Efficient Rapid Access to Biginelli for the Multicomponent Synthesis of 1,2,3,4-Tetrahydropyrimidines in Room-Temperature Diisopropyl Ethyl Ammonium Acetate

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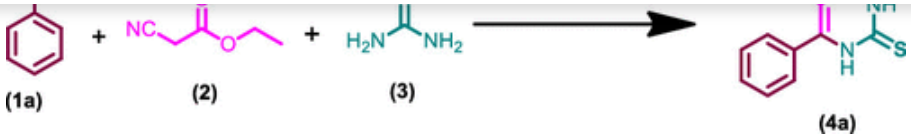
Abstract

The diisopropyl ethyl ammonium acetate (DIPEAc)-promoted Biginelli protocol has been developed for the first time by a successive one-pot three-component reaction of aldehydes, ethylcyanoacetate/ethyl acetoacetate, and thiourea/urea to afford pharmacologically promising 1,2,3,4-tetrahydropyrimidines in high yields at room temperature. The key benefits of the present scheme are the capability to allow a variability of functional groups, short reaction times, easy workup, high yields, recyclability of the catalyst, and solvent-free conditions, thus providing economic and environmental advantages. In addition, a series of 4-oxo-6-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles analogues were synthesized and selected for their in vitro antifungal and antibacterial activities.

Introduction

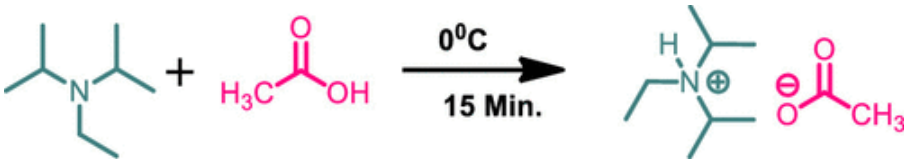
Jump To

Room-temperature ionic liquids (RTILs) have taken the attention of the chemical community all over the globe as a green alternative option to traditional ecofriendly media for catalysis, synthesis, separation, and other several chemical tasks. (1−7) RTILs include numerous exclusive properties, such as extensive liquid range, nonvolatility, low toxicity, high thermal stability, noncombustible, excellent solubility, and recyclability. (8) RTILs act as “neoteric solvents” for a wide range of industrial and chemical processes. In recent times, RTILs have been originating to be valuable as environmental friendly media for multitudinous organic revolutions. (9,10) On the other hand, multicomponent reactions (MCRs) are one of the more dominant and practical tackles in organic synthesis for the creation of pharmacologically relevant frameworks from the point of view of green chemistry. MCRs give benefits of atom economy, high yields, flexibility, target specificity, and especially one-pot operation; (11−13) the discrimination and returns of the MCRs are significantly affected by the choice of an appropriate catalyst. Thus, the introduction of a dynamic, inexpensive, mild, and environmental friendly catalyst for significant MCRs superior to analogues of pharmaceutical and biological prominence is in demand. In this paper, we have



Scheme 1. Synthesis of 4-Oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**4a**) by Using DIPEAc as RTIL

Scheme 2



Scheme 2. Synthesis of Diisopropylethylammonium Acetate (DIPEAc)

The pyrimidine moiety is an essential part of RNA and DNA, providing various biological properties such as potent fungicide and bactericide. (14) Some pyrimidine analogues are also known to acquire anticancer, (15) antimalarial, (16) antiviral, (17) antibacterial, (18,19) antifungal, (20,21) anticonvulsant, (22) and antihistamine (23) activities. Certain 3,4-dihydropyrimidines have developed as essential props of numerous calcium antihypertensive agents, adrenergic, channel blockers, and neuropeptide antagonists. (24) A number of natural marine products accommodate the 3,4-dihydropyrimidine nucleus, described in the literature for remarkable anti-HIV alkaloid batzelladine B activities (Figure 1). (25,26)

Thus, the enlargement of synthetic strategies for the creation of this molecule using an inexpensive, reusable, mild, and nontoxic catalyst is of enormous significance from the industrial and academic points of view. Even though various modes have been reported in the literature, the Biginelli MCR is moderately versatile because it can be implemented with numerous chemical takes in all three key components (i.e., aldehyde, β-ketoester, and thiourea or urea) paramount to a manifold of thiones/dihydropyrimidinones. (27) These reactions can be accomplished under a variability of tentative conditions, and several improvements have been reported in recent years, such as *p*-TsOH·H_2O, (28) H_3BO_3, (29) $[Al(H_2O)_6](BF_4)_3$, (30) thiamine hydrochloride, (31) imidazole-1-yl-acetic acid, (32) l-(+)-tartaric acid-dimethylurea, (32) $HClO_4$–SiO_2, (33,34) $SnCl_2·2H_2O$, (35) polymer-supported benzimidazolium-based ionic liquid, (36) basic IL, (37) Al-plante MCM-41, (38) $(NH_4)_2CO_3$, (39) $CeCl_3·7H_2O$, (40) $CaCl_2$, (39) $Ce(NH_4)_2(NO_3)_6$polyvinylsulfonic acid, (34) and $Fe(OTs)_3·6H_2O$. (41) However, numerous of these testified methods become infected with several disadvantages such as strong acidic conditions, use of hazardous or costly reagents, long reaction times, low yields of

component method in DIPEAc at room temperature to access a library of 1,2,3,4-tetrahydropyrimidine in good to excellent yields.

Results and Discussion

Jump To

Chemistry

To achieve optimized conditions for the Biginelli protocol based on the reaction of benzaldehyde (**1a**) (3 mmol), ethylcyanoacetate (**2**) (3 mmol), and thiourea (**3**) (3.2 mmol) as model substrates, we checked altered catalysts, temperatures, and solvents, and the results of this study are summarized in Table 1. It was found that when the reaction was carried out in the nonappearance of the catalyst in ethanol, no product was perceived, even after 9 h (Table 1, entry 1). To obtain the preferred product (**4a**), we tested the reaction using different catalysts such as Cs_2CO_3, *p*-TSA, β-CD, CTAB, SDS, ChCl:2urea, ChCl:2$ZnCl_2$, PEG-400, DIPEAc, and dicationic ionic liquid (Table 1, entries 2–11). Thus, room-temperature DIPEAc as the pre-eminent catalyst was tested for this reaction. In the presence of DIPEAc, compound **4a** was isolated in 93% yield after only 45 min at room temperature. The model reaction in water using phase transfer catalysts is found to be sluggish and formed the desired **4a** in less yields. Therefore, it can be thought that DIPEAc is green and a superior solvent and catalyst compared to the others shown in Table 1.

Table 1. Efficiency Comparison of Various Catalysts for the Synthesis of 4-Oxo-6-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4a)[a]

entry	catalyst	medium	time	yield[b] (%)/time (h)
1		EtOH	9 h	trace
2	Cs_2CO_3	EtOH	7 h	61
3	*p*-TSA	H_2O	7 h	68
4	β-CD	H_2O	6 h	65
5	CTAB	H_2O	6 h	59
6	SDS	H_2O	6 h	52

11	dicationic ionic liquid	dicationic ionic liquid	7 h	73

[a]Reaction conditions: aldehyde (3 mmol), ethylcyanoacetate (3 mmol), thiourea (3.2 mmol) in medium (5 mL), stirred at room temperature.
[b]Isolated yields b: no condensation. Bold values are for highlighting the good result.

The amount of the catalyst is another critical parameter in terms of reaction efficiency. To confirm the amount of the DIPEAc, the model reaction was examined by a set of experiments by the varying amounts from 1 to 5 mL; as the amount of DIPEAc increases gradually, a steady increase was observed in the product yield. DIPEAc (4 mL) furnishes **4a** in 96% yield at room temperature (Table 2, entries 1). Further increase in the amount of DIPEAc does not increase in the yield of the product. The model reaction was carried out without any catalyst and solvent; the trace amount of the product was achieved after a long period (Table 2, entry 1). Further, the efficiency of DIPEAc was checked by using 20 mol % DIPEAc in various solvents (Table 2, entries 7–12). In ethanol, the reaction takes place smoothly with high yield. While in water, MeOH, acetonitrile, DCM, CH_2Cl_2, and DMF reaction proceeds with lower yields at reflux temperature. None of the solvents exist the advantage of time and yield over the solvent-free condition. Hence, the solvent-free condition was regarded as the finest for the cost and environmental suitability.

Table 2. Solvent Effects on the Reaction of Aldehyde, Ethylcyanoacetate, and Thiourea for the Synthesis of 4-Oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4a)[a]

entry	DIPEAc	temp. (°C)	solvent	time (min)	yield (%)[b]
1	0	RT		24h	trace
2	1 mL	RT		45	60
3	2 mL	RT		45	75
4	3 mL	RT		45	80
5	4 mL	**RT**		**45**	**96**
6	5 mL	RT		45	95

11	20 mol %	reflux	CH_2Cl_2	320	52
12	20 mol %	reflux	DMF	320	50

[a]Reaction conditions: aldehyde (3 mmol), ethylcyanoacetate (3 mmol),thiourea (3.2 mmol) in solvent (5 mL), stirred at room temp.
[b]Isolated yields. Bold values are for highlighting the good result.

In summary, the highest efficiency and fastest reaction time for the model Biginelli reaction was observed at room temperature by using 4 mL of DIPEAc. Having ideal conditions in hand, the adaptability of the protocol was examined for the construction of 4-oxo-6-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (**4a–v**). Various substituents on aldehyde including methyl, methoxy, cyano, nitro, halogen (−Cl, −F, −Br), and hydroxyl moieties were used. The results of all reactions performed under these conditions are shown in Table 3. Aldehyde containing electron-donating groups such as −Me, −OMe, and electron-withdrawing group such as $-NO_2$ on the aromatic ring was compatible with this transformation, and corresponding 4-oxo-6-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (**4a–v**) were obtained in good to high yields. To our enchantment, halogen-substituted 2-benzylidene malononitrile gave the products with high yields (**4g**, **4h**, and **4l**). Moreover, sterically crowded di- and trisubstituted benzaldehyde provided the desired products in high yields (**4i**, **4j**, and **4r**). The heteroaryl aldehydes and aliphatic aldehydes also keep well under the present reaction conditions without any difficulties (**4m**, **4t**, and **4w–4zz**).

Table 3. Recycling of DIPEAc (IL) for The Synthesis of Compounds 4a and 4aa[a]

run	catalyst recovery	product yield (%)
1	96	96
2	92	93
3	91	90
4	90	89
5	80	78

The Biginelli formation of 1,2,3,4-tetrahydropyrimidine derivatives has been confirmed by spectroscopic techniques and physical data such as IR, ^{1}H NMR, ^{13}C NMR, and liquid chromatography–mass spectrometry (LCMS). According to the ^{1}H NMR spectrum of representative compound **4a**, the characteristic two singlet's at 11.71 and 8.96 for two protons of −NH group present in pyrimidine ring, 7.52–7.56 ppm and a doublet at 7.78–7.81 four protons present in phenyl ring confirmed the **4a**. ^{13}C NMR spectral data, in which the carbon signals of $-SCH_2$ and $-NCH_2$ groups, were resonated at 183.29 and 183.53 ppm, respectively. The signals at 166.22 point out the presence of the carbonyl carbon atom, while all further carbons gave peaks at expected values. Again, the construction of compound **4a** was confirmed by LCMS: *m*/*z* [M + Na]$^{+}$. The calculated *m*/*z* for compound **4a** $C_{11}H_7N_3OSNa^{+}$ is 252.2 and observed at 252.2 [M + Na]$^{+}$.

Figure 1

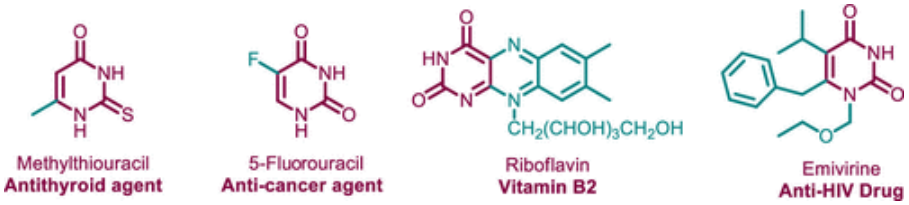


Figure 1. Pyrimidine-incorporated bioactive molecules.

Recycling of the Catalyst

Effectual reusability and recovery of the ionic liquid are other significant features of our proposed protocol. We check the reusability of the catalyst. The reaction was performed between aldehyde, ethylcyanoacetate, and thiourea under the optimized reaction conditions. DIPEAc was disconnected from the reaction mixture by the following procedure. After completion of the reaction, the reaction mixture was cooled to room temperature, and then, water and ethyl acetate were added. The product (**4a**) was extracted with ethyl acetate. As the DIPEAc is highly water-soluble, it goes into the aqueous layer. Evaporation of the aqueous layer under reduced pressure provided the catalyst (DIPEAc). Recyclability graph of catalytic efficiency of DIPEAc was tested for four consecutive cycles; the isolated yields were almost alike until the fourth recycling (Figure 2), but a reduction in the catalytic activity of DIPEAc was observed after the fifth cycle; the outcomes are summarized in Table 3. Furthermore, in order to explore the stability of DIPEAc during four consecutive runs, the IR spectra of the recovered DIPEAc (after four cycles) were matched with those of the fresh sample. As documented in Figure 3, the IR spectra displayed by the recovered catalyst were found to be almost similar to the fresh one.

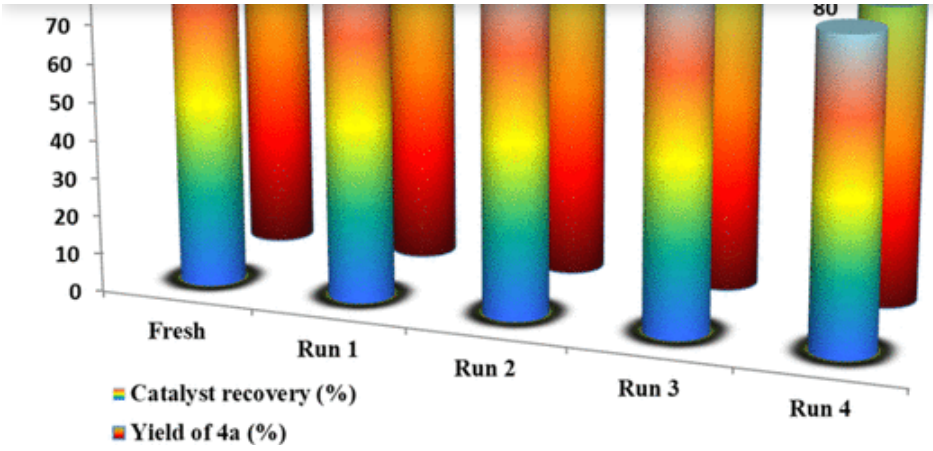


Figure 2. Reuse and recovery of DIPEAc and its effect on yield.

Figure 3

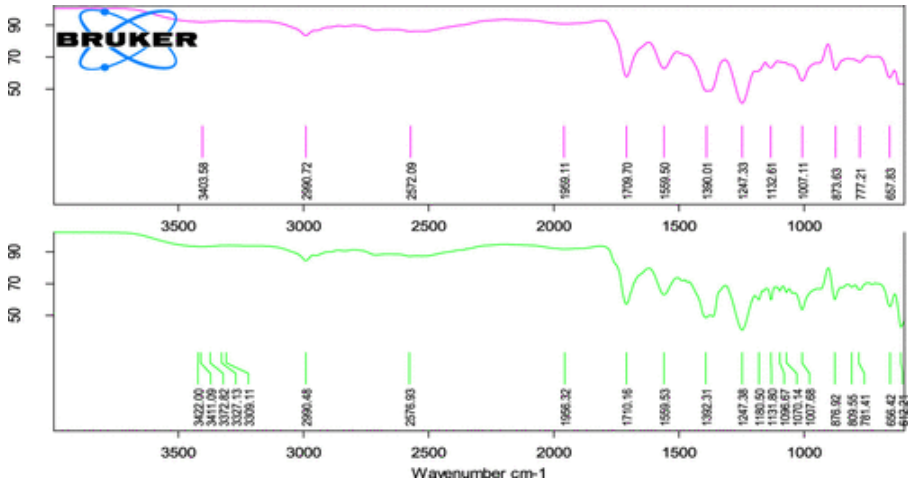


Figure 3. IR spectrum of reuse and recovery of DIPEAc (pink spectrum: fresh; green spectrum: after IV recycles).

Figure 4

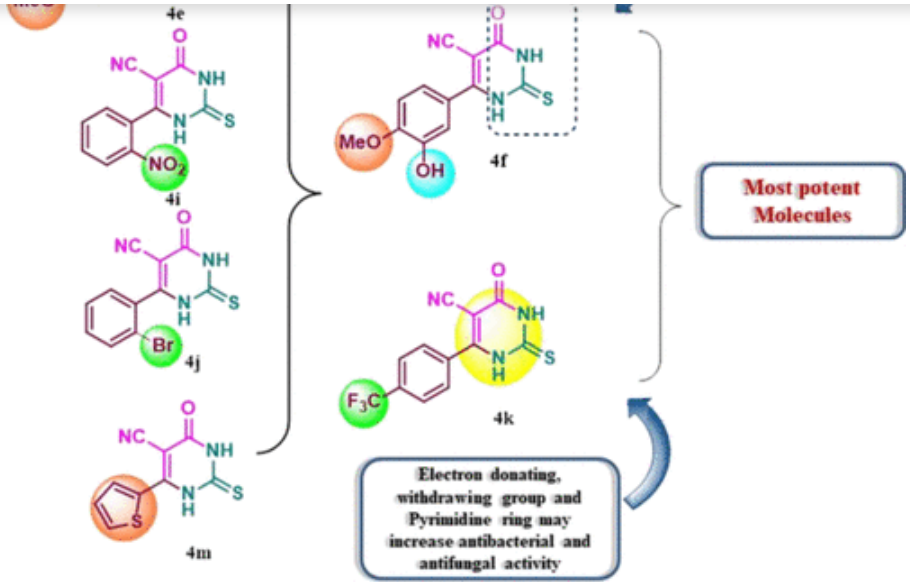


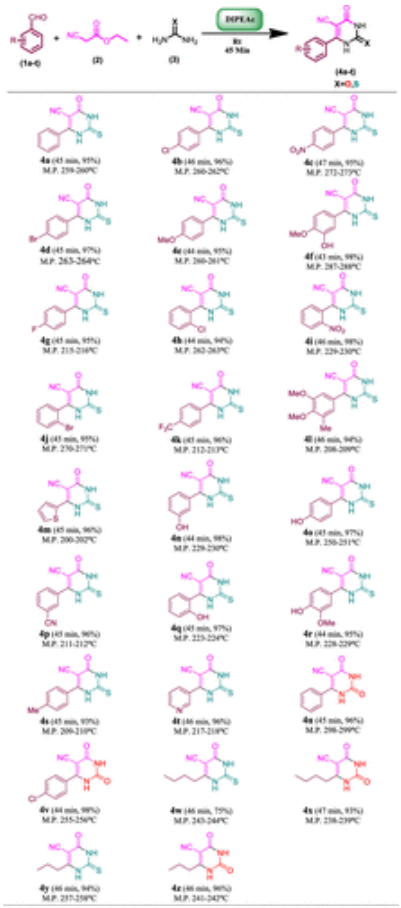
Figure 4. Structure–activity relationship of hybrid compounds.

Plausible Reaction Mechanism

To explain the mechanism of this one-pot three-component cyclocondensation leading to 1,2,3,4-tetrahydropyrimidine is accredited to the exclusive role of DIPEAc as a medium. It has the capacity to dissolve a number of inorganic/organic solutes readily. This might sensibly maintain the high concentrations of the reactants while initiating the reaction and even the progress of the reaction. Hence high to saturate the solutions of the reactants in the reaction mass would be responsible for degree acceleration of Biginelli reaction.

The stronger hydrogen bonding capability of DIPEAc and the motives for this could be elucidated as follows: (1) The use of DIPEAc elevated the solubility of reactants, which leads to superior interfacial area and lower mass transfer resistance. (43) (2) The stimulating effects of DIPEAc to the reaction could be endorsed to its polarity, hydrobonding, and hydrophobic effects. (44) Hydrophobic effect: The hydrophobic effect leads to extraordinary negative volume of initiation which means better stabilization of activated complexes than hydrophobic reactants in the reaction. Polarity effect: The high polarity of DIPEAc outcomes in the extra polar interpreted states than primary states, so the reaction promptness can be improved. Hydrogen-bonding effect: DIPEAc could initiate the reactants and intermediate products by forming the hydrogen bonds with the hydroxyl oxygen and carbonyl oxygen, respectively (Schemes 3and 4), constructing them easy to form consistent products. It was assumed that only polar protic solvents could give the preferred product, and the hydrogen-bonding effect is the core difference

Scheme 3



Scheme 3. Synthesis of 4-Oxo-6-aryl-2-thioxo-1,2,3,4-Tetrahydropyrimidine-5-carbonitriles (**4a–z**) by Using DIPEAc as RTIL[a]

[a] Reaction conditions: Aldehydes (**1a–z**) (3 mmol), ethylcyanoacetate/ethyl acetoacetate (3 mmol), and thiourea/urea (3.2 mmol) in DIPEAc (4 mL) stirred at room temp;

[b] isolated yields,

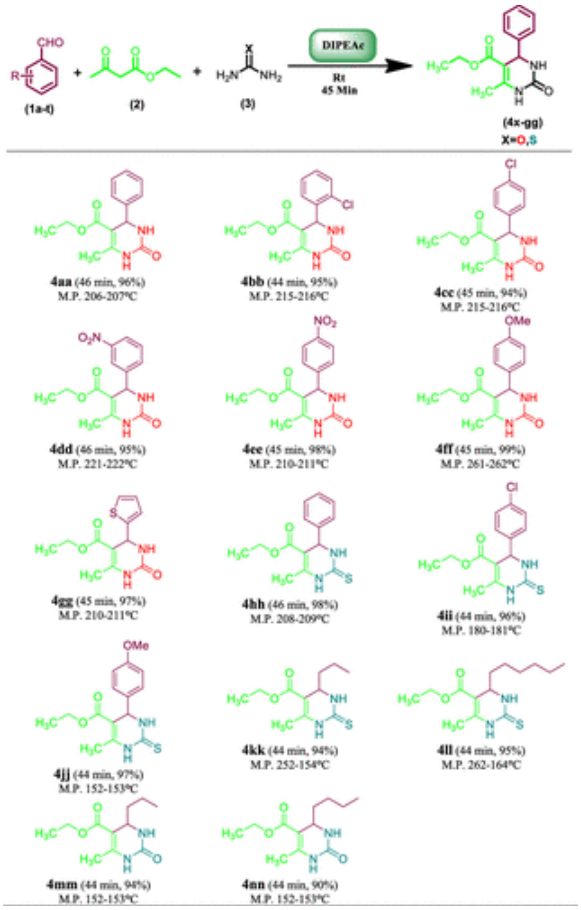
[c] melting points are in good contact with those reported in the literature. (36,50,51)

Antimicrobial Screening

Twenty analogues of 4-oxo-6-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (**4a–t**) were evaluated against four bacterial *Streptococcus pyogenes*, *Escherichia coli*,*S. aureus*, and *Pseudomonas aeruginosa*, and two fungal *C. Albicans* and *Aspergillus niger* strains. Ampicillin, rifampicin, and

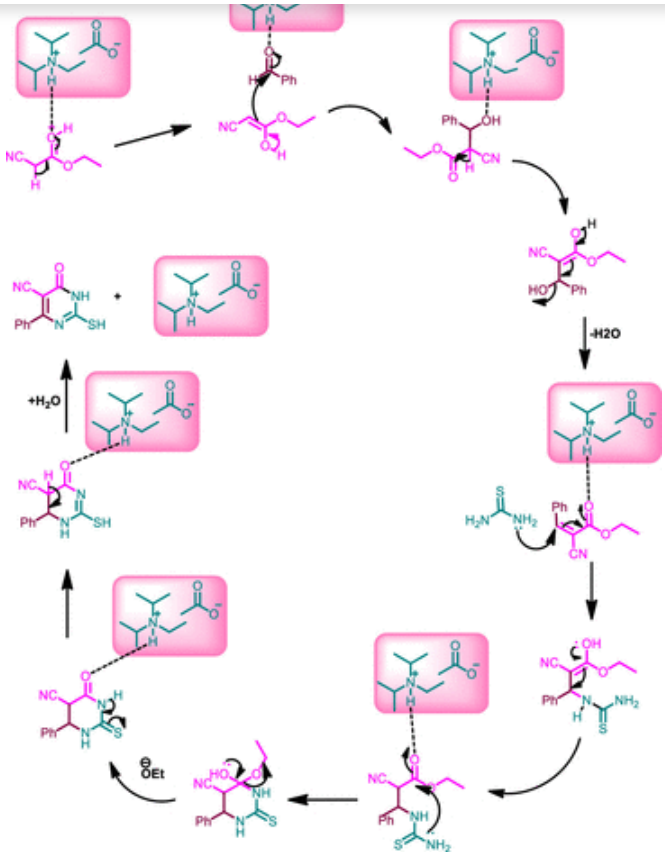
groups (−NO_2 and −CF_3) and electron-donating groups (−OH and −OCH_3) in the molecule (Figure 4). Compound **4f** showed good antibacterial activity against the Gram-positive strains, *P. aeruginosa*, *E. coli*, *Staphylococcus aureus*, and *S. pyogenes*. We imagine that the presence of −OH and −OCH_3 moieties in the molecule could contribute significantly to the antibacterial activities. Compound **4e** and **4i** showed decent antibacterial activity against *P. aeruginosa* and *E. coli* and less activity against *S. aureus*. Compounds **4e**, **4f**, **4i**, and **4n** showed decent antibacterial activity against all bacterial strains (Schemes 4 and 5).

Scheme 4



Scheme 4. Synthesis of Ethyl 6-Methyl-2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidine-5-carboxylates (**4aa–nn**) by Using DIPEAc as RTIL[a]

[a] Reaction conditions: aldehyde (**1aa–nn**) (3 mmol), ethylcyanoacetate/ethyl acetoacetate (3 mmol), thiourea/urea (3.2 mmol) in DIPEAc (4 mL), stirred at room temp;



Scheme 5. 4-Oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile

Table 4. Antimicrobial Screening of 4-Oxo-6-aryl-2-thioxo-1,2,3,4-Tetrahydropyrimidine-5-carbonitriles (4a–t)[a]

	minimum inhibitory concentration (MIC) in μg/mL			
compound	***E. c.* MTCC (443)**	***P. a.* MTCC (1688)**	***S. a.* MTCC (96)**	***S. p.* MTCC (442)**
4a	500	100	250	250
4b	250	500	500	100
4c	100	100	100	100
4d	100	200	250	250

4g	500	100	500	250
4h	100	100	200	250
4i	**12.5**	**25**	100	**50**
4j	100	500	100	100
4k	500	500	500	250
4l	500	250	500	250
4m	100	100	250	**50**
4n	**25**	100	250	100
4o	**50**	100	100	100
4p	100	200	100	250
4q	200	100	250	200
4r	500	200	200	250
4s	250	500	100	500
4t	50	50	200	200
ampicillin	100	100	250	100
griseofulvin				

[a] *E. c.*, *Escherichia coli*; *P. a.*, *Pseudomonas aeruginosa*; *S. a.*,*Staphylococcus aureus*; *S. p.*, *Streptococcus pyogenes*; *C.a.*, *Candida albicans*; *A. n.*, *Aspergillus niger*.

Compounds 4-oxo-6-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (**4a–t**) were also screened for their in vitro antifungal activity against two fungal strains such as *A. niger* and *Candida albicans* by

In conclusion, an environmentally and highly efficient green methodology has been established for the synthesis of functionalized 1,2,3,4-tetrahydropyrimidine derivatives using an inexpensive and recoverable room-temperature DIPEAc catalytic solvent-free system. This, to the best of our knowledge, has no examples. This reaction scheme exposes a number of advantages, such as uniqueness, high atom efficiency, mild reaction conditions, clean reaction profiles, easy workup procedure, and ecofriendliness. Furthermore, the prevention of hazardous organic solvents during the entire procedure (synthesis, ionic liquid preparation, and workup procedure) makes it a convenient and attractive method for the synthesis of these important compounds. In addition, a series of 4-oxo-6-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles analogs were screened for their in vitro antifungal and antibacterial activities. The consequences exposed that compounds **4e**, **4f**, and **4i** presented better antibacterial potency which is equal to the reference drug ampicillin. Compounds **4j**, **4k**, and **4m** were originated to be decent antifungal activity matched to the standard drug griseofulvin.

Experimental Section

Jump To

Materials and Methods

All of the reagents used were of laboratory grade. Melting points of all of the synthesized analogues were resolute in an open capillary tube and are uncorrected. The progress of the reaction was monitored by thin-layer chromatography on Merck's silica plates, and imagining was accomplished by iodine/ultraviolet light. IR spectra were acquired on a Bruker ALPHA (Eco-ATR) spectrometer. ^{1}H NMR spectra were recorded with a Bruker AvIII HD-400 MHz spectrometer operating at 400 MHz using DMSO solvent and tetramethylsilane (TMS) as the internal standard and chemical shift in δ ppm. Mass spectra were recorded on a Waters UPLCTQD (ESI-MS and APCI-MS) instrument, and elemental analysis was recorded on the CHNS auto-analyzer (Thermo Fischer EA1112 SERIES). Chemical shifts (δ) are reported in parts per million using TMS as an internal standard. The splitting pattern abbreviations are designed as singlet (s); doublet (d); double doublet (dd); bs (broad singlet), triplet (t); quartet (q); and multiplets (m).

Preparation of DIPEAc

General Procedure for the Synthesis of Diisopropylethylammonium Acetate (DIPEAc)

A mixture of *N*,*N*-diisopropylethylamine (3 mmol) and acetic acid (3 mmol) was stirred at 0–10 °C for 20 min. The viscous liquid, diisopropylethylammonium acetate, was achieved. (48,49)

dried, and purified by crystallization using ethanol as a solvent. The result is summarized in Table 4. The synthesis compound is confirmed by mp, IR, NMR, and mass spectra.

Spectral Analysis of Compounds

4-Oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4a)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2221.12 (CN stretching), 1722.36 (C═O stretching), 3244.37 (N−H stretching), 1448.54 (C═C aromatic stretching), 2902.28 (C−H stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 11.71 (s, 1H, NH), 8.96 (s, 1H, NH), 7.78−7.81 (d, 2H, Ar−H), 7.11−7.15 (d, 2H, Ar−H), 7.54−7.56 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 85.12, 118.62, 123.66, 128.62, 130.59, 131.52, 136.68, 138.64, 139.10, 162.22, 166.22, 183.29, 183.53 mass (LCMS): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_7N_3OSNa^+$, 252.2; found, 252.2. Anal. Calcd for $C_{11}H_7N_3OS$: N, 18.33; C, 57.63; S, 13.98; H, 3.08. Found: N, 18.33; C, 57.63; S, 13.98; H, 3.09.

4-(4-Chlorophenyl)-2-mercapto-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4b)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2205.85 (CN stretching), 1629.96 (C═O stretching), 3115.80 (N−H stretching), 1461.01 (C═C aromatic stretching), 2893.47 (C−H stretching) 896.64 (C−Cl stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 11.72 (s, 1H, NH), 8.97 (s, 1H, NH), 7.48−7.52 (d, 2H, Ar−H), 7.21−7.26 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 85.12, 119.53, 128.26, 130.22, 134.73, 135.19, 136.92, 162.66, 166.35, 184.23 mass (LCMS): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_6ClN_3OSNa^+$, 286.7; found, 286.7. Anal. Calcd for $C_{11}H_6ClN_3OS$: N, 15.94; C, 50.10; S, 12.16; H, 2.29. Found: N, 15.94; C, 50.10; S, 12.16; H, 2.29.

6-(4-Nitrophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4c)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2220.80 (CN stretching), 1630.96 (C═O stretching), 3145.80 (N−H stretching), 1460.01 (C═C aromatic stretching), 2800.47 C−H stretching) 890.64 (C−NO_2 stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 8.1 (s, 1H, NH), 8.97 (s, 1H, NH), 7.48−7.52 (d, 2H, Ar−H), 7.21−7.26 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 74.7, 115.8, 123.3, 123.3, 134.73, 126.6, 126.6, 137.7, 147.1, 169.1; 166.9, 175.2 mass (LCMS): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_6N_4O_3SNa^+$, 297.2; found, 297.2. Anal. Calcd for $C_{11}H_6N_4O_3S$: N, 20.43; C, 48.17; S, 11.69; H, 2.21. Found: N, 20.50; C, 48.23; S, 20.45; H, 2.28.

6-(4-Bromophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4d)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2200.80 (CN stretching), 1640.69 (C═O stretching), 3145.80

IR (ATR, υ cm^{-1}) characteristic absorptions: 2260.00 (CN stretching), 1620.69 (C═O stretching), 3245.80 (N−H stretching), 1520.02 (C═C aromatic stretching), 2850.26 (C−H stretching) 2830.12 (O−CH_3 stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 11.66 (s, 1H, NH), 11.29 (s, 1H, NH), 7.52−7.54 (d, 2H, Ar−H), 6.94−6.98 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 55.08, 75.2, 115.8, 121.1, 123.7, 124.2, 129.8, 130.1, 159.8, 166.9, 169.1, 175.2 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_9N_3O_2SNa^+$, 282.3; found, 282.3. Anal. Calcd for $C_{12}H_9N_3O_2S$: N, 16.21; C, 55.59; S, 12.36; H, 3.50. Found: N, 16.24; C, 55.60; S, 12.35; H, 3.50.

6-(3-Hydroxy-4-methoxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4f)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2200.80 (CN stretching), 1640.69 (C═O stretching), 3145.80 (N−H stretching), 1564.02 (C═C aromatic stretching), 2800.38 (C−H stretching) 2815.15 (O−CH_3 stretching), 3305.10 (O−H stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 12.32 (s, 1H, NH), 11.99 (s, 1H, NH), 9.12 (s, 1H, OH), 7.12 (d, 1H, Ar−H), 6.69−6.76 (s, 2H, Ar−H), 3.80 (s, 3H, OCH_3), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 56.3, 74.7, 112.1, 113.2, 115.9, 122.3, 127.9, 147.3, 149.4, 166.9, 169.1, 175.2 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_9N_3O_3SNa^+$, 398.3; found, 398.3. Anal. Calcd for $C_{12}H_9N_3O_3S$: N, 15.26; C, 52.36; S, 11.65; H, 3.30. Found: N, 15.25; C, 52.35; S, 11.66; H, 3.52.

6-(4-Fluorophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4g)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2211.10 (CN stretching), 1640.69 (C═O stretching), 3250.80 (N−H stretching), 1540.02 (C═C aromatic stretching), 2790.26 (C−H stretching) 1250.11 (C−F stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 12.33 (s, 1H, NH), 12.39 (s, 1H, NH), 7.36−7.40 (d, 2H, Ar−H), 7.24−7.28 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 75.7, 115.4, 115.8, 128.2, 127.9, 127.2, 162.3, 167.1, 169.5, 166.9, 175.2 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_6FN_3OSNa^+$, 270.2; found, 270.2. Anal. Calcd for $C_{11}H_6FN_3OS$: N, 15.55; C, 48.89; S, 12.97; H, 2.45. Found: N, 15.54; C, 48.85; S, 12.98; H, 2.44.

6-(2-Chlorophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4h)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2205.85 (CN stretching), 1629.96 (C═O stretching), 3115.80 (N−H stretching), 1461.01 (C═C aromatic stretching), 2893.47 (C−H stretching) 906.64 (C−Cl stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 11.66 (s, 1H, NH), 11.43 (s, 1H, NH), 7.48−7.52 (d, 2H, Ar−H), 7.21−7.26 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 85.12, 115.8, 126.7, 127.8, 129.3, 129.9, 131.1, 135.3, 166.9, 169.1; 175.2 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_6ClN_3OSNa^+$, 286.7; found, 286.7. Anal. Calcd for $C_{11}H_6ClN_3OS$: N, 15.02; C, 51.52; S, 11.46; H, 3.60. Found: N, 15.10; C,

130.0, 134.2, 145.6, 147.1, 166.2, 169.2, 178.2 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_6N_4O_3SNa^+$, 297.2; found, 297.2. Anal. Calcd for $C_{11}H_6N_4O_3S$: N, 20.43; C, 48.17; S, 11.69; H, 2.21. Found: N, 20.50; C, 48.23; S, 20.45; H, 2.28.

6-(2-Bromophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4j)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2250.80 (CN stretching), 1610.69 (C═O stretching), 3120.80 (N−H stretching), 1464.02 (C═C aromatic stretching), 2820.47 (C−H stretching) 960.64 (C−Br stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 12.53 (s, 1H, NH), 11.29 (s, 1H, NH), 7.49−7.53 (d, 2H, Ar−H), 7.33−7.38 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 76.3, 115.2, 118.6, 127.5, 128.6, 132.6, 138.2, 166.9, 169.1, 166.9; 169.7, 176.5 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_6BrN_3OSNa^+$, 331.1; found, 331.2. Anal. Calcd for $C_{11}H_6BrN_3OS$: N, 13.64; C, 42.88; S, 10.40; H, 1.96. Found: N, 13.10; C, 42.20; S, 10.30; H, 2.01.

4-Oxo-2-thioxo-6-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4k)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2190.80 (CN stretching), 1710.69 (C═O stretching), 3220.80 (N−H stretching), 1464.02 (C═C aromatic stretching), 2820.47 (C−H stretching) 1000.64 (C−CF_3 stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 12.26 (s, 1H, NH), 12.43 (s, 1H, NH), 7.42−7.46 (d, 2H, Ar−H), 7.27−7.30 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 76.8, 115.8, 124.1, 125.0, 125.1, 129.4, 130.2, 134.9, 166.8, 169.2; 178.3 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_6F_3N_3OSNa^+$, 320.2; found, 320.2. Anal. Calcd for $C_{12}H_6F_3N_3OS$: N, 14.14; C, 48.49; S, 10.79; H, 2.03. Found: N, 14.15; C, 48.48; S, 10.78; H, 2.08.

6-(3,4-Dimethoxy-5-methylphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4l)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2220.80 (CN stretching), 1650.69 (C═O stretching), 3045.80 (N−H stretching), 1564.02 (C═C aromatic stretching), 2800.38 (C−H stretching) 2875.15 (O−CH_3 stretching), 2875.15 (O−CH_3 stretching), 3305.10. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 12.66 (s, 1H, NH), 12.39 (s, 1H, NH), 7.14 (s, 1H, Ar−H), 6.84 (s, 1H, Ar−H), 3.83 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 16.1, 56.1, 60.3, 108.5, 115.7, 119.9, 125.4, 127.4, 145.2, 151.2, 166.9, 169.1, 175.2 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{13}N_3O_3SNa^+$, 326.3; found, 326.3. Anal. Calcd for $C_{14}H_{13}N_3O_3S$: N, 13.85; C, 55.43; S, 10.57; H, 4.32. Found: N, 13.85; C, 55.43; S, 10.57; H, 4.32.

4-Oxo-6-(thiophen-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4m)

6-(3-Hydroxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4n)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2200.80 (CN stretching), 1640.69 (C═O stretching), 3145.80 (N−H stretching), 1564.02 (C═C aromatic stretching), 2800.38 (C−H stretching) 3305.10 (O−H stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 12.32 (s, 1H, NH), 11.99 (s, 1H, NH), 9.45 (s, 1H, OH), 7.24−7.28 (d, 1H, Ar−H), 6.69−6.83 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 75.7, 112.1, 115.1, 115.8, 120.9, 130.0, 135.6, 158.4, 149.4, 166.9, 169.1, 175.2 mass (LCMS): m/z $[M + Na]^+$ calcd for $C_{11}H_7N_3O_2SNa^+$, 268.2; found, 268.2. Anal. Calcd for $C_{11}H_7N_3O_2S$: N, 17.13; C, 53.87; S, 13.07; H, 2.88. Found: N, 17.14; C, 53.88; S, 13.06; H, 2.87.

6-(4-Hydroxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4o)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2212.80 (CN stretching), 1660.69 (C═O stretching), 3100.80 (N−H stretching), 1564.02 (C═C aromatic stretching), 2800.38 (C−H stretching) 3300.10 (O−H stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 12.32 (s, 1H, NH), 11.99 (s, 1H, NH), 9.45 (s, 1H, OH), 7.31−7.35 (d, 1H, Ar−H), 6.35−6.39 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 75.7, 112.1, 115.1, 115.8, 120.9, 130.0, 135.6, 158.4, 149.4, 166.9, 169.1, 175.2 mass (LCMS): m/z $[M + Na]^+$ calcd for $C_{11}H_7N_3O_2SNa^+$, 268.2; found, 268.2. Anal. Calcd for $C_{11}H_7N_3O_2S$: N, 17.13; C, 53.87; S, 13.07; H, 2.88. Found: N, 17.14; C, 53.88; S, 13.06; H, 2.89.

6-(3-Cyanophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4p)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2212.80 (CN stretching), 2160.80, (CN stretching), 1660.69 (C═O stretching), 3100.80 (N−H stretching), 1600.02 (C═C aromatic stretching), 2800.38 (C−H stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 12.66 (s, 1H, NH), 12.39 (s, 1H, NH), 9.45 (s, 1H, OH), 7.80−7.83 (d, 1H, Ar−H), 7.61 (t, 1H, Ar−H), 7.89 (s, 1H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 75.2, 112.5, 115.8, 118.8, 129.3, 129.6, 131.4, 132.6, 134.9, 166.9, 169.1, 175.4 mass (LCMS): m/z $[M + Na]^+$ calcd for $C_{12}H_6N_4OSNa^+$, 277.3; found, 277.3. Anal. Calcd for $C_{12}H_6N_4OS$: N, 22.04; C, 56.59; S, 12.61; H, 2.38. Found: N, 22.05; C, 56.58; S, 12.62; H, 2.37.

6-(2-Hydroxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4q)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2220.10 (CN stretching), 1645.69 (C═O stretching), 3105.60 (N−H stretching), 1530.02 (C═C aromatic stretching), 2812.38 (C−H stretching) 3301.00 (O−H stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 12.32 (s, 1H, NH), 11.99 (s, 1H, NH), 9.45 (s, 1H, OH), 7.31−7.35 (d, 1H, Ar−H), 6.35−6.39 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 75.7, 112.1, 115.1, 115.8, 120.9, 130.0, 135.6, 158.4, 149.4, 166.9, 169.1, 175.2 mass (LCMS): m/z $[M + Na]^+$ calcd for

1H, NH), 9.12 (s, 1H, OH), 7.12 (d, 1H, Ar−H), 6.69−6.76 (s, 2H, Ar−H), 3.80 (s, 3H, OCH_3), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 56.3, 74.7, 112.1, 113.2, 115.9, 122.3, 127.9, 147.3, 149.4, 166.9, 169.1, 175.2 mass (LCMS): m/z $[M + Na]^+$ calcd for $C_{12}H_9N_3O_3SNa^+$, 398.3; found, 398.3. Anal. Calcd for $C_{12}H_9N_3O_3S$: N, 15.26; C, 52.36; S, 11.65; H, 3.30. Found: N, 15.27; C, 52.35; S, 11.66; H, 3.51.

4-Oxo-2-thioxo-6-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4s)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2200.80 (CN stretching), 1640.69 (C═O stretching), 3145.80 (N−H stretching), 1464.02 (C═C aromatic stretching), 2820.47 (C−H stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 12.12 (s, 1H, NH), 12.31 (s, 1H, NH), 7.68−7.70 (d, 2H, Ar−H), 7.33−7.38 (d, 2H, Ar−H), 2.41 (s, 3H, CH_3), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 21.3, 75.4, 116.8, 122.3, 123.3, 128.6, 128.8, 126.6, 130.7, 131.6, 166.9; 169.7, 175.5 mass (LCMS): m/z $[M + Na]^+$ calcd for $C_{12}H_9N_3OSNa^+$, 266.3; found, 266.3. Anal. Calcd for $C_{12}H_9N_3OS$: N, 17.27; C, 59.24; S, 13.18; H, 3.73. Found: N, 17.28; C, 59.25; S, 13.17; H, 3.74.

4-Oxo-6-(pyridin-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4t)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2221.10 (CN stretching), 1620.69 (C═O stretching), 3256.80 (N−H stretching), 1486.02 (C═C aromatic stretching), 3450.47 (pyridine ring stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 12.66 (s, 1H, NH), 12.39 (s, 1H, NH), 7.68−7.70 (d, 2H, Ar−H), 8.37 (s, 1H, Ar−H), 8.70 (s, 1H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 80.7, 115.8, 123.8, 131.6, 133.7, 149.5, 150.00, 166.9, 169.1, 175.2 mass (LCMS): m/z $[M + Na]^+$ calcd for $C_{10}H_6N_4OSNa^+$, 253.2; found, 253.2. Anal. Calcd for $C_{10}H_6N_4OS$: N, 24.33; C, 52.17; S, 13.92; H, 2.63. Found: N, 24.34; C, 52.18; S, 13.93; H, 2.64.

2,4-Dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4u)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2218.10 (CN stretching), 1732.69 (C═O stretching), 3256.80 (N−H stretching), 1486.02 (C═C aromatic stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 11.35 (s, 1H, NH), 10.98 (s, 1H, NH), 7.71−7.73 (d, 2H, Ar−H), 7.52−7.54 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 72.2, 115.8, 127.9, 128.3, 128.4, 128.6, 128.7, 131.6, 150.7, 161.6, 168.9 mass (LCMS): m/z $[M + Na]^+$ calcd for $C_{11}H_7N_3O_2Na^+$, 236.2; found, 236.2. Anal. Calcd for $C_{11}H_7N_3O_2$: N, 19.71; C, 61.97; H, 3.31. Found: N, 19.72; C, 61.98; H, 3.32.

6-(4-Chlorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4v)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2212.36 (CN stretching), 1640.69 (C═O stretching), 3301.80 (N−H stretching), 1510.02 (C═C aromatic stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 11.10 (s, 1H, NH), 10.30 (s, 1H, NH), 7.44−7.48 (d, 2H, Ar−H), 7.28−7.32 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6,

28.2, 64.8, 115.8, 116.2, 175.2, 182.4 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{11}N_3OSNa^+$, 232.3; found, 232.3. Anal. Calcd for $C_9H_{11}N_3OS$: N, 20.08; C, 51.66; H, 5.30; S, 15.32. Found: N, 20.02; C, 51.67; H, 5.31; S, 15.31.

6-Butyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4x)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2203.22 (CN stretching), 1660.60 (C═O stretching), 1760.10 (C═O stretching), 3300.10 (N−H stretching), 1552.12 (C═C aromatic stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.80 (s, 1H, NH), 10.10 (s, 1H, NH), 1.84 (t, 2H), 1.48 (d, 2H, Ar−H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 14.6, 21.2, 22.7, 28.9, 85.4, 116.5, 150.2, 161.3, 173.5 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{11}N_3O_2Na^+$, 216.2; found, 216.2. Anal. Calcd for $C_9H_{11}N_3O_2$: N, 21.75; C, 55.95; H, 5.74. Found: N, 21.71; C, 55.96; H, 5.73.

6-Butyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4y)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2203.22 (CN stretching), 1660.60 (C═O stretching), 3300.10 (N−H stretching), 1552.12 (C═C aromatic stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.50 (s, 1H, NH), 10.10 (s, 1H, NH), 1.98 (t, 2H), 1.30 (q, 1H), 1.38 (t, 2H), 0.93 (s, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 14.2, 21.1, 29.7, 64.9, 166.2, 175.2, 179.8 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_8H_9N_3OSNa^+$, 218.2; found, 218.2. Anal. Calcd for $C_8H_9N_3OS$: N, 21.52; C, 49.22; H, 4.65; S, 16.42. Found: N, 21.51; C, 49.23; H, 4.64; S, 16.41.

2,4-Dioxo-6-propyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4z)

IR (ATR, υ cm^{-1}) characteristic absorptions: 2203.22 (CN stretching), 1660.60 (C═O stretching), 1760.10 (C═O stretching), 3300.10 (N−H stretching), 1552.12 (C═C aromatic stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 9.50 (s, 1H, NH), 9.10 (s, 1H, NH), 1.88 (t, 2H), 1.40 (q, 1H), 1.38 (t, 2H), 0.98 (s, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 16.2, 23.1, 28.7, 65.9, 167.2, 176.2, 180.8 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_8H_9N_3OSNa^+$, 202.2; found, 202.2. Anal. Calcd for $C_8H_9N_3OS$: N, 23.45; C, 53.63; H, 5.06. Found: N, 23.46; C, 53.63; H, 5.07.

Ethyl 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4aa)

IR (ATR, υ cm^{-1}) characteristic absorptions: 3230.22 (NH stretching), 1697.60 (C═O stretching), 1760.10 (C═O stretching), 1552.12 (C═C aromatic stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 9.18 (s, 1H, NH), 7.73 (s, 1H, NH), 7.33−7.22 (m, 5H, Ar−H), 5.14 (d, 1H), 4.00−3.95 (q, 2H), 2.24 (s, 3H), 1.10−1.07 (t, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 14.09, 17.79, 53.98, 59.21, 99.29, 126.26, 127.28, 128.41, 144.88, 148.37, 152.15, 165.36 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{16}N_2O_3Na^+$, 283.3; found,

7.21 (t, 1H, Ar−H), 5.61 (d, 1H), 3.91−3.86 (q, 2H), 2.30 (s, 2H), 1.00−0.97 (t, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 13.95, 17.77, 53.40, 59.21, 90.83, 128.36, 131.75, 143.78, 148.68, 151.79, 165.36 mass (LCMS): m/z [M + Na]$^+$ calcd for $C_{14}H_{15}ClN_2O_3Na^+$, 317.7; found, 317.7. Anal. Calcd for $C_{14}H_{15}ClN_2O_3$: N, 9.50; C, 57.05; H, 5.13. Found: N, 9.51; C, 57.04; H, 5.13.

Ethyl 4-(4-Chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4cc)

IR (ATR, υ cm^{-1}) characteristic absorptions: 3228.22 (NH stretching), 1677.00 (C═O stretching), 1645.10 (C═O stretching), 1552.12 (C═C aromatic stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 9.21 (s, 1H, NH), 7.74 (s, 1H, NH), 7.40−7.38 (d, 2H, Ar−H), 7.25−7.23 (d, 2H, Ar−H), 5.14 (d, 1H), 4.01−3.95 (q, 2H), 2.24 (s, 3H), 1.11−1.07 (t, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 14.5, 17.77, 53.40, 59.21, 90.83, 128.36, 131.75, 143.78, 148.68, 151.79, 165.36 mass (LCMS): m/z [M + Na]$^+$ calcd for $C_{14}H_{15}ClN_2O_3Na^+$, 317.7; found, 317.7. Anal. Calcd for $C_{14}H_{15}ClN_2O_3$: N, 9.50; C, 57.05; H, 5.13. Found: N, 9.51; C, 57.04; H, 5.13.

Ethyl 6-Methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4dd)

IR (ATR, υ cm^{-1}) characteristic absorptions: 3323.12 (NH stretching), 1677.00 (C═O stretching), 1685.10 (C═O stretching), 1562.12 (C═C aromatic stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 9.33 (s, 1H, NH), 8.08 (s, 1H, NH), 8.16 (s, 1H, NH) 8.14−8.12 (d, 1H, Ar−H), 7.70−7.69 (d, 1H, Ar−H), 7.67−7.63 (t, 1H, Ar−H), 5.30 (s, 1H), 4.01−3.94 (q, 2H), 2.27 (s, 3H), 1.11−1.08 (t, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 13.97, 17.81, 53.53, 59.34, 98.32, 120.96, 122.30, 130.19, 132.94, 146.96, 147.63, 149.63, 151.63, 166.03 mass (LCMS): m/z [M + Na]$^+$ calcd for $C_{14}H_{15}N_3O_5Na^+$, 328.3; found, 328.3. Anal. Calcd for $C_{14}H_{15}N_3O_5$: N, 13.76; C, 55.08; H, 4.95. Found: N, 13.77; C, 55.09; H, 4.96.

Ethyl 6-Methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4ee)

IR (ATR, υ cm^{-1}) characteristic absorptions: 3224.12 (NH stretching), 1697.00 (C═O stretching), 1641.10 (C═O stretching), 1562.12 (C═C aromatic stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 9.35 (s, 1H, NH), 8.22−8.20 (d, 2H), 7.88 (s, 1H) 7.51−7.49 (d, 2H, Ar−H), 5.27 (d, 1H, Ar−H), 4.01−3.95 (q, 2H, Ar−H), 2.26 (s, 3H), 1.11−1.07 (t, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 14.02, 17.81, 53.67, 59.34, 98.32, 123.80, 127.64, 146.71, 149.36, 151.72, 151.98, 165.04 mass (LCMS): m/z [M + Na]$^+$ calcd for $C_{14}H_{15}N_3O_5Na^+$, 328.3; found, 328.3. Anal. Calcd for $C_{14}H_{15}N_3O_5$: N, 13.76; C, 55.08; H, 4.95. Found: N, 13.77; C, 55.09; H, 4.96.

59.15, 99.58, 113.17, 127.39, 137.05, 148.01, 152.16, 158.44, 165.38 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{18}N_2O_4Na^+$, 313.3; found, 313.3. Anal. Calcd for $C_{15}H_{18}N_2O_4$: N, 9.65; C, 62.06; H, 6.25. Found: N, 9.66; C, 62.06; H, 6.25.

Ethyl 6-Methyl-2-oxo-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4gg)

IR (ATR, υ cm^{-1}) characteristic absorptions: 3230.12 (NH stretching), 1701.00 (C═O stretching), 1646.10 (C═O stretching), 1562.12 (C═C aromatic stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 9.31 (s, 1H, NH), 7.90 (s, 1H) 7.35–7.34 (d, 1H, Ar–H), 6.93–6.88 (dd, 2H, Ar–H), 5.41 (d, 1H), 4.08–4.03 (q, 2H), 2.21 (s, 3H), 1.18–1.14 (t, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 14.15, 17.68, 49.35, 59.35, 99.78, 123.50, 124.63, 126.66, 148.65, 148.79, 152.23, 165.03 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}N_2O_3SNa^+$, 289.3; found, 289.3. Anal. Calcd for $C_{12}H_{14}N_2O_3S$: N, 10.52; C, 54.12; H, 5.30. Found: N, 10.52; C, 54.12; H, 5.30.

Ethyl 6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4hh)

IR (ATR, υ cm^{-1}) characteristic absorptions: 3230.12 (NH stretching), 3107.02 (NH stretching), 1697.00 (C═O stretching), 1697.43.10 (C═O stretching), 1562.12 (C═C aromatic stretching), ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 9.18 (s, 1H, NH), 7.73 (s, 1H) 7.33–7.22 (d, 1H, Ar–H), 5.14 (d, 1H), 4.08–3.95 (q, 2H), 2.24 (s, 3H), 1.10–1.07 (t, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 14.09, 17.79, 53.98, 59.21, 99.29, 126.26, 127.28, 128.41, 144.88, 148.37, 152.15, 165.36 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{16}N_2O_2SNa^+$, 299.3; found, 299.3. Anal. Calcd for $C_{14}H_{16}N_2O_2S$: N, 10.14; C, 60.85; H, 5.84; S, 11.60. Found: N, 1; C, 54.12; H, 5.84, S, 11.60.

Ethyl 4-(4-Chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4ii)

IR (ATR, υ cm^{-1}) characteristic absorptions: 3228.22 (NH stretching), 1677.00 (C═O stretching), 1645.10 (C═O stretching), 1552.12 (C═C aromatic stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 9.21 (s, 1H, NH), 7.74 (s, 1H, NH), 7.40–7.38 (d, 2H, Ar–H), 7.25–7.23 (d, 2H, Ar–H), 5.14 (d, 1H), 4.01–3.95 (q, 2H), 2.24 (s, 3H), 1.11–1.07 (t, 3H) ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 14.5, 17.77, 53.40, 59.21, 90.83, 128.36, 131.75, 143.78, 148.68, 151.79, 165.36 mass (LCMS): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{15}ClN_2O_2SNa^+$, 333.8; found, 333.8. Anal. Calcd for $C_{14}H_{15}ClN_2O_2S$: N, 9.01; C, 54.10; H, 4.86; S, 10.32. Found: N, 9.51; C, 57.04; H, 5.13; S, 10.32.

Ethyl 4-(4-Methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4ii)

10.46. Found: N, 9.15; C, 58.80; H, 5.15; S, 10.46.

Ethyl 6-Methyl-4-propyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4kk)

IR (ATR, υ cm^{-1}) characteristic absorptions: 3232.12 (NH stretching), 1721.00 (C═O stretching), 1562.12 (C═C aromatic stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 9.65 (s, 1H, NH), 8.10 (s, 1H) 4.51−3.72 (m, 3H), 2.16 (s, 3H), 1.46−1.23 (m, 4H), 1.19 (t, 3H), 0.85 (t, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 14.23, 14.69, 17.47, 18.17, 50.25, 59.52, 99.86, 136.28, 162.66, 174.35 mass (LCMS): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{18}N_2O_2SNa^+$, 265.3; found, 265.3. Anal. Calcd for $C_{11}H_{18}N_2O_2S$: N, 11.56; C, 54.52; H, 7.49; S, 13.23. Found: N, 11.56; C, 54.52; H, 7.49; S, 13.23.

Ethyl 4-Hexyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4ll)

IR (ATR, υ cm^{-1}) characteristic absorptions: 3332.12 (NH stretching), 1691.00 (C═O stretching), 1552.12 (C═C aromatic stretching). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 9.75 (s, 1H, NH), 8.23 (s, 1H) 4.11−3.88 (m, 3H), 2.16 (s, 3H), 1.46−1.23 (m, 4H),1.18 (t, 3H),0.85 (t, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 14.01, 14.26, 17.82, 21.95, 36.52, 49.99, 59.07, 99.39, 136.40, 160.83, 177.38 mass (LCMS): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{24}N_2O_2SNa^+$, 307.4; found, 307.4. Anal. Calcd for $C_{14}H_{24}N_2O_2S$: N, 9.85; C, 59.12; H, 8.51; S, 11.27. Found: N, 9.85; C, 59.12; H, 8.51; S, 11.27.

Ethyl 6-Methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4mm)

IR (ATR, υ cm^{-1}) characteristic absorptions: 3240.10 (N−H stretching), 1628.75 (C═O stretching), 3140.15, 1393.29 (C═C aromatic stretching), 2955.56 (C−H stretching) 1508.94 (CH_3 bending). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 8.95 (s, 1H, NH), 7.35 (s, 1H) 4.52−3.71 (m, 3H), 2.16 (s, 3H), 1.44−1.25 (m, 4H), 1.19 (t, 3H), 0.85 (t, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 14.23, 14.69, 17.47, 18.17, 50.25, 59.52, 99.86, 148.77, 153.27, 165.83 mass (LCMS): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{18}N_2O_3Na^+$, 249.3; found, 249.3. Anal. Calcd for $C_{11}H_{18}N_2O_3$: N, 12.38; C, 58.39; H, 8.02. Found: N, 12.38; C, 58.39; H, 8.01.

Ethyl 4-Butyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4nn)

IR (ATR, υ cm^{-1}) characteristic absorptions: 3230.21 (N−H stretching), 1640.75 (C═O stretching), 3146.15, 1343.29 (C═C aromatic stretching), 2945.56 (C−H stretching) 1518.94 (CH_3 bending). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 8.95 (s, 1H, NH), 7.35 (s, 1H) 4.52−3.71 (m, 3H), 2.16 (s, 3H), 1.44−1.25 (m, 4H), 1.19 (t, 3H), 0.85 (t, 3H), ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 14.23, 14.69, 17.47, 18.17, 50.25, 59.52, 99.86, 148.77, 153.27, 165.83 mass (LCMS): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{20}N_2O_3Na^+$, 263.03; found, 263.03. Anal. Calcd for $C_{12}H_{20}N_2O_3$: N, 11.66; C, 59.98; H, 8.39. Found: N, 11.66; C, 59.98; H, 8.39.

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Notes

The authors declare no competing financial interest.

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