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Synthesis, characterization and antimicrobial activity of new thioxo tetrahydropyrimidine derivatives

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A sequence of thioxotetrahydropyrimidenes derivatives, *N*-(4-chloro/methoxyphenyl)-3-formyl-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**s (4a-l)** were synthesized by the formylation of *N*-(4-chloro/methoxyphenyl)-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides **(3a-l)** by dry dimethyl formamide (DMF) and phosphorous oxychloride at room temperature. Formerly, compounds **(3a-l)** were synthesized by the condensation of *N*-(4-chloro/methoxyphenyl)-3-oxobutanamide **(1)**, various aromatic aldehydes **(2a-f)** and thiourea with catalytic amount of concentrated hydrochloric acid under reflux temperature. The structures of the synthesized various thioxotetrahydropyrimidenes have been characterized by using elemental analysis, Infrared, ^{1}H-NMR, ^{13}C-NMR spectroscopy and further supported by Mass spectroscopy. All the products have been screened for their *in-vitro* biological assay like antibacterial activity towards *Gram-positive* and *Gram-negative* bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40 µg/ml. It was showing that the compounds **4a, 4e, 4g, 4h, 4i** and **4l** displayed inspirational antibacterial and antifungal activity compared to the used reference standard.

1. Introduction

Among the extensive variety of heterocycles that have been discovered for developing pharmacologically significant molecules, tetrahydropyrimidines (THPMs) play a momentous role in the field of medicinal chemistry. It is thanks to their pharmacological activities such as anticancer,[1] antidiabetic[2], antibacterial[3], anti-HIV[4,5], calcium channel blockers[6], anti-depressent[7], analgesic[8], antihypertensive[9], antimalarial[10] and anti-inflammatory[11]. The literature survey exposed that the substitution of various groups on the tetrahydropyrimidine ring imparts different activities[12-14].

The one step method is the most widely used method as compared to multistep methods since they require time consumption reaction and give sophisticated yield with easy workup. Pietro Giacomo Biginelli (1860–1937) discovered a one-pot multicomponent reaction. He invented the procedure that would later be named Biginelli synthesis in his honour.[15] The scope of the original Biginelli reaction was gradually extended by variation of all three building blocks, allowing access to many multi-functionalized tetrahydropyrimidines. Huge numbers of tetrahydropyrimidines have been produced using the Biginelli reaction to date. Indeed, the most useful aza-nucleophile in Biginelli's chemistry is urea or *N*-methylurea. However, over the years were shown as quite rigid to apply thiourea or thiourea-based nucleophiles in Biginelli's chemistry.[16-19] This fact lies chiefly in its behaviour and massive sensitivity towards strong acids and bases, even the Lewis acid/base salt type. In the above-mentioned conditions with heating, it is very hard to apply thioureas in the Biginelli reaction

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with success. Furthermore, efficient synthesis of Biginelli's hybrids containing thiourea-based nucleophiles was and is quite motivating[20]. Considering this, our goal was to synthesize a small library of novel THPMs derivatives containing aryl aldehyde functionality by two step synthesis protocol to study their antimicrobial activity.

2. Results and Discussion

2.1 Chemistry and Spectroscopic discussion

The target compounds *N*-(4-chloro/methoxyphenyl)-3-formyl-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**s (4a-l)** were synthesized as charted in Reaction **Scheme 1**. The title compounds *N*-(4-chloro/methoxyphenyl)-3-formyl-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**s (4a-l)** were synthesized by a two-step procedure by Biginelli reaction and Vielsmeier-Hack reaction, respectively. Our main intention is to achieve the product with good yield, high purity and using green solvent for synthesis of compound **(3a-l)**. We have carried out the experiments with concentrated HCl and three different solvents i.e. dimethyl formamide (DMF), dioxane and ethanol. The data for the experiments is given in **Table 1.**

Table 1. Optimization conditions for the synthesis of compound **(3a-l)**

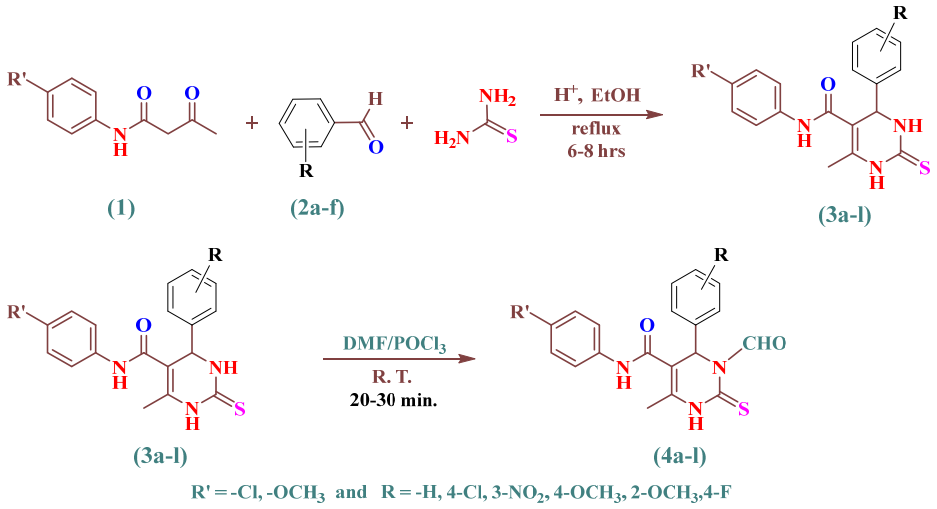
No.	Solvent	Time	Temperature	Yield
1	DMF	5-6 hrs	120 ºC	----
2	Ethanol (95%)	6-8 hrs	reflux	40-60 %
3	Dioxane	9-10 hrs	reflux	35-40 %

When the reaction was carried out in DMF solvent at 120 ºC temperature, the product was charred while the reaction was carried out with dioxane solvent, the products obtained was much impure with less yield. Finally, we have chosen, ethanol solvent with reflux temperature for synthesis of compound **(3a-l)** from *N*-(4-chloro/methoxyphenyl)-3-oxobutanamide **1** (0.01 mole), various substituted benzaldehyde **(2a-f)** (0.01 mole) and thiourea (0.01 mole) through Biginelli reaction. After that, by formylation by Vielsmeier-Hack reaction of suspension of *N*-(4-chloro/methoxyphenyl)-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide **(3a-l)** (0.01 mole) in 15 ml of dry DMF with dropwise addition of $POCl_3$ (0.02 mole) under stirring in an ice bath. After addition of $POCl_3$, stirring was continued at room temperature for another 20–30 minutes and then solution was poured into 200 ml ice water gives *N*-(4-chloro/methoxyphenyl)-3-formyl-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide**s (4a-l).**

After recrystallization of compounds **(4a-l)** from ethanol solvent, the purity of all compounds was checked by single spotted thin layer chromatography (TLC) as well as column chromatography filled with alumina adsorbent with solvent system ethyl acetate and hexane having ratio of 3:7 and their characterization is carried out by means of elemental analysis, Infrared, ^{1}H-NMR, ^{13}C-NMR spectroscopy and further supported by Mass spectroscopy.

Among all, the IR spectrum of compound **4i** showed bands at 3248 cm^{-1} which are due to N–H stretching of the pyrimidine ring. The compound showed a band at 3076 cm^{-1} which is due to aromatic C–H stretching vibration. Moderate bands observed at 3358 cm^{-1} is due to N–H stretching vibration of the amide group and weak overtone of N–H bending is observed at 3076 cm^{-1}. Weak band at 2766 is due to C–H stretching vibration of –CHO group. The band observed at 1467 cm^{-1} and 1520 cm^{-1} is due to aromatic C=C stretching vibration of phenyl ring and pyrimidine ring respectively. Bands observed at 1309 cm^{-1} and 1348 cm^{-1} are due to C–N stretching of amine and N=O symmetric stretching vibrations respectively. The bands observed at 1658 cm^{-1} and 1712 cm^{-1} is due to C=O stretching vibrations amide and aldehyde respectively. Bands observed at 1631 cm^{-1} and 1246 cm^{-1} are due to N–H bending vibration of amine and C–O–C stretching vibration of Ar–OCH_3 respectively. Moderate band observed at 1028 cm^{-1} is due to C=S stretching vibration. The mass spectrum of compound **4i** (by direct probe method) showed molecular ion peak at 426 m/z was observed in agreement with the molecular weight of the respective compound and base peak at 123 m/z for the most stable and abundant fragment. Some other peaks were obtained at 398, 304, 276, 217 and 108 m/z for various stable fragments. The ^{1}H-NMR spectrum of compound **4d** (in DMSO) showed two different singlet signals at 2.14 δ and 2.20 δ due to pyrimidine –NH– and -CH_3 group, respectively. Another two different singlet signals at 3.24 δ and 6.37 δ are observed due to 3H of –OCH_3 group and chiral–1H of the pyrimidine ring, respectively. The multiplate signal at 7.31-7.22 *δ* integrating for four protons is due to the aromatic ring which is attached to the pyrimidine ring. Two different doublets at 7.62 *δ* and 9.94 *δ* integrating for four protons is due to di-substituted phenyl ring. A singlet signal at 7.83 *δ* for one proton is obtained because of the –NH–CO– group. A singlet signal at 11.37 *δ* is observed due to the one proton of –CHO group. The ^{13}C-NMR spectrum of compound **4l** showed signals at 175.82, 167.54, 163.18, 160.92, 158.93, 138.98, 129.94, 128.54, 122.68, 115.37, 114.45, 106.43, 67.60, 55.84 and 17.94 δ corresponding to twenty different type of carbon atoms present in the compound. The most downfield signal appearing at 175.82 δ can be assigned to the carbonyl carbon of C=S group in the pyrimidine nucleus. The signals appearing at 167.54 δ and 163.18 δ can be assigned to carbonyl carbon of –CHO and –CONH– groups, respectively. The signals of carbon of the –OCH_3 and –CH_3 group appeared at 55.84 δ and 17.94 δ, respectively. The rest of the signals are corresponding to aromatic carbons of pyrimidine and phenyl nucleus.

All synthesized compounds were screened for their *in-vitro* biological assay like antibacterial activity towards *Gram-positive* and *Gram-negative* bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40 µg/ml.



Scheme 1. Synthesis of *N*-(4-chloro/methoxyphenyl)-3-formyl-6-methyl-4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides **(4a -l)**

2.2 biological activity

All the synthesized compounds have been evaluated for antimicrobial activity.

Antibacterial activity

The purified products were screened for their antibacterial activity using cup-plate agar diffusion method. The nutrient agar broth prepared by the usual method was inoculated aseptically with 0.5 ml of 24 hr. old subcultures of *Bacillus coccus*, *Staphylococcus aureus*, *Aerogenes*, *Pseudomonas aeruginosa* in separate conical flasks at 40-50 ºC and mixed well by gentle shaking. About 25 ml content of the flask was poured and evenly spreaded in a Petri dish (13 cm diameter) and allowed to set for 2 hr. The cups (10 mm diameter) were formed by the help of borer in agar medium and filled with 0.04 ml (40 µg) solution of sample in DMF. The plates were incubated at 37 ºC for 24 hrs. and the control was also maintained with 0.04 ml of DMF in a similar manner and the zone of inhibition of the bacterial growth were measured in *millimeters* and recorded in **Table-2**.

Antifungal activity

Aspergillus niger was employed for testing antifungal activity using the cup-plate method. The culture was maintained on *subouraud's agar slants*. Sterilized *sabouraud's agar* medium was inoculated with 72 hrs. old 0.5 ml suspension of fungal spores in a separate flask.

About 25 ml of inoculated medium was evenly spreaded in a Petri dish and allowed to sit for two hrs. The plates were incubated at 30 ºC for 48 hrs. After the completion of the incubation period, the zone of inhibition of growth in the form of diameter in *mm* was measured. Along the test solution in each Petri dish one cup was filled with solvent which acts as control. Standard drugs like *Amoxicillin*, *Benzyl Penicillin*, *Ciprofloxacin*, *Erythromycin* and *Greseofulvin* were used for comparison purposes. The zones of inhibition are recorded in **Table 2**.

From activity data, it is observed that compounds **4a** and **4l** were found to be active which is attributed to the presence of simple and 4-F-substituted benzene ring at C_4-position of pyrimidine nucleus, while compounds **4d**, **4f** and **4k** show moderate activity against *Bacillus coccus* with reference to standard drugs. Compound **4g** were found to be active due to the presence of a simple benzene ring at C_4-position of pyrimidine nucleus, while compound **4f** showed moderate activity against *Staphylococcus aureus.* Against *Aerogenes* strain, compounds **4a** and **4e** were found to be active which is attributed to the presence of simple and 2-OCH_3 substituted benzene ring at C_4-position of pyrimidine nucleus, while compounds **4d, 4i** and **4l** were found to be moderate active. Against *Pseudomonas aeruginosa,* compounds **4b, 4f** and **4l** are active due to the presence of 4-Cl and 4-F substituted benzene ring at C_4-position of pyrimidine nucleus than others. Compounds **4e** and **4i** were active because of presence of 2-OCH_3 and 3-NO_2 substituted benzene ring at C_4-position of pyrimidine nucleus while compounds **4b, 4h** and **4l** show moderate activity against *Aspergillus niger* as compared to standard drugs. Among thioxotetrahydropyrimidine derivatives, it was interesting to notice that the activity depends on the substituents rather than

the basic skeleton of the molecule. It was noticed that groups -F, -OCH_3, -Cl, -NO_2 and -H on the benzene ring at C_4-position of pyrimidine nucleus, enhanced their antimicrobial activity and are better antimicrobial agents.

Table 2: Antimicrobial screening results of compounds **4a-l**

Sample ID	R	R'	Zone of inhibition in *mm* Antibacterial activity				Antifungal
			B. coccus	***S. aureus***	***Aerogenes***	***Pseudomonas***	***A. niger***
4a	-H	4-Cl-	**24**	18	**22**	19	15
4b	4-Cl-	4-Cl-	16	20	19	**21**	**21**
4c	3-NO_2-	4-Cl-	20	19	15	20	18
4d	4-OCH_3-	4-Cl-	**21**	16	**20**	17	19
4e	2-OCH_3-	4-Cl-	19	18	**22**	18	**24**
4f	4-F-	4-Cl-	**21**	**21**	18	**21**	16
4g	-H	4-OCH_3-	20	**22**	19	14	18
4h	4-Cl-	4-OCH_3-	18	20	16	20	**21**
4i	3-NO_2-	4-OCH_3-	17	18	**21**	18	**22**
4j	4-OCH_3-	4-OCH_3-	15	19	17	12	14
4k	2-OCH_3-	4-OCH_3-	**21**	16	19	19	14
4l	4-F-	4-OCH_3-	**22**	20	**20**	**21**	**21**
Amoxicillin	-	-	**25**	**25**	**20**	**22**	**00**
Benzyl penicillin	-	-	**18**	**19**	**21**	**21**	**00**
Ciprofloxacin	-	-	**20**	**15**	**22**	**16**	**00**
Erythromycin	-	-	**22**	**21**	**19**	**23**	**00**
Greseofulvin	-	-	**00**	**00**	**00**	**00**	**26**

3. Conclusions

The synthetic method involves robust synthesis of thioxotetrahydropyrimidine **(4a-l)**, starting by one pot condensation of freshly prepared *N*-(4-chloro/methoxyphenyl)-3-oxobutanamide **(I)**, various substituted benzaldehyde **(2a-f)** and thiourea in ethanol solvent in presence of concentrated HCl with good yields followed by low temperature *N*-formylation by DMF/$POCl_3$. The method is endowed with several unique merits including gentle reaction conditions, short reaction time, broad substrate scope etc. The method has successfully applied for synthesis of a diverse library of twelve hybrid pyrimidines. Then after, these synthesized thioxotetrahydropyrimidine evaluated as anti-microbial agents against a group of antibacterial and antifungal strains. They were found to possess sensibly good antifungal activity and compounds **4a, 4e, 4g, 4i** and **4l** were found to be the most potent anti-microbial agents. It will be the topic of new research to substitute it with greener reagents and solvents, finding more effective anti-microbial agents. This work sanctions the high prominence of organic compounds in applied fields as reported before in the previous scientific papers.

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4. Experimental

4.1. Materials and Methods

Chemicals and solvents were purchased from Sigma-Aldrich Chemical Co., Merck chemical, Finar, and Spectrochem Ltd. Thin layer chromatography [silica gel G (E Merck) plates] was used to monitor the reactions. Visualization of TLC was achieved with UV light (254 and 365 nm) or with iodine vapor. Furthermore, recrystallization by ethanol solvent as well as column chromatography [alumina gel 63-200 µm] was used to purify the synthesized compounds. The melting point was determined by electrothermal apparatus using open capillary tubes and is uncorrected. IR spectra were recorded on a Shimadzu 8400 FTIR instrument in KBr disc and only significant absorbance levels (cm^{-1}) are listed. ^{1}H NMR spectra (400 MHz) were recorded on a "Bruker AVANCE III spectrometer" in DMSO solvent using TMS as internal standard. ^{13}C NMR spectra (400 MHz) were recorded in DMSO solvent. Chemical shift is given in ppm. Mass spectra were determined using a direct inlet probe on GCMS-QP2010 mass spectrometer (Shimadzu, Kyoto, Japan). Elemental analysis was performed on a Carlo Erba EA1108 elemental analyser.

4.2. General procedure

4.2.1 Procedure for the synthesis of N-(4-chloro/methoxyphenyl)-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides **(3a-l)**

The mixture of *N*-(4-chloro/methoxyphenyl)-3-oxobutanamide **(1)** (0.01 mole), substituted benzaldehydes **(2a-f)** (0.01 mole) and thiourea (0.74 gm, 0.01 mole) in ethanol (10 ml), containing 0.4 ml of concentrated HCl was heated under reflux for 6-8 hrs. The progress of the reaction was monitored by TLC (Thin-Layer Chromatography) using hexane-ethyl acetate (7:3) as an eluent and after competition of the reaction, the reaction mixture was allowed to stand at 5-10 ^{o}C for several

hours and precipitation was observed. The products were filtered and washed with chilled methanol and isolated as crystalline powder. and recrystallized from a mixture of ethanol + water to give analytically pure products. Compounds 3a, 3c, 3d and 3e were previously prepared by our research team[3]. While compound (3b)[21], (3g, 3i, 3j)[22] and 3h[23] were previously synthesized by using different catalysts and obtained results equivalent with literature data.

Physical and spectral data of N-(4-chlorophenyl)-6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide **(3c)**

Yield 42 %, m.p. 178 °C; IR(KBr): 3358 (N-H str. of amide), 3248 (N-H str. of pyrimidine), 3074 (C=C-H str.), 2936 (C-H str. of –CH_3), 1658 (C=O str. of amide), 1520 and 1467 (C=C str.), 1375 (N=O str. asym.), 1348 (N=O str. sym.), 1309 (C-N str.), 1024 (C=S str.), 752 (C-Cl str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.20 (s, 3H, -CH_3), 5.52 (s, 1H, pyrimidine-chiral-H), 7.40 - 7.85 (m, 4H, aromatic-H), 7.66 - 7.85 (dd, 2H, aromatic-H), 8.16 - 8.22 (dd, 2H, aromatic-H), 9.22 (s, 1H, pyrimidine-NH-), 9.62 (s, 1H, - NH-CO-), 9.81 (s, 1H, pyrimidine-NH-); EI-MS: m/z 402. ($C_{18}H_{15}ClN_4O_3S$); requried: C, 53.67; H, 3.75; N, 13.91 %; found: C, 53.66; H, 3.71; N, 13.90%.

Physical and spectral data of N-(4-chlorophenyl)-6-methyl-4-(4-flourophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide **(3f)**

Yield 49 %, m.p. 168 °C; IR(KBr): 3347 (N-H str. of amide), 3235 (N-H str. of pyrimidine), 3095 (C=C-H str.), 2989 (C-H str. of –CH_3), 1678 (C=O str. of amide), 1547 and 1453 (C=C str.), 1312 (C-N str.), 1024 (C=S str.), 879 (C-F str.), 755 (C-Cl str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.14 (s, 3H, -CH_3), 5.42 (s, 1H, pyrimidine-chiral-H), 7.42 (d, 2H, aromatic-H), 7.36 - 7.15 (dd, 4H, aromatic-H), 7.82 (d, 2H, aromatic-H), 9.17 (s, 1H, pyrimidine-NH-), 9.52 (s, 1H, -NH-CO-), 9.76 (s, 1H, pyrimidine-NH-); EI-MS: m/z 375. ($C_{18}H_{15}ClFN_3OS$); requried: C, 57.52; H, 4.02; N, 11.18 %; found: C, 57.46; H, 3.97; N, 11.15%.

Physical and spectral data of N-(4-methoxyphenyl)-6-methyl-4-(2-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide **(3k)**

Yield 41 %, m.p. 175 °C; IR (KBr): 3322 (N-H str. of amide), 3241 (N-H str. of pyrimidine), 3048 (C=C-H str.), 2955 (C-H str. of –CH_3), 1627 (C=O str. of amide), 1530 and 1432 (C=C str.), 1322 (C-N str.), 1239 (C-O-C str. of Ar–OCH_3), 1033 (C=S str.), 752 (C-H bending of o-disubstituted benzene) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.14 (s, 3H, -CH_3), 3.67 (s, 3H, Ar-OCH_3), 3.54 (s, 3H, Ar-OCH_3), 4.62 (s, 1H, pyrimidine-chiral-H), 6.82-6.98 (m, 4H, aromatic-H), 7.00 - 7.13 (dd, 2H, aromatic-H), 7.72 (d, 2H, aromatic-H), 9.47 (s, 1H, pyrimidine-NH-), 9.57 (s, 1H, -NH-CO-), 9.86 (s, 1H, pyrimidine-NH-); EI-MS: m/z 383. ($C_{20}H_{21}N_3O_3S$); requried: C, 62.24; H, 5.52; N, 10.96 %; found: C, 62.21; H, 5.45; N, 10.91%.

Physical and spectral data of N-(4-methoxyphenyl)-6-methyl-4-(4-flourophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide **(3l)**

Yield 51 %, m.p. 171 °C; IR (KBr): 3289 (N-H str. of amide), 3227 (N-H str. of pyrimidine), 3058 (C=C-H str.), 2985 (C-H str. of –CH_3), 1637 (C=O str. of amide), 1547 and 1429 (C=C str.), 1314 (C-N str.), 1224 (C-O-C str. of Ar–OCH_3), 1027 (C=S str.), 859 (C-F str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.13 (s, 3H, -CH_3), 3.74 (s, 3H, Ar-OCH_3), 5.56 (s, 1H, pyrimidine-chiral-H), 6.92 (d, 2H, aromatic-H), 7.15-7.28 (dd, 4H, aromatic-H), 7.74 (d, 2H, aromatic-H), 9.17 (s, 1H, pyrimidine-NH-), 9.40 (s, 1H, -NH-CO-), 9.76 (s, 1H, pyrimidine-NH-); EI-MS: m/z 371. ($C_{19}H_{18}FN_3O_2S$); requried: C, 61.44; H, 4.88; N, 11.31 %; found: C, 61.41; H, 4.85; N, 11.28 %.

4.2.2 Procedure for the synthesis of N-(4-chloro/methoxyphenyl)-3-formyl-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide **(4a-l)**

To a suspension of *N*-(4-chloro/methoxyphenyl)-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (0.01 mole) in 15 ml of dry DMF, $POCl_3$ (3.06 ml, 0.02 mole) was added dropwise under stirring in an ice bath. After addition of $POCl_3$, stirring was continued at room temperature for another 20 - 30 minutes. The progress of the reaction was monitored by TLC (Thin-Layer Chromatography) using hexane-ethyl acetate (6:4) as an eluent and after competition of the reaction, solution was poured into 200 ml ice water. The product was filtered and washed with chilled methanol and isolate the product as crystalline powder and recrystallized from ethanol and column chromatography with alumina gel adsorbent with solvent system ethyl acetate and hexane having ratio of 3:7 to give analytically pure products.

4.3 Spectral and physical data of compounds **(4a-l)**

4.2.3 N-(4-chlorophenyl)-3-formyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxa -mide **(4a)**

Yield 52 %, m.p. 166 °C; IR (KBr): 3342 (N-H str. of amide), 3245 (N-H str. of pyrimidine), 3070 (C=C-H str.), 2933 (C-H str. of –CH_3), 2745 (C-H str. of -CHO), 1715 (C=O str. of -CHO), 1634 (C=O str. of amide), 1518 and 1471 (C=C str.), 1027 (C=S str.), 755 (C-Cl str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.17 (s, 1H, pyrimidine-NH-), 2.21 (s, 3H, -CH_3), 6.34 (s, 1H, pyrimidine-chiral-H), 7.32 - 7.18 (m, 5H, aromatic-H), 7.61 (d, 2H, aromatic-H), 7.80 (s, 1H, -NH-CO-), 9.94 (d, 2H, aromatic-H), 11.37 (s, 1H, -CHO); ^{13}C NMR (400 MHz, DMSO): 175.82 (C=S), 167.54 (-CHO), 163.18 (-CO-NH-),

159.13, 143.37, 135.68, 133.36, 129.14, 128.54, 126.71, 121.68, 106.43, 67.60 and 17.94 (-CH_3) δ; EI-MS: m/z 385 [M^+], ($C_{19}H_{16}ClN_3O_2S$)); requried: C, 59.14; H, 4.18; N, 10.89 %; found: C, 59.11; H, 4.15; N, 10.83 %.

4.2.4 N-(4-chlorophenyl)-3-formyl-6-methyl-4-(4-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide **(4b)**

Yield 57 %, m.p. 160 ˚C; IR (KBr): 3338 (N-H str. of amide), 3236 (N-H str. of pyrimidine), 3066 (C=C-H str.), 2930 (C-H str. of –CH_3), 2747 (C-H str. of -CHO), 1718 (C=O str. of -CHO), 1629 (C=O str. of amide), 1528 and 1470 (C=C str.), 1032 (C=S str.), 758 (C-Cl str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.19 (s, 1H, pyrimidine-NH-), 2.18 (s, 3H, -CH_3), 6.29 (s, 1H, pyrimidine-chiral-H), 7.33 - 7.15 (m, 4H, aromatic-H), 7.63 (d, 2H, aromatic-H), 7.76 (s, 1H, -NH-CO-), 9.86 (d, 2H, aromatic-H), 11.14 (s, 1H, -CHO); ^{13}C NMR (400 MHz, DMSO): 175.80 (C=S), 167.49 (-CHO), 163.22 (-NH-CO-), 159.10, 141.36, 135.64, 133.30, 132.36, 129.08, 128.61, 126.11, 121.63, 106.40, 67.62 and 17.90 (-CH_3) δ; EI-MS: m/z 420 [M^+], ($C_{19}H_{15}Cl_2N_3O_2S$); requried: C, 54.30; H, 3.60; N, 10.00 %; found: C, 54.28; H, 3.57; N, 09.97 %.

4.2.5 N-(4-chlorophenyl)-3-formyl-6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide **(4c)**

Yield 51 %, m.p. 168 ˚C; IR (KBr): 3344 (N-H str. of amide), 3229 (N-H str. of pyrimidine), 3054 (C=C-H str.), 2953 (C-H str. of –CH_3), 2752 (C-H str. of -CHO), 1720 (C=O str. of -CHO), 1634 (C=O str. of amide), 1530 and 1452 (C=C str.), 1371 (N=O str. asym.), 1343 (N=O str. sym.), 1305 (C-N str.), 1035 (C=S str.), 780 and 720 (C-H bending of m-disubstituted benzene), 755 (C-Cl str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.10 (s, 1H, pyrimidine-NH-), 2.25 (s, 3H, -CH_3), 5.29 (s, 1H, pyrimidine-chiral-H), 7.68 - 7.29 (m, 4H, aromatic-H), 7.72 (d, 2H, aromatic-H), 7.87 (s, 1H, -NH-CO-), 9.81 (d, 2H, aromatic-H), 10.65 (s, 1H, -CHO); ^{13}C NMR (400 MHz, DMSO): 175.72 (C=S), 167.41 (-CHO), 163.12 (-NH-CO-), 159.07, 147.71, 135.64, 133.21, 129.23, 121.82, 106.32, 66.62 and 17.74 (-CH_3) δ; EI-MS: m/z 430 [M^+], ($C_{19}H_{15}ClN_4O_4S$); required: C, 52.96; H, 3.51; N, 13.00 %; found: C, 52.91; H, 3.47; N, 12.97 %.

4.2.6 N-(4-chlorophenyl)-3-formyl-6-methyl-4-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine -5-carboxamide **(4d)**

Yield 59 %, m.p. 172 ˚C; IR (KBr): 3321 (N-H str. of amide), 3224 (N-H str. of pyrimidine), 3047 (C=C-H str.), 2947 (C-H str. of –CH_3), 2771 (C-H str. of -CHO), 1714 (C=O str. of -CHO), 1630 (C=O str. of amide), 1530 and 1434 (C=C str.), 1254 (C-O-C str. of Ar–OCH_3), 1036 (C=S str.), 741 (C-Cl str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.14 (s, 1H, pyrimidine-NH-), 2.20 (s, 3H, -CH_3), 3.24 (s, 3H, -OCH_3), 6.37 (s, 1H, pyrimidine-chiral-H), 7.31 - 7.22 (m, 4H, aromatic-H), 7.62 (d, 2H, aromatic-H), 7.83 (s, 1H, -NH-CO-), 9.94 (d, 2H, aromatic-H), 11.37 (s, 1H, -CHO); ^{13}C NMR (400 MHz, DMSO): 175.89 (C=S), 167.50 (-CHO), 163.10 (-NH-CO-), 159.07, 158.54, 135.68, 133.31, 129.12, 125.69, 121.77, 114.23, 106.42, 67.54, 55.84 (-OCH_3) and 17.94 (-CH_3) δ; EI-MS: m/z 415 [M^+], ($C_{20}H_{18}ClN_3O_3S$)); requried: C, 57.76; H, 4.36; N, 10.10 %; found: C, 57.74; H, 4.31; N, 10.06 %..

4.2.7 N-(4-chlorophenyl)-3-formyl-6-methyl-4-(2-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine -5-carboxamide **(4e)**

Yield 59 %, m.p. 166 ˚C; IR (KBr): 3319 (N-H str. of amide), 3217 (N-H str. of pyrimidine), 3008 (C=C-H str.), 2948 (C-H str. of –CH_3), 2782 (C-H str. of -CHO), 1734 (C=O str. of -CHO), 1628 (C=O str. of amide), 1529 and 1428 (C=C str.), 1269 (C-O-C str. of Ar–OCH_3), 1021 (C=S str.), 752 (C-H bending of o-disubstituted benzene), 755 (C-Cl str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.24 (s, 1H, pyrimidine-NH-), 2.18 (s, 3H, -CH_3), 3.35 (s, 3H, -OCH_3), 6.31 (s, 1H, pyrimidine-chiral-H), 7.42 - 7.29 (m, 4H, aromatic-H), 7.68 (d, 2H, aromatic-H), 7.74 (s, 1H, -NH-CO-), 9.82 (d, 2H, aromatic-H), 11.32 (s, 1H, -CHO); ^{13}C NMR (400 MHz, DMSO): 175.71 (C=S), 167.52 (-CHO), 163.13 (-NH-CO-), 159.12, 156.51, 135.72, 133.27, 129.09, 127.79, 121.67, 120.56, 112.20, 106.31, 61.58, 56.24 (-OCH_3) and 17.91 (-CH_3) δ; EI-MS: m/z 415 [M^+], ($C_{20}H_{18}ClN_3O_3S$); requried: C, 57.76; H, 4.36; N, 10.10 %; found: C, 57.74; H, 4.31; N, 10.06 %.

4.2.8 N-(4-chlorophenyl)-3-formyl-6-methyl-4-(4-flourophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine -5-carboxamide **(4f)**

Yield 47 %, m.p. 188 ˚C; IR (KBr): 3330 (N-H str. of amide), 3247 (N-H str. of pyrimidine), 3056 (C=C-H str.), 2931 (C-H str. of –CH_3), 2741 (C-H str. of -CHO), 1714 (C=O str. of -CHO), 1619 (C=O str. of amide), 1518 and 1452 (C=C str.), 1042 (C=S str.), 887 (C-F str.), 755 (C-Cl str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.17 (s, 1H, pyrimidine-NH-), 2.14 (s, 3H, -CH_3), 6.41 (s, 1H, pyrimidine-chiral-H), 7.38 - 7.21 (m, 4H, aromatic-H), 7.72 (d, 2H, aromatic-H), 7.86 (s, 1H, -NH-CO-), 9.41 (d, 2H, aromatic-H), 11.07 (s, 1H, -CHO); ^{13}C NMR (400 MHz, DMSO): 175.81 (C=S), 167.51 (-CHO), 163.20 (-NH-CO-), 159.13, 141.31, 135.54, 133.32, 132.52, 129.18, 128.63, 126.16, 121.60, 106.33, 67.60 and 17.94 (-CH_3) δ; EI-MS: m/z 403 [M^+], ($C_{19}H_{15}ClFN_3O_2S$); requried: C, 56.51; H, 3.74; N, 10.40 %; found: C, 56.47; H, 3.71; N, 10.37 %.

4.2.9 N-(4-methoxyphenyl)-3-formyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbox -amide **(4g)**

Yield 58 %, m.p. 194 ˚C; IR (KBr): 3325 (N-H str. of amide), 3217 (N-H str. of pyrimidine), 3021 (C=C-H str.), 2935 (C-H str. of –CH_3), 2765 (C-H str. of -CHO), 1720 (C=O str. of -CHO), 1624 (C=O str. of amide), 1534 and 1430 (C=C str.), 1236 (C-O-C str. of Ar–OCH_3), 1032 (C=S str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.10 (s, 1H, pyrimidine-NH-), 2.13 (s, 3H, -CH_3), 3.09 (s, 3H, -OCH_3), 5.87 (s, 1H, pyrimidine-chiral-H), 7.31 - 7.11 (m, 5H, aromatic-H), 7.52 (d, 2H, aromatic-H), 7.75 (s, 1H, -NH-CO-), 9.74 (d, 2H, aromatic-H), 10.89 (s, 1H, -CHO); ^{13}C NMR (400 MHz, DMSO): 175.81 (C=S), 167.53 (-CHO), 163.13 (-NH-CO-), 159.11, 158.84, 143.35, 129.97, 128.46, 126.74, 122.67, 114.53, 106.40, 67.64, 55.80 (-OCH_3) and 17.91 (-CH_3) δ; EI-MS: m/z 381 [M^+], ($C_{20}H_{19}N_3O_3S$); requried: C, 62.98; H, 5.02; N, 11.02 %; found: C, 62.96; H, 5.00; N, 10.97 %.

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4.2.10 N-(4-methoxyphenyl)-3-formyl-6-methyl-4-(4-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine -5-carboxamide **(4h)**

Yield 47 %, m.p. 178 °C; IR (KBr): 3325 (N-H str. of amide), 3221 (N-H str. of pyrimidine), 3042 (C=C-H str.), 2956 (C-H str. of –CH_3), 2782 (C-H str. of -CHO), 1719 (C=O str. of -CHO), 1628 (C=O str. of amide), 1529 and 1428 (C=C str.), 1250 (C-O-C str. of Ar–OCH_3), 1032 (C=S str.), 758 (C-Cl str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.26 (s, 1H, pyrimidine-NH-), 2.38 (s, 3H, -CH_3), 3.12 (s, 3H, -OCH_3), 6.39 (s, 1H, pyrimidine-chiral-H), 7.54 - 7.21 (m, 4H, aromatic-H), 7.68 (d, 2H, aromatic-H), 7.89 (s, 1H, -NH-CO-), 9.74 (d, 2H, aromatic-H), 11.32 (s, 1H, -CHO); ^{13}C NMR (400 MHz, DMSO): 175.84 (C=S), 167.57 (-CHO), 163.15 (-NH-CO-), 158.94, 142.08, 132.37, 129.92, 128.56, 126.19, 122.67, 114.53, 106.40, 67.50, 55.82 (-OCH_3) and 17.91 (-CH_3) δ; EI-MS: m/z 415 [M^+], ($C_{20}H_{18}ClN_3O_3S$); requried: C, 57.76; H, 4.36; N, 10.10 %; found: C, 57.72; H, 4.33; N, 10.05 %.

4.2.11 N-(4-methoxyphenyl)-3-formyl-6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide **(4i)**

Yield 51 %, m.p. 182 °C; IR (KBr): 3358 (N-H str. of amide), 3248 (N-H str. of pyrimidine), 3076 (C=C-H str.), 2927 (C-H str. of –CH_3), 2766 (C-H str. of -CHO), 1712 (C=O str. of -CHO), 1658 (C=O str. of amide), 1520 and 1467 (C=C str.), 1374 (N=O str. asym.), 1348 (N=O str. sym.), 1309 (C-N str.), 1246 (C-O-C str. of Ar–OCH_3), 1028 (C=S str.), 782 and 724 (C-H bending of m-disubstituted benzene) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.18 (s, 1H, pyrimidine-NH-), 2.35 (s, 3H, -CH_3), 3.22 (s, 3H, -OCH_3), 5.33 (s, 1H, pyrimidine-chiral-H), 7.61 - 7.25 (m, 4H, aromatic-H), 7.62 (d, 2H, aromatic-H), 7.81 (s, 1H, -NH-CO-), 9.83 (d, 2H, aromatic-H), 11.05 (s, 1H, -CHO); ^{13}C NMR (400 MHz, DMSO): 175.78 (C=S), 167.48 (-CHO), 163.10 (-NH-CO-), 158.99, 147.74, 144.27, 133.03, 129.93, 129.31, 122.65, 121.85, 120.64, 114.53, 106.38, 66.54, 55.78 (-OCH_3) and 17.84 (-CH_3) δ; EI-MS: m/z 426 [M^+], ($C_{20}H_{18}N_4O_5S$)); requried: C, 56.33; H, 4.25; N, 13.14 %; found: C, 56.30; H, 4.21; N, 13.09 %.

4.2.12 N-(4-methoxyphenyl)-3-formyl-6-methyl-4-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidin -e-5-carboxamide **(4j)**

Yield 62 %, m.p. 200 ºC; IR (KBr): 3320 (N-H str. of amide), 3223 (N-H str. of pyrimidine), 3049 (C=C-H str.), 2945 (C-H str. of –CH_3), 2772 (C-H str. of -CHO), 1716 (C=O str. of -CHO), 1628 (C=O str. of amide), 1530 and 1435 (C=C str.), 1255 (C-O-C str. of Ar–OCH_3), 1034 (C=S str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.10 (s, 1H, pyrimidine-NH-), 2.14 (s, 3H, -CH_3), 3.23 (s, 3H, -OCH_3), 3.23 (s, 3H, -OCH_3), 6.22 (s, 1H, pyrimidine-chiral-H), 7.33 - 7.14 (m, 4H, aromatic-H), 7.68 (d, 2H, aromatic-H), 7.78 (s, 1H, -NH-CO-), 9.90 (d, 2H, aromatic-H), 11.17 (s, 1H, -CHO); ^{13}C NMR (400 MHz, DMSO): 175.85 (C=S), 167.53 (-CHO), 163.13 (-NH-CO-), 159.13, 158.84, 135.62, 129.84, 125.69, 122.57, 114.33, 106.36, 67.64, 55.82 (-OCH_3) and 17.90 (-CH_3) δ; EI-MS: m/z 411 [M^+], ($C_{21}H_{21}N_3O_4S$); requried: C, 61.30; H, 5.14; N, 10.21 %; found: C, 61.27; H, 5.11; N, 10.17 %.

4.2.13 N-(4-methoxyphenyl)-3-formyl-6-methyl-4-(2-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidin -e-5-carboxamide **(4k)**

Yield 60 %, m.p. 198 ºC; IR (KBr): 3320 (N-H str. of amide), 3222 (N-H str. of pyrimidine), 3049 (C=C-H str.), 2945 (C-H str. of –CH_3), 2774 (C-H str. of -CHO), 1719 (C=O str. of -CHO), 1630 (C=O str. of amide), 1530 and 1436 (C=C str.), 1251 (C-O-C str. of Ar–OCH_3), 1030 (C=S str.), 750 (C-H bending of o-disubstituted benzene) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.10 (s, 1H, pyrimidine-NH-), 2.11 (s, 3H, -CH_3), 3.23 (s, 3H, -OCH_3), 3.48 (s, 3H, -OCH_3), 6.27 (s, 1H, pyrimidine-chiral-H), 7.28 – 6.92 (m, 4H, aromatic-H), 7.68 (d, 2H, aromatic-H), 7.68 (s, 1H, -NH-CO-), 9.93 (d, 2H, aromatic-H), 11.12 (s, 1H, -CHO); ^{13}C NMR (400 MHz, DMSO): 175.85 (C=S), 167.50 (-CHO), 163.13 (-NH-CO-), 159.13, 158.84, 156.32, 129.84, 127.83, 122.57, 121.24, 120.74, 114.53, 106.36, 61.64, 56.21 (-OCH_3), 55.82 (-OCH_3) and 17.90 (-CH_3) δ; EI-MS: m/z 411 [M^+], ($C_{21}H_{21}N_3O_4S$) ; requried: C, 61.30; H, 5.14; N, 10.21 %; found: C, 61.27; H, 5.11; N, 10.17 %.

4.2.14 N-(4-methoxyphenyl)-3-formyl-6-methyl-4-(4-flourophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine -5-carboxamide **(4l)**

Yield 57 %, m.p. 176 °C; IR (KBr): 3321 (N-H str. of amide), 3242 (N-H str. of pyrimidine), 3044 (C=C-H str.), 2926 (C-H str. of –CH_3), 2738 (C-H str. of -CHO), 1710 (C=O str. of -CHO), 1628 (C=O str. of amide), 1520 and 1458 (C=C str.), 1237 (C-O-C str. of Ar–OCH_3), 1038 (C=S str.), 885 (C-F str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.32 (s, 1H, pyrimidine-NH-), 2.36 (s, 3H, -CH_3), 3.17 (s, 3H, -OCH_3), 6.12 (s, 1H, pyrimidine-chiral-H), 7.38 - 7.14 (m, 4H, aromatic-H), 7.54 (d, 2H, aromatic-H), 7.75 (s, 1H, -NH-CO-), 9.54 (d, 2H, aromatic-H), 11.12 (s, 1H, -CHO); ^{13}C NMR (400 MHz, DMSO): 175.82 (C=S), 167.54 (-CHO), 163.18 (-NH-CO-), 160.92, 158.93, 138.98, 129.94, 128.54, 122.68, 115.37, 114.45, 106.43, 67.60, 55.84 (-OCH_3) and 17.94 (-CH_3) δ; EI-MS: m/z 399 [M^+], ($C_{20}H_{18}FN_3O_3S$); requried: C, 60.14; H, 4.54; N, 10.52 %; found: C, 60.11; H, 4.51; N, 10.48 %.

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