (s, 1H, CH), 7.2-7.6 (m, 5H, Ar-H), 7.25 (d, 4H, Ar-H), 7.70 (s, 1H, NH), 9.1 (s, 1H, NH). Mass: [m/e (%)], M. Wt.: 327.1(M^+), 284.1, 201.1.

4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl) methanone (KT-04)

According to the general procedure DHPM KT-04 was obtained from benzoylactone ,p- chlorobenzaldehyde and thiourea in 71% yield, mp:240-243. IR (KBr) cm^{-1}: 3283 (N- H str.), 2927 (C-H str.), (>C=O), 1571, 1487, 1423, (ring skeleton), 1351 (CH3), 1201 (C=S). ^{1}H NMR 300 MHz (DMSO-d6, δ ppm): 1.73 (s, 3H, CH3), 5.36 (s, 1H, CH), 7.2-7.3(dd,J= 6 HZ, 4H, Ar-H), 7.4-7.5 (m, 5H, Ar-H) 9.63 (s, 1H, NH), 10.28 (s, 1H, NH). Mass: [m/e (%)], M. Wt.: 342, 339.

5-benzoyl-4-(3-hydroxy-4- methoxyphenyl)-6-methyl-3,4- dihydropyrimidin-2(1H)-one (KT-05)

According to the general procedure DHPM KT-05 was obtained from benzoylactone, vaniline and urea in 65% yield, mp:179- 180. IR (KBr) cm^{-1}: 3258 (O-H str. br), 2917 (C-H str.), 1684 (>C=O), 1596, 1514, 1450,1430 (ring skeleton), 1321 (CH3). ^{1}H NMR 300 MHz (DMSO-d6, δ ppm): 1.19 (s, 3H, CH3), 3.73 (s, 3H, OCH3), 4.79 (s, 1H, CH), 6.8-8.02 (m, 9H, Ar-H), 8.43 (s, 1H, NH), 8.60 (s, 1H, NH). Mass: [m/e (%)], M. Wt.: 337.

(4-(3-hydroxy-4-methoxyphenyl)-6- methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5 yl) (phenyl)methanone (KT-06)

According to the general procedure DHPM KT-06 was obtained from benzoylactone ,vaniline and thiourea in 66% yield, mp:183-184. IR (KBr) cm^{-1}: 3185 (O-H str. br), 2961 (C-H str.), 1715 (>C=O), 1597, 1566, 1514, 1462 (ring skeleton), 1365 (CH3), 1273 (C=S). ^{1}H NMR 300 MHz (DMSO-d6, δ ppm): 1.19 (s, 3H, CH3), 3.73 (s, 3H, OCH3), 4.79 (s, 1H, CH), 6.8-8.02 (m, 9H, Ar-H), 8.43 (s, 1H, NH), 8.60 (s, 1H, NH). Mass: [m/e (%)], M. Wt.: 355, 351.

Biological Acitvity:

The newly synthesized compounds were screened for their anti-bacterial activity against gram-negative bacteria (*Escherichia coli* and *Klebsiell*) and gram-positive bacteria (*Staphylococcus aureus*). In the liquid culture test, the decrease in the optical turbidity showed that the DHPMs had inhibited the bacterial growth in all cases.

Experimental Section

Melting points were determined in a melting point apparatus (Sentwin India). The TLC of the compound was performed on silica gel G coated glass plate with solvent system as ethyl-acetate : hexane (6:4). Chemicals used in this study are of analytical grade and some of them are used with further purification. IR spectra of a synthesized compound was obtained by preparing KBr pellet, using Perkin Elmer Spectrum 400 FT-IR spectrophotometer. ^{1}H-NMR studies were done on Avance-11 Bruker FT-NMR spectrophotometer 300 MHz using DMSO. Mass spectra was recorded on Water Q Tof Micro LS-MS Mass spectrophotometer.

General Procedure for the Synthesis of Benzoylacetone:

Benzoyl acetone was synthesized as per the method reported in Vogel textbook for Practical Organic Chemistry[11]. General Procedure for the Synthesis of DHPMs: Benzoylacetone 0.1 M, benzaldehyde 0.1M and urea 0.15 M were taken in a round bottom flask taking methanol as solvent and the contents were dissolved by gently heating the flask. Conc. HCl (5-6 drops) was added to the flask and was then refluxed for 6-8 hrs. The completion of the reaction was monitored by TLC. After cooling at the room temperature the solid crystalline product was filtered and washed with chilled methanol and then recrystallized from ethanol to obtain the new DHPMs (Figure 2).

Procedure for anti-microbial activity:

The synthesized DHPMs were screened against *Escherichia coli, Klebsiella, Staphylococcus aureus* for anti-microbial activity which were grown in nutrient broth (N.B.) medium overnight in incubator shaker at 37^{o}C. Nutrient broth solution was prepared by dissolving 1.3 g of solid N.B. in 100 ml of distilled water in a 250mL flask. The flask containing the N.B., other glass wares (flasks, test tubes etc.) and tips of the micropipette were autoclaved before use. Then three flasks were taken. In the first flask 20ml N.B. and 1ml of bacterial culture were added. This flask was considered as the control in which the normal bacterial growth took place. In the second flask, 20mL of N.B., 1mL bacterial culture and 0.002g (dissolved in 1ml ethanol) of DHPMs were added. In the third flask, 20mL of N.B. and 0.002g (dissolved in 1ml ethanol) of compounds were added (this flask was considered as the reference of second flask). Then all these flasks were kept in the incubator shaker at 30^{o}C for 1hr. After 1hr, 3ml of suspension from each flask was taken to determine the optical density at 600 nm in UV-Visible Spectrophotometer. The flasks were again placed in the incubator shaker, the second reading was taken after one hour. This procedure was repeated for 7-8 hrs to obtain the growth curve of the bacteria under observation.

Conclusion

Total six 5-benzoyl-6-methyl-4- (substituted)phenyl-3,4-dihydropyrimidin- 2(1H)-ones were synthesized in the research work. The compounds are characterized by IR, ^{1}H NMR, Mass spectral analysis. From the anti-microbial activity data the synthesized compounds, it is evident that some of the newly synthesized compounds particularly KT-01, KT-02, KT-03, KT-05 and KT-06 are showing promising activity against the screened microbes. When the new DHPMs were screened against *E.coli*, compounds KT-03 and KT-06 showed significant inhibition of the cell culture within 8 hrs of study period. Among these two compounds, KT-03 is more potent and it gives O. D. of only 0.167 as compared to KT-06 (O.D. = 0.410) after incubation of 8 hrs. When these compounds were screened against *Klebsiella,* compound KT-05 and KT-06 showed significant inhibition of the bacteria cell culture. (For KT-05, O.D. = 0.417 & for KT-06, O.D. = 0.782) as compared to other homologues of these compounds. Against *Klebsiella* KT-05 may be considered as the most active. Lastly, the screening against *S. aureus* results reveals that compounds KT-01 and KT-02 were the most potent among their series. O. D. of KT- 01 = 0.199 and KT-02 = 0.229 after 8 hrs of incubation period. From these results, it is clear that KT-01 is most potent against *S. aureus* in all synthesized compounds. In conclusion, we have synthesized new DHPMs using classical Biginelli approach. All the newly synthesized compounds were screened against 3 different bacterial strains namely *Escherichia coli, Klebsiella* and *Staphylococcus aureus.* The screening results reveal that among all the compounds, KT-01 is the most potent DHPM against *S. aureus.*

Acknowledgements

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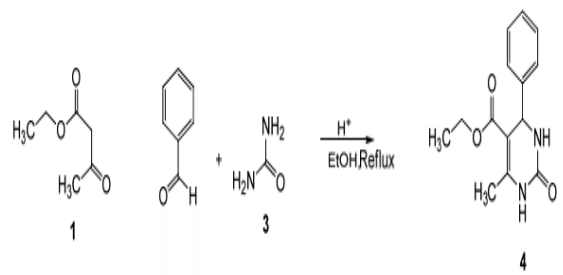

Figure 1 Biginelli Reaction

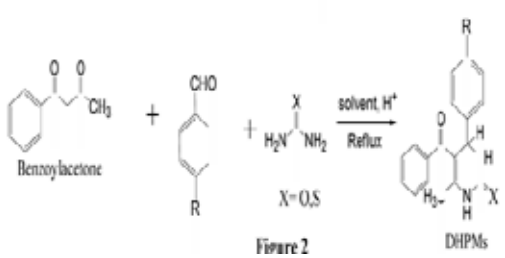

Figure 2

Table 1:Physical data of 5-benzoyl-6-methyl-4-(substituted) phenyl-3,4-dihydropyrimidin-2(1H)ones .

Substitution			Molecular formula	Molecular weight	Melting Point (^{o}C)	Rf value	% of Yield
Z	R	X					
KT-01	H	O	C18H16N2O2	292.33	210-213	0.5	67
KT-02	H	S	C18H16N2OS	308.40	220-222	0.45	63
KT-03	4-Cl	O	C18H15ClN2O2	326.78	236-238	0.53	70
KT-04	4-Cl	S	C18H15ClN2OS	342.84	240-243	0.58	71
KT-05	3-OH, 4-OCH3	O	C19H18N2O4	338.36	179-180	0.63	65
KT-06	3-OH, 4-OCH3	S	C19H18N2O3S	354.42	183-184	0.58	66

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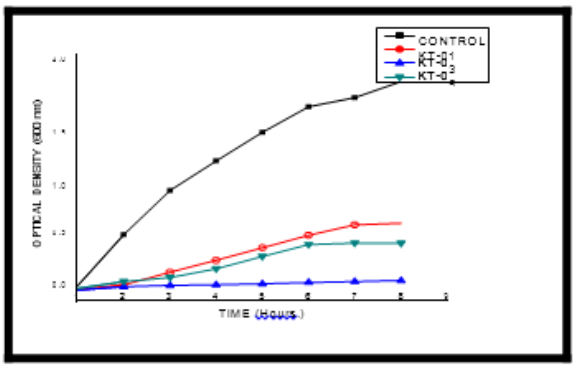
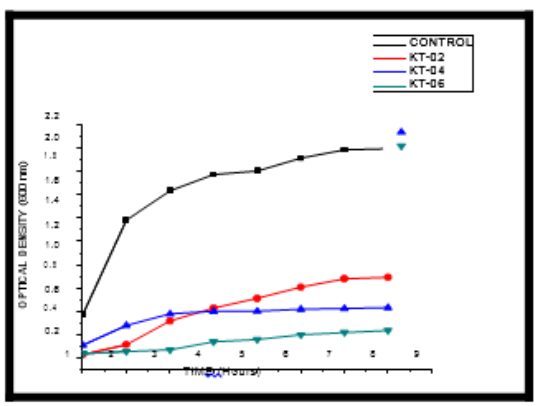
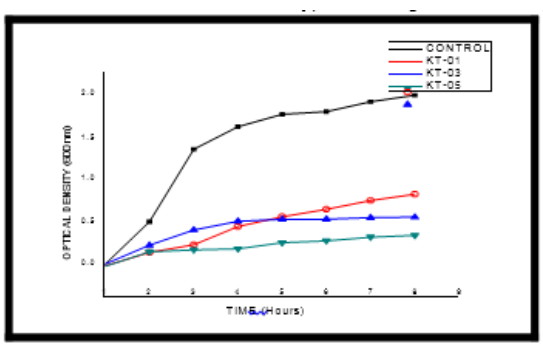


A



B

Inhibition of the *E. coli* growth by DHPMs (A) Urea Derivatives (B) Thiourea Derivatives



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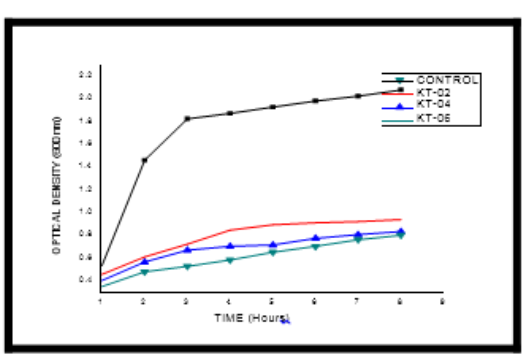
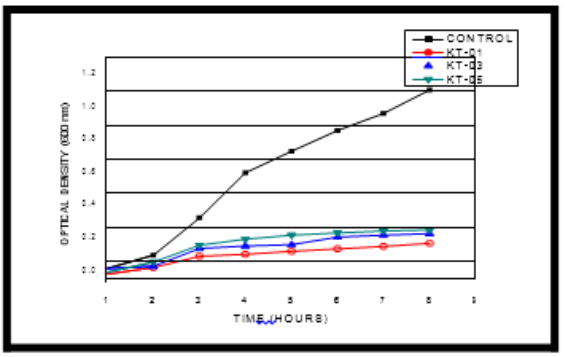
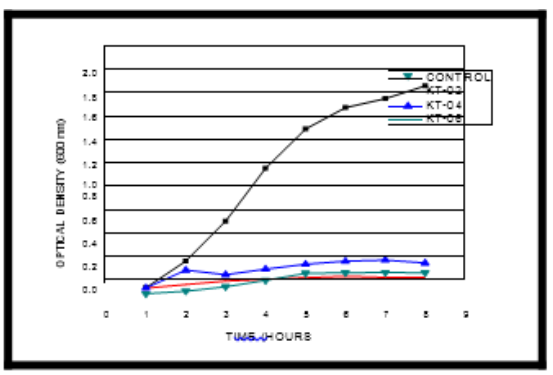


D

Inhibition of the Klebsiella growth by DHPMs (C) Urea Derivatives (D) Thiourea Derivatives



E



F

Inhibition of the Staphylococcus aureus growth by DHPMs (E) Urea Derivatives (F) Thiourea Derivatives

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