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Microwave-assisted synthesis of -CF_3 functionalized 3,4-dihydropyrimidinone/thione/imine derivatives by using potassium phthalimide (PPI) as a green and reusable organocatalyst and their anti-microbial evaluation

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One-pot synthesis of novel -CF_3 functional group containing 3,4-dihydropyrimidinone/thione/imine derivatives **8a-l**, **9a-l** and **10a-l** has been successfully performed in high yields through the reaction of aromatic aldehydes, β-dicarbonyl compound, urea/thiourea/guanidine hydrochloride by using potassium phthalimide (PPI) as organocatalyst under solvent-free conditions under microwave irradiation at 300 W. PPI has been introduced as an efficient and biodegradable organocatalyst in Biginelli condensation with excellent reusability. The good yield of products, fast reaction time, simple work-up procedure, as well as usage of nontoxic, reusable, and easily recoverable catalyst under magnetic starring have been counted as advantages of the applied process. This organocatalyst can be removed after completion of reaction and reused several times under the same reaction conditions without significant loss of catalyst activity. The anti-microbial activity of all newly synthesised Biginelli products has been investigated against a variety of microorganisms such as *E. coli*, *S. aureus*, *S. pyogenes*, *P. aeruginosa*, *C. albicans*, *A. niger* and *A. clavatus*.

Keywords: Biginelli reaction, -CF_3 functional group, 3,4-Dihydropyrimidinone/thione/imine derivatives, Potassium phthalimide (PPI), One-pot synthesis, Microwave irradiation, Solvent-free, Anti-microbial activity

In the synthesis of organic compounds, microwave irradiation[1] plays a vital role and provides several advantages over traditional heating, including a high yield of product, a short reaction time, and a straightforward work-up process. Biginelli's reaction[2,3] is a three-component one-pot reaction, discovered in 1893, is widely used in the production of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones (Fig. 1). Many natural marine alkaloids[4], medicines, inhibitors, and drug candidates contain 3,4-dihydropyrimidin-2(1*H*)-ones/thiones as essential structural units. An aldehyde, *β*-ketoester, and urea or thiourea are cyclocondensed with acidic catalysts to produce 3,4-dihydropyrimidin-2(1*H*)-ones/3,4-dihydropyrimidin-2(1*H*)-thiones (DHPMs)[5]. Biginelli compounds are the generally known as DHPMs. Due to its applicability in the area of drugs and pharmaceuticals, aryl substituted DHPMs[6] and their derivatives have received a lot of interest in recent years. The heterocyclic scaffolds containing the dihydropyrimidin moiety are found in a wide range of biological activity such as anti-bacterial[7,8], carbonic anhydrase inhibitory[9], anti-fungal[10], anti-leishmania[11], anti-microbial[12], anti-cancer[13], vasodilator[14], anti-HIV[15], and Alzheimer's disease[16]. Because of these interesting features of 3,4-dihydropyrimidin derivatives[17], much attention has been paid to the development of environmentally friendly methods for synthesising this heterocyclic scaffold.

Various catalysts and reaction conditions were used to develop numerous Biginelli reactions. Different organocatalysts[6,18-21] such as phosphoric acids of phytic acid phthalimide-*N*-sulfonic acid[22], chiral phosphoric acids[23], 2-ethylhexanoic acid[24], PEG-embedded[25,26] thiourea dioxide (PEG.TUD), imidazol-1-yl-acetic acid[27], triphenylphosphine (PPh_3)[28], 3-nitrophenylboronic acid[29], 1-methylimidazoliumtri-fluoroacetate[30], tartaric acid[31], xanthan sulfuric acid[32] were reported. Although many of these protocols have one or more limitations, such as long reaction time, complex workup process, need of expensive catalysts and organic solvents. As a result, the development of a catalytically efficient, quick, simple, solventless and environmentally friendly technique for the synthesis

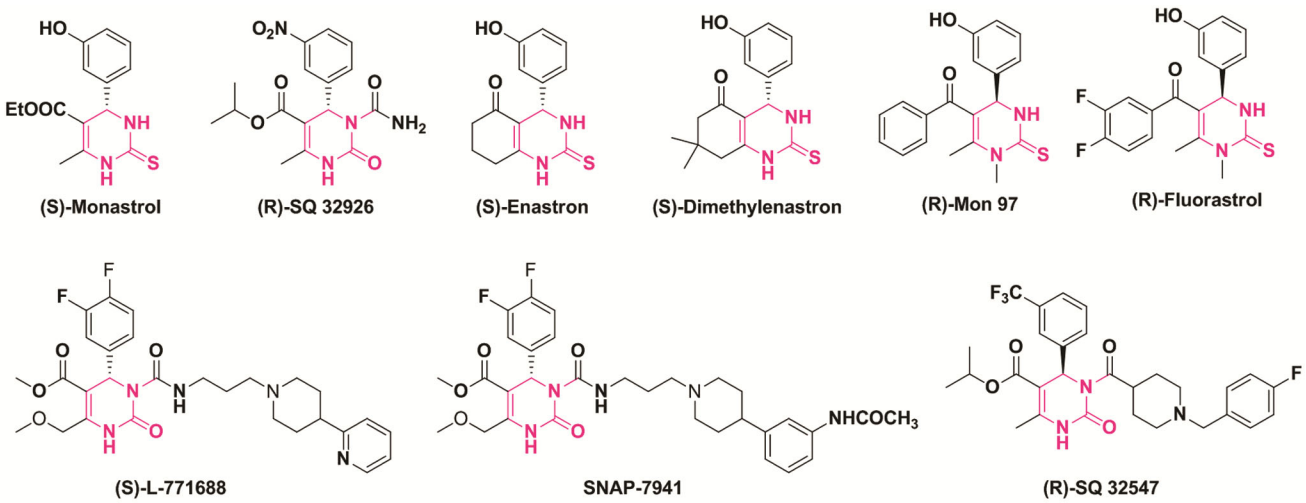


Fig. 1 — 3,4-dihydropyrimidin-2(1*H*)-ones/thiones scaffold containing bioactive compounds

of dihydropyrimidine has gained a lot of attention in recent years.

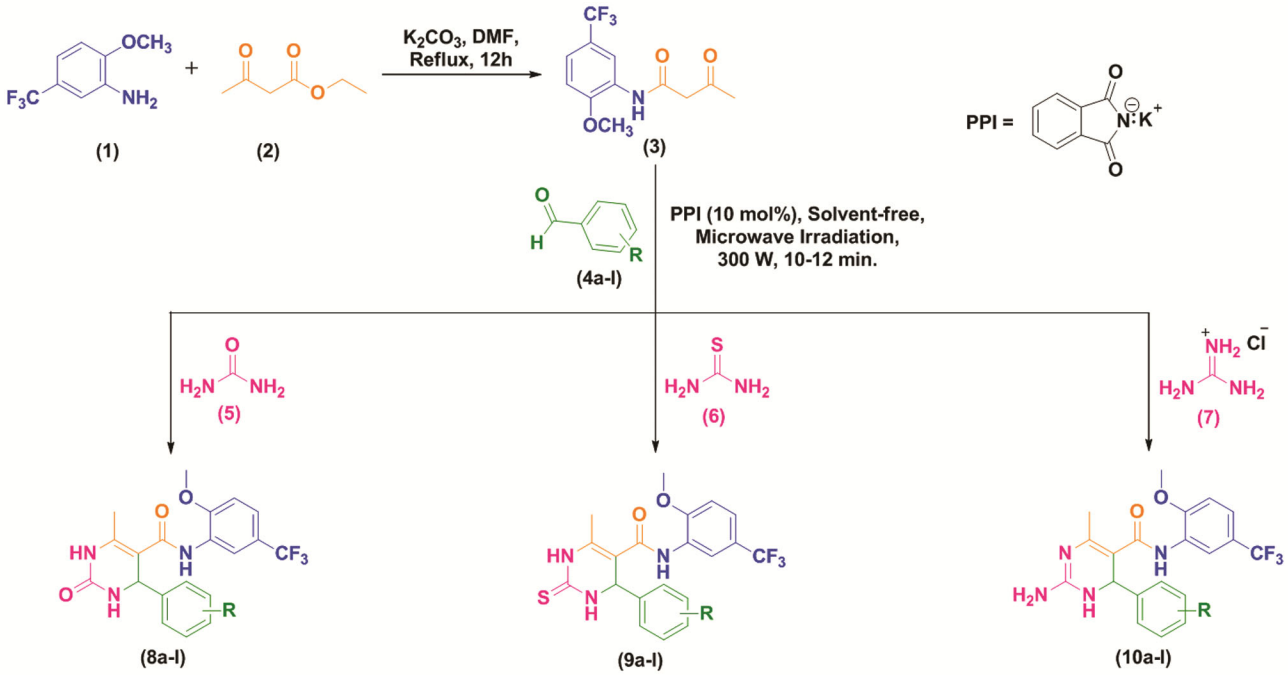
Fluorine containing organic compounds are developed to improve pharmacological qualities such as solubility, metabolic and oxidative stability, lipophilicity, and bioavailability. The trifluoromethyl group (-CF_3)[33-36] is of current interest among fluorine-containing functional groups because of its unusual structural and electrical properties, which can be valuable in materials, agriculture, and medicinal science[37,38]. Indeed, -CF_3-containing medicines and agrochemicals have shown improved efficacy along with reduced negative effects[39]. Due to these fascinating features, we have decide to take -CF_3 functionalized *β*-ketoester, *i.e.*, *N*-(2-methoxy-5-(trifluoromethyl) phenyl)-3-oxobutanamide in this one-pot Biginelli reaction[40].

Nowadays, organocatalysis is being extensively investigated due to its attractive characteristics like high efficiency, low cost, environmentally benign, transition metals-free conditions, experimental simplicity, and ability to recover. In organic transformation[41], it's been difficult to expand solid base catalytic systems. Potassium phthalimide (PPI)[42] is a reusable organo-catalyst that is efficient, mild, and cheap. It was used in the Gabriel procedure as a reagent[43] for preparing primary amines and the production of phthalimide derivatives. It is also been used as a catalyst for the synthesis of various important organic compounds such asisocyanurates[44], 3,3'-arylmethylene-bis(4-hydroxyquinolin-2(1*H*)-ones)[45], and amino-benzochromenes[46]. Kiyani and co-workers[47] have demonstrated one-step multi-component synthesis of Hantzsch 3,4-dihydro-pyrimidin-2(1*H*)-ones/thiones derivatives catalysed by PPI under solvent-free conditions at 120°C. Inspired from them, we have decide to carryout Biginelli reaction with PPI by using novel *β*-ketoester, *i.e.*, *N*-(2-methoxy-5-(trifluoromethyl) phenyl)-3-oxobutanamide under microwave irradiation technique. To the best of our knowledge, the use of PPI as the catalyst for the preparation of this novel class of Biginelli's derivatives under microwave irradiation condition has not been reported so far.

We present here a simple, efficient, and environmentally friendly method for the synthesis of -CF_3 functional group containing 3,4-dihydropyrimidinone/thione/imine derivatives **8a-l**, **9a-l** and **10a-l** through a one-pot three-component condensation reaction of *N*-(2-methoxy-5-(trifluoromethyl)phenyl)-3-oxobutanamide, urea/thiourea/guanidine hydrochloride hydrochloride, and aromatic aldehydes using PPI as a bio-degradable recyclable catalyst under microwave irradiation conditions (Scheme 1).

Experimental Section

All substances were purchased from commercial sources and were analytical grade, unless otherwise noted. The experiments were carried out in a modified Samsung microwave oven. The melting points were calculated without adjustment using an Optimelt MPA 100 melting point instrument. On a Perkin Elmer FT-IR 377 spectrophotometer, KBr was utilised to record FT-IR spectra. Proton NMR spectra were acquired using a Bruker AV 400 MHz



Scheme 1 — Potassium phthalimide (PPI) catalyzed synthesis of -CF_3 functional group containing 3,4-dihydropyrimidinone/thione/imine derivatives **8a-l**, **9a-l** and **10a-l**

spectrometer with DMSO as the solvent and TMS as the internal reference. The mass spectra were collected in the United States at the Advion expression CMS. The ion source is electron spray ionisation, and the mobile phase is acetone (ESI). The elemental analysis was carried out using a CHN elemental analyzer. Thin layer chromatography (TLC) was done using Merck pre-coated silica gel 60 F_{254} aluminium sheets, visible by UV light, and was used to track the progress of the reactions.

Preparation of *N*-(2-methoxy-5-(trifluoromethyl) phenyl)-3-oxobutanamide, 3

In 3-neck RBF, 2-methoxy-5-(trifluoromethyl) aniline (1 mmol) and K_2CO_3 (1.2 mmol) were dissolved into DMF (2 mL). To this solution ethyl acetoacetate (1 mmol) was added. Reaction mixture was then stirred under reflux condition for 12h. The reaction progress was checked by TLC to ensure complete consumption of the starting materials. After completion of the reaction, reaction mass was quenched with ice-cold water (25 mL). The obtained solid was filter through watman filter paper using Buckner funnel under vacuum. Suck well dry to get crude product. The pure products was obtained after recrystallization from hot ethanol. The obtained compound was confirmed by ESI-MS spectral analysis. MS (ESI) *m/z* for (275.08): 276.1 $(M+1)^+$.

General protocol for the preparation of 3,4-dihydro pyrimidinone/thione/imine derivatives 8a-l, 9a-l and 10a-l

A mixture of To begin, aryl benzaldehydes **4a-l** (1 mmol), *N*-(2-methoxy-5-(trifluoromethyl)phenyl)-3-oxobutanamide **3** (1 mmol), and urea/thiourea/ guanidine hydrochloride **(5/6/7)** (1.2 mmol), and PPI (10 mol%) was taken in 50 mL RBF. Put the RBF in microwave oven and the reaction mixture was irradiated at 300 W for 10-12 min. The progress of the reaction mixture was monitored by TLC analysis. After completion of the reaction, the reaction mixture was cooled to RT and poured into 25 mL ice-water. Obtained precipitated solid was filtered off, washed with cold distilled water (10 mL), and air-dried to obtain crude products. The pure products **8a-l**, **9a-l** and **10a-l** was obtained after recrystallization from hot ethanol. After removal of the water from the filtered solution, the catalyst is recovered and used for the subsequent reaction.

Spectral data of synthesized compounds

***N*-(2-Methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 8a**: Off white solid. IR (KBr): 3345 (-N-H), 3112 (-N-H), 3072 (-C-H), 1708 (-CO-NH),1265 (-C-F), 1246 cm^{-1} (-C-O); ^1H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydro-

pyrimidine-CH_3), 3.85 (s, 3H, -OCH_3), 5.61 (s, 1H, dihydropyrimidine-ring-CH), 7.09-7.11 (m, 5H, ArH), 7.22-7.24 (d, 1H,*J* = 8.4 Hz,ArH), 7.30-7.32 (d, 1H,*J* = 8.8 Hz,ArH), 8.27 (s, 1H, ArH),8.33 (s, 1H, -CONH),9.04 (s, 1H, -NH), 10.05 (s, 1H, -NH); ESI-MS: *m/z* (405.13): 406.13$(M+1)^+$. Elemental analysis: Calculated for $C_{20}H_{18}F_3N_3O_3$ (405.38): C 69.26%, H 4.48%, N 10.37%. Found: C 69.25%, H 4.46%, N 10.36%.

4-(2-Bromophenyl)-*N*-(2-methoxy-5-(trifluoro methyl)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide, 8b: White solid. IR (KBr): 3344 (-N-H), 3108 (-N-H), 3075 (-C-H), 1715 (-CO-NH),1263 (-C-F), 1243 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.22 (s, 3H, dihydropyrimidine-CH_3), 3.84 (s, 3H, -OCH_3), 5.58 (s, 1H, dihydropyrimidine-ring-CH), 7.20-7.25 (m, 3H, ArH), 7.26-7.28 (d, 1H,*J* = 8.8 Hz,ArH), 7.38-7.40 (d, 1H,*J* = 8.6 Hz,ArH), 7.54-7.56 (d, 1H,*J* = 8.6 Hz, ArH), 8.27 (s, 1H, ArH),8.30 (s, 1H, -CONH),9.03 (s, 1H, -NH), 10.06 (s, 1H, -NH); ESI-MS: *m/z* (483.04): 485.04$(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{17}BrF_3N_3O_3$ (484.27): C 49.60%, H 3.54%, N 8.68%. Found: C 49.59%, H 3.53%, N 8.67%.

4-(4-Fluorophenyl)-*N*-(2-methoxy-5-(trifluoro-methyl)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide, 8c: Off white solid. IR (KBr): 3342 (-N-H), 3107 (-N-H), 3073 (-C-H), 1712 (-CO-NH),1261 (-C-F), 1242 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.82 (s, 3H, -OCH_3), 5.60 (s, 1H, dihydropyrimidine-ring-CH), 7.08-7.10 (d, 2H,*J* = 8.8 Hz,ArH), 7.15-7.17 (d, 2H,*J* = 8.4 Hz,ArH), 7.26-7.28 (d, 1H,*J* = 8.8 Hz,ArH), 7.38-7.40 (d, 1H,*J* = 8.6 Hz,ArH), 8.27 (s, 1H, ArH),8.31 (s, 1H, -CONH),9.05 (s, 1H, -NH), 10.02 (s, 1H, -NH); ESI-MS: *m/z* (423.12): 424.12 $(M+1)^+$. Elemental analysis: Calculated for $C_{20}H_{17}F_4N_3O_3$ (423.37): C 56.74%, H 4.05%, N 9.93%. Found: C 56.73%, H 4.04%, N 9.92%.

***N*-(2-Methoxy-5-(trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide, 8d**: White solid. IR (KBr): 3342 (-N-H), 3109 (-N-H), 3070 (-C-H), 1707 (-CO-NH),1263 (-C-F), 1245 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.20 (s, 3H, dihydropyrimidine-CH_3), 3.84 (s, 6H, 2×-OCH_3), 5.59 (s, 1H, dihydropyrimidine-ring-CH), 6.87-6.89 (d, 2H,*J* = 8.4 Hz,ArH), 7.11-7.12 (d, 2H,*J* = 8.6 Hz,ArH), 7.25-7.27 (d, 1H,*J* = 8.8 Hz,ArH), 7.36-7.38 (d, 1H,*J* = 9.2 Hz,ArH), 8.26 (s, 1H, ArH), 8.34 (s, 1H, -CONH), 9.06 (s, 1H, -NH), 10.06 (s, 1H, -NH); ESI-MS: *m/z* (435.14): 436.14 $(M+1)^+$. Elemental analysis: Calculated for $C_{21}H_{20}F_3N_3O_4$ (435.40): C 57.93%, H 4.63%, N 9.65%. Found: C 57.92%, H 4.62%, N 9.64%.

4-(2-Chloro-4-hydroxyphenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 8e: Light yellow solid. IR (KBr): 3340 (-N-H), 3109 (-N-H), 3072 (-C-H), 1710 (-CO-NH),1263 (-C-F), 1240 (-C-O), 652 cm^{-1} (-C-Cl); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.20 (s, 3H, dihydropyrimidine-CH_3), 3.80 (s, 3H, -OCH_3), 5.58 (s, 1H, dihydropyrimidine-ring-CH), 6.77-6.79 (d, 1H,*J* = 8.4 Hz,ArH),6.84 (s, 1H,-OH),7.13-7.15 (d, 1H,*J* = 8.4 Hz,ArH), 7.24-7.26 (d, 1H,*J* = 8.4 Hz,ArH), 7.37-7.39 (d, 1H,*J* = 9.2 Hz,ArH),7.52 (s, 1H, ArH),8.25 (s, 1H, ArH), 8.32 (s, 1H, -CONH), 9.00 (s, 1H, -NH), 9.99 (s, 1H, -NH). MS (ESI) *m/z* for (455.09): 457.08 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{17}ClF_3N_3O_4$ (455.82): C 52.70%, H 3.76%, N 9.22%. Found: C 52.69%, H 3.75%, N 9.21%.

4-(2-Chloro-4-methoxyphenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 8f: Off white solid. IR (KBr): 3342 (-N-H), 3111 (-N-H), 3070 (-C-H), 1712 (-CO-NH),1264 (-C-F), 1244 (-C-O), 654 cm^{-1} (-C-Cl); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.20 (s, 3H, dihydropyrimidine-CH_3), 3.81 (s, 6H, 2×-OCH_3), 5.59 (s, 1H, dihydropyrimidine-ring-CH), 6.78-6.80 (d, 1H,*J* = 8.4 Hz,ArH),6.85 (s, 1H, ArH),7.14-7.16 (d, 1H,*J* = 8.8 Hz,ArH), 7.24-7.26 (d, 1H,*J* = 8.2 Hz,ArH), 7.36-7.38 (d, 1H,*J* = 8.8 Hz,ArH), 8.27 (s, 1H, ArH),8.34 (s, 1H, -CONH),9.02 (s, 1H, -NH), 10.05 (s, 1H, -NH); ESI-MS: *m/z* (469.10): 471.10 $(M+2)^+$. Elemental analysis: Calculated for $C_{21}H_{19}ClF_3N_3O_4$ (469.85): C 53.68%, H 4.08%, N 8.94%. Found: C 53.67%, H 4.06%, N 8.93%.

4-(2-Bromo-4-fluorophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 8g: Pale yellow solid. IR (KBr): 3340 (-N-H), 3113 (-N-H), 3072 (-C-H), 1713 (-CO-NH),1265 (-C-F), 1246 (-C-O), 665 cm^{-1} (-C-Br); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.20 (s, 3H, dihydropyrimidine-CH_3), 3.80 (s, 3H, -OCH_3), 5.60 (s, 1H, dihydropyrimidine-ring-CH), 6.76-6.78 (d, 1H,*J* = 8.6 Hz,ArH),6.84 (s, 1H, ArH),7.16-7.18 (d, 1H,*J* = 8.4 Hz,ArH), 7.25-7.27 (d,

1H,*J* = 8.4 Hz,ArH), 7.35-7.37 (d, 1H,*J* = 8.8 Hz,ArH), 8.26 (s, 1H, ArH),8.30 (s, 1H, -CONH),9.00 (s, 1H, -NH), 10.03 (s, 1H, -NH); ESI-MS: *m/z* (501.03): 503.03 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{16}BrF_4N_3O_3$ (502.26): C 47.83%, H 3.21%, N 8.37%. Found: C 47.82%, H 3.20%, N 8.36%.

4-(2-Chlorophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 8h: White solid. IR (KBr): 3342 (-N-H), 3109 (-N-H), 3076 (-C-H), 1718 (-CO-NH),1264 (-C-F), 1244 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.83 (s, 3H, -OCH_3), 5.59 (s, 1H, dihydropyrimidine-ring-CH), 7.22-7.26 (m, 3H, ArH), 7.28-7.30 (d, 1H,*J* = 8.4 Hz,ArH), 7.39-7.41 (d, 1H,*J* = 8.8 Hz,ArH), 7.55-7.57 (d, 1H,*J* = 8.4 Hz, ArH), 8.28 (s, 1H, ArH),8.34 (s, 1H, -CONH),9.04 (s, 1H, -NH), 10.05 (s, 1H, -NH); ESI-MS: *m/z* (439.09): 441.09 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{17}ClF_3N_3O_3$ (439.82): C 54.62%, H 3.90%, N 9.55%. Found: C 54.61%, H 3.89%, N 9.54%.

4-(4-Chlorophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 8i: White solid. IR (KBr): 3344 (-N-H), 3109 (-N-H), 3074 (-C-H), 1714 (-CO-NH),1263 (-C-F), 1244 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.22 (s, 3H, dihydropyrimidine-CH_3), 3.81 (s, 3H, -OCH_3), 5.59 (s, 1H, dihydropyrimidine-ring-CH), 7.12-7.14 (d, 2H,*J* = 8.4 Hz,ArH), 7.18-7.20 (d, 2H,*J* = 8.8 Hz,ArH), 7.27-7.29 (d, 1H,*J* = 8.2 Hz,ArH), 7.39-7.41 (d, 1H,*J* = 8.6 Hz,ArH), 8.25 (s, 1H, ArH),8.34 (s, 1H, -CONH),9.06 (s, 1H, -NH), 10.04 (s, 1H, -NH); ESI-MS: *m/z* (439.09): 441.09 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{17}ClF_3N_3O_3$ (439.82): C 54.62%, H 3.90%, N 9.55%. Found: C 54.61%, H 3.89%, N 9.54%.

***N*-(2-Methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-oxo-4-(*p*-tolyl)-1,2,3,4-tetrahydro pyrimidine-5-carboxamide, 8j**: White solid. IR (KBr): 3342 (-N-H), 3107 (-N-H), 3070 (-C-H), 1712 (-CO-NH),1260 (-C-F), 1241 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.23 (s, 3H, dihydropyrimidine-CH_3), 2.35 (s, 3H, Ar-CH_3), 3.82 (s, 3H, -OCH_3), 5.60 (s, 1H, dihydropyrimidine-ring-CH), 7.13-7.15 (d, 4H,*J* = 8.8 Hz,ArH), 7.28-7.30 (d, 1H,*J* = 8.4 Hz,ArH), 7.39-7.41 (d, 1H,*J* = 8.6 Hz,ArH), 8.28 (s, 1H, ArH),8.36 (s, 1H, -CONH),9.08 (s, 1H, -NH), 10.05 (s, 1H, -NH); ESI-MS: *m/z* (419.15): 420.15 $(M+1)^+$. Elemental analysis: Calculated for $C_{21}H_{20}F_3N_3O_3$ (419.40): C 60.14%, H 4.81%, N 10.02%. Found: C 60.12%, H 4.80%, N 10.01%.

***N*-(2-Methoxy-5-(trifluoromethyl)phenyl)-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 8k**: Dark yellow solid. IR (KBr): 3345 (-N-H), 3111 (-N-H), 3075 (-C-H), 1716 (-CO-NH),1265 (-C-F), 1245 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.22 (s, 3H, dihydropyrimidine-CH_3), 3.81 (s, 3H, -OCH_3), 5.59 (s, 1H, dihydropyrimidine-ring-CH), 7.20-7.22 (d, 2H,*J* = 8.4 Hz,ArH), 7.27-7.29 (d, 1H,*J* = 8.8 Hz,ArH), 7.41-7.43 (d, 1H,*J* = 8.8 Hz,ArH), 8.25 (s, 1H, ArH),8.32-8.34 (d, 2H,*J* = 8.8 Hz,ArH),8.40 (s, 1H, -CONH),9.07 (s, 1H, -NH), 10.05 (s, 1H, -NH); ESI-MS: *m/z* (450.12): 451.12 $(M+1)^+$. Elemental analysis: Calculated for $C_{20}H_{17}F_3N_4O_5$ (450.37): C 53.34%, H 3.80%, N 12.44%. Found: C 53.33%, H 3.79%, N 12.43%.

4-(2-Chloro-4-nitrophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 8l: Dark yellow solid. IR (KBr): 3340 (-N-H), 3113 (-N-H), 3072 (-C-H), 1713 (-CO-NH),1360 (-N-O), 1265 (-C-F), 1246 (-C-O), 651 cm^{-1} (-C-Cl); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.81 (s, 3H, -OCH_3), 5.59 (s, 1H, dihydropyrimidine-ring-CH), 6.78-6.80 (d, 1H,*J* = 8.2 Hz,ArH),6.83 (s, 1H, ArH),7.15-7.17 (d, 1H,*J* = 8.8 Hz,ArH), 7.24-7.26 (d, 1H,*J* = 8.8 Hz,ArH), 7.34-7.36 (d, 1H,*J* = 9.2 Hz,ArH), 8.27 (s, 1H, ArH),8.33 (s, 1H, -CONH),9.04 (s, 1H, -NH), 10.06 (s, 1H, -NH); ESI-MS: *m/z* (484.08): 486.07 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{16}ClF_3N_4O_5$ (484.82): C 49.55%, H 3.33%, N 11.56%. Found: C 49.54%, H 3.32%, N 11.55%.

***N*-(2-Methoxy-5-(trifluoromethyl)phenyl)-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 9a**: Off white solid. IR (KBr): 3346 (-N-H), 3115 (-N-H), 3073 (-C-H), 1706 (-CO-NH),1267 (-C-F), 1248 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.22 (s, 3H, dihydropyrimidine-CH_3), 3.86 (s, 3H, -OCH_3), 5.42 (s, 1H, dihydropyrimidine-ring-CH), 7.19-7.27 (m, 5H, ArH), 7.31-7.33 (d, 1H,*J* = 8.2 Hz,ArH), 7.48-7.50 (d, 1H,*J* = 8.4 Hz,ArH), 8.12 (s, 1H, ArH), 8.93 (s, 1H, -CONH), 9.54 (s, 1H, -NH), 10.25 (s, 1H, -NH); ESI-MS: *m/z* (421.11): 422.11$(M+1)^+$. Elemental analysis: Calculated for $C_{20}H_{18}F_3N_3O_2S$

(421.44): C 57.00%, H 4.31%, N 9.97% S 7.61%. Found: C 57.00%, H 4.30%, N 9.96%, S 7.60%.

4-(2-Bromophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 9b: Light yellow solid. IR (KBr): 3344 (-N-H), 3108 (-N-H), 3075 (-C-H), 1715 (-CO-NH),1263 (-C-F), 1243 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.20 (s, 3H, dihydropyrimidine-CH_3), 3.85 (s, 3H, -OCH_3), 5.38 (s, 1H, dihydropyrimidine-ring-CH), 7.19-7.39 (m, 3H, ArH), 7.44-7.46 (d, 1H,*J* = 8.4 Hz,ArH), 7.47-7.49 (d, 1H,*J* = 8.8 Hz,ArH), 7.52-7.54 (d, 1H,*J* = 8.4 Hz, ArH), 8.12 (s, 1H, ArH), 8.96 (s, 1H, -CONH), 9.51 (s, 1H, -NH), 10.19 (s, 1H, -NH); ESI-MS: *m/z* (499.02): 501.02 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{17}BrF_3N_3O_2S$ (500.33): C 48.01%, H 3.42%, N 8.40%, S 6.41%. Found: C 48.00%, H 3.41%, N 8.39%, S 6.40%.

4-(4-Fluorophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 9c: White solid. IR (KBr): 3346 (-N-H), 3105 (-N-H), 3075 (-C-H), 1713 (-CO-NH),1264 (-C-F), 1243 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.82 (s, 3H, -OCH_3), 5.40 (s, 1H, dihydropyrimidine-ring-CH), 7.05-7.07 (d, 2H,*J* = 8.4 Hz,ArH), 7.16-7.18 (d, 2H,*J* = 8.4 Hz,ArH), 7.46-7.48 (d, 1H,*J* = 8.8 Hz,ArH), 7.52-7.54 (d, 1H,*J* = 8.8 Hz,ArH), 8.15 (s, 1H, ArH), 8.95 (s, 1H, -CONH), 9.55 (s, 1H, -NH), 10.19 (s, 1H, -NH); ESI-MS: *m/z* (439.10): 440.10 $(M+1)^+$. Elemental analysis: Calculated for $C_{20}H_{17}F_4N_3O_2S$ (439.43): C 54.67%, H 3.90%, N 9.56%, S 7.30%. Found: C 54.66%, H 3.89%, N 9.55%, S 7.29%.

***N*-(2-Methoxy-5-(trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 9d**: White solid. IR (KBr): 3342 (-N-H), 3109 (-N-H), 3070 (-C-H), 1707 (-CO-NH),1263 (-C-F), 1245 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.20 (s, 3H, dihydropyrimidine-CH_3), 3.84 (s, 6H, 2×-OCH_3), 5.59 (s, 1H, dihydropyrimidine-ring-CH), 6.87-6.89 (d, 2H,*J* = 8.4 Hz,ArH), 7.15-7.17 (d, 2H,*J* = 8.4 Hz,ArH), 7.43-7.45 (d, 1H,*J* = 8.4 Hz,ArH), 7.56-7.58 (d, 1H,*J* = 8.8 Hz,ArH), 8.16 (s, 1H, ArH), 8.94 (s, 1H, -CONH), 9.56 (s, 1H, -NH), 10.16 (s, 1H, -NH); ESI-MS: *m/z* (451.12): 452.12 $(M+1)^+$. Elemental analysis: Calculated for $C_{21}H_{20}F_3N_3O_3S$ (451.46): C 55.87%, H 4.47%, N 9.31%, S 7.10%. Found: C 55.86%, H 4.46%, N 9.30%, S 7.09%.

4-(2-Chloro-4-hydroxyphenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 9e: Yellow solid. IR (KBr): 3343 (-N-H), 3112 (-N-H), 3074 (-C-H), 1715 (-CO-NH),1265 (-C-F), 1240 (-C-O), 654 cm^{-1} (-C-Cl); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.82 (s, 3H, -OCH_3), 5.60 (s, 1H, dihydropyrimidine-ring-CH), 6.77-6.79 (d, 1H,*J* = 8.4 Hz,ArH),6.84 (s, 1H, -OH),7.13-7.15 (d, 1H,*J* = 8.4 Hz,ArH), 7.24-7.26 (d, 1H,*J* = 8.4 Hz,ArH), 7.37-7.39 (d, 1H,*J* = 9.2 Hz,ArH), 7.52 (s, 1H, ArH), 8.25 (s, 1H, ArH), 8.32 (s, 1H, -CONH), 9.00 (s, 1H, -NH), 9.99 (s, 1H, -NH); ESI-MS: *m/z* (471.06): 473.06 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{17}ClF_3N_3O_3S$ (471.88): C 50.91%, H 3.63%, N 8.91%, S 6.79%. Found: C 50.91%, H 3.62%, N 8.90%, S 6.78%.

4-(2-Chloro-4-methoxyphenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 9f: Light yellow solid. IR (KBr): 3345 (-N-H), 3114 (-N-H), 3072 (-C-H), 1714 (-CO-NH),1265 (-C-F), 1246 (-C-O), 652 cm^{-1} (-C-Cl); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.83 (s, 6H, 2×-OCH_3), 5.60 (s, 1H, dihydropyrimidine-ring-CH), 6.78-6.80 (d, 1H,*J* = 8.4 Hz,ArH),6.85 (s, 1H, ArH),7.24-7.66 (d, 1H,*J* = 8.4 Hz,ArH), 7.34-7.36 (d, 1H,*J* = 8.8 Hz,ArH), 7.56-7.58 (d, 1H,*J* = 9.2 Hz,ArH), 8.17 (s, 1H, ArH), 8.92 (s, 1H, -CONH), 9.54 (s, 1H, -NH), 10.25 (s, 1H, -NH); ESI-MS: *m/z* (485.08): 487.08 $(M+2)^+$. Elemental analysis: Calculated for $C_{21}H_{19}ClF_3N_3O_3S$ (485.91): C 51.91%, H 3.94%, N 8.65%, S 6.60%. Found: C 51.90%, H 3.93%, N 8.64%, S 6.59%.

4-(2-Bromo-4-fluorophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 9g: Pale yellow solid. IR (KBr): 3345 (-N-H), 3116 (-N-H), 3078 (-C-H), 1715 (-CO-NH),1266 (-C-F), 1247 (-C-O), 662 cm^{-1} (-C-Br); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.20 (s, 3H, dihydropyrimidine-CH_3), 3.82 (s, 3H, -OCH_3), 5.58 (s, 1H, dihydropyrimidine-ring-CH), 6.76-6.78 (d, 1H,*J* = 8.6 Hz,ArH),6.84 (s, 1H, ArH),7.16-7.18 (d, 1H,*J* = 8.4 Hz,ArH), 7.24-7.26 (d, 1H,*J* = 8.8 Hz,ArH), 7.56-7.58 (d, 1H,*J* = 8.6 Hz,ArH), 8.16 (s, 1H, ArH), 8.98 (s, 1H, -CONH), 9.52 (s, 1H, -NH), 10.23 (s, 1H, -NH); ESI-MS: *m/z* (517.01): 519.01 $(M+2)^+$. Elemental analysis: Calculated for $C_{21}H_{19}ClF_3N_3O_3S$ (518.32): C 46.35%, H 3.11%, N 8.11%, S 6.19%. Found: C 46.34%, H 3.11%, N 8.10%, S 6.18%.

4-(2-Chlorophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 9h: White solid. IR (KBr): 3340 (-N-H), 3114 (-N-H), 3078 (-C-H), 1720 (-CO-NH),1262 (-C-F), 1246 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.82 (s, 3H, -OCH_3), 5.60 (s, 1H, dihydropyrimidine-ring-CH), 7.22-7.26 (m, 3H, ArH), 7.28-7.30 (d, 1H,*J* = 8.8 Hz,ArH), 7.39-7.41 (d, 1H,*J* = 8.4 Hz,ArH), 7.55-7.57 (d, 1H,*J* = 9.2 Hz, ArH), 8.18 (s, 1H, ArH), 8.94 (s, 1H, -CONH), 9.53 (s, 1H, -NH), 10.25 (s, 1H, -NH); ESI-MS: *m/z* (455.07): 457.07 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{17}ClF_3N_3O_2S$ (455.88): C 52.69%, H 3.76%, N 9.22%, S 7.03%. Found: C 52.68%, H 3.75%, N 9.21%, S 7.02%.

4-(4-Chlorophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 9i: White solid. IR (KBr): 3346 (-N-H), 3112 (-N-H), 3078 (-C-H), 1711 (-CO-NH),1263 (-C-F), 1245 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.82 (s, 3H, -OCH_3), 5.61 (s, 1H, dihydropyrimidine-ring-CH), 7.12-7.14 (d, 2H,*J* = 8.8 Hz,ArH), 7.19-7.21 (d, 2H,*J* = 8.4 Hz,ArH), 7.37-7.39 (d, 1H,*J* = 8.6 Hz,ArH), 7.49-7.51 (d, 1H,*J* = 9.2 Hz,ArH), 8.15 (s, 1H, ArH), 8.99 (s, 1H, -CONH), 9.57 (s, 1H, -NH), 10.24 (s, 1H, -NH); ESI-MS: *m/z* (455.07): 457.07 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{17}ClF_3N_3O_2S$ (455.88): C 52.69%, H 3.76%, N 9.22%, S 7.03%. Found: C 52.68%, H 3.75%, N 9.21%, S 7.02%.

***N*-(2-Methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-thioxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 9j**: Off white solid. IR (KBr): 3346 (-N-H), 3108 (-N-H), 3078 (-C-H), 1716 (-CO-NH),1266 (-C-F), 1249 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.23 (s, 3H, dihydropyrimidine-CH_3), 2.35 (s, 3H, Ar-CH_3), 3.82 (s, 3H, -OCH_3), 5.60 (s, 1H, dihydropyrimidine-ring-CH), 7.15-7.17 (d, 4H,*J* = 8.4 Hz,ArH), 7.38-7.40 (d, 1H,*J* = 8.4 Hz,ArH), 7.46-7.48 (d, 1H,*J* = 8.8 Hz,ArH), 8.18 (s, 1H, ArH), 8.96 (s, 1H, -CONH), 9.58 (s, 1H, -NH), 10.25 (s, 1H, -NH); ESI-MS: *m/z* (435.12): 436.12 $(M+1)^+$. Elemental analysis: Calculated for $C_{21}H_{20}F_3N_3O_2S$ (435.47): C 57.92%, H 4.63%, N 9.65%, S 7.36%. Found: C 57.91%, H 4.62%, N 9.64%, S 7.35%.

***N*-(2-Methoxy-5-(trifluoromethyl)phenyl)-6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 9k**: Yellow solid. IR (KBr): 3345 (-N-H), 3111 (-N-H), 3075 (-C-H), 1716 (-CO-NH),1265 (-C-F), 1245 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.82 (s, 3H, -OCH_3), 5.61 (s, 1H, dihydropyrimidine-ring-CH), 7.20-7.22 (d, 2H,*J* = 8.4 Hz,ArH), 7.38-7.40 (d, 1H,*J* = 8.8 Hz,ArH), 7.42-7.44 (d, 1H,*J* = 8.6 Hz,ArH), 8.15 (s, 1H, ArH),8.31-8.33 (d, 2H,*J* = 9.2 Hz,ArH),9.00 (s, 1H, -CONH), 9.57 (s, 1H, -NH), 10.25 (s, 1H, -NH); ESI-MS: *m/z* (466.09): 467.09 $(M+1)^+$. Elemental analysis: Calculated for $C_{20}H_{17}F_3N_4O_4S$ (466.44): C 51.50%, H 3.67%, N 12.01%, S 6.87%. Found: C 51.49%, H 3.66%, N 12.00%, S 6.86%.

4-(2-Chloro-4-nitrophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide, 9l: Dark yellow solid. IR (KBr): 3342 (-N-H), 3117 (-N-H), 3075 (-C-H), 1716 (-CO-NH),1363 (-N-O), 1266 (-C-F), 1248 (-C-O), 652 cm^{-1} (-C-Cl); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.82 (s, 3H, -OCH_3), 5.59 (s, 1H, dihydropyrimidine-ring-CH), 6.78-6.80 (d, 1H,*J* = 8.4 Hz,ArH),6.83 (s, 1H, ArH),7.18-7.20 (d, 1H,*J* = 8.8 Hz,ArH), 7.44-7.46 (d, 1H,*J* = 8.4 Hz,ArH), 7.54-7.56 (d, 1H,*J* = 9.2 Hz,ArH), 8.17 (s, 1H, ArH), 8.93 (s, 1H, -CONH), 9.54 (s, 1H, -NH), 10.26 (s, 1H, -NH); ESI-MS: *m/z* (500.05): 502.05 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{16}ClF_3N_4O_4S$ (500.88): C 47.96%, H 3.22%, N 11.19%, S 6.40%. Found: C 47.95%, H 3.21%, N 11.18%, S 6.39%.

2-Amino-*N*-(2-methoxy-5-(trifluoromethyl) phenyl)-4-methyl-6-phenyl-1,6-dihydropyrimidine-5-carboxamide, 10a: Off white solid. IR (KBr): 3345 (-N-H), 3112 (-N-H), 3072 (-C-H), 1708 (-CO-NH),1265 (-C-F), 1246 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.85 (s, 3H, -OCH_3), 5.61 (s, 1H, dihydropyrimidine-ring-CH), 6.75(s, 2H, -NH_2),7.09-7.11 (m, 5H, ArH), 7.22-7.24 (d, 1H,*J* = 8.4 Hz,ArH), 7.30-7.32 (d, 1H,*J* = 8.8 Hz,ArH), 8.27 (s, 1H, ArH), 8.33 (s, 1H, -CONH), 10.05 (s, 1H, -NH); ESI-MS: *m/z* (404.15): 405.15$(M+1)^+$. Elemental analysis: Calculated for $C_{20}H_{19}F_3N_4O_2$ (404.39): C 59.40%, H 4.74%, N 13.85%. Found: C 59.39%, H 4.73%, N 13.84%.

2-Amino-6-(2-bromophenyl)-N-(2-methoxy-5-(trifluoromethyl)phenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxamide, 10b: Light yellow solid. IR (KBr): 3344 (-N-H), 3108 (-N-H), 3075 (-C-H),

1715 (-CO-NH),1263 (-C-F), 1243 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.20 (s, 3H, dihydropyrimidine-CH_3), 3.85 (s, 3H, -OCH_3), 5.38 (s, 1H, dihydropyrimidine-ring-CH), 6.70(s, 2H, -NH_2),7.19-7.39 (m, 3H, ArH), 7.44-7.46 (d, 1H,*J* = 8.4 Hz,ArH), 7.47-7.49 (d, 1H,*J* = 8.8 Hz,ArH), 7.52-7.54 (d, 1H,*J* = 8.4 Hz, ArH), 8.12 (s, 1H, ArH), 8.96 (s, 1H, -CONH),10.04 (s, 1H, -NH); ESI-MS: *m/z* (482.06): 484.05$(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{18}BrF_3N_4O_2$ (483.29): C 49.71%, H 3.75%, N 11.59%. Found: C 49.70%, H 3.74%, N 11.58%.

2-Amino-6-(4-fluorophenyl)-N-(2-methoxy-5-(trifluoromethyl)phenyl)-4-methyl-1,6-dihydro-pyrimidine-5-carboxamide, 10c: Off white solid. IR (KBr): 3342 (-N-H), 3107 (-N-H), 3073 (-C-H), 1712 (-CO-NH),1261 (-C-F), 1242 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.82 (s, 3H, -OCH_3), 5.60 (s, 1H, dihydropyrimidine-ring-CH), 6.73(s, 2H, -NH_2),7.08-7.10 (d, 2H,*J* = 8.8 Hz,ArH), 7.15-7.17 (d, 2H,*J* = 8.4 Hz,ArH), 7.26-7.28 (d, 1H,*J* = 8.8 Hz,ArH), 7.38-7.40 (d, 1H,*J* = 8.6 Hz,ArH), 8.27 (s, 1H, ArH), 8.31 (s, 1H, -CONH),10.03 (s, 1H, -NH); ESI-MS: *m/z* (422.14): 423.14 $(M+1)^+$. Elemental analysis: Calculated for $C_{20}H_{18}F_4N_4O_2$ (422.38): C 56.87%, H 4.30%, N 13.26%. Found: C 56.86%, H 4.29%, N 13.25%.

2-Amino-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-6-(4-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxamide, 10d: White solid. IR (KBr): 3342 (-N-H), 3109 (-N-H), 3070 (-C-H), 1707 (-CO-NH),1263 (-C-F), 1245 cm^{-1} (-C-O); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.20 (s, 3H, dihydropyrimidine-CH_3), 3.84 (s, 6H, 2×-OCH_3), 5.59 (s, 1H, dihydropyrimidine-ring-CH), 6.72(s, 2H, -NH_2),6.97-6.99 (d, 2H,*J* = 8.4 Hz,ArH), 7.15-7.17 (d, 2H,*J* = 8.4 Hz,ArH), 7.43-7.45 (d, 1H,*J* = 8.4 Hz,ArH), 7.56-7.58 (d, 1H,*J* = 8.8 Hz,ArH), 8.16 (s, 1H, ArH), 8.94 (s, 1H, -CONH),10.06 (s, 1H, -NH); ESI-MS: *m/z* (434.16): 435.16 $(M+1)^+$. Elemental analysis: Calculated for $C_{21}H_{21}F_3N_4O_3$ (434.42): C 58.06%, H 4.87%, N 12.90%. Found: C 58.05%, H 4.86%, N 12.89%.

2-Amino-6-(2-chloro-4-hydroxyphenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxamide, 10e: Light yellow solid. IR (KBr): 3340 (-N-H), 3109 (-N-H), 3072 (-C-H), 1710 (-CO-NH),1263 (-C-F), 1240 (-C-O), 652 cm^{-1} (-C-Cl); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.20 (s, 3H, dihydropyrimidine-CH_3), 3.80 (s, 3H, -OCH_3), 5.58 (s, 1H, dihydropyrimidine-ring-CH), 6.72(s, 2H, -NH_2),6.84 (s, 1H, -OH),6.97-6.99 (d, 1H,*J* = 8.4 Hz,ArH), 7.13-7.15 (d, 1H,*J* = 8.4 Hz,ArH), 7.24-7.26 (d, 1H,*J* = 8.4 Hz,ArH), 7.37-7.39 (d, 1H,*J* = 9.2 Hz,ArH), 7.52 (s, 1H, ArH), 8.25 (s, 1H, ArH), 8.32 (s, 1H, -CONH),10.04 (s, 1H, -NH); ESI-MS: *m/z* (454.10): 456.10 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{18}ClF_3N_4O_3$ (454.83): C 52.81%, H 3.99%, N 12.32%. Found: C 52.80%, H 3.98%, N 12.31%.

2-Amino-6-(2-chloro-4-methoxyphenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxamide, 10f: Light yellow solid. IR (KBr): 3345 (-N-H), 3114 (-N-H), 3072 (-C-H), 1714 (-CO-NH),1265 (-C-F), 1246 (-C-O), 652 cm^{-1} (-C-Cl); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.83 (s, 6H, 2×-OCH_3), 5.60 (s, 1H, dihydropyrimidine-ring-CH), 6.70(s, 2H, -NH_2),6.78-6.80 (d, 1H,*J* = 8.4 Hz,ArH),6.95 (s, 1H, ArH),7.24-7.66 (d, 1H,*J* = 8.4 Hz,ArH), 7.34-7.36 (d, 1H,*J* = 8.8 Hz,ArH), 7.56-7.58 (d, 1H,*J* = 9.2 Hz,ArH), 8.17 (s, 1H, ArH), 8.92 (s, 1H, -CONH),10.05 (s, 1H, -NH); ESI-MS: *m/z* (468.12): 470.11 $(M+2)^+$. Elemental analysis: Calculated for $C_{21}H_{20}ClF_3N_4O_3$ (468.86): C 53.80%, H 4.30%, N 11.95%. Found: C 53.79%, H 4.29%, N 11.94%.

2-Amino-6-(2-bromo-4-fluorophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxamide, 10g: Pale yellow solid. IR (KBr): 3340 (-N-H), 3113 (-N-H), 3072 (-C-H), 1713 (-CO-NH),1265 (-C-F), 1246 (-C-O), 665 cm^{-}1 (-C-Br); 1H NMR (400MHz, DMSO-d6): δ 2.20 (s, 3H, dihydropyrimidine-CH_3), 3.80 (s, 3H, -OCH_3), 5.60 (s, 1H, dihydropyrimidine-ring-CH), 6.74(s, 2H, -NH_2),6.81-6.83(d, 1H,*J* = 8.6 Hz,ArH),6.94 (s, 1H, ArH),7.16-7.18 (d, 1H,*J* = 8.4 Hz,ArH), 7.25-7.27 (d, 1H,*J* = 8.4 Hz,ArH), 7.35-7.37 (d, 1H,*J* = 8.8 Hz,ArH), 8.26 (s, 1H, ArH), 8.30 (s, 1H, -CONH), 10.03 (s, 1H, -NH); ESI-MS: *m/z* (500.05): 502.05 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{17}BrF_4N_4O_2$ (501.28): C 47.92%, H 3.42%, N 11.18%. Found: C 47.91%, H 3.41%, N 11.17%.

2-Amino-6-(2-chlorophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-4-methyl-1,6-dihydro-pyrimidine-5-carboxamide, 10h: White solid. IR (KBr): 3340 (-N-H), 3114 (-N-H), 3078 (-C-H), 1720 (-CO-NH),1262 (-C-F), 1246 cm^{-1} (-C-O); ^{1}H NMR

(400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.82 (s, 3H, -OCH_3), 5.60 (s, 1H, dihydropyrimidine-ring-CH), 6.72(s, 2H, -NH_2),7.22-7.26 (m, 3H, ArH), 7.28-7.30 (d, 1H,*J* = 8.8 Hz,ArH), 7.39-7.41 (d, 1H,*J* = 8.4 Hz,ArH), 7.55-7.57 (d, 1H,*J* = 9.2 Hz, ArH), 8.18 (s, 1H, ArH), 8.94 (s, 1H, -CONH),10.04 (s, 1H, -NH); ESI-MS: *m/z* (438.11): 440.10 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{18}ClF_3N_4O_2$ (438.84): C 54.74%, H 4.13%, N 12.77%. Found: C 54.73%, H 4.12%, N 12.76%.

2-Amino-6-(4-chlorophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-4-methyl-1,6-dihydro-pyrimidine-5-carboxamide, 10i: White solid. IR (KBr): 3344 (-N-H), 3109 (-N-H), 3074 (-C-H), 1714 (-CO-NH),1263 (-C-F), 1244 cm^{-1} (-C-O); ^1H NMR (400MHz, DMSO-d_6): δ 2.22 (s, 3H, dihydropyrimidine-CH_3), 3.81 (s, 3H, -OCH_3), 5.59 (s, 1H, dihydropyrimidine-ring-CH), 6.73(s, 2H, -NH_2),7.12-7.14 (d, 2H,*J* = 8.4 Hz,ArH), 7.18-7.20 (d, 2H,*J* = 8.8 Hz,ArH), 7.27-7.29 (d, 1H,*J* = 8.2 Hz,ArH), 7.39-7.41 (d, 1H,*J* = 8.6 Hz,ArH), 8.25 (s, 1H, ArH), 8.34 (s, 1H, -CONH), 10.04 (s, 1H, -NH); ESI-MS: *m/z* (438.11): 440.10 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{18}ClF_3N_4O_2$ (438.84): C 54.74%, H 4.13%, N 12.77%. Found: C 54.73%, H 4.12%, N 12.76%.

2-Amino-*N*-(2-methoxy-5-(trifluoromethyl) phenyl)-4-methyl-6-(*p*-tolyl)-1,6-dihydro pyrimidine-5-carboxamide, 10j: Off white solid. IR (KBr): 3346 (-N-H), 3108 (-N-H), 3078 (-C-H), 1716 (-CO-NH),1266 (-C-F), 1249 cm^{-1} (-C-O); ^1H NMR (400MHz, DMSO-d_6): δ 2.23 (s, 3H, dihydropyrimidine-CH_3), 2.35 (s, 3H, Ar-CH_3), 3.82 (s, 3H, -OCH_3), 5.60 (s, 1H, dihydropyrimidine-ring-CH), 6.75(s, 2H, -NH_2),7.15-7.17 (d, 4H,*J* = 8.4 Hz,ArH), 7.38-7.40 (d, 1H,*J* = 8.4 Hz,ArH), 7.46-7.48 (d, 1H,*J* = 8.8 Hz,ArH), 8.18 (s, 1H, ArH), 8.96 (s, 1H, -CONH),10.05 (s, 1H, -NH); ESI-MS: *m/z* (418.16): 419.17 $(M+1)^+$. Elemental analysis: Calculated for $C_{21}H_{21}F_3N_4O_2$ (418.42): C 60.28%, H 5.06%, N 13.39%. Found: C 60.27%, H 5.05%, N 13.38%.

2-Amino-*N*-(2-methoxy-5-(trifluoromethyl) phenyl)-4-methyl-6-(4-nitrophenyl)-1,6-dihydro-pyrimidine-5-carboxamide, 10k: Dark yellow solid. IR (KBr): 3345 (-N-H), 3111 (-N-H), 3075 (-C-H), 1716 (-CO-NH),1265 (-C-F), 1245 cm^{-1} (-C-O); ^1H NMR (400MHz, DMSO-d_6): δ 2.22 (s, 3H, dihydropyrimidine-CH_3), 3.81 (s, 3H, -OCH_3), 5.59 (s, 1H, dihydropyrimidine-ring-CH), 6.76(s, 2H, -NH_2),7.20-7.22 (d, 2H,*J* = 8.4 Hz,ArH), 7.27-7.29 (d, 1H,*J* = 8.8 Hz,ArH), 7.41-7.43 (d, 1H,*J* = 8.8 Hz,ArH), 8.25 (s, 1H, ArH),8.32-8.34 (d, 2H,*J* = 8.8 Hz,ArH),8.40 (s, 1H, -CONH), 10.05 (s, 1H, -NH); ESI-MS: *m/z* (449.13): 450.13 $(M+1)^+$. Elemental analysis: Calculated for $C_{20}H_{18}F_3N_5O_4$ (449.39): C 53.45%, H 4.04%, N 15.58%. Found: C 53.44%, H 4.03%, N 15.57%.

2-Amino-6-(2-chloro-4-nitrophenyl)-*N*-(2-methoxy-5-(trifluoromethyl)phenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxamide, 10l: Dark yellow solid. IR (KBr): 3342 (-N-H), 3117 (-N-H), 3075 (-C-H), 1716 (-CO-NH),1363 (-N-O), 1266 (-C-F), 1248 (-C-O), 652 cm^{-1} (-C-Cl); ^1H NMR (400MHz, DMSO-d_6): δ 2.21 (s, 3H, dihydropyrimidine-CH_3), 3.82 (s, 3H, -OCH_3), 5.59 (s, 1H, dihydropyrimidine-ring-CH), 6.72(s, 2H, -NH_2),6.80-6.82(d, 1H,*J* = 8.4 Hz,ArH),6.93 (s, 1H, ArH),7.18-7.20 (d, 1H,*J* = 8.8 Hz,ArH), 7.44-7.46 (d, 1H,*J* = 8.4 Hz,ArH), 7.54-7.56 (d, 1H,*J* = 9.2 Hz,ArH), 8.17 (s, 1H, ArH), 8.93 (s, 1H, -CONH),10.06 (s, 1H, -NH); ESI-MS: *m/z* (483.09): 485.09 $(M+2)^+$. Elemental analysis: Calculated for $C_{20}H_{17}ClF_3N_5O_4$ (483.83): C 49.65%, H 3.54%, N 14.48%. Found: C 49.64%, H 3.53%, N 14.47%.

Antibacterial and antifungal activity

Antimicrobial activity of all newly synthesized -CF_3 functional group containing 3,4-dihydro-pyrimidinone/thione/imine derivatives **8a-l**, **9a-l** and **10a-l** was tested against two gram-positive bacterial strains (*Staphylococcus aureus* MTCC 96, *Streptococcus pyogenes* MTCC 442), two gram-negative bacterial strains (*Escherichiacoli* MTCC 443, *Pseudomonas aeruginosa* MTCC 1688) as well as three fungal strains (*Candida albicans* MTCC 227, *Aspergillus clavatus* MTCC 1323, and *Aspergillus niger* MTCC 282) using the agar dilution method. Standard control medications for antibacterial activity included ampicillin, ciprofloxacin, and chloramphenicol, while antifungal activity included Nystatin and Greseofulvin.

Results and Discussion

To begin, benzaldehyde **4a**, *N*-(2-methoxy-5-(trifluoromethyl)phenyl)-3-oxobutanamide **(3)**, and urea **5** were treated under solvent-free conditions at 120°C in the absence of a catalyst as well as in the presence of varying quantities of PPI ranging from 2.5 to 20 mol% (Table 1).When the reaction was carried out without the use of a catalyst, the product **8a** was only generated in 23% yield after 12 hours, as shown in Table 1. The reaction yield was raised to 56% with a

2.5 percent catalyst increase, and the reaction time was lowered from 12 to 8 hours (Table 1, entry 2). The yield of compound **8a** production was enhanced from 63 to 78% when the amount of PPI was raised from 5 to 15 mol%, and the reaction time was further lowered to 6h (Table 1, entries 3-5). However, when the PPI concentration was increased to 20 mol%, no significant increase in the **8a** yield was seen (Table 1, entry 6). As a result, a catalyst with a concentration of 10 mol% PPI was chosen to carry out the subsequent reactions.

We also looked examined how temperature affected yield and reaction time (Table 1, entries 7-11). Lower product **8a** formation was seen when the reaction was carried out at 50 °C. The yield was improved by gradually increasing the temperature from 70 to 110°C. Increases in temperature to 130 °C had no discernible influence on the reaction yield. In the presence of 10 mol% PPI, it was discovered that the reaction temperature should be 120°C.

Furthermore, the model reaction was investigated in a variety of solvents with different boiling points, including acetonitrile, DMF, ethanol, dichloromethane, THF, and water in order to find the best solvent (Table 2, entries 1-6). The reaction times were long, as seen in Table 2. It was determined that 10 mol% PPI was sufficient, and 120 °C and without use of any solvent were the ideal reaction conditions for the completion of the reaction. As a result, all subsequent reactions were carried out at 120 °C with 10 mol% PPI under solvent-free conditions.

After successfully attaining optimal reaction conditions under thermal heating, we conducted a model reaction under microwave irradiation (MWI). Surprisingly, when the reaction was irritated under microwave irradiation with 10 mol% PPI under solvent-free condition at 300W, we achieved the maximum yield of product **8a** with the shortest reaction time (10 minute) (Table 3, entry 1). After that we evaluated the application of various microwave irradiation powers (Table 3, entries 2-4). When the microwave irradiation power was increased from 300W to 600W, the product yield fell. This happens when the product deteriorates at higher temperatures. As a consequence, 10 mol% PPI under solvent-free condition at 300 W is the optimal condition for this reaction.

Following the optimization of the reaction conditions, the generality of the reaction was assessed by using several aryl aldehydes with electron-donating and electron-withdrawing groups, as well as urea, thiourea, or guanidine hydrochloride hydrochloride. With this technique, both electron-withdrawing and electron-donating substituents bearing aryl aldehyde interacted easily, yielding high product yields. It appears that steric factors affect the reactivity of some aryl aldehydes with substituents in the *ortho*-position, since they showed less reactivity than the other aromatic aldehydes, resulting in a slightly lower yield of products. (Table 4, entries 2, 5, 6, 7, 8, 12, 14, 17, 18, 19, 20, 24, 26, 29, 30, 31, 32, and 36).The results are presented in Table 4, which shows that most of these reactions generally proceeded extremely cleanly with no side products. TLC and elemental analyses confirmed the purity of the produced compounds. Spectral analysis was used to characterize the final products' structure (IR, ESI-MS, ^{1}H and ^{13}C NMR).

Table 1 — Effect of the amounts of catalyst PPI and temperature on the synthesis of compound **8a**

Entry	PPI loading (mol%)	Temperature (°C)	Time (h)	Yield (%) [a]
1	–	120	12	23
2	2.5	120	8	56
3	5	120	8	63
4	10	120	6	78
5	15	120	6	78
6	20	120	6	79
7	10	50	6	25
8	10	70	6	39
9	10	90	6	58
10	10	110	6	72
11	10	130	6	78

[a]Isolated yields

Table 2 — Effect of solvent on the synthesis of compound **8a**

Entry	Solvent	Condition	Time (h)	Yield (%) [a]
1	Acetonitrile	Reflux	6	66
2	DMF	Reflux	6	73
3	Ethanol	Reflux	6	74
4	Dichloromethane	Reflux	6	62
5	THF	Reflux	6	68
6	Water	Reflux	6	53

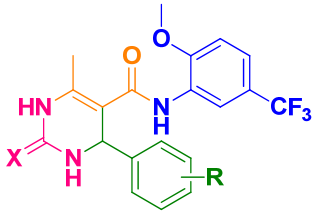
[a] Isolated yields

Table 3 — Effect of Microwave irradiation (MWI) on the synthesis of compound **8a**

Entry	PPI loading (mol%)	Condition	Time (min)	Yield (%) [a]
1	10	MWI, 300 W	10	93
2	10	MWI, 150 W	10	74
3	10	MWI, 150 W	15	76
4	10	MWI, 600 W	10	91

[a] Isolated yields

Table 4 — Preparation of 3,4-dihydropyrimidinone/thione/imine derivatives **8a-l**, **9a-l**, and **10a-l**

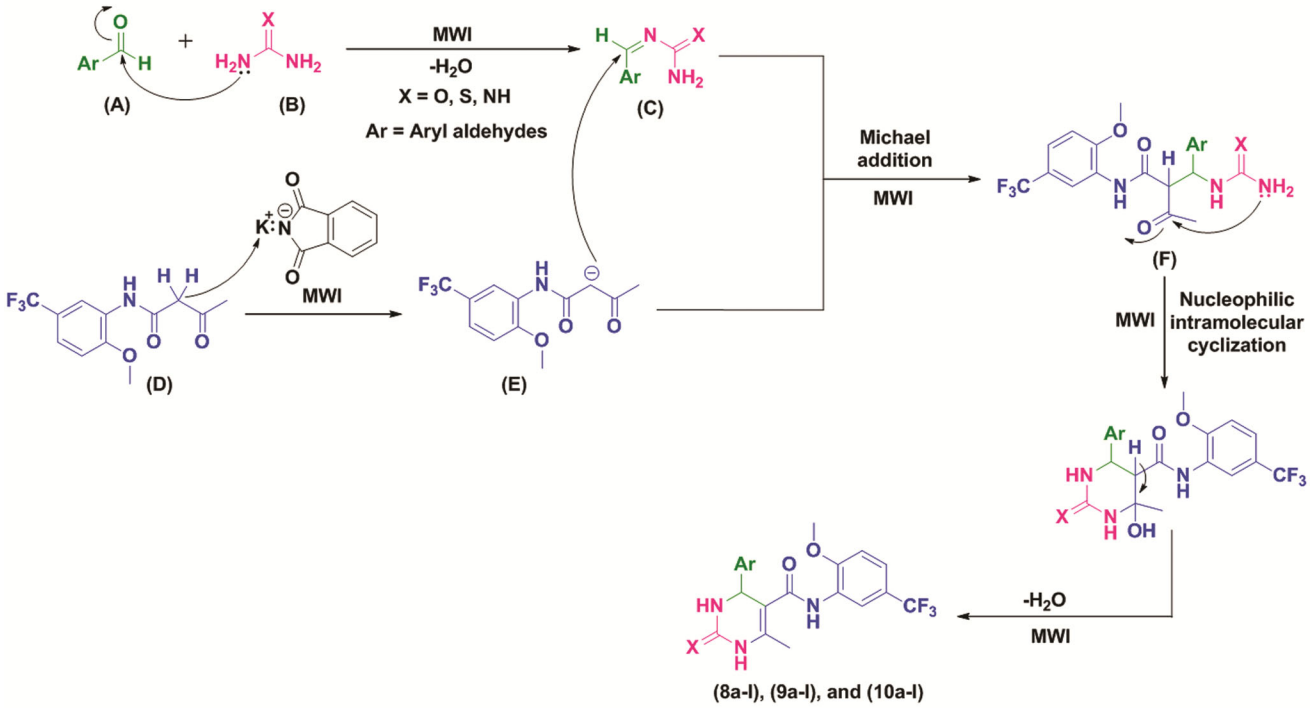


Entry	Compd	R	X	Time (min)	Yield (%)[a]	m.p. (°C)
1	**8a**	H	O	10	93	241-243
2	**8b**	2-Br	O	12	89	253-254
3	**8c**	4-F	O	10	92	212-214
4	**8d**	4-OMe	O	10	94	230-231
5	**8e**	2-Cl-4-OH	O	12	88	228-230
6	**8f**	2-Cl-4-OMe	O	11	91	211-212
7	**8g**	2-Br-4-F	O	12	89	225-227
8	**8h**	2-Cl	O	12	87	202-204
9	**8i**	4-Cl	O	10	94	217-219
10	**8j**	4-Me	O	11	93	223-225
11	**8k**	4-NO_2	O	12	91	242-244
12	**8l**	2-Cl-4-NO_2	O	12	88	239-241
13	**9a**	H	S	11	94	221-222
14	**9b**	2-Br	S	12	90	235-236
15	**9c**	4-F	S	10	92	218-220
16	**9d**	4-OMe	S	11	94	227-229
17	**9e**	2-Cl-4-OH	S	12	89	241-242
18	**9f**	2-Cl-4-OMe	S	11	90	213-215
19	**9g**	2-Br-4-F	S	12	88	238-240
20	**9h**	2-Cl	S	12	87	219-220
21	**9i**	4-Cl	S	10	94	228-229
22	**9j**	4-Me	S	11	92	226-228
23	**9k**	4-NO_2	S	12	91	244-245
24	**9l**	2-Cl-4-NO_2	S	12	89	237-239
25	**10a**	H	NH	11	94	232-234
26	**10b**	2-Br	NH	12	90	248-249
27	**10c**	4-F	NH	10	92	228-230
28	**10d**	4-OMe	NH	10	94	223-224
29	**10e**	2-Cl-4-OH	NH	12	89	236-238
30	**10f**	2-Cl-4-OMe	NH	11	90	222-223
31	**10g**	2-Br-4-F	NH	12	88	238-240
32	**10h**	2-Cl	NH	12	87	240-241
33	**10i**	4-Cl	NH	10	94	216-218
34	**10j**	4-Me	NH	10	93	225-227
35	**10k**	4-NO_2	NH	12	91	231-233
36	**10l**	2-Cl-4-NO_2	NH	12	88	237-239

[a] Isolated yield

A plausible mechanism for the formation of 3,4-dihydropyrimidinone/thione/imine derivatives **8a-l**, **9a-l** and **10a-l** is shown in Scheme 2.

Following dehydration, aldehyde (**A**) was condensed with urea, thiourea, or guanidine hydrochloride hydrochloride (**B**), yielding an imine intermediate (**C**). The oxyanion intermediate (**E**) is formed when PPI removes acidic hydrogen of CH_2 group of *N*-(2-methoxy-5-(trifluoromethyl)phenyl)-3-oxobutanamide (**D**). Finally intermediate (**E**) reacted with intermediate (**C**) through a Michael addition reaction to formed intermediate (**F**). The target compounds **8a-l**, **9a-l** and **10a-l** were produced by the intramolecular cyclization and dehydration intermediate (**F**).



Scheme 2 — Proposed reaction mechanism

IR spectra showed characteristic NH starching peaks nearer 3120 and 3340 cm^{-1} is corresponding to two -NH starching peaks. In addition, C-H starching peaks nearer 3070 cm^{-1} is corresponding to -CH_3 group. In addition, C=O starching peaks nearer 1620 cm^{-1} is corresponding to –CONH2 group. Furthermore, In addition, C-F starching peaks nearer 1250 cm^{-1} is corresponding to -CF_3 group. The ^{1}H NMR spectrum exhibited a singlet nearer 2.2 ppm, which indicated a proton of the dihydropyrimidine-CH_3, while singlet nearer 5.6 ppm, which indicated a proton of the dihydropyrimidine-ring-CH. In addition, one singlet nearer 3.8 ppm indicated three protons of -OCH_3 group. In addition, peaks between 6.8 and 8.5 ppm were observed for respective aromatic protons. Furthermore, singlet nearer 9.0 ppm indicated protons of CONH group, while singlet nearer 10 ppm, which indicated a proton of the -NH. The ESI-MS spectra of compounds **8a-l**, **9a-l** and **10a-l** show corresponding $(M+1)^+$ peak as well as $(M+2)^+$ in case of chloro and bromo substituted derivatives.

Using the model reaction, the reusability of the catalyst was also investigated. The filtrate containing the PPI catalyst was subjected to evaporation under reduced pressure after the product was separated by filtration, and the solid was recovered. The recycled

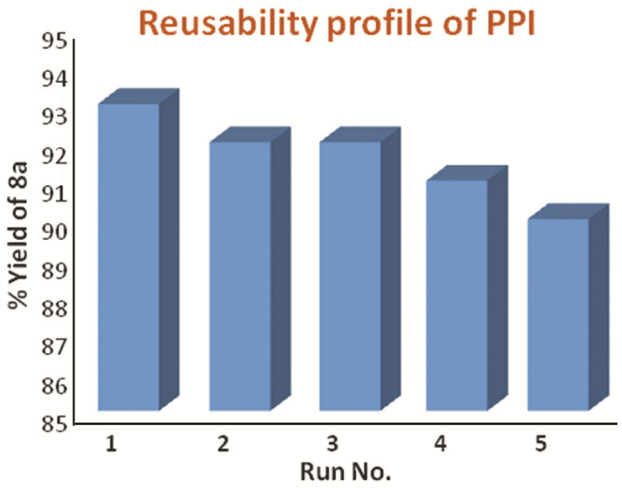


Fig. 2 — Reusability profile of PPI

solid catalyst was employed for five consecutive runs of the same model reaction under optimum conditions using the same solid catalyst (Fig. 2). The decrease in yield is most likely due to a modest loss in the catalyst's catalytic efficiency or a reduction in the amount of catalyst recovery owing to the handling.

Antimicrobial activity

In vitro antibacterial activity

The antibacterial activity of all newly synthesized scaffolds was tested *in vitro* (Table 5). In comparison

Table 5 — *In vitro* antibacterial activity of 3,4-dihydropyrimidinone/thione/imine derivatives **8a-l**, **9a-l** and **10a-l**

	MIC (μg/mL)			
Compd	*E.coli* MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenus* MTCC 442
8a	125	200	250	200
8b	200	250	200	250
8c	100	125	50	100
8d	62.5	100	50	100
8e	100	100	100	125
8f	62.5	62.5	25	62.5
8g	100	100	100	125
8h	62.5	125	100	200
8i	125	100	62.5	100
8j	100	125	100	200
8k	250	200	250	125
8l	200	250	200	200
9a	200	250	200	200
9b	250	200	200	250
9c	100	100	100	100
9d	62.5	62.5	50	62.5
9e	100	125	62.5	100
9f	62.5	100	25	62.5
9g	125	100	125	100
9h	125	125	100	62.5
9i	100	100	62.5	100
9j	125	125	125	100
9k	250	200	200	250
9l	200	250	250	200
10a	100	200	100	200
10b	200	125	200	250
10c	200	100	200	125
10d	100	62.5	50	100
10e	125	125	100	62.5
10f	62.5	100	50	100
10g	125	200	200	125
10h	100	100	100	100
10i	100	125	100	200
10j	125	200	200	125
10k	200	200	250	200
10l	125	250	200	200
Ampicillin	100	100	250	100
Ciprofloxacin	25	25	50	50
Chloramphenicol	50	50	50	50

to standard antibiotics, the bioassay study revealed that 3,4-dihydropyrimidinone/thione/imine derivatives **8a-l**, **9a-l** and **10a-l** showed outstanding effectiveness against the all investigated bacteria. In general, most of the substances examined were more effective against both Gram-positive and Gram-negative bacteria (Fig. 3, Fig. 4, and Fig. 5).

The Gram-positive bacterial strain with the highest sensitivity to the compounds investigated was *S. aureus*. Furthermore, when compared to Ciprofloxacin (MIC = 25 μg/mL), compounds **8f** and **9f** with electron donating groups (-Cl & -OMe) on the aryl ring demonstrated exceptional inhibitory efficacy against gram positive *S. aureus* bacteria at the lowest minimum inhibitory concentration (MIC) of 25 μg/mL. Furthermore, compounds **8c, 8d, 9d, 10d**,and **10f**(containing electron-rich groups on the aryl ring such as -Cl, -F, -OH, -OMe) showed outstanding efficacy with MIC values of 50 μg/mL against *S. aureus* when compared to standard drug Ampicillin, as well as equipotent activity when compared to standard drugs Chloramphenicol (MIC = 50 μg/mL) and Ciprofloxacin (MIC = 50 μg/mL).

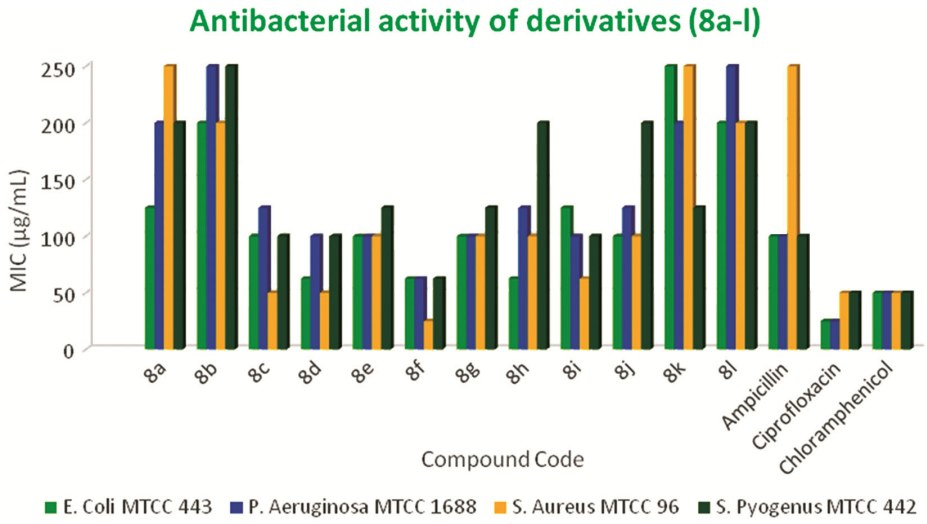


Fig. 3 — Antibacterial activity of 3,4-dihydropyrimidinone **8a-l**

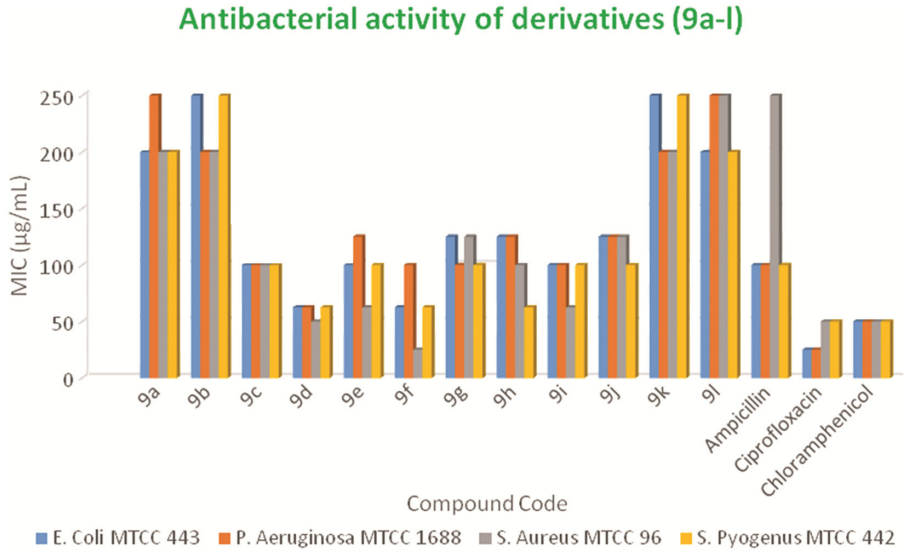


Fig. 4 — Antibacterial activity of 3,4-dihydropyrimidinone **9a-l**

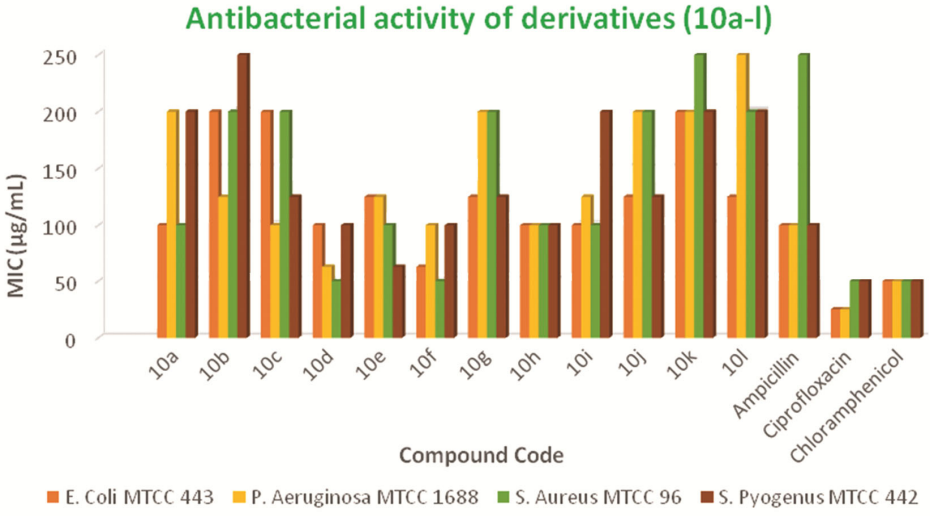


Fig. 5 — Antibacterial activity of 3,4-dihydropyrimidinone **10a-l**

Additionally, derivatives **8i**, **9e**, and **9i** having electron donating substituents on the aryl ring showed good efficacy against *S. aureus* bacteria, with MIC = 62.5 μg/mL, which is better than Ampicillin (MIC = 250 μg/mL). Furthermore, the majority of the compounds had good antibacterial efficacy against *S. aureus*, with MIC values ranging from 100 to 250 μg/mL.

Furthermore, when compared to the common antibiotic Ampicillin, analogues **8f**, **9d**, **9f**, **9h**, and **10e** (MIC = 62.5 μg/mL) showed outstanding efficiency against *S. pyogenes*. Furthermore, the examined derivatives **8c**, **8d**, **8i**, **9c**, **9e**, **9g**, **9i**, **9j**, **10d**, **10f**, and **10h** were found to be equally effective against S. pyogenes as Ampicillin (MIC = 100 μg/mL), but 50% less effective than Ciprofloxacin (MIC = 50 μg/mL) and Chloramphenicol (MIC = 50 μg/mL). Other compounds examined demonstrated relatively moderate activity against *S. pyogenes*.

Antibacterial activity of all developed compounds against the two Gram-negative pathogens studied revealed that analogues **8d**, **8f**, **8h**, **9d**, **9f**, and **10f** (MIC = 62.5 μg/mL) were more effective against *E. coli* than Ampicillin (MIC = 100 μg/mL). Furthermore, the derivatives **8c**, **8e**, **8g**, **8j**, **9c**, **9e**, **9i**, **10a**, **10d**, **10h**,and **10i** with MIC = 100 μg/mL were similarly effective against *E. coli* as Ampicillin (MIC = 100 μg/mL), but 50% less potent than Chloramphenicol (MIC = 50 μg/mL). Furthermore, the rest of the compounds had moderate antibacterial efficacy against *E. coli*, with MIC values ranging from 125 to 250 μg/mL.Furthermore, when compared to the standard antibiotic Ampicillin (MIC = 100 μg/mL), compounds **8f, 9d, and 10d** (MIC = 62.5 μg/mL) demonstrated excellent potency against *P. Aeruginosa* strain. Furthermore, when compared to Ampicillin (MIC = 100 μg/mL), compounds **8d**, **8e**, **8g**, **8i**, **9c**, **9f**, **9g**, **9i**, **10c**, **10f**, and **10h** showed good activity with MIC values of 100 μg/mL against gram negative *P. Aeruginosa* bacterial strain.

In vitro antifungal activity

According to results revealed from antifungal activity, all of the screened compounds **8a-l**, **9a-l** and **10a-l** exhibited sensitivity to *C. albicans* strains, while certain variants showed activity against the other two fungal strains (Table 6).

Table 6 — *In vitro* antifungal activity of 3,4-dihydropyrimidinone/thione/imine derivatives **8a-l**, **9a-l** and **10a-l**

Compd	MIC (μg/mL)		
	C. albicans MTCC 227	A. *niger* MTCC 282	A. *clavatus* MTCC 1323
8a	1000	250	1000
8b	500	500	250
8c	500	1000	500
8d	200	200	1000
8e	500	500	250
8f	1000	1000	500
8g	200	250	1000
8h	500	1000	1000
8i	250	500	500
8j	500	250	500
8k	100	500	250
8l	200	1000	100
9a	500	500	500
9b	500	200	1000
9c	250	250	500
9d	500	250	250
9e	1000	500	250
9f	500	1000	1000
9g	250	500	1000
9h	500	250	500
9i	250	250	250
9j	200	500	250
9k	200	250	250
9l	100	100	200

(*Contd*.)

Table 6 — *In vitro* antifungal activity of 3,4-dihydropyrimidinone/thione/imine derivatives **8a-l**, **9a-l** and **10a-l** — (*Contd.*)

Compd	MIC (µg/mL)		
	C. albicans MTCC 227	A. *niger* MTCC 282	A. *clavatus* MTCC 1323
10a	500	200	250
10b	500	1000	500
10c	250	250	250
10d	200	500	250
10e	250	1000	1000
10f	500	500	1000
10g	250	200	500
10h	200	500	500
10i	500	500	1000
10j	500	1000	500
10k	100	100	200
10l	200	250	500
Nystatin	100	100	100
Greseofulvin	500	100	100

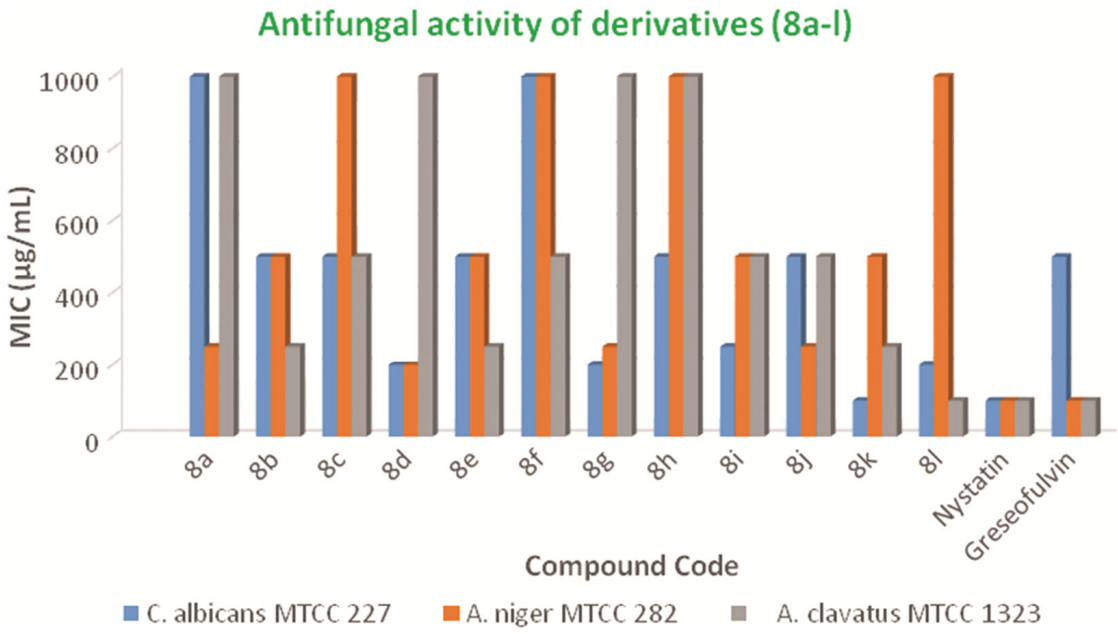


Fig. 6 — Antifungal activity of 3,4-dihydropyrimidinone **8a-l**

When compared to the standard medicine Greseofulvin (MIC = 500 g/mL) and Nystain (MIC = 100 g/mL), derivatives **8k**, **9l**, and **10k** showed excellent effectiveness against *C. albicans*. Furthermore, when compared to the reference medication Greseofulvin, compounds **8d**, **8k**, **8l**, **9j**, **9k**, **10d**, **10h**, and **10l** showed good potency with MIC = 200 g/mL against *C. albicans*. The remaining compounds, on the other hand, have moderate activity against *Candida albicans*, with MIC values ranging from 250 to 1000 g/mL (Fig. 6). Additionally, derivatives **9l**,and **10k** possessing electron-withdrawing -NO_2 group on aryl ring (MIC = 100 µg/mL) displayed equipotent activity compared to both standard drugs Nystain and Greseofulvin against the *A. niger* strain. Likewise, analogue**8l** possessing electron-withdrawing -NO_2 group on aryl ring (MIC = 100 µg/mL) displayed equipotent activity compared to both standard drugs Nystain and Greseofulvin against the *A. clavatus* strain.Furthermore, the rest of the compounds had moderate antibacterial efficacy against *A. niger* and *A. Clavatus* (Fig. 7 and Fig. 8).

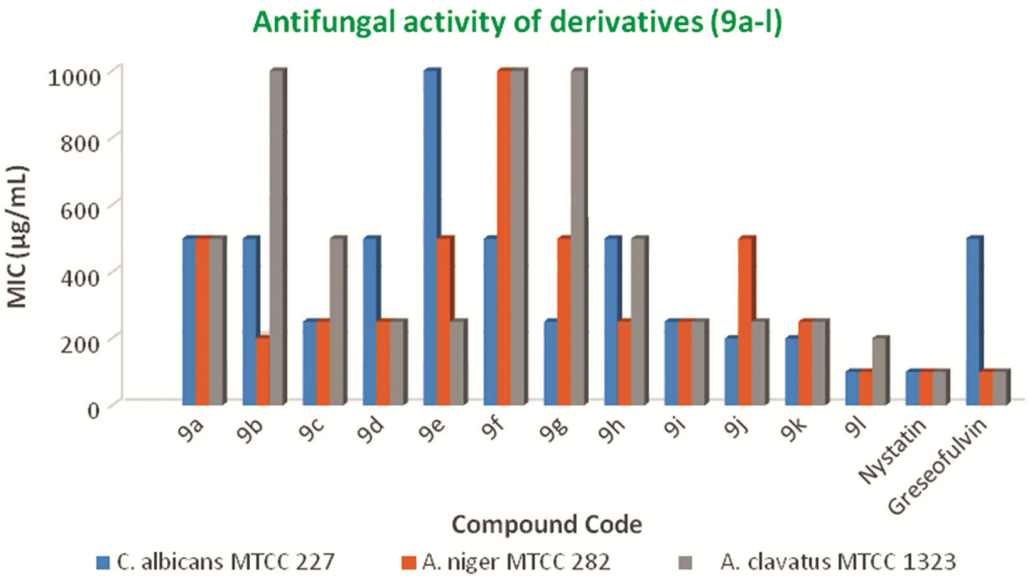


Fig. 7 — Antifungal activity of 3,4-dihydropyrimidinone **9a-l**

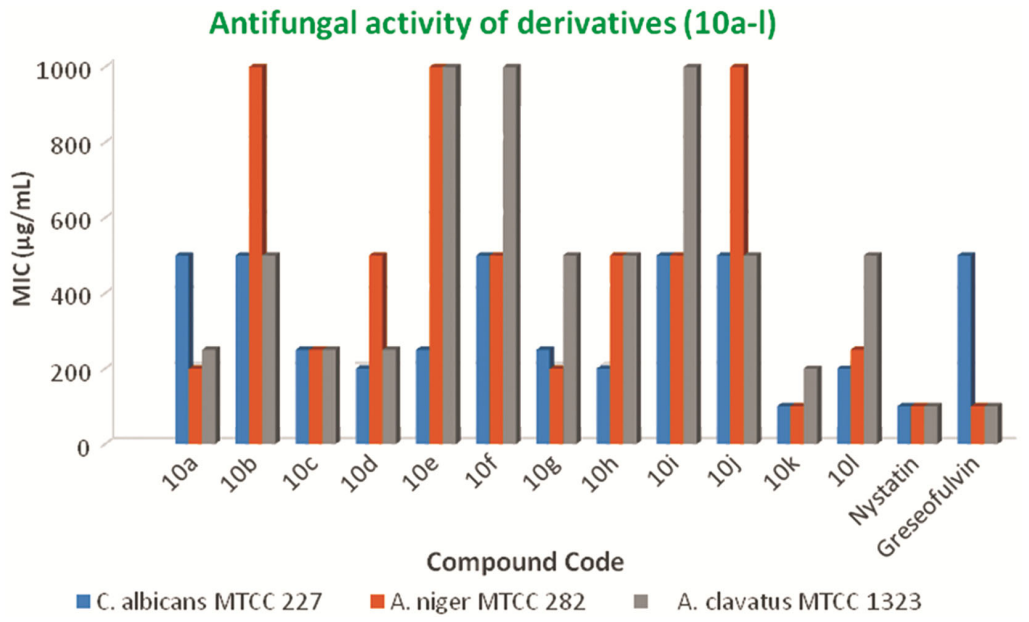


Fig. 8 — Antifungal activity of 3,4-dihydropyrimidinone **10a-l**

Conclusions

Finally, using PPI as an environmentally friendly solid and biodegradable organocatalyst under solvent-free conditions, a simple, one-pot, and efficient procedure for the synthesis of novel -CF_3 functional group containing 3,4-dihydropyrimidinone/thione/imine derivatives **8a-l**, **9a-l** and **10a-l** has been developed. The reusability of the PPI, microwave heating, ease of workup procedure, and avoidance of harmful organic solvents, safety and cleanliness, and great yields of the end products are all notable advantages of this approach. The 3,4-dihydro-pyrimidinone/thione/imine derivatives **8d**, **8f**, **8h**, **9d**, **9f**, and **10f** had excellent antibacterial activity against *E. coli*, *S. aureus*, *S. pyogenes*, and *P. aeruginosa*, whereas the derivatives **9l** and **10k** had excellent antifungal activity against *C. albicans*, *A. niger*, and *A. clavatus*.

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