ORIGINAL ARTICLE

Microwave assisted one-pot catalyst free green synthesis of new methyl-7-amino-4-oxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1H-pyran[2,3-d]pyrimidine-6-carboxylates as potent in vitro antibacterial and antifungal activity

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ABSTRACT

An efficiently simple protocol for the synthesis of methyl 7-amino-4-oxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1H-pyran[2,3-d]pyrimidine-6-carboxylates via one-pot three component condensation pathway is established via microwave irradiation using varied benzaldehyde derivatives, methyleyanoacetate and thio-barbituric acid in water as a green solvent. A variety of functionalized substrates were found to react under this methodology due to its easy operability and offers several advantages like, high yields (78–94%), short reaction time (3–6 min), safety and environment friendly without used any catalyst. The synthesized compounds (4a–4k) showed comparatively good in vitro antimicrobial and antifungal activities against different strains. The Compounds 4a, 4b, 4c, 4d, 4e and 4f showed maximum antimicrobial activity against Staphylococcus aureus, Bacillus cereus (gram-positive bacteria), Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa (gram-negative bacteria). The synthesized compound 4f showed maximum antifungal activity against Aspergillus Niger and Penicillium chrysogenum strains. Streptomycin is used as standard for bacterial studies and Mycostatin as standards for fungal studies. Structure of all newly synthesized products was characterized on the basis of IR, 1H NMR, 13C NMR and mass spectral analysis.

Introduction

Nitrogen and oxygen-containing heterocycles serve both as a biomimetic and reactive pharmacophores due to their diverse therapeutic property thus, plays vital role in natural and synthetic organic chemistry [1,2]. Certain annulated uracils have received considerable attention in medicinal chemistry as their wide biological activities such as, antibacterial,
antifungal, antileishmanial agents, antimalarial, antimetabolite, antitumor, antiviral, antihypertensive activity and emerged as an integral backbone of several medicinal drugs [3–8]. The assorted medicinal agents are composed of several uracil rings in which Pyranopyrimidines create a significant status. Hence, these multifaceted uracils, fascinated large efforts toward their synthetic manipulation of annulated Pyrano[2,3-d]pyrimidine derivatives.

The development of environmentally benign and clean protocol has become the goal of synthetic methodology in aqueous conditions as water plays a vital role in life processes, ambient reaction medium, unique reactivity and selectivity in organic synthesis [9–11]. Thus, there is a need for developing multicomponent reactions (MCRs) paths in water without using any harmful organic solvents and catalysts.

Green chemistry has now become a subject of demanding research emerged in the early 1990s [12], which is now widely adopted to meet the fundamental scientific challenges so as to protect the humans and environment, to achieve commercial viability and to reduce hazardous wastes as well as eliminate the use of conventional volatile organic solvents [13–15]. Thus microwave-irradiated multi-component reactions showed attractive synthetic strategy for rapid-efficient library generation and provided these potential green chemistry techniques in present scenario for various heterocyclic syntheses [16]. Here, microwave irradiations couples directly with colliding molecules of the entire reaction mixture, leads to rapid temperature rise at the moment of fruitful collision. As a result mere a reaction contents get heated and not the vessel; gives better homogeneity and selective heating of polar molecules to impart advantages viz: environmentally friendly, improved bond forming efficiency (BFE), time saving, experimental simplicity, and atom economy [17–19]. In recent years, synthesis of Pyrano[2,3-d]pyrimidine derivatives were reported using plethora of reagents under traditional thermal condition [20], microwave irradiation [21], ultrasonic irradiation [22], solvent and catalyst free condition [23,24], using different catalysts such as, Zn[(L)PROLINE]; [25], diammonium hydrogen phosphate (DAHP) [26], L-proline [27], ionic liquids [28] and DABCO [29]. Reported methods appearing in the literature usually require forcing conditions, prolonged reaction time, effluent pollution, high cost of catalyst; create wastes, complex synthetic pathway, low yields, and involved organic solvents as well high energy to proceed. Thus, investigation has been carried out under microwave-organic reaction enhancement (MORE) techniques for synthesis of targeted products. Moreover, to the best of our knowledge there is no report on the use of methylcyanoacetate as reactant for the synthesis of annulated pyrano[2,3-d]pyrimidines. Therefore we report here, to explore the catalyst free efficient, simple and fast green pathway synthesis of highly functionalized methyl 7-amino-4-oxo-5-phenyl-2-thioxo-2, 3, 4, 5-tetrahydro-1H-Pyran-2, 3-d] pyrimidine-6-carboxylate derivatives via one-pot three-component domino Knoevenagel-Michael addition reaction under microwave irradiation (Scheme 1).

**Experimental**

**Instruments and analysis**

Melting points were determined by open capillary method and were uncorrected. IR spectra were recorded on a Perkin–Elmer 298 spectrophotometer using KBr pellet. 1H NMR spectra were obtained on a Bruker instrument (400 MHz) and 13C NMR spectra were (100 MHz) recorded in DMSO-d6 as solvent with TMS as internal standard. Chemical shifts are reported in ppm. Mass spectra were measured using high resolution GC–MS (DFS) thermo spectrometers with EI (70 EV). Molecular ion peak was observed in agreement with molecular weight of respective compound. Reactions have been monitored by thin layer chromatography on 0.2-mm pre-coated plates of silica gel G60 F254 (Merck). Microwave irradiation was carried out in a Microwave Oven, Model No. NNK 571 MF (2450 MHz, 1000 W) equipped with a 35 mL vessel. The in vitro antimicrobial and antifungal activity of synthesized compounds has studied in pharmacy department, Kashmir University.

General procedure for the preparation of methyl 7-amino-4-oxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1H-pyran-2,3-d] pyrimidine-6-carboxylate derivatives (4a–k).

**Conventional heating**

Benzaldehyde derivatives 1 (1 mmol), methylcyanoacetate 2, (1.2 mmol), thiobarbituric acid 3 (1 mmol) and water (8–10 mL) as solvent were taken in an RB flask and stirred at 48 °C, 60 °C and at room temperature without using catalyst. The reaction was monitored by thin layer chromatography using eluent petroleum ether and ethyl acetate (7:3 ratio). The solid compound was filtered, washed with cold water and recrystallization from 95% ethanol to obtain pure product methyl 7-amino-4-oxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1H-Pyran-2,3-d|pyrimidine-6-carboxylate derivatives.

![Scheme 1](image)

Scheme 1 Microwave and conventional synthesis of methyl 7-amino-4-oxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1H-pyran-2,3-d|pyrimidine-6-carboxylate derivatives (4a–k).
Microwave assisted one-pot catalyst free green synthesis

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A mixture of benzaldehyde derivatives 1 (1 mmol), methylkynoanacetate 2, (1.2 mmol), thio-barbituric acid 3, (1 mmol) and water (3.0 mL) was placed into Teflon vessel and subjected to microwave irradiation under catalyst free conditions for a given time at power of 250 W and 120 °C. After completion of the reaction as followed by TLC examination at an interval of 30 s using eluent petroleum ether:ethylacetate (7:3 ratio). The reaction mixture was cooled to room temperature and poured into cold water, causing the precipitation of the product. The solid product was filtered under vacuum, washed with water and subsequently recrystallized from 95% ethanol to yield the pure product in excellent yield (78-94%).

Selected spectral data

Methyl 7-aminooxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylate 4a

M.p. 221–223 °C; –IR (KBr) (vmax): 3387 (NH), 3328, 3103 (NH), 3072 (C–H), 2159 (C=O), 1768 (C–O), 1654 (C–C) cm–1; 1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H, NH), 10.80 (s, 1H, NH), 7.27–7.11 (m, 4H, Ar–H), 7.08 (s, 1H, Ar–H), 6.82 (s, 2H, NH3), 3.94 (s, 1H, Ar–H), 3.61 (s, 3H, CH3); 13C NMR (100 MHz, DMSO-d6) δ 179.43 (>C=O), 170.23 (>C=S), 159.49 (>C=O), 155.08 (>C=N–H), 151.65 (C–4), 140.52 (C–11), 128.59 (C–16), 127.61 (C–14), 93.41 (C–5), 84.22 (C–9), 52.03 (CH3), 39.43 (C–10); –EI–MS, m/z (C15H13N2O4S): 347 (M+), 331, 319, 316, 253.

Methyl 7-aminooxo-5-(p-tolyl)-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylate 4b

M.p. 286–287 °C; –IR (KBr) (vmax): 3304 (NH), 3312, 3196 (NH), 3032 (C–H), 2107 (C=O), 1734 (C–O), 1629 (C–C) cm–1; 1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H, NH), 10.80 (s, 1H, NH), 7.04 (d, J = 6.7 Hz, 2H, Ar–H), 6.95 (s, 2H, Ar–H), 6.82 (s, 2H, NH3), 3.94 (s, 1H, Ar–H), 3.61 (s, 3H, CH3), 2.19 (s, 3H, CH3); 13C NMR (100 MHz, DMSO-d6) δ 179.44 (>C=S), 170.24 (–COCH3), 159.49 (>C=O), 155.08 (>C=N–H), 151.65 (C–4), 128.59 (C–16), 127.61 (C–14), 93.41 (C–5), 84.22 (C–9), 52.03 (CH3), 39.43 (C–10); –EI–MS, m/z (C15H13N2O4S): 345 (M+), 315, 303, 300, 253, 239.

Methyl 7-aminooxo-5-4-hydroxyphenyl)-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylate 4f

M.p. 182–182 °C; –IR (KBr) (vmax): 3634 (OH), 3510 (NH2), 3415, 3309 (NH), 3137 (C–H), 2204 (C=O), 1654 (C–C), 1431 (C–C) cm–1; 1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H, NH), 10.80 (s, 1H, NH), 6.98 (d, J = 6.8 Hz, 2H, Ar–H), 6.82 (s, 2H, NH3), 6.61 (d, J = 2.7 Hz, 2H, Ar–H), 6.05 (s, 1H, OH), 3.94 (s, 1H, Ar–H), 3.61 (s, 3H, CH3); 13C NMR (100 MHz, DMSO-d6) δ 179.43 (>C=S), 170.23 (–COCH3), 159.49 (>C=O), 157.19 (>C=N–H), 155.08 (>C=N–H), 151.65 (C–4), 129.31 (C–16), 129.20 (C–120), 115.15 (C–13), 93.41 (C–5), 84.21 (C–9), 52.03 (CH3), 39.43 (C–10). –EI–MS, m/z (C15H13N2O4S): 347 (M+), 331, 319, 316, 253.

Biological evaluation

Synthesized compounds (4a–4k) were screened for their in vitro antimicrobial activity against Staphylococcus aureus, Bacillus cereus (gram-positive bacteria), Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa (gram-negative bacteria) and also tested for their in vitro antifungal activity against Aspergillus Niger and Penicillium chrysogenum strains. The minimum inhibitory concentration (MIC) of µg/mL values is carried out by the disc-diffusion technique [30,31] to assess the activity of the chosen compounds. Samples were dissolved in dimethyl sulfoxide (DMSO) for dilution to prepare stock of 1 mg/mL−1 and Whatman filter paper disks (No. 1) were impregnated with the solutions. The impregnated disks were placed on the surface of solidified nutrient agar dishes seeded by the test bacteria and sabourauds dextrose agar dishes seeded by the test fungi. The medium in the plates was allowed to stand at room temperature for 10 min and was set to solidify in a refrigerator for 30 min. The minimum inhibitory concentrations (MICs) were measured in millimeters by the end of the incubation period 48 h at 37 °C (for bacteria) and 72–91 h at 28 °C (for fungi). Streptomycin (25 µg mL−1) is used as standard for bacterial studies and Mycostatin (25 µg mL−1) as standards for fungal studies. The results are described in Table 4.

Results and discussion

Chemistry

Herein, we wish to report the synthesis of methyl 7 amino-4-oxo-5-phenyl-2-thioxo-2, 3, 4, 5-tetrahydro-1H-Pyran[2,3-d]pyrimidine-6-carboxylate derivatives from aromatic aldehydes 1 (1 mmol), methylkynoanacetate 2 (1.2 mmol), thio-barbituric acid 3 (1 mmol) using water (3.0 mL) as solvent under microwave irradiation. Initially, the same reaction has also monitored under conventional heating (48 °C and 60 °C). The result showed that reaction completed in 3–6 min with excellent yield (78–94%) under microwave irradiation as compared to conventional heating were obtained moderate yields (69–86%) in 2–6 h at 48 °C and (71–87%) in 1–4 h at 60 °C respectively. Further the yields (67–82%) of targeted compounds were obtained in 2–7 h under room temperature (Table 1). Therefore, microwave irradiation reducing the reaction time and improving the reaction yields. The nature of different substituents containing electron-withdrawing groups (such as nitro group, halide) or electron-donating groups (such as hydroxyl group, alkoxyl group) did not showed strongly obvious effects in terms of reaction time and yield of products. In order to optimize the reaction condition of different solvents for the model product 4f, using reaction mixture of 4-hydroxy benzaldehyde 1 (1 mmol), methylkynoanacetate 2 (1.2 mmol) and thio-barbituric acid 3 (1 mmol) under conventional heating (48 °C and 60 °C), room temperature and microwave irradiation 120 °C (Scheme 2). Results are summarized in Table 2, showed that best conversion was obtained using water as solvent in reaction medium. Mechanistically, the formation
of the product is a sequence of reactions involving Knoevenagel condensation of methylecyanacetic acid with aromatic aldehydes by loss of water molecule, followed by Michael addition of thio-barbituric acid on electron deficient C-atom and an intra molecular heterocyclization that leads to the formation of the pyrano[2,3-d]pyrimidine derivatives [29]. A reasonable mechanism for the formation of targeted products via three component reaction is outlined in (Scheme 3).

The structure of model compound 4f was confirmed by IR, $^1$H NMR, $^{13}$C NMR and mass spectrometric analysis. The IR spectrum showed absorptions at 3634, 3510, 3309, 3137 cm$^{-1}$ due to the OH, NH$_2$, two NH, C−H, C=N, C=O, C−C groups respectively. The $^1$H NMR spectrum showed the presence of two amido protons (NH) as singlet at $\delta$ 10.98–10.80 and other peaks at $\delta$ 6.98 (d, $J$ = 6.8 Hz, 2H, Ar=H), 6.82 (s, 2H, NH$_2$), 6.61 (d, $J$ = 7.0 Hz, 2H, Ar=H), 6.05 (s, 1H, OH), 3.94 (s, 1H, Ar=H), 3.61 (s, 3H, OCH$_3$) (Fig. 1). The $^{13}$C NMR spectrum showed 13 peaks at $\delta$ 179.43 (>C=S), 170.23 (==COCH$_3$), 159.49 (>C=O), 157.19 (>C=OH), 155.08 (>C=NH$_2$), 151.65 (C-4), 129.31 (C-16), 129.20 (C-12), 115.15 (C-13), 93.41 (C-5), 84.21 (C-9), 52.03 (CH$_3$), 39.43 (C-10) (Fig. 2). The mass spectrum of 4f revealed a strong molecular ion peak at $m/z$ 347 (M$^+$) in agreement with molecular weight of compound.

Further, we have worked on systematic evaluation of different catalysts for the model product 4f, by reacting a mixture of 4-hydroxy benzaldehyde (1 mmol), methylecyanacetic acid (1.2 mmol) and thio-barbituric acid (1 mmol) using water (3.0 mL) as solvent under microwave irradiation (Table 3). We found that yield of model product 4f is 94% without using catalyst. These results indicated that time taken for the synthesis of model product 4f using different catalysts is 5–20 min with poor yield 57–82% (Table 3). We observed that due to more addition of catalysts the product formation is very low and the removal of catalysts by simple washing is difficult.

The structural assignment of 4(a–k) was confirmed by IR, $^1$H NMR, $^{13}$C NMR and mass spectrometric analysis. The IR spectra exhibited sharp bands regions at 3634 cm$^{-1}$ (OH), 3304–3510 cm$^{-1}$ (NH$_2$), 3103–3329 cm$^{-1}$ (NH), 2107–2201 cm$^{-1}$ (CN) and 1676–1768 cm$^{-1}$ (C=O) groups. $^1$H NMR spectra of the synthesized products exhibited the following characteristic signals: protons of two amido groups (NH) on pyrimidine ring are directly attached to electronegative nitrogen atoms showed deshield the protons toward downfield and the removal of catalysts by simple washing is difficult.

The significant peaks observed at $\delta$ 10.98–10.80 ppm. Protons of primary amine (NH$_2$) are directly attached to the electronegative nitrogen atom observed broad singlet in the region of 6.80–3.85 ppm. Hydroxyl proton observed at 6.05 ppm and methoxy protons observed broad singlet at 3.81–3.84 ppm. Upon studying the $^1$H NMR spectrum a characteristic sharp singlet is observed toward up-field region at 2.19 ppm. This signal is assigned to the three equivalent methyl protons at Para position of phenyl ring. Thus, by observing and assigning the peaks in the NMR spectrum and by the calculation of the $J$ values for each of the proton it can be clearly suggested the proposed structure for synthesized compounds has been confirmed. The $^{13}$C NMR spectrum of synthesized compounds showed 12–14 peaks at different $\delta$ values. The significant peaks observed at $\delta$ 179.44 (>C=S), 170.24 (==COCH$_3$), 159.50 (>C=O), 157.19 (>C=OH), 155.08 (>C=NH$_2$), 149.31 (>C=NO$_2$),
Systematic fragmentation pattern was observed in mass spectral analysis. Molecular ion peak was observed in agreement with molecular weight of compounds.

In vitro antibacterial and antifungal activity

Electron donating substituents viz; –OH, CH₃, –OCH₃ and C₆H₅ on the annulated pyrano[2,3-d] pyrimidine skeleton increases solubility in the solvent showed high in vitro antimicrobial and antifungal activity. The synthesized compound 4f showed maximum antibacterial activity against S. aureus, B. cereus (gram-positive bacteria), E. coli, K. pneumonia, P. aeruginosa (gram-negative bacteria) and also enhanced maximum antifungal activity against A. Niger and P. chrysogenum strains. The Compounds 4a, 4b, 4c, 4d and 4e showed maximum antibacterial activity against gram-positive and gram-negative bacteria like; S. aureus, B. cereus, E. coli, K.

### Table 2 Optimization of different solvents for the synthesis of 4f product under conventional heating (48 °C and 60 °C), room temperature and microwave irradiation at 120 °C.

| Solvent  | Room temperature | Conventional method | Microwave irradiation |
|----------|------------------|---------------------|----------------------|
|          | Time (h) | Yield (%) | Time (h) | Yield (%) | Time (h) | Yield (%) | Time (min) | Yield (%) |
| Ethanol  | 3        | 72        | 3        | 69        | 2        | 71        | 4        | 76        |
| Water    | 4        | 82        | 3        | 78        | 2        | 83        | 5        | 94        |
| DMF      | 2        | 62        | 2        | 71        | 1        | 62        | 4        | 61        |
| DMSO     | 2        | 57        | 2        | 61        | 2        | 58        | 10       | 42        |
| CH₂Cl₂   | 3        | 61        | 3        | 62        | 2        | 56        | 4        | 67        |
| EtOH:H₂O | 1        | 78        | 1        | 67        | 1        | 64        | 5        | 72        |
| Solvent less | 8      | 63        | 6        | 56        | 5        | 59        | 12       | 58        |

*a* Isolated yields.

### Table 3 Optimization of catalysts for the synthesis of 4f product under microwave irradiation.

| Entry | Catalyst | Mole% | Solvent | Time (min) | Yield (%) |
|-------|----------|-------|---------|------------|-----------|
| 1     | DBU      | 20 mol| H₂O     | 15         | 82        |
| 2     | DABCO    | 20 mol| H₂O     | 12         | 71        |
| 3     | K₂CO₃    | 20 mol| H₂O     | 20         | 57        |
| 4     | Et₃N     | 2–3 Drops| H₂O | 11         | 64        |
| 5     | No catalyst | – | H₂O | 5          | 94        |

*a* Isolated yields.

**Table 4 Antibacterial and antifungal activity methyl 7-amino-4-oxo-5-phenyl-2-thioxo-2, 3, 4, 5-tetrahydro-1H-pyran[2, 3-d] pyrimidine-6-carboxylate derivatives (4a–4k).**

| Compd. | MIC (µg/mL) | MIC (µg/mL) |
|--------|-------------|-------------|
|        | Gram positive | Gram negative |
|        | S. aureus | B. cereus | E. coli | K. pneumonia | P. aeruginosa | A. Niger | P. chrysogenum |
| 4a     | 12        | 18        | 17      | 21          | 19          | +       | –          |
| 4b     | 15        | 12        | 16      | 19          | 21          | +       | +          |
| 4c     | 16        | 19        | 15      | 18          | 16          | –       | +          |
| 4d     | 17        | 21        | 17      | 17          | 20          | + +     | +          |
| 4e     | 13        | 15        | 16      | 14          | 12          | +       | +          |
| 4f     | 21        | 18        | 21      | 22          | 18          | + +     | +          |
| 4g     | –         | 10        | 7       | 3           | 13          | –       | –          |
| 4h     | 11        | –         | 9       | –           | 4           | +       | +          |
| 4i     | 10        | 12        | 8       | 11          | 9           | +       | –          |
| 4j     | –         | 8         | 10      | 11          | –           | –       | +          |
| 4k     | 13        | 11        | 13      | 12          | 10          | +       | +          |

*Inhibition zone around the disks for antibacterial activity: 18–28 mm: very strong activity; 11–17 mm: strong activity; 6–16 mm: moderate weak activity; 0–5 mm weak activity; dash denotes no activity.

*Zone area for antifungal activity: +++ = 23–32 mm, ++ = 12–22 mm, + = 0–11 mm, dash (–) = no activity.

*Streptomycin* for antibacterial activity and *Mycostatin* for antifungal activity.
Scheme 2  Microwave and conventional synthesis of 4f model compound.

Scheme 3  Proposed mechanism for the synthesis of new methyl 7-amino-4-oxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylate derivatives under microwave irradiation.

Fig. 1  $^1$H NMR spectra of synthesized model compound 4f.
pneumonia, P. aeruginosa. The compound 4g has antibacterial activity against P. aeruginosa (gram-negative bacteria). Whereas the compounds 4i and 4k have moderate antibacterial activity against S. aureus, B. cereus (gram-positive bacteria), E. coli, K. pneumonia, P. aeruginosa (gram-negative bacteria). The compounds 4g and 4j have least antibacterial activity against B. cereus, E. coli and K. pneumonia strains and showed no antibacterial activity against S. aureus (gram-positive). The compound 4h has no antibacterial activity against B. cereus (gram-positive) and K. pneumonia (gram-negative).

The compounds 4d and 4f have maximum antifungal activity against A. Niger and P. chrysogenum strains. The compounds 4a, 4c, 4i, 4h and 4k have moderate antibacterial activity against A. Niger strain and compounds 4c, 4g and 4j have no antifungal activity against A. Niger strain. The compounds 4b, 4c, 4d, 4e, 4g, 4h, 4j and 4k have antifungal activity against P. chrysogenum strain. Whereas the compounds 4a and 4i have no antifungal activity against P. chrysogenum strain. These findings suggest that rather than disrupting cell membranes, the compounds acted outside the cell and became attached to surface groups of the bacterial cells enhanced its activity. The good activity is attributed in the presence of pharmacologically active benzaldehyde, —OH, CH₃, —OCH₃, —Cl and —NO₂ groups attached to phenyl ring on the pyran ring shows extensive effect on the membrane potential associated with bactericidal activity (Table 4).

Conclusions

Microwave-assisted methodology developed catalyst free, simple and green pathway for the synthesis of methyl 7 amino-4-oxo-5-phenyl-2-thioxo-2, 3, 4, 5-tetrahydro-1H-Pyran [2, 3-d] pyrimidine-6-carboxylate derivatives. The advantages of this ecofriendly and safe procedure provide spectacular accelerations, higher yields under milder reaction conditions, short reaction time and simple work up. The relevant studies showed that steric, electronic effects and polar parameters of the benzaldehyde substituents on pyran ring were important for both in vitro antimicrobial and antifungal activities.

Conflict of Interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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