RESEARCH ARTICLE

Experimental Antioxidant Activities of Synthetic 3,4-Dihydropyrimidine Derivatives

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ABSTRACT

The synthesized of five new pyrimidine derivatives was prepared from the condensation in one pot reaction of ethyl acetoacetate, substituted aromatic aldehydes, urea, and FeCL3.6H2O, with 5 to 10 drops of hydrochloride acid as catalyst in reflexing ethanol. The yield of the product was found to be in the range of 55 to 90%. The antioxidant efficiency of synthesized compounds was estimated by using the 2, 2-diphenyl-1-picrylhydrazyl (DPPH) method, hydroxyl method, nitric oxide method, and superoxide radical scavenging assay method. The compounds 6a, 6e, and 6c demonstrated considerable radical scavenging activity, resulting in the presence of electron-donating substituent on replaced aldehydes. The confirmation compounds by spectral data by proton and ^{13}C-nuclear magnetic resonance, infrared spectra, and MS spectra.

Keywords: One-pot reaction, dihydropyrimidines, DHPMs, Antioxidant.

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INTRODUCTION

The derivatives of 3,4-dihydropyrimidine-2-one play a significant part in the history of heterocyclic chemistry and are used as primary synthons and pharmacophores in the realm of organic chemistry. Because of the biological, antibacterial, antiviral, anti-HIV, and anti-tumor properties of 3,4-dihydropyrimidine compounds as well as other medicinal properties and their practical significance, new synthetic methods and synthesis have been developed. These compounds are widely used in the pharmaceutical industry. They need to be derived into new forms.[1-4] Dihydropyrimidine-2-ones inhibited the kinesin motor protein after exerting their anticancer effects. Due to the unique role these proteins play in mitosis, the development of more selective antimitotics with better side effect profiles may be facilitated by focusing on the Kinesin spindle protein (KSP, or Eg5), the most prominent target of the mitotic kinesin family,[5] and designing of drugs that own to their different importance use in chemotherapeutic treatment. This nucleus has been the focus of a significant amount of research effort. The biomimetic qualities and reactive pharmacophores of pyrimidines are shown to be responsible for their many therapeutic benefits, including antiviral activity,[6] anticancer activity,[7] antibacterial effects,[8] antihypertensive activity[9] tyrosine kinase inhibitory effect,[10] COX-2 inhibitory effect[11] and calcium channel blockade activity.[12-14] Presence of bases of pyrimidine, the main building blocks of DNA and RNA, is one of the probable causes for their efficiencies. The ring of pyrimidine is found in various vitamins such as riboflavin, folic acid, and thiamine. The nucleus of pyrimidine is also found in barbituric acid, which is utilized in hypnotics. We were interested in creating new dihydro pyrimidine derivatives because of these intriguing biological characteristics, and we tested their *in-vitro* antifungal, antibacterial, and anticancer effects.

MATERIALS AND METHODS

All chemical compounds were obtained from Merck, Mumbai. The melting points were estimated on a Veego VMP-1 capillary device in capillaries (open type) and were not corrected. Compound purity was achieved by thin-layer chromatography (TLC) on silica gel G in different solvent systems utilizing vapors of iodine-like detecting agents. The recording of IR spectra was done by using a Jasco FTIR-410 spectrometer in potassium bromide pellets and it is expressed in cm^{-1}. ^{1}H-NMR spectra were recorded on Brucker 400 MHz spectrophotometers using tetramethylsilane as the internal standard. Chemical shifts are expressed in δ (ppm). Mass spectra were recorded on Jeol 5×10^2/DA-6000

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Synthesis; general procedure of 3,4-dihydropyrimidine-2-one derivatives 2(a-e)

A mixture of 3,4-dihydro pyrimidine compounds 2a,2b,2c,2d and 2e (1 or 0.02-mole) substituted phenyl aldehydes and (0.01 mole) of ethyl acetoacetate with (0.015 mole) urea/ thiourea in 25 mL of ethanol in the presence of $FeCl_3$ (5%mmole) in 3 mL of hydrochloric acid, was refluxed for 15 hours like appear in Figure 1. Thin-layer chromatography was utilized to complete of monitor reaction. The product was filtered, washed by using isopropanol, and finally dried. To obtain title compounds 3,4-dihydropyrimidine 2a.2b,2c,2d and 2e at 75 to 92% yield.

A mixture of 3,4-dihydro pyrimidine compounds 2a (2.7 g, 0.02 mole) of 4-aminoacetophenone and 2.8 mL 0.02 mole of ethyl acetoacetate with 1.9g, 0.025-mole thiourea, yield = 55%, mp = 250–252°C, Black solid, IR (KBr) 3194, 3302, 2978, 1674, 1180, 1445, mass spectra: 305, 290, 275, 245, 217, 193, 178, 92, 87, 76 m/z.

Ethyl -4-(2-hydroxynaphthalene -1-yl)-3,4--dihydrpopyrimidine –one) 2b

A mixture of 3,4-dihydropyrimidine compounds 2b (1.7 g, 0.01 mole) of 2-hydroxy -1-naphthaleneaminoacetophenone and 1.4 mL 0.01 mole of ethyl acetoacetate with 0.9 g, 0.015mole urea, yield = 89, mp = 255–257°C, brown solid, IR (KBr): 3062, 3340, 2985, 1728, 1627. ^{1}H-NMR (DMSO-$d6$) δ 1.288 (t, 3H, –CH3), 1.8 (s, 3H, –CH3), 4.21 (q, 2H,CH2), 5.07. (S, 1H,CH), 7.04–7.96 (m, 6H), 9.3 (s, 1H), 9.7 (s, 1H). 10.5 (s, 1H, OH). ^{13}C-NMR (DMSO) 23, 60, 83, 116–130, 169, Mass spectra =326, 309, 297, 279, 235, 183169, 154, 129, 115, 89, 79, 57, 42 M/Z.

Ethyl -4-(2-Bromophenyl -1-yl)-3,4--dihydrpopyrimidine -2–one) 2c:

A mixture of 3,4-dihydropyrimidine compounds 2c (2.3 g, 0.02 mole) of 2-bromobenzaldehyde and (2.8 mL, 0.02 mole) of ethyl acetoacetate with 0.5 g, 0,025 mole) urea, yield = 86%, mp = 207–208°C, brown solid, IR (KBr): 3224, 3348, 2978, 1712, 1635, 1458. ^{1}H-NMR (DMSO-$d6$) δ 1.00 (t, 3H, –CH3), 2.32 (t 3H, –CH3), 3.9 (q, 2H, CH2), 5.67. (S, 1H, CH), 7.17–7.59 (m, 4H), 7.74 (s, 1H, NH), 9.3 (s, 1H,NH), 9.7 (s, 1H). 10.5 (s, 1H, OH). ^{13}C-NMR (DMSO- d6):13, 94, 17.62, 59.03, 98.21, 122, 132 164.

Diethyl-4,4-(1,4-phenylene) bis3,4-dihydropyrimidine -2-one 2d:

A mixture of 3,4-dihydropyrimidine compounds 2d (1.34 g, 0.01 mole) of terephthaldehyde and (2.8 mL, 0.02 mole) of ethyl acetoacetate with 1.8 g, 0,03 mole) urea, yield = 90%, MP=DC C0, White solid, IR(KBr): 3122, 3310, 3249, 2981, 1707, 11448, ^{1}H-NMR (DMSO-$d6$) δ 1.07 (t, 3H, –CH3), 2.21 (t 3H, –CH), 3.9 (q, 2H, CH2), 5.08. (S, 1H, CH), 7.15 (m, 4H), 7.69 (s, 1H, NH), 9.17(s, 1H, NH). ^{13}C-NMR (DMSO- d6): 14, 17, 59, 99, 126–143, 165.

4-(4-aminophenyl)-5-(ethoxymethyl)-4,6-dimethyl-3,4-dihydropyrimidine-2(1H)-thione (2a):

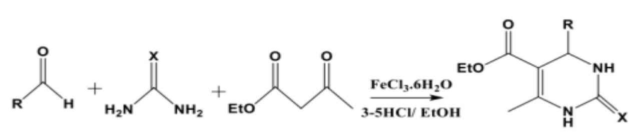

Figure 1: 3,4-Dihydropyrimidine derivatives (2a-e)

Ethyl -4-(4-acetamidophenyl) 3,4-dihydropyrimidine -2-one 2e

A mixture of 3,4-dihydropyrimidine compounds 2e (1.63 g, 0.01 mole) of N-(4-Formylphenyl) acetamide and (1.4 mL, 0.01 mole) of ethyl acetoacetate with 0.9 g, 0,015 mole)urea, yield = 75%, mp = 233–237, C0, yellow solid, IR (KBr): 3072, 33127, 3194, 2982, 1697, 1640, 1510. ^{1}H-NMR (DMSO-$d6$) δ 1.11 (t, 3H, –CH3), 2.24 (t 3H, –CH), 3.98 (q, 2H, CH_2), 5.09 (S, 1H, CH), 7.14–7.5 (m, 4H), 7.7 (s, 1H, NH) 9.19 (s, 1H, NH),). 9.95 (s,1H, HN-CO): ^{13}C-NMR (DMSO- d6): 14, 17, 59 99, 118–139, 168, mass spectra =317, 302, 288, 275, 265, 244, 231, 183, 155, 137 M/Z.

3-DPPH Radical Scavenging Activity

DPPH radicals estimated antioxidant activity of 2(a-e), and the results displayed in Table 1 demonstrate that these free radicals are stable and that their radical characteristic is neutralized in molecules that can donate H atoms.[13] The antioxidant-induced decrease in the DPPH radical's absorbance at 517 nm was used to determine the radical's potential for reduction. It is a given that organic compounds, such as those that donate electrons (amine, hydroxyl, and bromo) can resist oxidative stresses and behave like agents known as free radical trapping agents. Table 1 shows the compounds 2a, 6b, 6c, and 2e scavenging activity on DPPH. Various amounts (10, 15, 20, and 25 μL) of each solution of tubes holding 5 mL of methanolic solution (0.004%) of reagent were filled with methanolic DHPM derivatives. Every exam solution was created in three copies. The combinations of solutions were shaken and left for two hours. The following formula was used to determine the percentage of DPPH radical scavenging activity in each sample and standard:

%DPPH radical scavenging activity = [1 _(At / Ao)] x 100

RESULTS AND DISCUSSION

The new five 3,4-dihydro pyrimidine derivatives 2(a–e) were synthesized according to Figure 2. Reaction of of ethyl acetoacetate, aromatic aldehydes, urea, thiourea, and FeCL3.6H2O, with 5 to 10 drops of hydrochloride acid as catalyst in reflexing ethanol. To maximize purity and completeness, TLC was conducted at each stage of the reaction. Using ^{1}H-NMR, IR, and mass spectral analysis, all synthesized compounds were identified. The IR spectra of 3, 4-dihydro pyrimidine derivatives give seven stretching vibration bands at 3062–3194, 2978, 1658–1728, 1180–1273, 1627–1666, 3294–3441 and 1442–1510, respectively. The 1H-NMR spectra of these compounds gave signals at 3.9 to 4.2 ppm for CH2 and 1.00 to 1.28 ppm for the CH3 group. For example 2a compound appeared singlet at 9.7 ppm for the NH group, multiplied signals at 7.04 to 7.96 ppm and 10.5 ppm for OH group also, the pyrimidine cycle containing one aromatic

Table 1: Reducing power activity, free radical scavenging activity of 3,4-dihydro pyrimidine derivatives and standard in antioxidant activity

Compounds	*DPPH(IC) µg/mL*
2a	3.01
2c	4.92
2e	2.99
BHT	2.19

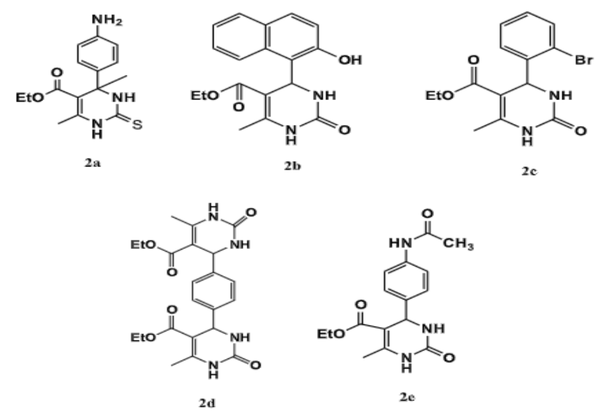

Figure 2: Structures of the compounds (2a-2e)

proton C4-H shown at chemical shift s.07 ppm >The ^{13}C-NMR spectra of 2b compound of carbonyl ester shown at signal at 168 ppm while carbonyl amide at chemical shift 154 ppm, the two carbons atoms of pyrimidine ring with methyl or methylene group of ester shown at 131, 148, 14, 17, 15, respectively.

CONCLUSION

The synthesis of 3,4-dihydropyrimidin2-one has been successfully turned into an antioxidant. The antioxidant activity of ethyl4-(2-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 2e was carried out against some common pathogenic bacteria. Significant anti microbal. The results show that the synthesized compounds were toxic against the bacteria. The comparison of the antibacterial and antifungal activity of these compounds with standard compounds shows the presence of methoxy and halogen Clr Br groups.

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