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Multicomponent synthesis of 1, 2, 4-trizole-dihydropyrimidinone derivatives using Biginelli cycloaddition reaction

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Abstract

An operationally simple protocol was employed for synthesis of series of new 1, 2, 4-triazole-dihydropyrimidinone derivatives. Firstly 1-(4-(1H-1, 2, 4-triazol-1-yl) phenyl) ethanone was synthesized using 4-fluroacetophenone, 1, 2, 4-triazole, an.K_2CO_3 in DMF solvent for 12 hrs at 110^0C. then 1-(4-(1H-1,2,4-triazol-1-yl)phenyl) ethanone was refluxed with dimethyl foramide dimethylacetal (DMF-DMA) for 6 hrs gives product 1-(4-(1H-1,2,4-triazol-1-yl)phenyl)-3-(dimethylamino)prop-2-en-1-one (enaminone). Lastly different substituted aromatic aldehyde, urea and 1-(4-(1H-1, 2, 4-triazol-1-yl) phenyl)-3-(dimethylamino) prop-2-en-1-one (enaminone) was refluxed in glacial acetic acid for 12 hrs yields series of new 1,2,4-triazole-dihydropyrimidinone derivatives. The synthesized compound were characterized by mass, ^{1}H NMR and ^{13}C NMR spectroscopy followed by antibacterial and antifungal activity.

Keywords: 1, 2, 4-triazole, DMF-DMA, aromatic aldehyde, urea

Introduction

Heterocyclic compounds containing bridgehead nitrogen are imperative for survival as they are part of crucial building blocks like amino acids, nucleotides, many coenzymes, metabolic regulators etc. Triazoles are one of the most essential nitrogen containing five membered heterocycles containing two carbon and three nitrogen atoms. There are two isomeric forms namely 1, 2, 3-triazole and 1, 2, 4-triazole [1, 2] (fig.1).

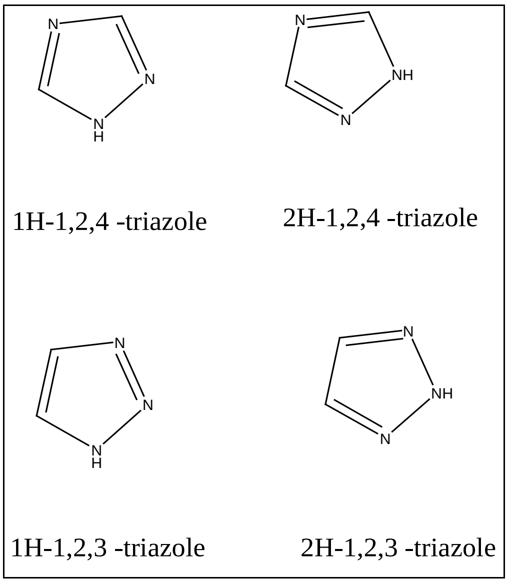


Fig 1

The properties of triazoles have been utilized in many directions for years. The important structural accent of triazole ring with desirable electron feature is beneficial for triazole derivatives for easily binding of variety of enzymes and receptars in biological scenario to show activity against various diseases. They also having broad range of applications in pharmaceutical, agrochemical, supramolecular chemistry, organic synthesis[3-6]. Triazole and their fused heterocyclic compound derivatives serve interesting biological activities such as antibacterial[7], antifungal[8], antihypertensive[9], anti-inflammatory[10] anticancer[11], antitumor[12], antimalerial[13], antitubercular[14], analgesic [15]. Triazole derivatives had shown potent antiviral activities against H1N1 influenza virus [16]. Among derivatives of triazole, have been used in medical field as an antifungal agent such as Fluconazole, Itraconazole, Voriconazole, Triazolam, Furaciline, Alprazolam, Estazolam etc [17]. This disease is especially dangerous for people with minimized immunity, malnutrition, the elderly and alcohol abusers.

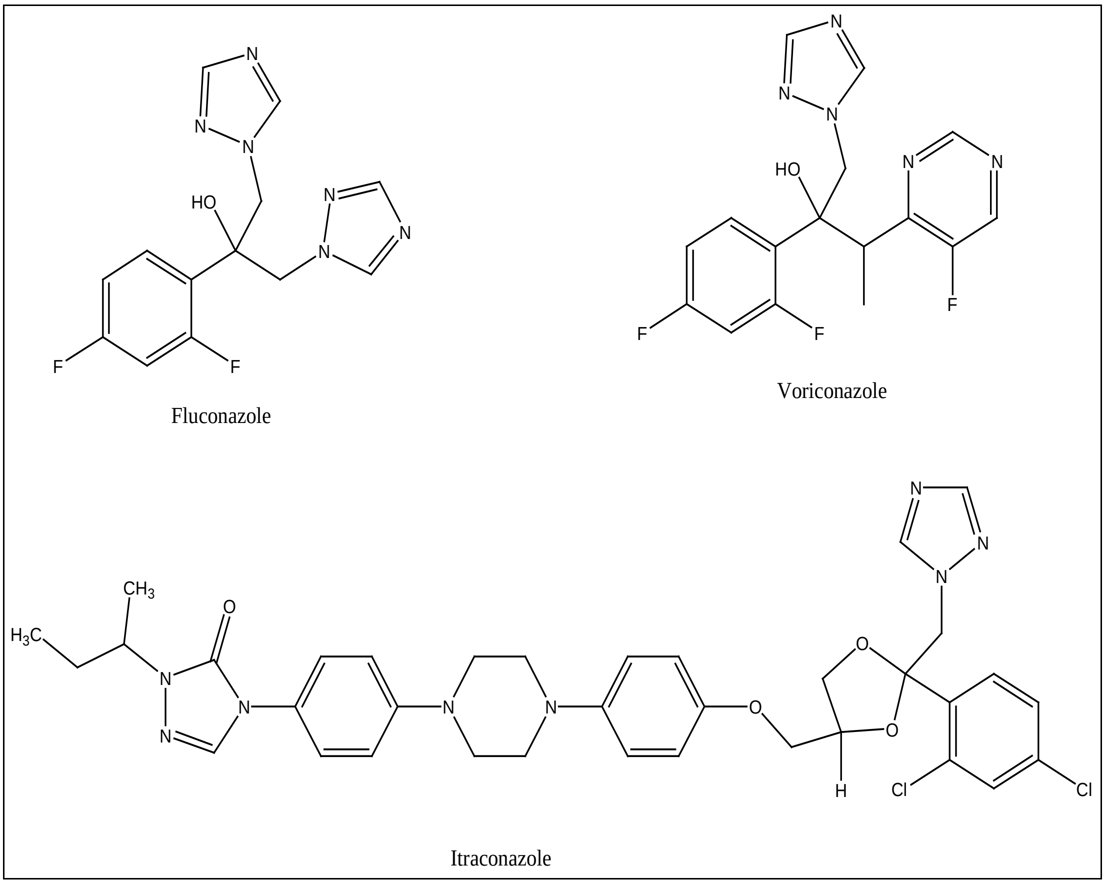


Fig 2

On the other side, dihydropyrimidinone also serve as interesting and multifaceted pharmacological activities such as antiviral [18], antitumor [19], antidiabetic [20], antifungal and antibacterial [21]. As a consequence, dihydropyrimidinone derivatives synthesis containing contradictory substitution patterns has attracted marked attention as its discovery 120 years ago in 1893 by the Italian chemist Pietro Biginelli [22]. Among them, the Biginelli multicomponent reaction, involving a multicomponent condensation of aldehyde, β-ketoester, and urea in presence of different acidic or basic catalyst. By taking advantage from literature survey for above both (triazole and dihydropyrimidinone) bioactive heterocyclic moiety, most of researcher design and synthesized scaffolds exhibit significant biological activity. Guillermo *et al.* developed 1,2,3-triazole derivatives of dihydropyrimidinone as acidic corrosion inhibitor for steel [22], Hassen *et al.* design and synthesized dihydropyrimidinone/1,2,3-triazole hybrid molecule as an antiviral agent [23], Elisabete *et al.* design and synthesized a Novel 1,2,3-triazole-dihydropyrimidinone hybrids and evaluated anticancer activity [24]. Synthesis of Dihydropyrimidinone derivaives with imidazole moiety were synthesized by Biginelli reaction [25]. By considering all these above facts and literature survey suggested that compounds including these two important scaffolds (dihydropyrimidinone and triazole) should possess pharmaceutical activity so the target of present work is to synthesize new compounds containing dihydropyrimidinone derivatives with 1,2,4-triazole moiety.

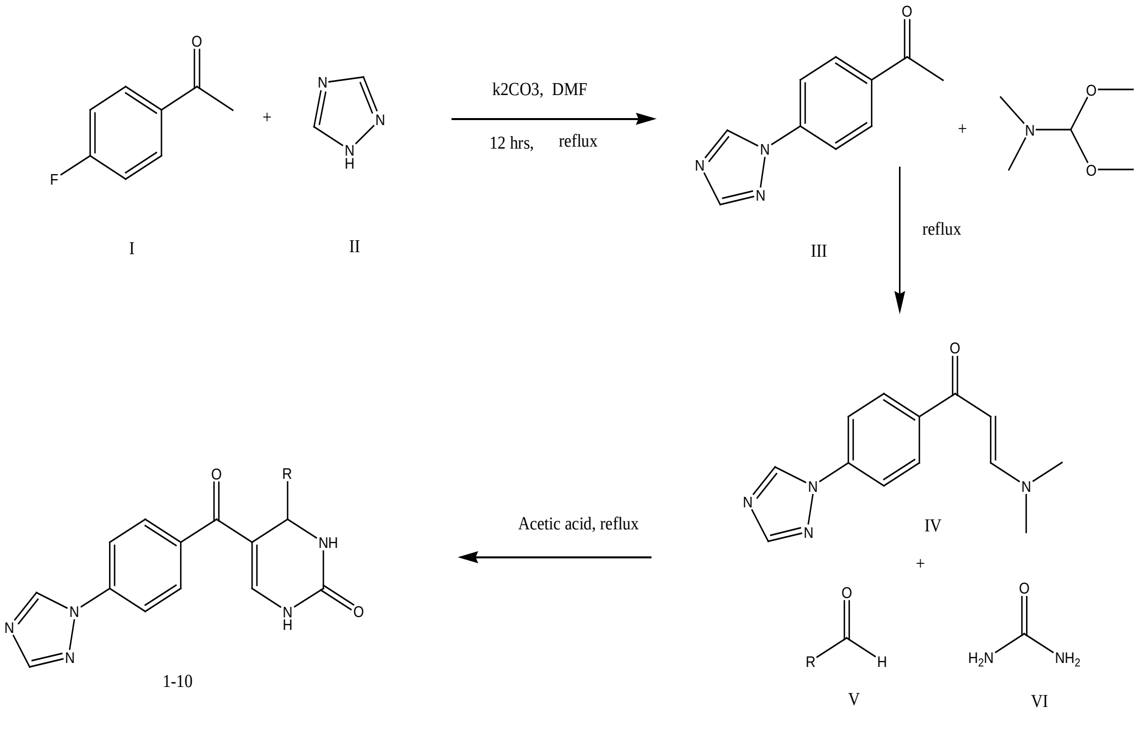
Experimental

All the chemicals were purchased from local suppliers and were used directly as received without further purification. The progress of reaction was monitored by Thin layer chromatography was accomplished on precoated plates of TLC silica gel 60 F_{254}. Visualization was made with UV light (254 or 365nm). The mobile phase used for developing chromatogram is Methanol: DCM (1:10). The ^1H NMR spectra were recorded on BRUKER- 400 MHz (Model: AV 400) spectrometer in DMSO-d6 solvent using TMS as an internal reference and Chemical shifts were supposed to be due to the presence of the solvent. Mass spectra were recorded on MS8040 Mass Spectrometer.

***Synthesis of (4-(1H-1, 2, 4-triazol-1-yl) phenyl) ethanone*:** A mixture of 4-fluro acetophenone (0.047 mol) and 1,2,4-triazole (0.047 mol) was taken in presence of potassium carbonate (0.056 mol) in DMF solvent. The reaction mixture refluxed for 12 hours, then reaction mixture was left to cool slowly at room temperature followed by addition of water to reaction mixture and extracted with ethyl acetate (3x 50 ml). The organic layer was dry over an. Na_2SO_4 and was concentrated under vacuum to get product. The obtained product was recrystallized from absolute ethanol.

Synthesis of (E)-1-(4-(1H-1,2,4-triazol-1-yl)phenyl)-3-(dimethylamino)prop-2-en-1-one: A mixture of (E)-1-(4-(1H-1,2,4-triazol-1-yl)phenyl) ethanone (0.02 mol) and dimethyl formamide-dimethyl acetal (DMF-DMA) (0.02 mol) was refluxed for 10 hours under solvent free condition on heating mantle. After the completion of reaction, the reaction mixture was slowly cooled to room temperature. The precipitate was obtained. Diethyl ether was added to the precipitate, and filtration was performed under vacuum. The obtained product (E)-1-(4-(1H-1, 2, 4-triazol-1-yl) phenyl)-3-(dimethylamino) prop-2-en-1-one was recrystallized from absolute ethanol.

General Synthesis of the Trizole derivatives of Dihydropyrimidinone: A mixture of (E)-1-(4-(1H-1, 2, 4-triazol-1-yl)phenyl)-3-(dimethylamino)prop-2-en-1-one (0.002 mol), different substituted benzaldehydes (0.002 mol), urea (0.002 mol), and glacial acetic acid (10 mL) was refluxed for 3hours. The precipitates were obtained by pouring the reaction mixture into the ice cold water. The products were isolated by Buchner filtration under vacuum. The products were washed three times with cold water followed by hexane. The physicochemical properties of different triazole derivatives are shown in Table. 1. In the ^{1}H-NMR spectra, the signals of the individual protons of the compounds were verified on the basis of multiplicity, chemical shifts, and coupling constant. Analytical and Spectral data for the compounds were in good agreement with the expected structures of the compounds.



Scheme.1: Reaction scheme for synthesis of triazole derivatives of dihydropyrimidinone

Fig 3

Name of structure

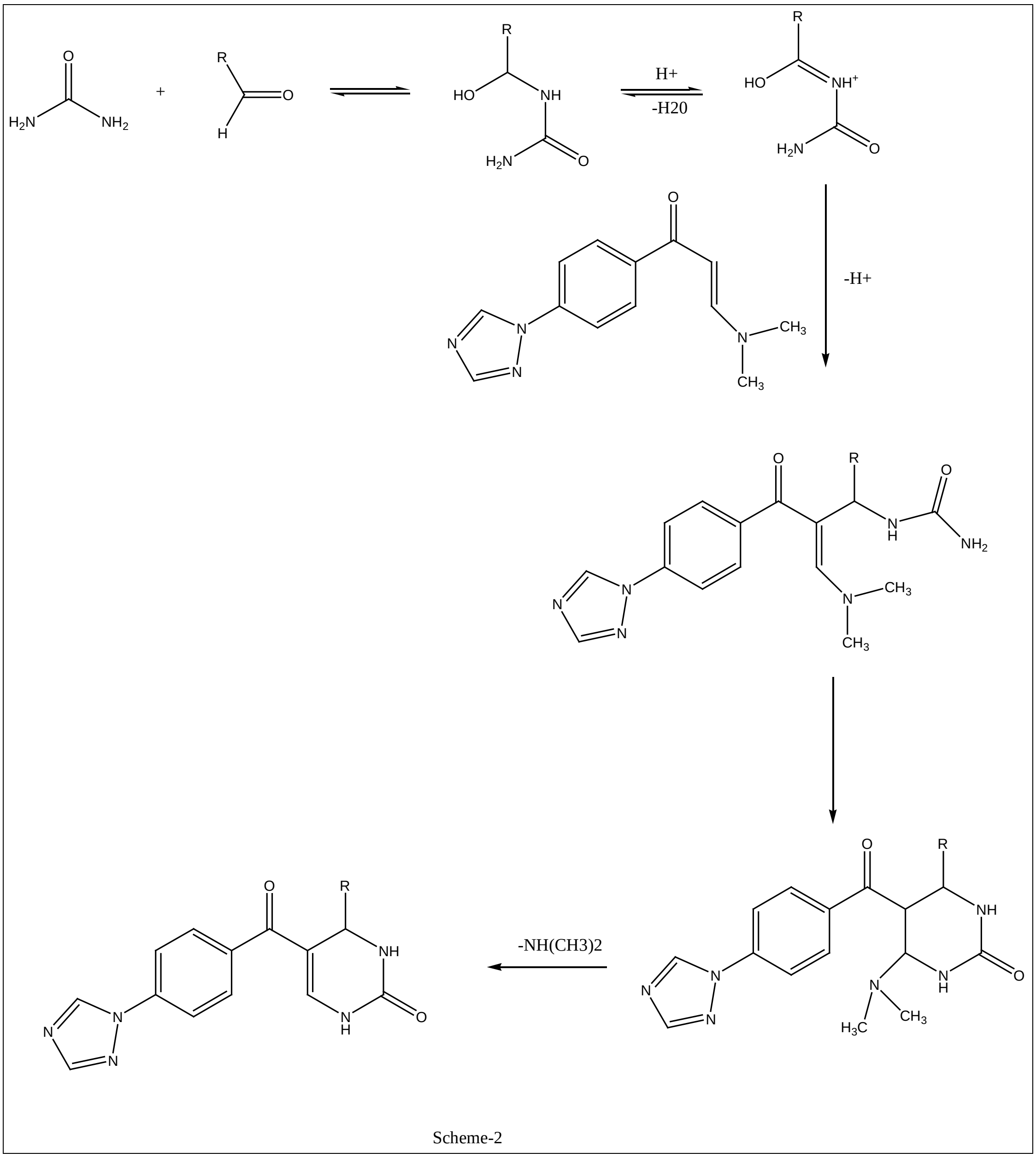
a. 5-[4-(1H-triazole-1-yl)benzoyl]-4-phenyl-3,4-dihydropyrimidin-2(1H)-one: ^{1}H NMR: 400 MHz, DMSO-d6): δ=9.38 (1H, s, triazole H), 8.27 (1H, s, triazole H), 7.11 (1H, s, =CH), 5.44 (1H, d, J=2.8Hz), 7.20-7.96 (m, 9H, Ar-H), 9.42 (s, 1H, NH), 7.88 (s, 1H, NH). MS: m/z=346
b. 5-[4-(1H-triazole-1-yl)benzoyl]-4-(2-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one: ^{1}H NMR: 400 MHz, DMSO-d6): δ=9.37 (1H, s, triazole H), 8.28 (1H, s, triazole H), 3.83 (3H, s,OCH_3) 7.13 (1H, s, =CH), 5.71 (1H, d, J=2.4Hz), 6.89-7.97 (m, 8H, Ar-H), 9.34 (s, 1H, NH), 7.43 (s, 1H, NH). MS: m/z=376
c. 5-[4-(1H-triazole-1-yl)benzoyl]-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one: ^{1}H NMR: 400 MHz, DMSO-d6): δ=9.38 (1H, s, triazole H), 8.27 (1H, s, triazole H), 7.12 (1H, s, =CH), 5.44 (1H, d, J=2.8Hz), 7.34-7.96 (m, 8H, Ar-H), 9.49 (s, 1H, NH), 7.91 (s, 1H, NH). MS: m/z=380
d. 5-[4-(1H-triazole-1-yl)benzoyl]-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one: ^{1}H NMR: 400 MHz, DMSO-d6): δ=9.37 (1H, s, triazole H), 8.26 (1H, s, triazole H), 7.17 (1H, s, =CH), 6.12 (1H, d, J=2.0Hz), 7.50-8.10 (m, 8H, Ar-H), 9.60 (s, 1H, NH), 7.90 (s, 1H, NH). MS: m/z=391
e. 5-[4-(1H-triazole-1-yl)benzoyl]-4-(3-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one: ^{1}H NMR: 400 MHz, DMSO-d6): δ=9.38 (1H, s, triazole H), 8.27 (1H, s, triazole H), 3.74 (3H, s,OCH_3) 7.11 (1H, s, =CH), 5.42 (1H, d, J=2.8Hz), 6.83-8.13 (m, 8H, Ar-H), 9.42 (s, 1H, NH), 7.87 (s, 1H, NH). MS: m/z=376

f. 5-[4-(1H-triazole-1-yl)benzoyl]-4-(4-trifluromethylphenyl)-3,4-dihydropyrimidin-2(1H)-one: ^{1}H NMR: 400 MHz, DMSO-d6): δ=9.37 (1H, s, triazole H), 8.26 (1H, s, triazole H), 7.14 (1H, s, =CH), 5.52 (1H, d, J=2.8Hz), 7.56-8.12 (m, 8H, Ar-H), 9.52 (s, 1H, NH), 7.95 (s, 1H, NH). MS: m/z=414

g. 5-[4-(1H-triazole-1-yl)benzoyl]-4-(4-trifluromethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one: ^{1}H NMR: 400 MHz, DMSO-d6): δ=9.38 (1H, s, triazole H), 8.27 (1H, s, triazole H), 7.14 (1H, s, =CH), 5.48 (1H, d, J=2.8Hz), 7.23-7.96 (m, 8H, Ar-H), 9.50 (s, 1H, NH), 7.93 (s, 1H, NH). MS: m/z=430 Table.1: Physicochemical properties of compounds:

Table 1

Compound	R	Yield (%)
1	C_6H_5	70
2	2-OCH_3- C_6H_4	68
3	4-Cl- C_6H_4	75
4	4-NO_2- C_6H_4	72
5	3-OCH_3- C_6H_4	68
6	2-NO_2- C_6H_4	75
7	4-CF_3- C_6H_4	68
8	4-OCF_3- C_6H_4	68
9	4-F- C_6H_4	65
10	4-OCH_3- C_6H_4	70



Scheme-2

Fig 4

Results and Discussion

As shown in scheme 1, reaction of 4-fluoro acetophenone with 1, 2, 4-triazole in presence of potassium carbonate and DMF solvent for refluxing 12 hrs yields (4-(1H-1, 2, 4-triazol-1-yl) phenyl) ethanone (III). (E)-1-(4-(1H-1, 2, 4-triazol-1-yl) phenyl)-3-(dimethylamino) prop-2-en-1-one (IV) was synthesized by refluxing (4-(1H-1, 2, 4-triazol-1-yl) phenyl) ethanone (III) with Dimethyl formamide-Dimethylacetal (DMF-DMA) under solvent free condition for 10 hrs. To prepare final triazole- dihydro pyrimidinone derivatives, a mixture of substituted aromatic aldehyde (V), enaminone (IV) and urea (VI) in glacial acetic acid was refluxed for 3 hrs.) The ethylenic protons indicate that the enaminone existed in the E- configuration [26]. Compounds shows broad spectrum and having δ value in between 7.43-7.95 ppm and 9.34-9.60 ppm indicates presence of two NH protons. The racemic proton of dihydropyrimidinone moiety is observed at 7.11-7.44 ppm δ value as doublet (J=2.8Hz). The δ value in between 7.11-7.17 ppm indicates presence of allylic proton which appears as singlet. [13]C NMR and mass spectra of some compounds confirm the presence of compound.

The possible reaction mechanism for dihydropyrimidinone derivative containing 1, 2, 4-triazole (1–10) involves the acid-catalyzed formation of iminium ion intermediate from the substituted aryl aldehydes and urea. Reaction of iminium ion by enaminone of 1, 2, 4-triazole produces ureidenone, which cyclizes to form hexahydropyrimidine. Removal of N (CH3)2 group from hexahydropyrimidine in presence of glacial acetic acid produces final dihydropyrimidinone derivative (1–10) containing 1, 2, 4-triazole moiety (Scheme 2)

Conclusions

In conclusion, a series of dihydropyrimidinone derivatives with 1,2,4-triazole derivatives were synhesized wih simple and efficient method having high purity of compound. The starting material was synthesized by 4-fluro acetophenone with 1,2,4-triazole in presence of potassium carbonate in DMF solvent for 12 hrs which gives product acetophenone triazole compound. The enaminone were synthesized by treating acetophenone triazole with Dimethylformamide Dimethylacetal (DMF-DMA) under solvent free condition. The new dihydropyrimidinone derivatives were obtained from reaction of enaminone, substituted aryl aldehyde and urea in presence of glacial acetic acid.

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