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New Simple Synthesis of 6-Phenyl-5,6-Dihydropyrimidin-2(1h)-One

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Abstract: A novel non Biginelli reaction has been developed for the synthesis of 6-phenyl-5,6-dihydro-pyrimidin-2(1H)-one as a simple semisynthetic new molecule from reaction of urea with cinnamaldehyde under mild acidic condition. The molecule has been synthesized and its antitumor activity was studied against four human cancer cell lines.

Key words: Urea · Cinnamaldehyde · Cyclization · Dihydropyrimidine · Anticancer

INTRODUCTION

Urea is a small organic compound and widely used in organic synthesis. Urea reaction with aldehydes is considered as one of the most important reactions of urea, as most aldehydes form resins from reaction with urea. Furthermore, urea can react directly with formaldehyde [1], acetaldehyde [2] or cinnamaldehyde [3] producing resins. It can, also, react with formaldehyde, acetaldehyde or propionaldehyde in aqueous medium to form sprayable sources of nitrogen which have prolonged fertilizer activity [4]. Such reactions did not include structure identification of their released products. On the other hand, in traditional organic synthesis, reaction of urea with aldehydes leads to condensation products, for example ethylidenediurea from urea acetaldehyde condensation [5] and 1-(3-phenylallylidene) urea from urea cinnamaldehyde condensation [6]. Clearly, the same reactants lead to different products depending on reaction conditions. The widely used reaction for construction of dihidropyrimidinione (Biginelli reaction) is a multiple-component chemical reaction depending on 3 components β-dicarbonyl compounds (e.g. ethyl acetoacetate), an aryl aldehyde (such as benzaldehyde) and urea [7]. Given the above observations, the development of a new general method for constructing the 6-phenyl-5,6-dihydropyrimidin-2(1H)-one skeleton starting from the reaction of urea with cinnamaldehyde in methanol under acidic condition remains a worthwhile proposition.

MATERIALS AND METHODS

Melting points are recorded on Gallenkamp electric melting point apparatus. The IR spectra cm^{-1} (KBr) were recorded on Perkin Elmer Infrared Spectrophotometer Model 157, Grating. The ^{1}H NMR and ^{13}C NMR spectra were recorded onJEOL-ECA500 using TMS as an internal reference and DMSO-d6 as solvent. The mass spectra (EI) were recorded on 70 eV with Kratos MS equipment and a Varian MAT311A Spectrometer.Elemental analyses were performed on Carlo Erba 1108. (National Research Center, Egypt). Reactions were monitored on Merck silicagel 60 F254 aluminum sheets. TLC spots were visualized by inspection of plates under UV light (254 and 365 nm). All commercial reagents were obtained either from Aldrich, Algomhoria or Oxford and used without any further purification.

6-Phenyl-5,6-Dihydropyrimidin-2(1H)-One(I): To a solution of urea (0.2 mol) in methanol (40 ml) was added cinnamaldehyde (0.2 mol) and HCL%33(10dps). The resulting mixture was refluxed for 5 min. the residue was filtered and washed with ethanol to give I as a white solid (90%). mp: 200°C. IR(KBr): cm-1 = 1697.3(C=O), 2935(CH aliphatic), 3086(CH phenyl), 3228(NH); MS m/e calc. 175 (M+); ^{1}HNMR(CDCl3, 500MHz) δ: 1.5-1.9(m, 2H, CH_2 of pyrimidine), 4.7(t, 1H, CH of pyrimidine), 5.8(S,1H,NH) exchangable with D_2O, 7.2-7.5(m, 6H, benzene ring and CH=N); ^{13}CNMR(DMSO-d6, 500MHz)δ: 54(CH of pyrimidine), 36(CH_2 of pyrimidine),125-130 (6C of

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phenyl), 163(C=O), 164(C=N); ^{13}C DEPT (Distortionless Enhancement by Polarization Transfer) NMR δ: 36 $^{-}$ve (CH_2 of pyrimidine ring), 54 $^{+}$ve (CH of pyrimidine ring), 126-130 $^{+}$ve (5 CH of phenyl and CH=N) and no peaks after 130; 2D NMR HMQC (Heteronuclear multiple-quantum correlation spectroscopy) all carbons discussed at ^{13}C NMR are related to protons at^{1} H NMR.

RESULTS AND DISCUSSION

The 6-phenyl-5,6-dihydropyrimidin-2(1H)-one (I) was synthesized starting from the reaction of urea with cinnamaldehyde in methanol under mild acidic condition by adding 10 drops of HCL%33 (Scheme 1).

According to the old literature [5,6], urea-cinnamaldehyde reaction would have the possibility of other two condensed products 1-(3-phenylallylidene) urea (II) or 1,1'-(3-phenylprop-2-ene-1,1-diyl)diurea(III) (Scheme 2). A characteristic data for compound I was obtained, in mass specrum base peak at m/e = 43 is a strong evidence for presence of CONH not $CONH_2$. Also DEPT show intense peak at δ=36 negative which is a strong evidence for presence of CH_2 of pyrimidine ring. HMQC show multiplet peaks for aliphatic $CHCH_2$ of dihidropyrimidine ring.

Compound I, was tested against four human cancer cell lines MCF-7 (human breast cancer cell line), HELA (human cervical cancer cell line), HCT116

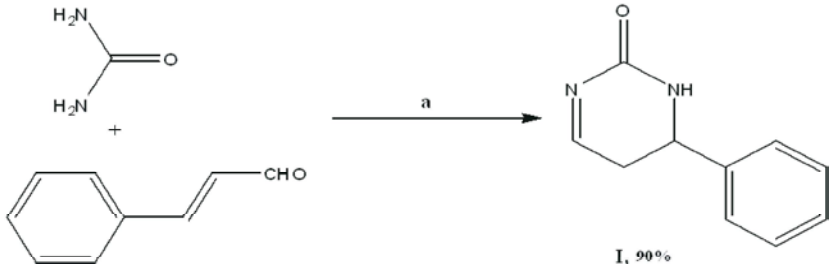
Table 1: Cytotoxicity of compound I against various cancer cell lines

	IC_{50}(μg/ml) in indicated cell line			
Compound	MCF-7	HELA	HCT116	HEPG2
I	3.5	3.9	12.3	17
5-FU	6.5	9.5	89.8	28.2

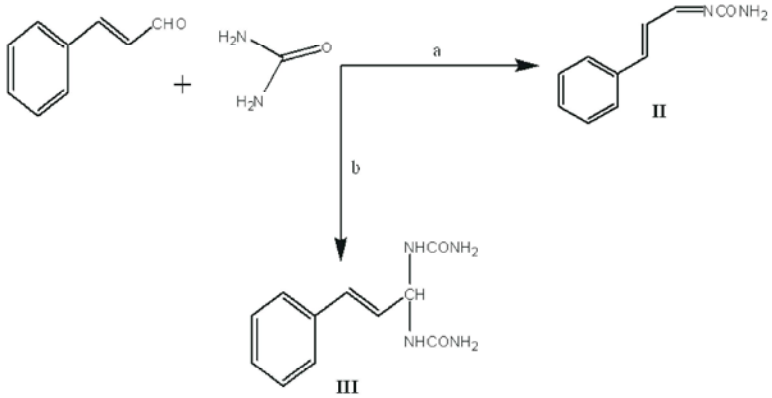
Table 2: Physico-chemical properties of I[(a)]

Compound	%ABS	TPSA	Molecular weight	MlogP	HBDH	M_NO	Lipinski's violations
I	94.7	41.460	174.2	1.478	1	3	0
5-FU	86.32	65.72	130.1	-0.005	2	4	0

[(a)]% ABS (percentage of absorption); TPSA (topological polar surface area); MlogP (Moriguchi estimation of logP); HBDH (Number of Hydrogen bond donor protons); M_NO (Total number of Nitrogen and Oxygen atoms)



Scheme 1: (a) Methanol, HCL 10dps, stirring, 70°C, 5 min



Scheme 2: (a): Dry benzene, TFA, rt, 2hrs. (b): aq. Solution, rt, 1hr, evaporation

(human colorectal cancer cell line) and HEPG2 (human liver cancer cell line) by sulforhodamine B (SRB) assay [8] and shown to have IC_{50}(the half maximal (50%) inhibitory concentration) better than the widely used anticancer drug 5- fluorouracil(5-FU) (Table 1).

A computational study designed to predict the ADME(absorption, distribution, metabolism, elimination) properties of new molecule was performed and the results are presented in (Table 2). Topological polar surface area (TPSA) is a good indicator of drug absorbance in the intestines, Caco-2 monolayers penetration and blood-brain barrier crossing [9]. TPSA was used to calculate the percentage of absorption (%ABS) according to the equation: [%ABS = 109 - 0.345 × TPSA], as reported by Zhao *et al*. [10] In addition, Lipinski's rule of five[11] was also calculated. The molecule have ideal ADME properties showing high percentage of intestinal absorption, with value 94.7% and not violated any of the Lipinski's parameters, an important characteristic for future drug- development.

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