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Synthesis and Biological Evaluation of Some Novel Sulfonylurea and Sulfonamide Derivatives under Phase Transfer Catalysis Conditions

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Abstract: Classes of novel sulfonylurea and sulfonamide derivatives **3-13** were synthesized via three different roots, using pharmacologically active functionalized pyrimidine or piperidine-2,6-dione derivatives and p-toluene sulfonyl chloride under phase transfer conditions (PTC). The structures of all the newly synthesized compounds were characterized by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. The title compounds were screened for antibacterial activity against two-gram positive bacterial strains such as Staphylococcus aureus and Bacillus subtilis and two-gram negative bacterial strains such as Escherichia coli and Pseudomonas aeruginosa and also screened for antifungal activity against Fusarium oxysporum, Candida albicans and Aspergillus niger pathogens. Compounds **3b**, **4b**, **6b, 6d, 8b, 11b, 13**b and **13e** exhibited potent activity and remaining derivatives showed moderate to weak activity against bacteria and fungi

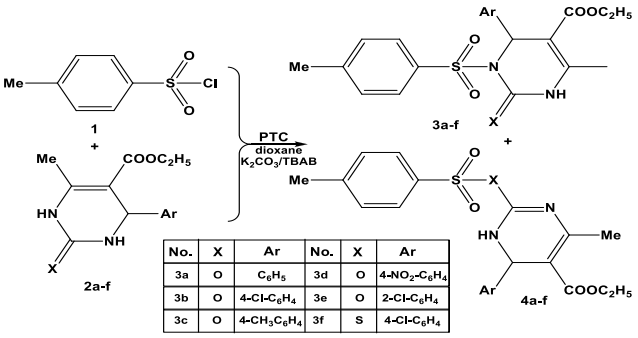
Keywords: Sulfonylureas, Sulfonamide, Pyrimidine, PTC, Antibacterial activity, Antifungal activity.

1 Introduction

Sulfonamide-based medicines were the second antimicrobial agents, still widely used today for the treatment of various bacterial, protozoal and fungal infections [1] and the first effective chemotherapeutic agents to be available in safe therapeutic dosage ranges [2]. They were the mainstay of therapy for bacterial infections in human beings before the introduction of Penicillin in 1941 [3]. Compounds containing sulfonyl groups have long been a research focus as a result of their biological importance, chemical applications and some of the aryl sulfonamide derivatives are a common substructure class present in a large number of active pharmaceutical ingredients (APIs) [4]. Sulfonamide derivatives occupy a unique position in the drug industry with their potent antibacterial and antimicrobial properties [5]. The applications of sulfonamides has greatly extended from their primary function as antitumor [6], hypoglycemic [7], antithyroid [8], anti-carbonic anhydrase [9], anti-inflammatory [10], diuretic [11], COX-inhibitors, dihydropteroate synthetase (DHPS)-the key enzyme involved in folate synthesis, anti-impotence drugs [12].

2 Results and Discussion

Based on overview of the literature and ubiquitous medicinal and biological importance of sulfonylurea and sulfonamide derivatives have led to the great challenge for researchers for designing of these new biological active libraries which may be useful in search of potential drug candidates, drug intermediates and development of new synthetic methodologies. As a part of our research, we have synthesized a series of novel ethyl 6-methyl-2-oxo-4-phenyl-3-tosyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **3a-f** from the reaction of p-toluene sulfonylchloride**1** with ethyl 6-methyl-2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **2a-f** (Biginelli products) [13] under phase transfer catalysis conditions [dioxane/K_2CO_3/TBAB], where two products were isolated one from dioxane layer and was identified as 6-methyl-2-oxo(thioxo)-4-aryl-1-tosyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **3a-f** in

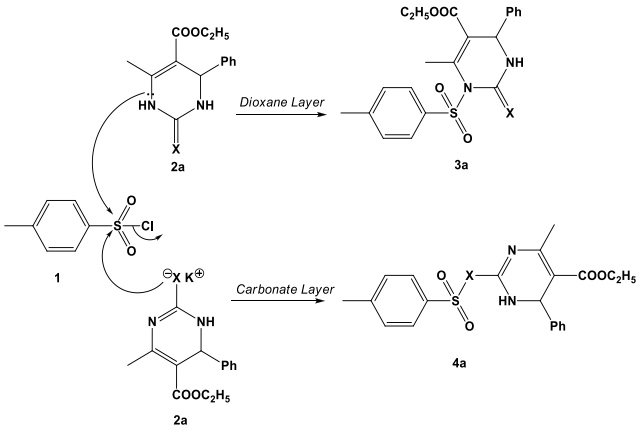


No.	X	Ar	No.	X	Ar
3a	O	C_6H_5	3d	O	4-NO_2-C_6H_4
3b	O	4-Cl-C_6H_4	3e	O	2-Cl-C_6H_4
3c	O	4-$CH_3C_6H_4$	3f	S	4-Cl-C_6H_4

Scheme 1

moderate yield 35-55 % and another one from carbonate layer after acidification with acetic acid and was identified as ethyl 4-methyl-6-aryl-2-tosyloxy(tosylthio)-1,6-dihydropyrimidine-5-carboxylate **4a-f** in poor yields 10-25%, Scheme 1.

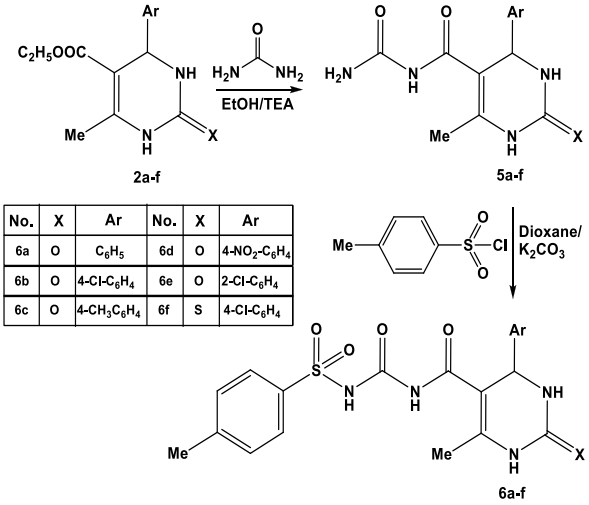
The reaction pathway in dioxane layer was assumed to follow a preliminary nucleophilic attack of the secondary amine into the sulfonyl chloride moiety with subsequent elimination of HCl molecule. While the nucleophilic attack into the sulfony chloride was preceded by the thiol group of the tautomeric form of compound **2a**, Scheme 2.



Scheme 2

The IR spectrum of compound **3a** was revealed absorption bands at 3297, 1718, 1695, 1396 cm^{-1} corresponding to NH, $C=O_{ester}$, $C=O_{amide}$ and S=O stretching respectively. Where the ^{1}H-NMR spectrum of compound **3a** showed a singlet at δ 9.24 ppm corresponding to NH proton, multiplet between δ 7.78-7.22 ppm for aromatic protons, a singlet at δ 5.28 ppm for CH-Ar proton, a quartet at δ 4.01 ppm for OCH_2 protons, two singlets at δ 2.32 and 2.18 ppm for two CH_3 protons and a triplet at δ 1.01 ppm for CH_3 protons. The ^{13}C-NMR of compound **3a** revealed signals at 14.1, 21.3, 22.5, 53.2, 59.1, 100.2, 116.3, 121.6, 123.5, 126.8, 127.7, 129.5, 131.3, 136.6, 164.1 and 168.9. While the IR spectrum of compound **4a** showed absorption bands at 3305, 1726 and 1401 cm^{-1} characteristic for NH, C=O and S=O stretching respectively. The ^{1}H-NMR spectrum of compound **4a** exhibited a singlet at δ 9.18 for NH proton, a multiplet between δ 7.72-7.28 ppm for aromatic protons, a singlet at δ 5.36 ppm for CH-Ar proton, a quartet at δ 4.01 ppm for OCH_2 protons, two singlets at δ 2.30 and 2.22 ppm for two CH_3 protons and a triplet at δ 1.01 ppm for CH_3 protons. The ^{13}C-NMR of compound **3a** revealed signals at 14.2, 19.2, 21.1, 53.4, 59.0, 100.2, 115.8, 121.7, 123.1, 126.5, 127.3, 128.2, 129.5, 133.7, 134.5, 161.5 and 168.6.

Attempts to obtain new sulfonylurea derivatives were made, therefore the Biginelli products were allowed to react with urea and the obtained products were the reacted with p-toluene sulfonyl chloride under mild alkaline conditions where a new series of sulfonylurea derivatives **6a-f** were obtained, Scheme 3.

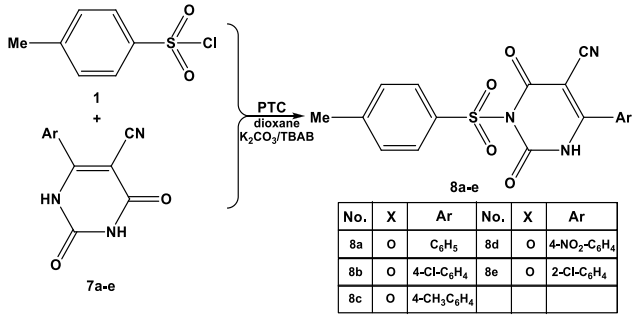


No.	X	Ar	No.	X	Ar
6a	O	C_6H_5	6d	O	4-NO_2-C_6H_4
6b	O	4-Cl-C_6H_4	6e	O	2-Cl-C_6H_4
6c	O	4-$CH_3C_6H_4$	6f	S	4-Cl-C_6H_4

Scheme 3

The absence of OCH_2CH_3 group in the ^{1}H-NMR spectrum of compound **5a** confirm the reaction of urea at the ester group, where the IR spectrum of compound **6a** showed absorption bands at 3314, 3296, 3223, 1698 and 1666 cm^{-1} for NH and CO stretching. ^{1}H-NMR spectrum of compound **6a** displayed four singlets at 10.23, 9.22 and 7.98 ppm for 4 NH protons, a multiplet between 7.64 and 7.32 ppm for aromatic protons, a singlet at 5.32 ppm for CH proton and two singlets at 2.32 and 2.22 ppm for 2 CH_3 protons.

In an extension of our work, p-toluene sulfonyl chloride was reacted with 2,4-dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile **7a-e** [14] under mild alkaline conditions (dioxane/TEA) to give 2,4-dioxo-6-aryl-3-tosyl-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile **8a-e** in poor yields, so the reaction was achieved under phase transfer catalysis [dioxane/K_2CO_3/TBAB] where the desired cyclic sulfonylureas **8a-e** were obtained from dioxane layer in good yields, Scheme 4.



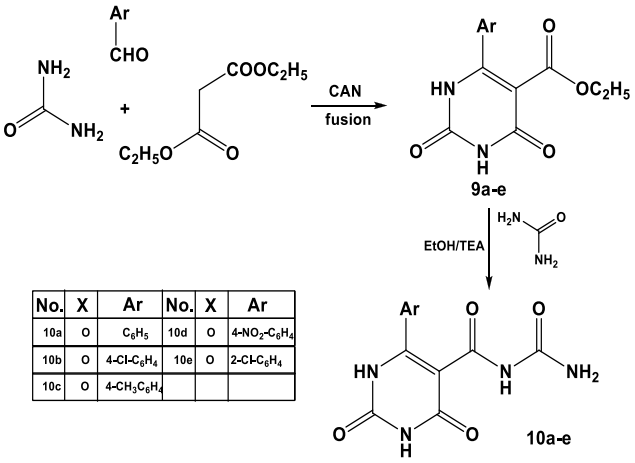
No.	X	Ar	No.	X	Ar
8a	O	C_6H_5	8d	O	4-NO_2-C_6H_4
8b	O	4-Cl-C_6H_4	8e	O	2-Cl-C_6H_4
8c	O	4-$CH_3C_6H_4$			

Scheme 4

The IR spectrum of compound **8a** showed absorption maxima at 3287, 2202, 1707, and 1387 cm^{-1} corresponding

to NH, CN, C=O and S=O stretching respectively, where the ^{1}H-NMR spectrum displayed a broad band at 9.26 ppm characteristic for NH group, a multiplet band between 7.74-7.26 ppm characteristic for aromatic protons, a singlet at 2.32 for methyl protons. ^{13}C-NMR spectrum of compound **8a** was found to be with accordance with the proposed structure.

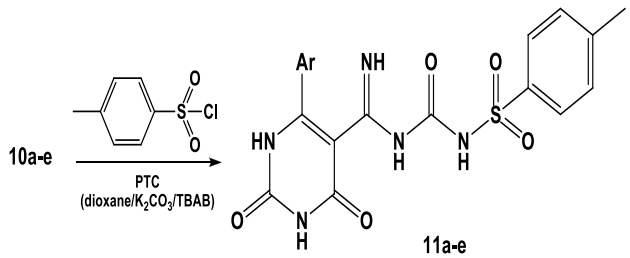
Searching for new sulfonylurea derivatives has prompted us to look for different synthetic protocols. Therefore, the multi-component reaction between diethyl malonate, aromatic aldehyde and urea under solvent free conditions in the presence of a catalytic amount of ceric ammonium nitrate (CAN) afforded the corresponding pyrimidine derivatives namely: ethyl 2,4-dioxo-6-aryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **9a-e**, which in turn were allowed to react with another molecule of urea under mild alkaline conditions (EtOH/TEA) to give the corresponding urea derivatives **10a-e**, Scheme 5.



No.	X	Ar	No.	X	Ar
10a	O	C_6H_5	10d	O	4-NO_2-C_6H_4
10b	O	4-Cl-C_6H_4	10e	O	2-Cl-C_6H_4
10c	O	4-$CH_3C_6H_4$			

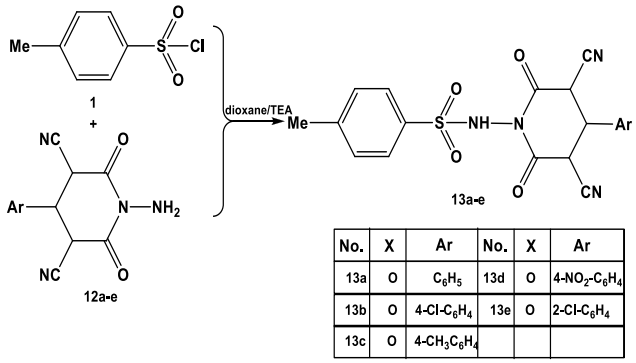
Scheme 5

When compounds **10a-e** were subjected to reaction with p-toluene sulfonyl chloride under phase transfer catalysis condition [dioxane/K_2CO_3/TBAB] gave the corresponding sulfonyl urea derivatives namely: 2,4-dioxo-6-phenyl-N-(tosylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide **11a-e**, Scheme 6.



Scheme 6

On the other hand, compound **1** was reacted with 1-amino-2,6-dioxo-4-arylpiperidine-3,5-dicarbonitrile **12a-e** [15] under mild alkaline conditions (dioxane/TEA) where the corresponding sulfonamide derivatives **13a-e** were obtained in good yields, Scheme 7.



No.	X	Ar	No.	X	Ar
13a	O	C_6H_5	13d	O	4-NO_2-C_6H_4
13b	O	4-Cl-C_6H_4	13e	O	2-Cl-C_6H_4
13c	O	4-$CH_3C_6H_4$			

Scheme 7

Analytical and spectral data of the synthesized compounds are in agreement with the proposed structure (see Experimental section).

3 Biological Evaluations

3.1 Antimicrobial evaluation

Table 1. Antimicrobial Activities of the newly Synthesized Compounds.

Inhibition zone (mm)							
Comp. No.	**Gram-negative**		**Gram-positive**		**Fungi**		**Yeast**
	E. Coli	***p. putida***	***B. subtilis***	***S. lactis***	***A. niger***	***P. sp.***	***C. albicans***
3a	10	12	12	9	8	10	0
3b	14	14	12	14	10	12	0
3c	8	10	6	8	10	10	0
4a	12	12	8	12	12	10	0
4b	15	12	10	13	10	8	0
4c	14	10	10	12	8	8	0
6a	10	12	10	12	8	10	0
6b	15	12	12	10	10	10	0
6c	12	10	8	8	8	12	0
8a	10	11	13	11	10	8	0
8b	14	12	14	15	12	12	2
8c	10	8	9	7	6	7	0
11b	12	10	11	10	8	8	0
11d	13	10	12	8	7	7	0
13a	12	15	12	12	12	10	0
13b	16	15	14	14	12	12	4
13c	15	15	12	10	12	10	2
Ampicillin	24	20	19	22	24	14	14
Chloram-phenicol	22	21	18	19	20	12	0

The newly synthesized heterocyclic compounds listed in Table 1 were tested for their antimicrobial activity against

the following microorganisms: Escherichia coli, Pseudomonas putida, Bacillus subtilis, Streptococcus lactis, Aspergillus niger, Penicillium sp. and Candida albicans. The preliminary screening of the investigated compounds was performed using the filter paper disc-diffusion method. The most active compounds were **3b**, **4a,b**, **6b**, **8b,c**, **11b** and **13b,d**, which were slightly inhibitory to the microorganisms. The rest of compounds showed weak to moderate sensitivity to the tested organisms, and the results are summarized in Table 1.

E. coli = Escherichia coli; P. putida = Pseudomonas putida; B. subtilis = Bacillus subtilis; S. lactis = Streptococcus lactis; A. niger = Aspergillus niger; P. sp. = Penicilliumsp; C. albicans = Candida albicans. The sensitivity of microorganisms to the tested compounds is identified in the following manner *: Highly sensitive = Inhibition zone 15-20 mm; Moderately sensitive = Inhibition zone: 10-15 mm; Slightly sensitive = Inhibition zone: 5-10 mm; Not sensitive = Inhibition zone: 0 mm;* Each result represents the average of triplicate readings. The newly synthesized compounds were screened for their antimicrobial activities and they showed moderate to potent activity against their corresponding pathogens.

3.2 Experimental

All melting points were determined on a Koffler melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Brukeravance 400 MHz spectrometer using TMS as internal reference (chemical shifts in δ, ppm), and IR spectra were obtained on a Nicolet 710 FT-IR spectrometer (KBr, ν_{max} in cm^{-1}).

Reaction of p-toluene sulfonyl chloride 1 with ethyl 6-methyl-2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 2a-i (Biginelli products) under PTC conditions:

General procedure:

An equimolar mixture of p-toluene sulfonyl chloride **1** (1.905 g, 0.01 mol) and Biginelli product **2a-f** (0.01 mol) was dissolved in 50 mL dry dioxane and then treated with ~ 7g anhydrous potassium carbonate and a catalytic amount of tetrabutylammonium bromide (TBAB). The reaction mixture was stirred at 60 °C for 4-6 h, and then left to cool. Potassium carbonate was removed by filtration, washed thoroughly with dioxane and the dioxane layer was collected and evaporated under reduced pressure where the corresponding sulfonylurea derivatives **3a-f** were obtained and recrystallized from ethanol into the desired products. Carbonate were dissolved in water the acidified with AcOH and left at room temperature overnight, the obtained solid were filtered off and recrystallized from aqueous ethanol affording compounds **4a-f**.

Ethyl6-methyl-2-oxo-4-phenyl-1-tosyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3a: Yield: 58%, m.p.: 262-264 °C, IR (KBr, ν, cm^{-1}): 3297 (NH), 1718 (C=O), 1695 (C=O) and 1396 (S=O), ^{1}H-NMR (DMSO, δ, ppm): 9.24 (s, 1H, NH), 7.78-7.22 (m, 9H, CH-arom.), 5.28 (s, 1H, CH), 4.01 (q, J= 7.0 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 1.01 (t, J= 7.0 Hz, 3H CH_3), ^{13}C-NMR (DMSO, δ, ppm): 14.1, 21.3, 22.5, 53.2, 59.1, 100.2, 116.3, 121.6, 123.5, 126.8, 127.7, 129.5, 131.3, 136.6, 164.1, 168.9.

Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1-tosyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3b: Yield: 62%, m. p.: 246-248 °C, IR (KBr, ν, cm^{-1}): 3307 (NH), 1723 (C=O), 1696 (C=O), 1399 (S=O), ^{1}H-NMR (DMSO, δ, ppm): 9.22 (s, 1H, NH), 7.81-7.26 (m, 8H, CH-arom.), 5.36 (s, 1H, CH), 3.99 (q, J= 7.0 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 1.00 (t, J= 7.0 Hz, 3H CH_3), ^{13}C-NMR (DMSO, δ, ppm): 14.2, 17.5, 18.8, 53.3, 59.2, 100.1, 116.3, 122.3, 124.1, 126.5, 127.1, 127.8, 128.5, 131.3, 134.6, 154.5, 166.5.

Ethyl 6-methyl-2-oxo-4-p-tolyl-1-tosyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3c: Yield: 60%, m. p.: 250-252 °C, IR (KBr, ν, cm^{-1}): 3303 (NH), 1733 (C=O), 1693 (C=O), 1396 (S=O), ^{1}H-NMR (DMSO, δ, ppm): 9.23 (s, 1H, NH), 7.81-7.26 (m, 8H, CH-arom.), 5.36 (s, 1H, CH), 4.00 (q, J= 7.0 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2,18 (s, 3H, CH_3), 1.00 (t, J= 7.0 Hz, 3H CH_3), ^{13}C-NMR (DMSO, δ, ppm): 14.2, 17.5, 18.8, 53.3, 59.2, 100.1, 116.3, 122.3, 124.1, 126.5, 127.1, 127.8, 128.5, 131.3, 134.6, 154.5, 166.5.

Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1-tosyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3d: Yield: 62%, m. p.: 255-257 °C, IR (KBr, ν, cm^{-1}): 3311 (NH), 1730 (C=O), 1691 (C=O), 1395 (S=O), ^{1}H-NMR (DMSO, δ, ppm): 9.23 (s, 1H, NH), 7.85-7.25 (m, 8H, CH-arom.), 5.36 (s, 1H, CH), 4.01 (q, J= 7.0 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 1.01 (t, J= 7.0 Hz, 3H CH_3), ^{13}C-NMR (DMSO, δ, ppm): 14.0, 17.7, 18.8, 53.2, 59.2, 100.1, 116.3, 122.3, 124.1, 126.5, 127.1, 127.8, 128.5, 132.3, 134.6, 154.5, 168.5.

Ethyl 4-(2-chlorophenyl)-6-methyl-2-oxo-1-tosyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3e: Yield: 52%, m. p.: 235-258 °C, IR (KBr, ν, cm^{-1}): 3310 (NH), 1735 (C=O), 1695 (C=O), 1398 (S=O), ^{1}H-NMR (DMSO, δ, ppm): 9.25 (s, 1H, NH), 7.80-7.25 (m, 8H, CH-arom.), 5.35 (s, 1H, CH), 4.00 (q, J= 7.0 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 1.02 (t, J= 7.0 Hz, 3H CH_3), ^{13}C-NMR (DMSO, δ, ppm): 14.1, 17.8, 18.7, 53.3, 59.2, 100.1, 116.5, 122.2, 124.4, 126.5, 127.2, 127.8, 128.5, 132.1, 133.3, 134.5, 154.5, 168.5.

Ethyl 4-(4-chlorophenyl)-6-methyl-2-thioxo-1-tosyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 3f: Yield: 65%, m. p.: 278-280 °C, IR (KBr, ν, cm^{-1}): 3309 (NH),

1734 (C=O), 1690 (C=O), 1398 (S=O), 1223 (C=S), ^{1}H-NMR (DMSO, δ, ppm): 9.20 (s, 1H, NH), 7.82-7.25 (m, 8H, CH-arom.), 5.36 (s, 1H, CH), 4.00 (q, J= 7.0 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 1.02 (t, J= 7.0 Hz, 3H CH_3), ^{13}C-NMR (DMSO, δ, ppm): 14.1, 17.8, 18.7, 53.3, 59.2, 100.1, 116.5, 122.2, 124.4, 126.5, 127.2, 127.8, 128.5, 132.1, 133.3, 166.2, 168.5.

Ethyl 4-methyl-6-phenyl-2-(tosyloxy)-1,6-dihydropyrimidine-5-carboxylate 4a:

Yield: 17 %, m.p.: 224-226 °C, IR (KBr, ν, cm^{-1}): 3254 (NH), 1728 (C=O), and 1395 (S=O), ^{1}H-NMR (DMSO, δ, ppm): 9.28 (s, 1H, NH), 7.78-7.28 (m, 9H, CH-arom.), 5.35 (s, 1H, CH), 4.01 (q, J= 7.0 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 1.01 (t, J= 7.0 Hz, 3H CH_3), ^{13}C-NMR (DMSO, δ, ppm): 14.4, 21.5, 22.5, 53.2, 59.1, 100.1, 116.3, 121.6, 123.5, 126.8, 127.7, 129.5, 131.3, 132,5, 133.6, 136.6, 168.9.

Ethyl 6-(4-chlorophenyl)-4-methyl-2-(tosyloxy)-1,6-dihydropyrimidine-5-carboxylate 4b:Yield: 20 %, m.p.: 246-248 °C, IR (KBr, ν, cm^{-1}): 3258 (NH), 1728 (C=O), and 1399 (S=O), ^{1}H-NMR (DMSO, δ, ppm): 9.25 (s, 1H, NH), 7.82-7.38 (m, 8H, CH-arom.), 5.35 (s, 1H, CH), 4.01 (q, J= 7.0 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 1.01 (t, J= 7.0 Hz, 3H CH_3), ^{13}C-NMR (DMSO, δ, ppm): 14.1, 21.5, 22.5, 53.3, 59.2, 100.1, 116.1, 121.6, 123.6, 126.7, 127.7, 129.5, 131.2, 132,5, 133.2, 168.9.

Ethyl 4-methyl-6-p-tolyl-2-(tosyloxy)-1,6-dihydropyrimidine-5-carboxylate 4c:

Yield: 12 %, m.p.: 230-232 °C, IR (KBr, ν, cm^{-1}): 3252 (NH), 1732 (C=O), and 1396 (S=O), ^{1}H-NMR (DMSO, δ, ppm): 9.23 (s, 1H, NH), 7.78-7.35 (m, 8H, CH-arom.), 5.32 (s, 1H, CH), 4.01 (q, J= 7.0 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 1.01 (t, J= 7.0 Hz, 3H CH_3), ^{13}C-NMR (DMSO, δ, ppm): 14.1, 21.5, 21.7, 22.6, 53.3, 59.3, 100.1, 116.1, 121.7, 123.6, 126.7, 127.7, 129.5, 131.2, 132.5, 133.1, 168.5.

Ethyl 4-methyl-6-(4-nitrophenyl)-2-(tosyloxy)-1,6-dihydropyrimidine-5-carboxylate 4d: Yield: 16 %, m.p.: 203-205 °C, IR (KBr, ν, cm^{-1}): 3267 (NH), 1730 (C=O), and 1401 (S=O), ^{1}H-NMR (DMSO, δ, ppm): 9.25 (s, 1H, NH), 7.82-7.35 (m, 8H, CH-arom.), 5.35 (s, 1H, CH), 4.01 (q, J= 7.0 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 1.01 (t, J= 7.0 Hz, 3H CH_3), ^{13}C-NMR (DMSO, δ, ppm): 14.5, 21.5, 21.5, 22.6, 53.3, 59.5, 100.1, 116.1, 121.7, 125.6, 126.7, 127.8, 129.5, 131.2, 132.5, 133.1, 168.8.

Ethyl 6-(2-chlorophenyl)-4-methyl-2-(tosyloxy)-1,6-dihydropyrimidine-5-carboxylate 4e: Yield: 10 %, m.p.: 222-225 °C, IR (KBr, ν, cm^{-1}): 3260 (NH), 1730 (C=O), and 1400 (S=O), ^{1}H-NMR (DMSO, δ, ppm): 9.25 (s, 1H, NH), 7.80-7.35 (m, 8H, CH-arom.), 5.35 (s, 1H, CH), 4.01 (q, J= 7.0 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 1.01 (t, J= 7.0 Hz, 3H CH_3).

Ethyl 6-(4-chlorophenyl)-4-methyl-2-(tosylthio)-1,6-dihydropyrimidine-5-carboxylate 4f: Yield: 10 %, m.p.: 262-264 °C, IR (KBr, ν, cm^{-1}): 3255 (NH), 1733 (C=O), and 1396 (S=O), ^{1}H-NMR (DMSO, δ, ppm): 9.23 (s, 1H, NH), 7.72-7.36 (m, 8H, CH-arom.), 5.32 (s, 1H, CH), 4.01 (q, J= 7.0 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 1.01 (t, J= 7.0 Hz, 3H CH_3).

Synthesis of N-carbamoyl-6-methyl-2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide 5a-f:

An equimolar mixture of Biginelli product **2a-f** (0.01 mol) and urea (0.75 g, 0.0125 mol) in ethanol (25 mL) was treated with few drops of TEA catalyst. The reaction mixture was heated under reflux for 3 h and then solvent was removed under reduced pressure and the residual mass was collected, washed with water and used without further purification.

Reaction of N-carbamoyl-6-methyl-2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide 5a-f with p-toluene sulfonyl chloride:

An equimolar mixture of compound **5a-f** (0.001 mol) and p-toluene sulfonyl chloride (1.9 g, 0.001 mol) was dissolved in dry dioxane (30 mL) was treated with anhydrous K_2CO_3 (~5 g). The reaction mixture was stirred at 60 °C for 3 h, potassium carbonate was removed by filtration and the dioxane was evaporated under reduced pressure. The residual mass was then triturated with light petroleum (40-60 °C) and the formed solid was collected by filtration and recrystallized from the proper solvent to give compound **6a-f**.

6-Methyl-2-oxo-4-phenyl-N-(tosylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide 6a: Yield: 78 %, m.p.: 206-208 °C, IR (KBr, ν, cm^{-1}): 3314, 3296, 3233 (4 NH), 1698 (CO), 1666 (CO); ^{1}H-NMR (DMSO, δ, ppm): 10.23 (s, 1H, NH), 9.22 (br, 2H, 2NH), 7.98 (s, 1H, NH), 7.64-7.32 (m, 9H, CH-arom.), 5.32 (s, 1H, CH), 2.32 (s, 3H, CH_3). 2.22 (s, 3H, CH_3); ^{13}C-NMR (DMSO, δ, ppm): 16.1, 22.4, 53.8, 101,3, 116.0, 121.3, 122.5, 123.7, 126.2, 128.6, 129.2, 131.5, 132.8, 162.5, 166.3, 168.9.

4-(4-Chlorophenyl)-6-methyl-2-oxo-N-(tosylcarbamoyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide 6b: Yield: 86 %, m.p.: 233-235 °C, IR (KBr, ν, cm^{-1}): 3322, 3290, 3231 (4 NH), 1696 (CO), 1668 (CO); ^{1}H-NMR (DMSO, δ, ppm): 10.25 (s, 1H, NH), 9.23 (br, 2H, 2NH), 7.99 (s, 1H, NH), 7.72-7.42 (m, 8H, CH-arom.), 5.35 (s, 1H, CH), 2.30 (s, 3H, CH_3). 2.22 (s, 3H, CH_3); ^{13}C-NMR (DMSO, δ, ppm): 16.0, 22.4, 53.3, 101.1, 116.1, 121.2, 122.8, 123.8, 126.2, 129.9, 131.7, 133.1, 133.8, 162.0, 166.5, 169.5.

6-Methyl-2-oxo-4-p-tolyl-N-(tosylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide 6c: Yield: 80%,

m.p.: 255-257 °C, IR (KBr, ν, cm^{-1}): 3315, 3293, 3222 (4 NH), 1690 (CO), 1665 (CO); ^{1}H-NMR (DMSO, δ, ppm): 10.22 (s, 1H, NH), 9.23 (br, 2H, 2NH), 7.97 (s, 1H, NH), 7.66-7.38 (m, 8H, CH-arom.), 5.32 (s, 1H, CH), 2.31 (s, 3H, CH_3). 2.21 (s, 3H, CH_3); ^{13}C-NMR (DMSO, δ, ppm): 14.0, 22.5, 53.3, 101.1, 116.3, 121.5, 122.5, 123.0, 124.2, 126.5, 127.8, 129.5, 131.2, 162.1, 166.0, 168.1.

6-Methyl-4-(4-nitrophenyl)-2-oxo-N-(tosylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide 6d: Yield: 85%, m.p.: 270-272 °C, IR (KBr, ν, cm^{-1}): 3328, 3290, 3232 (4 NH), 1698 (CO), 1669 (CO); ^{1}H-NMR (DMSO, δ, ppm): 10.25 (s, 1H, NH), 9.23 (br, 2H, 2NH), 8.01 (s, 1H, NH), 7.76-7.35 (m, 8H, CH-arom.), 5.35 (s, 1H, CH), 2.32 (s, 3H, CH_3), 2.22 (s, 3H, CH_3).

4-(2-Chlorophenyl)-6-methyl-2-oxo-N-(tosylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide 6e:Yield: 77%, m.p.: 258-260 °C, IR (KBr, ν, cm^{-1}): 3311, 3293, 3233 (4 NH), 1690 (CO), 1665 (CO); ^{1}H-NMR (DMSO, δ, ppm): 10.21 (s, 1H, NH), 9.22 (br, 2H, 2NH), 7.97 (s, 1H, NH), 7.65-7.30 (m, 8H, CH-arom.), 5.33 (s, 1H, CH), 2.32 (s, 3H, CH_3), 2.20 (s, 3H, CH_3).

4-(4-Chlorophenyl)-6-methyl-2-thioxo-N-(tosylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide 6f: Yield: 87%, m.p.: 238-240 °C, IR (KBr, □, cm^{-1}): 3326, 3290, 3223 (4 NH), 1692 (CO), 1668 (CO); ^{1}H-NMR (DMSO, δ, ppm): 10.23 (s, 1H, NH), 9.23 (br, 2H, 2NH), 7.97 (s, 1H, NH), 7.62-7.32 (m, 8H, CH-arom.), 5.35 (s, 1H, CH), 2.32 (s, 3H, CH_3), 2.22 (s, 3H, CH_3).

Synthesis of 2,4-dioxo-6-aryl-3-tosyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile 8a-e:

Compound **7a-e** (0.01 mol) was dissolved in dioxane (25 mL) and then treated with anhydrous potassium carbonate (~ 5g). The reaction mixture was stirred at room temperature and then p-toluene sulfonyl chloride (1.9 g, 0.01 mol) was added in small portions with continuous stirring. A catalytic amount of TBAB was added and temperature was raised to 70 °C and the reaction was further stirred at this temperature for 4h. The reaction mixture was left to cool and carbonate was removed filtration, dioxane was evaporated under reduced pressure. The residual mass was triturated with light petroleum (40-60 °C) and the obtained solid was collected and recrystallized from the proper solvent into compound **8a-e**.

2,4-Dioxo-6-phenyl-3-tosyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile 8a: Yield: 57%, m.p.: 226-228 °C, IR (KBr, ν, cm^{-1}): 3261 (NH), 2212 (CN), 1695 (CO), 1672 (CO); ^{1}H-NMR (DMSO, δ, ppm): 9.23 (br, 1H, NH), 7.75-7.30 (m, 9H, CH-arom.), 2.32 (s, 3H, CH_3).

6-(4-Chlorophenyl)-2,4-dioxo-3-tosyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile 8b: Yield: 68%, m.p.: 240-242 °C, IR (KBr, ν, cm^{-1}): 3268 (NH), 2202 (CN), 1690 (CO), 1666 (CO); ^{1}H-NMR (DMSO, δ, ppm): 9.25 (br, 1H, NH), 7.77-7.38 (m, 8H, CH-arom.), 2.30 (s, 3H, CH_3).

2,4-Dioxo-6-p-tolyl-3-tosyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile 8c: Yield: 65%, m.p.: 255-257 °C, IR (KBr, ν, cm^{-1}): 3265 (NH), 2211 (CN), 1691 (CO), 1667 (CO); ^{1}H-NMR (DMSO, δ, ppm): 9.23 (br, 1H, NH), 7.75-7.38 (m, 8H, CH-arom.), 2.30 (s, 3H, CH_3), 2.22 (s, 3H, CH_3).

6-(4-Nitrophenyl)-2,4-dioxo-3-tosyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile 8d:Yield: 76%, m.p.: 235-237 °C, IR (KBr, ν, cm^{-1}): 3244 (NH), 2202 (CN), 1690 (CO), 1665 (CO); ^{1}H-NMR (DMSO, δ, ppm): 9.22 (br, 1H, NH), 7.70-7.35 (m, 8H, CH-arom.), 2.31 (s, 3H, CH_3).

6-(2-Chlorophenyl)-2,4-dioxo-3-tosyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile 8e: Yield: 56%, m.p.: 244-246 °C, IR (KBr, ν, cm^{-1}): 3248 (NH), 2205 (CN), 1695 (CO), 1667 (CO); ^{1}H-NMR (DMSO, δ, ppm): 9.23 (br, 1H, NH), 7.65-7.35 (m, 8H, CH-arom.), 2.32 (s, 3H, CH_3).

Synthesis of ethyl 2,4-dioxo-6-aryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 9a-e:

A mixture of aromatic aldehyde (10 mmol), diethyl malonate (1.53 mL, 10 mmol), urea (0.9 g, 15 mmol) and ceric ammonium nitrate (10 mmol%) was heated with stirring at 80-90 ^{o}C for 20-3-0 minutes. The progress of reaction was monitored by TLC, after completion of the reaction, crushed ice was added, the solid product was filtered off, washed with ice-cold water, dried and recrystalized from ethanol. Structures of the obtained compounds were established on the basis of their spectral data (IR, ^{1}HNMR and ^{13}NMR spectroscopy).

Synthesis of N-carbamoyl-2,4-dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide 10a-e:

An equimolar mixture of compounds **9a-e** (0.01 mol) and urea (0.75 g, 0.0125 mol) in ethanol (25 mL) was treated with few drops of TEA catalyst. The reaction mixture was heated under reflux for 3 h and then solvent was removed under reduced pressure and the residual mass was collected, washed with water and used without further purification.

Synthesis of 2,4-dioxo-6-phenyl-N-(tosylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide 11a-e:

Compound **10a-e** (0.01 mol) was dissolved in dioxan (25 mL) and then treated with anhydrous potassium carbonate (~ 5g). The reaction mixture was stirred at room temperature and then p-toluene sulfonyl chloride (1.9 g, 0.01 mol) was added in small portions with continuous stirring. A catalytic amount of TBAB was added and temperature was raised to 70 °C and the reaction was further stirred at this temperature for 4h. The reaction

mixture was left to cool and carbonate was removed filtration, dioxane was evaporated under reduced pressure. The residual mass was triturated with light petroleum (40-60 °C) and the obtained solid was collected and recrystallized from the proper solvent into compound **11a-e**.

2,4-dioxo-6-phenyl-N-(tosylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboximidamide 11a:

Yield: 76%, m.p.: 214-216 °C, IR (KBr, ν, cm^{-1}): 3304, 3248 (2NH), 1698 (CO), 1667 (CO); ^{1}H-NMR (DMSO, δ, ppm): 10.12 (br, 1H, NH), 9.23 (br, 2H, 2NH), 7.75-7.35 (m, 10H, CH-arom.+ NH), 2.32 (s, 3H, CH_3).

6-(4-chlorophenyl)-2,4-dioxo-N-(tosylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboximidamide 11b:

Yield: 80%, m.p.: 232-234 °C, IR (KBr, ν, cm^{-1}): 3308, 3289, 3240 (3NH), 1698 (CO), 1668 (CO); ^{1}H-NMR (DMSO, δ, ppm): 10.23 (br, 1H, NH), 10.12 (br, 1H, NH) 9.23 (br, 2H, 2NH), 7.75-7.35 (m, 8H, CH-arom., 2.32 (s, 3H, CH_3).

2,4-dioxo-6-p-tolyl-N-(tosylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboximidamide 11c:

Yield: 78%, m.p.: 220-222 °C, IR (KBr, ν, cm^{-1}): 3310, 3280, 3240 (3NH), 1696 (CO), 1666 (CO); ^{1}H-NMR (DMSO, δ, ppm): 10.23 (br, 1H, NH), 10.12 (br, 1H, NH) 9.23 (br, 2H, 2NH), 7.70-7.35 (m, 8H, CH-arom., 2.32 (s, 3H, CH_3), 2.22 (s, 3H, CH_3).

6-(4-nitrophenyl)-2,4-dioxo-N-(tosylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboximidamide 11d:

Yield: 82%, m.p.: 244-246 °C, IR (KBr, ν, cm^{-1}): 3315, 3288, 3245 (3NH), 1699 (CO), 1675 (CO); ^{1}H-NMR (DMSO, δ, ppm): 10.25 (br, 1H, NH), 10.12 (br, 1H, NH) 9.25 (br, 2H, 2NH), 7.78-7.38 (m, 8H, CH-arom., 2.32 (s, 3H, CH_3).

6-(2-chlorophenyl)-2,4-dioxo-N-(tosylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-5-carboximidamide 11e:

Yield: 68%, m.p.: 240-242 °C, IR (KBr, ν, cm^{-1}): 3312, 3280, 3244 (3NH), 1695 (CO), 1668 (CO); ^{1}H-NMR (DMSO, δ, ppm): 10.22 (br, 1H, NH), 10.12 (br, 1H, NH) 9.23 (br, 2H, 2NH), 7.77-7.35 (m, 8H, CH-arom., 2.32 (s, 3H, CH_3).

Synthesis of N-(3,5-dicyano-4-aryl-2,6-dioxopiperidin-1-yl)-4-methylbenzene -sulfonamide 13a-e:

An equimolar mixture of 1-amino-2,6-dioxo-4-arylpiperidine-3,5-dicarbonitrile **12a-e** (0.005 mol) and p-toluene sulfonyl chloride (0.95 g, 005 mol) in dioxane (25 mL) was treated with few drops of TEA catalyst and the reaction mixture was refluxed for 3 hrs. Dioxane was evaporated under reduced pressure and the formed solid was collected and recrystallized from the proper solvent to give compound **13a-e**.

N-(3,5-dicyano-2,6-dioxo-4-phenylpiperidin-1-yl)-4-methylbenzenesulfonamide 13a:

Yield: 78%, m.p.: 240-242 °C, IR (KBr, ν, cm^{-1}): 3281 (NH), 2202 (CN), 1695 (CO); ^{1}H-NMR (DMSO, δ, ppm): 9.23 (br, 1H, NH), 7.70-7.35 (m, 9H, CH-arom., 5.65 (d, 2H, 2 CH-CN). 5.32 (t, 1H, CH-Ph), 2.32 (s, 3H, CH_3).

N-(4-(4-chlorophenyl)-3,5-dicyano-2,6-dioxopiperidin-1-yl)-4-methylbenzenesulfonamide 13b:

Yield: 82%, m.p.: 262-264 °C, IR (KBr, ν, cm^{-1}): 3288 (NH), 2206 (CN), 1696 (CO); ^{1}H-NMR (DMSO, δ, ppm): 9.25 (br, 1H, NH), 7.72-7.35 (m, 8H, CH-arom., 5.62 (d, 2H, 2 CH-CN). 5.38 (t, 1H, CH-Ph), 2.32 (s, 3H, CH_3).

N-(3,5-dicyano-2,6-dioxo-4-p-tolylpiperidin-1-yl)-4-methylbenzenesulfonamide 13c:

Yield: 75%, m.p.: 258-260 °C, IR (KBr, ν, cm^{-1}): 3265 (NH), 2208 (CN), 1695 (CO); ^{1}H-NMR (DMSO, δ, ppm): 9.23 (br, 1H, NH), 7.77-7.38 (m, 8H, CH-arom., 5.60 (d, 2H, 2 CH-CN). 5.35 (t, 1H, CH-Ph), 2.32 (s, 3H, CH_3), 2.2 (s, 3H, CH_3).

N-(3,5-dicyano-4-(4-nitrophenyl)-2,6-dioxopiperidin-1-yl)-4-methylbenzenesulfonamide 13d:

Yield: 80%, m.p.: 265-268 °C, IR (KBr, ν, cm^{-1}): 3268 (NH), 2212 (CN), 1699 (CO); ^{1}H-NMR (DMSO, δ, ppm): 9.25 (br, 1H, NH), 7.78-7.40 (m, 8H, CH-arom., 5.65 (d, 2H, 2 CH-CN). 5.35 (t, 1H, CH-Ph), 2.32 (s, 3H, CH_3).

N-(4-(2-chlorophenyl)-3,5-dicyano-2,6-dioxopiperidin-1-yl)-4-methylbenzenesulfonamide 13e:

Yield: 72%, m.p.: 244-246 °C, IR (KBr, ν, cm^{-1}): 3256 (NH), 2211 (CN), 1698 (CO); ^{1}H-NMR (DMSO, δ, ppm): 9.23 (br, 1H, NH), 7.75-7.38 (m, 8H, CH-arom., 5.65 (d, 2H, 2 CH-CN). 5.36 (t, 1H, CH-Ph), 2.32 (s, 3H, CH_3).

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