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# Microwave-assisted multicomponent synthesis of antiproliferative 2,4-dimethoxy-tetrahydropyrimido[4,5-b]quinolin-6(7H)-ones $\dagger$ 

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#### Abstract

In this study, we demonstrate a simple, highly efficient, rapid and convenient series of 2,4-dimethoxy-tetrahydropyrimido[4,5-b]quinolin-6(7H)-ones 4a-v. Microwave irradiation facilitates the one-pot multicomponent reaction of different aromatic aldehydes, 6-amino-2,4-dimethoxypyrimidine and dimedone using glacial acetic acid. Metal-free multicomponent synthesis, shorter reaction time, higher product yield, easy product purification without column chromatography and outstanding green credential parameters are the key features of this protocol. We analysed $4 \mathrm{a}-\mathrm{v}$ against six human tumour cell lines for antiproliferative activity. $4 \mathrm{~h}, 4 \mathrm{o}, 4 \mathrm{q}$ and 4 v show good antiproliferative activity with a good in silico ADMET profile. Furthermore, $4 \mathrm{~h}, 4 \mathrm{o}, 4 \mathrm{q}$ and 4 v also show drug-likeness properties by obeying drug-like filters.


## 1. Introduction

The worldwide burden of tumours and cancer has been steadily increasing and is expected to continue to rise in the next decades because of population ageing and urban lifestyles. ${ }^{1}$ So, the need to develop antitumor agents has also increased in recent times. Previously we reported antiproliferative activity of pyrimidine and quinoline based heterocycles against six human tumour cell lines. In this work, we developed novel pyrimidine and quinoline based heterocycles to develop a new potent antiproliferative agent. ${ }^{2,3}$ Multicomponent reactions (MCRs) facilitated by microwave irradiation are an effective strategy from the perspective of green chemistry. ${ }^{4}$ Microwave irradiation is a powerful tool in heterocyclic chemistry as well as drug discovery. ${ }^{4,5}$ When MW radiation comes into contact with solvent, bubbles develop, grow and then burst, generating hot regions of high temperature and pressure. These hot regions generate enough energy to progress the reaction due to the elevation in number of species. These species produce sufficient kinetic energy to exceed the activation energy barrier. ${ }^{6}$ Microwave irradiation has numerous benefits, such as being

[^0]homogeneous and quick heating, having shorter reaction times, higher reaction rates, lower energy consumption and low waste production. ${ }^{7,8}$ As a result, synthesis utilizing MCRs under MW irradiation proceeds effortlessly and in a benign way.

In 2010, pyrimido[4,5-b]quinolines (PQs) were reported as a new class of antitumor agents and found PQ I as a potent antitumor agent. ${ }^{9}$ Other research groups then worked on PQs and explored more antitumor PQs (II-III) (Fig. 1a). ${ }^{10,11}$ Thus, PQs are the best candidate to explore new antitumor agents. Some mechanisms for the anticancer effects of pyrimido[4,5-b] quinolines were reported including the inhibition of vascular epithelial growth factor receptor tyrosine kinase, ${ }^{12}$ topoisomerases I and Epidermal growth factor receptor. ${ }^{13}$ In other case, pyrimido[4,5-b]quinolines showed the anticancer effects through caspase- 3 activation. They also inhibited tubulin polymerization, arrested cell cycle at G2/M phase and induced apoptosis. ${ }^{14}$ Methoxy group containing heterocycles have more potential of antitumor or anticancer activity. For instance, II and III of Fig. 1a contain methoxy group in their molecules. Many anticancer drugs like bosutinib, ${ }^{15}$ brigatinib, ${ }^{16}$ cabazitaxel, ${ }^{17}$ erdafitinib, ${ }^{18}$ lurbinectedin ${ }^{19}$ and trabectedin ${ }^{20}$ contain methoxy group in their chemical structure. So, here we developed methoxy group containing PQs i.e., 2,4-dimethoxy-tetrahydropyrimido[4,5-b]quinolin-6(7H)-ones (2,4-dimethoxyTHPQs).

In our previous work, 2,4-dimethoxy-THPQs were synthesised by conventional heating in acetic acid medium. ${ }^{21}$ To improve the protocol, irradiation of microwave was used for acceleration of multicomponent synthesis. Irradiation of microwave was used in the synthesis of heterocycle because it
a) Potent antitumour Pyrimido[4,5-b]quinolines

(I)
$\mathrm{IC}_{50}=6.9 \mu \mathrm{~g} / \mathrm{ml}$ (EAC)

(II)
$\mathrm{IC}_{50}=15.8 \pm 1.7 \mu \mathrm{M}$ (CNE2)
$=17.1 \mu \mathrm{M} \pm 1.4$ (KB)
$=18.9 \pm 1.5$ (MGC-803)

(III)
$\mathrm{IC}_{50}=3.62 \mu \mathrm{M}$ (MCF-7)
b) Naik's work: Microwave assisted synthesis of pyrimido[4,5-b]quinoline from 2-chloro-3formylquinoline

c) Quiroga's work: Microwave assisted synthesis of pyrimido[4,5-b]quinoline by cyclization

d) Mosslemin's work: Microwave assisted multicomponent synthesis of pyrimido[4,5-b]quinoline

e) This work:


Fig. 1 (a) Representative PQs with antiproliferative activity. (b-d) Reported synthetic strategies to obtain PQs. (e) Synopsis of the synthetic methodology reported in this work.
offers unique advantages. It reduces the time of the reaction and enhances the yield. ${ }^{22}$ Fig. 1 show previous work on microwave-assisted synthesis of PQs. The microwave-assisted reaction of 2-chloro-3-formylquinoline with urea/thiourea produced PQs in 9-10 minutes (Fig. 1b). ${ }^{23}$ Microwave-assisted cyclisation reaction of 2,4-diamino-6-chloro-pyrimidine-5carbaldehydes in the presence of acetic acid produced PQs
(Fig. 1c). ${ }^{24}$ The microwave-assisted multicomponent reaction of aldehyde, amine and (thio)barbituric acid also produced PQs (Fig. 1d). ${ }^{25}$ In this work, 2,4-dimethoxy-THPQs were synthesised by microwave-assisted multicomponent reaction of aldehydes, dimedone and 6-amino-2,4-dimethoxypyrimidine in continuation of our work on exploring novel bioactive heterocycles (Fig. $1 \mathrm{e}) .{ }^{26-32}$ 2,4-dimethoxy-THPQs were then evaluated for in vitro
antiproliferative activity against six human tumour cell lines. Furthermore, the most potent 2,4-dimethoxy-THPQs are evaluated by in silico ADMET and drug-likeness properties.

## 2. Results and discussions

### 2.1. Chemistry

In the above concept, we selected $p$-chlorobenzaldehyde 1a, 6-amino-2,4-dimethoxypyrimidine 2 and dimedone 3 as model substrates to explore the microwave irradiated multicomponent synthesis of $4 \mathbf{a}$ (Scheme 1). In order to check the effect of the selected solvent and catalyst, we optimised the rection by different reaction conditions (Table 1). Complete conversation of 1a into 4 a did not observe in catalyst-free condition with ethanol and water (Table 1, entry 1-3). As discussed earlier, $p$ TSA is the best catalyst for similar reactions. So, we utilised it for optimisation (Table 1, entry 4-7). Best results were observed when glacial acetic acid was used as a solvent. At room temperature, $p$-TSA/AcOH converted 1a to 4 a in 25 minutes. In comparison, $p$-TSA/AcOH converted $1 \mathbf{1 a}$ to $\mathbf{4 a}$ in 10 minutes under reflux. Similar results are also observed in the case of glacial acetic acid only (Table 1, entry 8 and 9). So, we decided to proceed with the best-optimised condition (Table 1, entry 9) in which desired product 4 a was obtained in only 10 minutes by glacial acetic acid under reflux.

In order to check the effect of microwave irradiation power, we optimised the rection by applying different microwave irradiation power (Table 2). The best results were obtained by applying 75 W MW with the highest $84 \%$ isolated yield in only 5 minutes.

We also carried out a reaction with a similar protocol with conventional heating (Table 1, entry 10). It produced 4 a in 90 minutes by glacial acetic acid under reflux with $73 \%$ isolated yield. To evaluate the greenness of the conventional vs. microwave synthesis, the green metrics (see ESI $\dagger$ for the definition of

Table 2 Optimization of the power of microwave irradiation for synthesis of $4 a^{a}$

| Entry | Power (W) | Time (Min) | Yield $^{b}(\%)$ |
| :--- | :--- | :---: | :--- |
| 1 | 200 | 10 | 78 |
| 2 | 150 | 10 | 82 |
| 3 | 150 | 5 | 83 |
| 4 | 100 | 10 | 82 |
| 5 | 75 | 10 | 80 |
| 6 | 75 | 5 | $\mathbf{8 4}$ |
| 7 | 50 | 5 | 83 |

${ }^{a}$ Reaction condition: $1 \mathrm{mmol} p$-chlorobenzaldehyde $1 \mathrm{a}, 1 \mathrm{mmol} 6$ -amino-2,4-dimethoxypyrimidine 2 and 1 mmol dimedone $3,3 \mathrm{~mL}$ acetic acid, reflux. ${ }^{b}$ Isolated yield.


Scheme 1 Three-component synthesis of 4a from p-chlorobenzaldehyde, 6-amino-2,4-dimethoxypyrimidine and dimedone.

Table 1 Optimization of solvent and catalyst for the preparation of compound 4a under Microwave irradiation ${ }^{a}$

| Entry | Catalyst | Solvent ${ }^{b}$ | Temperature | Time (min) | Conversion relative to aldehyde ${ }^{c}$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | - | Water | RT | - | - |
| 2 | - | Ethanol | RT | - | - |
| 3 | - | Ethanol | Reflux | 35 | Incomplete |
| 4 | $p$-TSA (20 mol\%) | Ethanol | Reflux | 45 | 100\% |
| 5 | $p$-TSA (20 mol\%) | Acetonitrile | Reflux | 30 | 100\% |
| 6 | $p$-TSA (20 mol\%) | Acetic acid | RT | 25 | 100\% |
| 7 | $p$-TSA (20 mol\%) | Acetic acid | Reflux | 10 | 100\% |
| 8 | - | Acetic acid | RT | 25 | 100\% |
| 9 | - | Acetic acid | Reflux | 10 | 100\% |
| 10 | - | Acetic acid | Reflux | 90 | $100 \%{ }^{\text {d }}$ |

[^1] solvent. ${ }^{c}$ Observed from TLC analysis. ${ }^{d}$ Obtained by conventional heating.

Table 3 Green metrics (AE, AEf, CE, RME, OE and MP) analysis for conventional and microwave synthesis of 4 a

${ }^{a}$ Isolated yield. Abbreviation: AE: atom economy, AEf: atom efficiency, CE: carbon efficiency, RME: reaction mass efficiency, OE: optimum efficiency, MP: mass productivity.
green metrics and detailed calculation process) were conducted and the results are shown in Tables 3 and 4 . The AE for both conventional $v s$. microwave synthesis is $91.74 \%$ due to the same reactants. AEf, CE, RME, OE and MP of microwave is higher
than the conventional method. Whereas PMI, E-factor, SI and WI of microwave is lower than the conventional method. So, from both ways, the microwave process is greener than the

Table 4 Green metrics (PMI, E-factor, SI and WI) analysis for conventional and microwave synthesis of $4 \mathrm{a}^{a}$

| Method | Time (min) | PMI | E-factor | SI |  |
| :--- | ---: | ---: | ---: | ---: | ---: |
| Conventional | 90 | 105.17 | 104.17 | 34.71 |  |
| Microwave | 5 | 91.59 | 90.59 | 30.23 | 68.97 |

Lower the value, greener the process


[^2]

${ }^{a}$ Reaction condition: 1 mmol aldehyde $1,1 \mathrm{mmol} 6$-amino-2,4-dimethoxypyrimidine 2 and 1 mmol dimedone $3,3 \mathrm{~mL}$ AcOH, 75 W MW, Reflux. Isolated yields are mentioned with the product.
conventional method for the reaction of model substrates 1a, 2 and 3.

With the best optimal reaction condition in hand, we then explore the substrate scope of this 2,4-dimethoxy-THPQ derivative using different substituted aromatic/heteroaromatic
aldehyde 1a-v with dimedone 2 and 6-amino-2,4dimethoxypyrimidine 3 . Under this optimal reaction conditions, reaction performed smoothly with both electronreleasing and electron-withdrawing substituted aldehydes and give excellent yield up to $87 \%$.


Scheme 2 A plausible reaction root for the formation of 2,4-dimethoxy-THPQs.

Using this green protocol, we synthesize twenty-two 2,4-dimethoxy-THPQs $\mathbf{4 a}-\mathbf{v}$ from variety of substrate (Table 5). In primary investigation, formation of desired product was confirmed by TLC analyses using mixture of $30 \%$ ethyl acetate and $70 \% n$-hexane. The desired product was obtained with minor impurities, which were easily removed by washing of icecold diethyl ether. The derivatives $\mathbf{4 p}$-t were purified by washing with ice-cold aqueous methanol. The derivative $\mathbf{4 u}$ was soluble in water when reaction mixture poured into water, after 20 minutes pure solid product was formed which was isolated by filtration.

The structure of all the synthesized compound were characterised via. ${ }^{1} \mathrm{H}$ NMR, ${ }^{13} \mathrm{C}$ NMR and either HRMS or LCMS analysis. Furthermore, we developed a single crystal of product $4 f$ and 40 and it was studied using single-crystal X-ray diffraction (SCXRD). The structure of $\mathbf{4 f}$ and $\mathbf{4 0}$ were fully confirmed by results of the analysis. The single-crystal XRD data of $\mathbf{4 f}$ shows that it was crystalises in monoclinic crystal system, space group $C 2 / c$ with unit cell dimension $a=17.3963(6) \AA, b=22.485(1) \AA, c$ $=14.0877(9) \AA$, $\alpha=90^{\circ}, \beta=127.7461(13)^{\circ}, \gamma=90^{\circ}, V=$ 4357.3(4) $\AA^{3}, Z=8$, density $=1.206 \mathrm{~g} \mathrm{~cm}^{-3}$ and linear absorption coefficient $0.084 \mathrm{~mm}^{-1}$. The product 40 crystalises in triclinic crystal system, space group $P-1$ with unit cell dimension $a=6.0680(2) \AA, b=13.0347(5) \AA, c=13.5866(5) \AA, \alpha=$ $103.302(3)^{\circ}, \beta=95.6327(18)^{\circ}, \gamma=103.2902(19)^{\circ}, V=1004.76(7)$ $\AA^{3}, Z=2$, density $=1.469 \mathrm{~g} \mathrm{~cm}^{-3}$ and linear absorption coefficient $2.072 \mathrm{~mm}^{-1}$. XRD data were deposited online to Cambridge Crystallographic Data Centre (CCDC). CCDC deposition number 2157101 and 2149724 contain the ESI crystallographic data for this paper.

Herein, we proposed plausible reaction root based on the literature reports, ${ }^{33,34}$ (Scheme 2). Firstly, Knoevenagel
condensation was carried out in between aromatic aldehyde and dimedone in presence of acetic acid under microwave irradiation and resulting in the formation of possible Knoevenagel adduct ( $K$ ) by elimination of first water molecule. In next step, 6-amino-2,4-dimethoxy aniline readily undergoes nucleophilic attack on this Knoevenagel adduct ( K ) and produce an imine derivative. In the final step, this imine derivative undergoes intramolecular ring-closing step via $\mathrm{C}-\mathrm{N}$ bond formation by elimination of second water molecule in presence of acetic acid and furnished the final product.

### 2.2. Antiproliferative activity

The antiproliferative activity of 2,4-dimethoxy-THPQs was $\mathbf{4 a - v}$ studied in a panel of six human solid tumour cell lines. From the initial set of compounds $\mathbf{4 a}-\mathbf{v}$ derivatives, $\mathbf{4 c}-\mathbf{e}, \mathbf{4 l}$ and $\mathbf{4 s}$ were not tested due to their poor solubility under the experimental conditions. The results reported as $50 \%$ growth inhibition $\left(\mathrm{GI}_{50}\right)$ are shown in Table 6. The results are best compared in the $\mathrm{GI}_{50}$ range plot (Fig. 2). The data from the $\mathrm{GI}_{50}$ range plot reveals that most of the compounds have similar activity across the cell line panel. The most active compounds of the series ( $\mathbf{4 h}$, $\mathbf{4 o}, \mathbf{4 q}$ and $\mathbf{4 v}$ ) displayed $\mathrm{GI}_{50}$ values at comparable range that the one displayed by CDDP. From the results, it is not possible to obtain a clear structure-activity relationship (SAR). For instance, compound $\mathbf{4 h}$ holds an electron-donating group (OMe) at para position and 40 has an electron-withdrawing group ( Br ), whilst $\mathbf{4 q}$ bears a nitro group in ortho position.

### 2.3. ADMET prediction

Potent antiproliferative 2,4-dimethoxy-THPQs 4h, 4o, 4q and $\mathbf{4 v}$ were evaluated for in silico ADMET prediction which is important drug profiling for novel drug discovery. ${ }^{35}$ Various filters

| Compound | A549 (lung) | HBL-100 (breast) | HeLa (cervix) | SW1573 (lung) | T-47D (breast) | WiDr (colon) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 4 a | $13 \pm 5.1$ | $24 \pm 7.9$ | $17 \pm 5.8$ | $27 \pm 0.71$ | $26 \pm 6.5$ | $17 \pm 1.6$ |
| 4b | $29 \pm 4.2$ | $38 \pm 8.1$ | $28 \pm 4.8$ | $37 \pm 7.5$ | $33 \pm 5.7$ | $31 \pm 9.1$ |
| 4f | $30 \pm 4.5$ | $41 \pm 8.6$ | $33 \pm 0.87$ | $38 \pm 0.95$ | $32 \pm 1.7$ | $39 \pm 6.5$ |
| 4 g | $38 \pm 1.6$ | $41 \pm 12$ | $34 \pm 3.4$ | $46 \pm 1.4$ | $33 \pm 10$ | $49 \pm 12$ |
| 4h | $37 \pm 4.8$ | $\mathbf{1 . 6} \pm \mathbf{0 . 4 7}$ | $27 \pm 1.4$ | $43 \pm 6.5$ | $23 \pm 3.1$ | $42 \pm 8.4$ |
| 4 i | $45 \pm 9.7$ | $64 \pm 31$ | $40 \pm 14$ | $15 \pm 6.0$ | $37 \pm 4.7$ | $44 \pm 7.5$ |
| 4j | $28 \pm 5.5$ | $35 \pm 7.8$ | $34 \pm 11$ | $21 \pm 7.0$ | $39 \pm 16$ | $44 \pm 21$ |
| 4k | $51 \pm 7.7$ | $81 \pm 17$ | >100 | $60 \pm 2.6$ | $83 \pm 29$ | $83 \pm 18$ |
| 4m | $24 \pm 1.3$ | $29 \pm 13$ | $13 \pm 6.1$ | $30 \pm 0.87$ | $21 \pm 7.1$ | $30 \pm 3.6$ |
| 4n | $19 \pm 3.5$ | $24 \pm 3.7$ | $27 \pm 4.6$ | $32 \pm 5.4$ | $17 \pm 1.6$ | $26 \pm 1.1$ |
| 40 | $7.7 \pm 2.4$ | $19 \pm 7.9$ | $8.3 \pm 1.1$ | $20 \pm 1.3$ | $16 \pm 3.2$ | $12 \pm 5.8$ |
| 4p | $23 \pm 6.1$ | $33 \pm 4.2$ | $15 \pm 0.4$ | $21 \pm 8.6$ | $27 \pm 1.9$ | $31 \pm 4.6$ |
| 4q | $12 \pm 4.7$ | $10 \pm 3.2$ | $4.0 \pm 0.98$ | $8.0 \pm 0.45$ | $10 \pm 2.8$ | $19 \pm 0.88$ |
| 4r | $25 \pm 3.4$ | $35 \pm 5.1$ | $30 \pm 8.9$ | $47 \pm 15$ | $32 \pm 0.14$ | $36 \pm 1.9$ |
| 4t | $30 \pm 1.9$ | $37 \pm 15$ | $25 \pm 11$ | $17 \pm 0.77$ | $48 \pm 12$ | $35 \pm 0.4$ |
| 4u | $47 \pm 15$ | $88 \pm 21$ | $71 \pm 26$ | $35 \pm 1.7$ | $92 \pm 13$ | $80 \pm 29$ |
| 4v | $9.5 \pm 0.15$ | $17 \pm 7.9$ | $11 \pm 3.4$ | $6.0 \pm 0.10$ | $16 \pm 6.3$ | $14 \pm 4.1$ |
| CDDP | $4.9 \pm 0.2$ | $1.9 \pm 0.2$ | $1.8 \pm 0.5$ | $2.7 \pm 0.4$ | $17 \pm 3.3$ | $23 \pm 4.3$ |



Fig. $2 \mathrm{Gl}_{50}$ range plot against human solid tumour cell lines. Cisplatin (CDDP) was used as reference anticancer drug (blue bar). Green bars indicate the most active compounds.
such as Lipinski filter, Ghose filter, Veber filter, Egan filter and Muegge filter are help to predict drug likeness based on their physicochemical properties. $\mathbf{4 h}, \mathbf{4 o}, \mathbf{4 q}$ and $\mathbf{4 v}$ were evaluated for their ADMET properties with the help of the online web server SwissADME (http://www.swissadme.ch). Calculated physicochemical properties of are summarised in Table 7.

Bioavailability radar plot of 2,4-dimethoxy-THPQs $\mathbf{4 h}, \mathbf{4 0}, \mathbf{4 q}$ and $\mathbf{4 v}$ show in Fig. 3 display that all four 2,4-dimethoxy-THPQs have drug like radar plot. Calculated bioavailability score found as 0.55 for all 2,4 -dimethoxy-THPQs. To predict the gastrointestinal absorption and blood-brain barrier permeability of 2,4-dimethoxy-THPQs $\mathbf{4 h}, \mathbf{4 0}, \mathbf{4 q}$ and $\mathbf{4 v}$, BOILED-Egg delineation was used. BOILED-Egg delineation of these 2,4-dimethoxyTHPQs is illustrated in Fig. 4. "The white region is the physicochemical space of molecules with highest probability of being absorbed by the gastrointestinal tract, and the yellow region (yolk) is the physicochemical space of molecules with highest probability to permeate to the brain". ${ }^{\mathbf{3 6}} \mathbf{4 h}, \mathbf{4 q}$ and $\mathbf{4 v}$ show high gastrointestinal absorbance, and they have no blood-brain permeability. While 40 show blood-brain permeability. Red dots for $\mathbf{4 o}$ and $\mathbf{4 v}$ denoted that they are not P-gp substrates while blue dots for $\mathbf{4 h}$ and $\mathbf{4 q}$ denoted that they are P-gp substrates.

## 3. Experimental section

### 3.1. General methods

For synthesis, all chemical reagents were purchased from the TCI, Sigma-Aldrich and Sisco Research Laboratories Pvt. Ltd and used without further purification. The microwave-assisted reactions were performed in a "SINEO UWave-1000 Microwave, UV, US Synthesis Extraction Reactor". The progress of all chemical reactions was monitored by thin-layer chromatography (TLC, on aluminium plates pre-coated with F254 silica gel 60). Melting points of all solid compounds were determined by the open capillary tube method and are uncorrected. High-resolution mass spectra (HRMS) were acquired using Agilent technologies model G6564 QTOF. The samples were ionized in positive ion mode using a MALDI or ESI ionization sources. The LCMS analysis was collected on an MS-Agilent 6120 quadrupole. Nuclear magnetic resonance spectra ( ${ }^{1} \mathrm{H}$ NMR \& ${ }^{13} \mathrm{C}$ NMR) were recorded on a Bruker 500 MHz WB FT-NMR spectrometer having

Table 7 Physicochemical properties of $4 h, 4 o, 4 q$ and $4 v$ with various filters for drug-likeness ${ }^{a}$

| Comp. | MW | RB | HBA | HBD | MR | TPSA | $\mathrm{X} \log \mathrm{P}$ | $\mathrm{W} \log \mathrm{P}$ | $\mathrm{M} \log \mathrm{P}$ | NR | NC | NH | Atom |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 4h | 425.48 | 5 | 7 | 1 | 118.58 | 91.8 | 3.62 | 3.14 | 1.97 | 4 | 23 | 8 | 58 |
| 40 | 444.32 | 3 | 5 | 1 | 113.3 | 73.34 | 4.36 | 3.89 | 3.18 | 4 | 21 | 7 | 50 |
| 4q | 410.42 | 4 | 7 | 1 | 114.42 | 119.16 | 3.5 | 3.03 | 1.7 | 4 | 21 | 9 | 52 |
| 4v | 450.35 | 3 | 5 | 1 | 111.17 | 101.58 | 4.41 | 3.95 | 2.78 | 4 | 19 | 8 | 47 |


| Lipinski filter | Ghose filter | Veber filter | Egan filter | Muegge filter |
| :---: | :---: | :---: | :---: | :---: |
| $\mathrm{MW} \leq 500$ | $160 \leq \mathrm{MW} \leq 480$ | $\mathrm{RB} \leq 10$ | WlogP $\leq 5.88$ | $200 \leq \mathrm{MW} \leq 600$ |
| $\mathrm{M} \log \mathrm{P} \leq 4.15$ | $\begin{aligned} & -0.4 \leq \mathrm{W} \log \mathrm{P} \leq \\ & 5.6 \end{aligned}$ | TPSA $\leq 140$ | TPSA $\leq 131.6$ | $\begin{aligned} & -2 \mathrm{X} \log \mathrm{P} \leq 5 ; \text { TPSA } \\ & \leq 150 \end{aligned}$ |
| $\mathrm{HBA} \leq 10$ | $40 \leq \mathrm{MR} \leq 130$ |  |  | $\begin{aligned} & \mathrm{NR} \leq 7 ; \mathrm{NC}>4 ; \mathrm{NH} \\ & >1 ; \mathrm{RB} \leq 15 ; \mathrm{HBA} \leq \\ & 10 ; \mathrm{HBD} \leq 5 \end{aligned}$ |
| $\mathrm{HBD} \leq 5$ | $20 \leq$ atoms $\leq 70$ |  |  |  |

${ }^{a}$ Abbreviation: MW: molecular weight; RB: rotational bond; HBA: H-bond acceptor; HBD: H-Bond Donor; MR: Molecular Refractivity; TPSA: Topological Polar Surface Area; NR: No. of ring; NC: No. of Carbon; NH: No. of Heteroatoms.


Fig. 3 Bioavailability radar of 2,4-dimethoxy-THPQs $4 h, 4 o, 4 q$ and $4 v$
proton noise decoupling mode with a standard 5 mm probe using $\mathrm{CDCl}_{3}$ and DMSO- $d_{6}$ solution. Abbreviations are used for the ${ }^{1} \mathrm{H}$ NMR signal are as follows: $\mathrm{s}=$ singlet, $\mathrm{d}=$ doublet, $\mathrm{t}=$ triplet, $\mathrm{q}=$ quartet $\mathrm{dd}=$ double doublet, $\mathrm{td}=$ triple doublet, $\mathrm{m}=$ multiplet. The chemical shifts are reported in parts per million and coupling constants $(J)$ are provided in Hertz.

### 3.2. General procedure for synthesis of 2,4-dimethoxyTHPQs 4a-v

A mixture of aromatic aldehydes ( $\mathbf{1}, 1 \mathrm{mmol}$ ), 6 -amino-2,4dimethoxypyrimidine ( $2,1 \mathrm{mmol}$ ), dimedone ( $3,1 \mathrm{mmol}$ ) and acetic acid ( 3 mL ) were charged into a microwave vessel. The


Fig. 4 BOILED-Egg model of 2,4-dimethoxy-THPQs 4h, $4 \mathrm{o}, 4 \mathrm{q}$ and 4 v .
reaction mixture was heated at $110^{\circ} \mathrm{C}(75 \mathrm{~W})$ by MW irradiation for 5 min . The reaction progress was monitored on TLC using $n$ hexane:ethyl acetate ( $70: 30, \mathrm{v} / \mathrm{v}$ ) as mobile phase. After complete consumption of starting material, the reaction mixture was cooled to room temperature and poured into 20 mL cold water. The obtained crude product was filtered and dried in an oven. Further purification, the crude product was stirred in 5 mL ice-cold diethyl ether or methanol as mentioned in results and discussion to obtain pure product. The products $\mathbf{4 f}$ and $\mathbf{4 o}$ were crystallised by a slow evaporation method using a mixture of 20 mL dichloromethane and 3 mL methanol.
3.2.1. 5-(4-Chlorophenyl)-2,4-dimethoxy-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one (4a). White solid, mp. $208-210{ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta$, ppm): 8.46 (s, 1H, NH), 7.26 (d, $J=8.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), 7.17 (d, $J=$ $8.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), 5.17 ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{CH}$ ), $3.92\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.89(\mathrm{~s}$, $3 \mathrm{H}, \mathrm{OCH}_{3}$ ), $2.46\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.26\left(\mathrm{~d}, J=16 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.19$ (d, $\left.J=16 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.09\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.00\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) ( $\left.\delta, \mathrm{ppm}\right): 195.0,168.8,163.4,156.5$, 150.3, 144.5, 131.8, 129.3, 128.1, 111.6, 95.9, 54.4, 54.1, 50.6, 41.2, 33.8, 32.6, 29.4, 27.3; HRMS(ESI-MS) $400.0996[\mathrm{M}+\mathrm{H}]^{+}$.
3.2.2. 2,4-Dimethoxy-8,8-dimethyl-5-phenyl-5,8,9,10-tetrahydropyrimido $[4,5-b]$ quinolin-6(7H)-one (4b). White solid, mp $244-246{ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 8.05(\mathrm{~s}, 1 \mathrm{H}$, NH ), 7.31 (d, $J=7.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 7.20(\mathrm{t}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH})$, $7.11(\mathrm{t}, J=7.25 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}), 5.21(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.91(\mathrm{~s}, 3 \mathrm{H}$, $\left.\mathrm{OCH}_{3}\right), 3.89\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.45\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.26(\mathrm{~d}, J=16.5 \mathrm{~Hz}$, $\left.1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.19\left(\mathrm{~d}, J=16 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.09\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.01(\mathrm{~s}$, $3 \mathrm{H}, \mathrm{CH}_{3}$ ); ${ }^{13} \mathrm{C}-\mathrm{NMR}\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right.$ ) ( $\delta, \mathrm{ppm}$ ): 195.0, 168.8, 163.3, 156.5, 149.9, 145.9, 128.0, 127.9, 126.2, 112.1, 96.3, 54.4, 54.1, 50.7, 41.3, 34.2, 32.6, 29.4, 27.3; MS(MM-ES + APCI) 364.20 $[\mathrm{M}-\mathrm{H}]^{-}$.
3.2.3. 5-(2-Chlorophenyl)-2,4-dimethoxy-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one (4c). White solid, $\mathrm{mp} 306-308{ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta$, ppm): 7.43 (s, 1H, NH), 7.36 (dd, $J=8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 7.25 (dd, $J=$ $8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}), 7.11(\mathrm{td}, J=7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}), 7.04(\mathrm{td}, J=8 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{ArH}), 5.51(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.90\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.83(\mathrm{~s}, 3 \mathrm{H}$, $\left.\mathrm{OCH}_{3}\right), 2.45-2.35\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.23\left(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right)$, $2.15\left(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.09\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.02(\mathrm{~s}, 3 \mathrm{H}$, $\mathrm{CH}_{3}$ ); ${ }^{13} \mathrm{C}-\mathrm{NMR}\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right.$ ) ( $\left.\delta, \mathrm{ppm}\right): 194.8,169.0,163.5$, 156.1, 149.8, 142.8, 133.3, 131.7, 129.7, 127.4, 126.3, 54.5, 53.9, $50.5,41.5,33.7,32.5,29.3,27.4$; HRMS(+ESI) $400.1422[\mathrm{M}+\mathrm{H}]^{+}$.
3.2.4. 5-(3-Chlorophenyl)-2,4-dimethoxy-8,8-dimethyl-5,8,9,10-tetrahydropyrimido $[4,5-b]$ quinolin- $6(7 H)$-one (4d). White solid, mp $240-242{ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta$, ppm): 7.56 (s, 1H, NH), 7.23-7.21 (m, 2H, ArH), 7.15-7.09 (m, $2 \mathrm{H}, \mathrm{ArH}), 5.16(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.92\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.90(\mathrm{~s}, 3 \mathrm{H}$, $\mathrm{OCH}_{3}$ ), $2.44\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.26\left(\mathrm{~d}, J=16 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.20(\mathrm{~d}, J$ $\left.=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.10\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.02\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) ( $\delta, \mathrm{ppm}$ ): 194.8, 168.9, 163.5, 156.0, 149.7, 147.7, 133.9, 129.2, 127.9, 126.5, 126.3, 111.6, 95.6, 54.7, 54.2, 50.6, 41.4, 34.1, 32.7, 29.2, 27.4; MS(MM-ES + APCI) 398.20 $[\mathrm{M}-\mathrm{H}]^{+}$.
3.2.5. 2,4-Dimethoxy-5-(3-methoxyphenyl)-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one
White solid, $\mathrm{mp} 224-226{ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta$, ppm): 7.18 (s, 1H, NH), 7.13-6.65 (m, 4H, ArH), 5.18 (s, 1H, CH), $3.90\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.89\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.75\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.44$ (d, $J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), $2.39\left(\mathrm{~d}, J=17 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.25(\mathrm{~d}, J$ $\left.=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.21\left(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.09(\mathrm{~s}, 3 \mathrm{H}$, $\left.\mathrm{CH}_{3}\right), 1.02\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-\mathrm{NMR}\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm})$ : 194.9, 168.8, 163.3, 159.4, 156.1, 149.4, 147.3, 128.9, 120.3, 113.9, 112.1, 111.4, 96.0, 55.1, 54.5, 54.1, 50.6, 41.5, 34.1, 32.7, 29.3, 27.4; MS(MM-ES + APCI) $394.20[\mathrm{M}-\mathrm{H}]^{+}$.
3.2.6. 2,4-Dimethoxy-5-(4-methoxyphenyl)-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one White solid, mp 198-200 ${ }^{\circ} \mathrm{C}$; ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta$, ppm): $8.60(\mathrm{~s}, 1 \mathrm{H}, \mathrm{NH}), 7.23(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 6.74(\mathrm{~d}, J=$ $8.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), 5.16 ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{CH}$ ), 3.91 ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{OCH}_{3}$ ), $3.90(\mathrm{~s}$, $3 \mathrm{H}, \mathrm{OCH}_{3}$ ), $3.73\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.46-2.45\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.27-$ $2.18\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 1.08\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.01\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-\mathrm{NMR}$ $\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 195.2,168.7,163.1,157.9,156.5$, $150.2,138.5,129.3,128.8,113.5,113.4,112.0,96.5,55.1,54.3$, 54.0, 50.7, 41.1, 33.2, 32.5, 29.4, 27.3; MS(MM-ES + APCI) 394.20 [ $\mathrm{M}-\mathrm{H}]^{+}$.
3.2.7. 5-(2,4-dimethoxyphenyl)-2,4-dimethoxy-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one (4g). White solid, mp $138-140{ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta$, ppm): 8.33 (s, 1H, NH), 7.30 (d, $J=8.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 6.39 (dd, $J=$ $8.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}), 6.35(\mathrm{~d}, J=2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}), 5.24(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH})$, $3.89\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.85\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.75\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.71$ $\left(\mathrm{s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.42\left(\mathrm{~d}, J=17 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.35(\mathrm{~d}, J=16.5 \mathrm{~Hz}$, $\left.1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.21\left(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.13(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CH}_{2}$ ), $1.07\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 0.97\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-\mathrm{NMR}(125 \mathrm{MHz}$, $\mathrm{CDCl}_{3}$ ) ( $\left.\delta, \mathrm{ppm}\right): 195.1,168.6,162.9,159.2,158.5,156.9,150.3$, 131.6, 126.0, 110.5, 103.7, 98.6, 95.7, 55.2, 55.2, 54.3, 53.9, 50.7, 41.3, 32.5, 31.5, 29.6, 26.7; HRMS(+ESI) $426.2021[\mathrm{M}+\mathrm{H}]^{+}$.
3.2.8. 5-(3,4-dimethoxyphenyl)-2,4-dimethoxy-8,8-
dimethyl-5,8,9,10-tetrahydropyrimido $[4,5-b] q u i n o l i n-6(7 H)$-one (4h). White solid, mp 208-210 ${ }^{\circ} \mathrm{C}$; ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta$, ppm): 8.46 (s, 1H, NH), 6.97-6.70 (m, 3H, ArH), 5.17 (s, 1H, CH), $3.921\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.916\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.84\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$, $3.80\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.47\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.27(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CH}_{2}$ ), $2.22\left(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.09\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.03(\mathrm{~s}$, $3 \mathrm{H}, \mathrm{CH}_{3}$ ); ${ }^{13} \mathrm{C}-\mathrm{NMR}\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 195.2,168.8$, 163.1, 156.5, 150.1, 148.4, 147.4, 138.9, 119.5, 112.0, 111.7, 110.8, 96.4, 55.8, 55.7, 54.4, 54.1, 50.6, 41.2, 33.6, 32.5, 29.6, 27.2; HRMS(+ESI) $426.2026[\mathrm{M}+\mathrm{H}]^{+}$.
3.2.9. 5-(2,5-dimethoxyphenyl)-2,4-dimethoxy-8,8-dimethyl-5,8,9,10-tetrahydropyrimido $[4,5-b]$ quinolin- $6(7 H)$-one (4i). White solid, mp $206-208{ }^{\circ} \mathrm{C}$; ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta$, ppm): 7.26, 7.21 (s, 2H, NH $+\mathrm{CDCl}_{3}$ ), $6.95(\mathrm{~d}, J=3 \mathrm{~Hz} 1 \mathrm{H}, \mathrm{ArH})$, 6.71 (d, $J=9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}), 6.65-6.63$ (m, H, ArH), 5.28 (s, 1H, $\mathrm{CH}), 3.89\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.83\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.75\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$, $3.71\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.42\left(\mathrm{~d}, J=17 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.30(\mathrm{~d}, J=$ $\left.17 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.21\left(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.14(\mathrm{~d}, J=$ $\left.16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.08\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 0.99\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-\mathrm{NMR}$ $\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 194.8,168.7,163.1,153.1,152.1$, 134.4, 117.2, 112.0, 111.9, 110.7, 95.4, 56.2, 55.6, 54.4, 54.0, 50.6, 41.59, 32.55, 32.0, 29.4, 27.0; HRMS(+ESI) $426.2020[\mathrm{M}+\mathrm{H}]^{+}$.
3.2.10. 5-(4-ethoxyphenyl)-2,4-dimethoxy-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one (4j). White solid, mp 192-194 ${ }^{\circ} \mathrm{C}$; ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta$, ppm): 8.49 (s, 1H, NH), 7.21 (d, $J=9 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 6.73$ (d, $J=$ $8.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), $5.15(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.97-3.92\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 3.91$ $\left(\mathrm{s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.89\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.46-2.44\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.27-$ $2.18\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 1.35\left(\mathrm{t}, J=7 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.08\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right)$, $1.00\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-\mathrm{NMR}\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 195.2$, 168.7, 163.1, 157.4, 157.3, 156.5, 150.1, 138.3, 129.3, 128.8,
113.9, 112.1, 96.5, 63.2, 54.3, 54.0, 50.7, 41.1, 33.2, 32.5, 29.4, 27.3, 14.9; HRMS(+ESI) 410.2076 [M + H] .
3.2.11. 5-(3-hydroxyphenyl)-2,4-dimethoxy-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one (4k). Light brown solid, mp 292-294 ${ }^{\circ} \mathrm{C}$; ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right.$ and DMSO- $d_{6}$ ) ( $\delta, \mathrm{ppm}$ ): $9.73(\mathrm{~s}, 1 \mathrm{H}, \mathrm{NH}), 8.89(\mathrm{~s}, 1 \mathrm{H}, \mathrm{OH}), 6.95$ ( $\mathrm{t}, J=8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}$ ), 6.70-6.68 (m, 2H, ArH), 6.53-6.51 (m, 1H, $\mathrm{ArH}), 5.01(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.88\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.87\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$, $2.47\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.19\left(\mathrm{~d}, J=16 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.10(\mathrm{~d}, J=16 \mathrm{~Hz}$, $\left.1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.07\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.00\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-\mathrm{NMR}(125$ $\mathrm{MHz}, \mathrm{CDCl}_{3}$ and $\left.\mathrm{DMSO}-d_{6}\right)(\delta, \mathrm{ppm}): 194.5,168.4,163.2,157.1$, $156.8,151.5,147.9,128.8,118.7,114.5,113.2,110.7,95.8,54.5$, 53.9, 50.8, 33.8, 32.5, 29.4, 27.4; HRMS(+ESI) 382.1793 [M + H $]^{+}$.
3.2.12. 5 -([1, $1^{\prime}$-biphenyl]-4-yl)-2,4-dimethoxy-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one (41). White solid, mp $246-248{ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta$, ppm): 8.06 (s, 1H, NH), 7.53 (d, $J=7 \mathrm{~Hz}, 2 \mathrm{H}, \operatorname{ArH}$ ), 7.44 (d, $J=$ $8.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 7.40-7.37(\mathrm{~m}, 4 \mathrm{H}, \mathrm{ArH}), 7.30-7.26(\mathrm{~m}, 1 \mathrm{H}$, $\mathrm{ArH}), 5.25(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.920\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.915\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$, $2.47\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.27\left(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.22(\mathrm{~d}, J=$ $\left.16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.10\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.03\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-\mathrm{NMR}$ $\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 195.1,168.9,163.3,156.4,150.1$, 145.0, 141.1, 139.0, 128.6, 128.4, 127.0, 126.9, 126.8, 112.0, 96.2, 54.5, 54.2, 50.7, 41.3, 33.9, 32.7, 29.4, 27.4; HRMS(+ESI) $442.2121[\mathrm{M}+\mathrm{H}]^{+}$.
3.2.13. 2,4-Dimethoxy-8,8-dimethyl-5-( $p$-tolyl)-5,8,9,10-tetrahydropyrimido $[4,5-b]$ quinoline- $6(7 H)$-one ( $4 m$ ). White solid, mp 208-210 ${ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 8.68(\mathrm{~s}, 1 \mathrm{H}$, $\mathrm{NH}), 7.21(\mathrm{~d}, J=8 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 7.01(\mathrm{~d}, J=8 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 5.19$ $(\mathrm{s}, 1 \mathrm{H}, \mathrm{CH}), 3.901\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.897\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.49-2.42$ $\left(\mathrm{m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.26\left(\mathrm{~d}, J=14.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.23(\mathrm{~d}, J=15.5 \mathrm{~Hz}$, $\left.1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.08\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.01\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-\mathrm{NMR}(125$ $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 195.2,168.7,163.1,156.6,150.4,143.1$, $135.6,128.8,127.7,112.0,96.5,54.3,54.1,50.7,41.1,33.7,32.6$, 29.5, 27.4, 21.2; HRMS(+ESI) $380.1969[\mathrm{M}+\mathrm{H}]^{+}$.
3.2.14. 5-(4-fluorophenyl)-2,4-dimethoxy-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one (4n). White solid, mp $200-202{ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta$, $\mathrm{ppm}): 8.47(\mathrm{~s}, 1 \mathrm{H}, \mathrm{NH}), 7.29-7.26(\mathrm{~m}, 2 \mathrm{H}, \mathrm{ArH}), 6.91-6.86(\mathrm{~m}$, $2 \mathrm{H}, \mathrm{ArH}), 5.18(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.92\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.90(\mathrm{~s}, 3 \mathrm{H}$, $\mathrm{OCH}_{3}$ ), $2.47\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.26\left(\mathrm{~d}, J=16 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.20(\mathrm{~d}, J$ $\left.=16 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.09\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.00\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-\mathrm{NMR}$ $\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 195.1,168.8,162.8(\mathrm{~d}, J=127.9 \mathrm{~Hz})$, $160.3,156.5,150.2,141.8(\mathrm{~d}, J=2.9 \mathrm{~Hz}), 129.3(\mathrm{~d}, J=7.8 \mathrm{~Hz})$, 114.7 (d, $J=21.2 \mathrm{~Hz}$ ), 111.9, 96.2, 54.4, 54.1, 50.6, 41.2, 33.6, 32.6, 29.4, 27.3; HRMS(+ESI) $384.1719[\mathrm{M}+\mathrm{H}]^{+}$.
3.2.15. 5-(4-bromophenyl)-2,4-dimethoxy-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one (40). Light brown solid, $\mathrm{mp} 214-216{ }^{\circ} \mathrm{C}$; ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ ( $\delta, \mathrm{ppm}$ ): 8.47 (s, 1H, NH), 7.32 (d, $J=8.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ), 7.20 (d, $J$ $=7.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 5.16(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.92\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.89(\mathrm{~s}$, $3 \mathrm{H}, \mathrm{OCH}_{3}$ ), $2.46\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.26\left(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.19$ ( $\mathrm{d}, J=16 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), $1.09\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.00\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) ( $\delta, \mathrm{ppm}$ ): 195.0, 168.8, 163.4, 156.5, 150.3, 145.0, 131.1, 129.7, 120.0, 111.5, 95.8, 54.4, 54.1, 50.6, 41.2, 33.9, 32.6, 29.4, 27.3; MS(MM-ES + APCI) $442.20[\mathrm{M} \mathrm{-} \mathrm{H}]^{-}$.
3.2.16. 2,4-Dimethoxy-8,8-dimethyl-5-(4-nitrophenyl)-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one (4p). Light yellow solid, mp $234-236{ }^{\circ} \mathrm{C}$; ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ ( $\delta, \mathrm{ppm}$ ): 8.87 (s, 1H, NH), 8.09 (d, $J=8.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 7.50(\mathrm{~d}, J$ $=8.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 5.29(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.94\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.90(\mathrm{~s}$, $3 \mathrm{H}, \mathrm{OCH}_{3}$ ), $2.53\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.28\left(\mathrm{~d}, J=16 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.19$ (d, $J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), $1.11\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.00\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right)$; ${ }^{13} \mathrm{C}-\mathrm{NMR}\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 195.0,168.8,163.6,156.6$, $153.2,151.1,146.3,128.9,123.4,110.7,95.0,54.6,54.3,50.1$, 41.1, 34.8, 32.6, 29.4, 27.2; HRMS(+ESI) $411.1660[\mathrm{M}+\mathrm{H}]^{+}$.
3.2.17. 2,4-Dimethoxy-8,8-dimethyl-5-(2-nitrophenyl)-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one (4q). Light yellow solid, $\mathrm{mp} 270-272{ }^{\circ} \mathrm{C}$; ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ ( $\delta, \mathrm{ppm}$ ): 7.79 (s, 1H, NH), 7.78-7.77 (m, 1H, ArH), 7.43-7.35 (m, $2 \mathrm{H}, \mathrm{ArH}$ ), $7.24-7.22(\mathrm{~m}, 1 \mathrm{H}, \mathrm{ArH}), 6.03(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.91(\mathrm{~s}, 3 \mathrm{H}$, $\mathrm{OCH}_{3}$ ), $3.82\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.47-2.43\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.25(\mathrm{~d}, J=$ $\left.16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.16\left(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.10(\mathrm{~s}, 3 \mathrm{H}$, $\mathrm{CH}_{3}$ ), 1.01 (s, $3 \mathrm{H}, \mathrm{CH}_{3}$ ); ${ }^{13} \mathrm{C}-\mathrm{NMR}\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}):$ 194.7, 169.0, 163.6, 156.0, 150.3, 148.8, 140.2, 132.4, 130.8, 126.9, 124.2, 111.3, 95.3, 54.6, 54.2, 50.4, 41.4, 32.6, 30.2, 29.1, 27.6; HRMS(+ESI) $411.1660[\mathrm{M}+\mathrm{H}]^{+}$.
3.2.18. 2,4-Dimethoxy-8,8-dimethyl-5-(2-nitrophenyl)-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one (4r). Off white solid, $\mathrm{mp} 236-238{ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta$, ppm): 8.38 (s, 1H, NH), 8.13 (s, 1H, ArH), 7.99 (d, $J=8 \mathrm{~Hz}, 1 \mathrm{H}$, ArH), 7.74 (d, $J=7.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}), 7.40(\mathrm{t}, J=8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH})$, $5.30(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.94\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.90\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.52(\mathrm{~s}$, $\left.2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.28\left(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.19(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CH}_{2}$ ), $1.11\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.02\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-\mathrm{NMR}(125 \mathrm{MHz}$, $\mathrm{CDCl}_{3}$ ) ( $\left.\delta, \mathrm{ppm}\right): 195.0,168.8,163.6,156.3,150.8,148.3,147.9$, $134.5,128.8,122.8,121.5,110.9,95.2,54.6,54.3,50.5,41.2,34.6$, 32.6, 29.4, 27.3; HRMS(+ESI) $411.1660[\mathrm{M}+\mathrm{H}]^{+}$.
3.2.19. 2,4-Dimethoxy-8,8-dimethyl-5-(naphthalen-1-yl)-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(7H)-one (4s). Off white solid, $\mathrm{mp} 180-182{ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta$, ppm): 8.79 (s, 1H, NH), 8.56-8.36 (m, 1H, ArH), 6.73 (d, $J=$ $8.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}), 5.15(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.97-3.92\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 3.91$ $\left(\mathrm{s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.89\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.46-2.44\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.27-$ $2.18\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 1.35\left(\mathrm{t}, \mathrm{J}=7 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.08\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right)$, $1.00\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-\mathrm{NMR}\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 195.3$, 169.0, 163.0, 156.2, 133.4, 131.1, 128.1, 127.0, 126.7, 125.5, 125.3, 125.0, 113.4, 97.5, 54.4, 53.8, 50.5, 41.1, 32.5, 29.7, 29.4, 27.3; HRMS(+ESI) $415.2121\left[\mathrm{M}+\mathrm{NH}_{4}\right]^{+}\left[-\mathrm{H}_{2} \mathrm{O}\right]$.
3.2.20. 5-(6-bromobenzo[d][1,3]dioxol-5-yl)-2,4-dimethoxy-8,8-dimethyl-5,8,9,10-tetrahydropyrimido $[4,5-b]$ quinolin-6(7H)one (4t). White solid, mp 296-298 ${ }^{\circ} \mathrm{C}$; ${ }^{1} \mathrm{H}$-NMR ( 500 MHz , $\left.\mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 7.40(\mathrm{~s}, 1 \mathrm{H}, \mathrm{NH}), 6.92(\mathrm{~s}, 1 \mathrm{H}, \mathrm{ArH}), 6.75(\mathrm{~s}, 1 \mathrm{H}$, ArH), 7.74 (d, $J=7.5 \mathrm{~Hz}, 1 \mathrm{H}, \operatorname{ArH}), 5.88$ (dd, $J=8 \mathrm{~Hz}, 2 \mathrm{H}$, $\left.\mathrm{OCH}_{2} \mathrm{O}\right), 5.43(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.91\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.87\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$, $2.45-2.37\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.24\left(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.18(\mathrm{~d}, J$ $\left.=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.10\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.05\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) ( $\left.\delta, \mathrm{ppm}\right): 195.0,169.1,163.4,155.8$, 149.6, 147.2, 146.5, 114.0, 112.5, 111.7, 110.4, 101.5, 95.7, 54.5, 53.9, 50.6, 41.5, 35.5, 32.6, 29.1, 27.7; HRMS(+ESI) 488.0807 [M + $\mathrm{H}]^{+}$.
3.2.21. 5-(2-Butyl-5-chloro-1H-imidazole-4-yl)-2,4-dime-thoxy-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinolin$\mathbf{6 ( 7 H )}$ )one ( $\mathbf{4 u}$ ). Light brown solid, $\mathrm{mp} 212-214{ }^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}(500$ $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 9.91(\mathrm{~s}, 1 \mathrm{H}, \mathrm{NH}), 8.00(\mathrm{~s}, 1 \mathrm{H}, \mathrm{NH}), 5.22(\mathrm{~s}$, $1 \mathrm{H}, \mathrm{CH}), 3.94\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.90\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.58(\mathrm{td}, J=$ $\left.7.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 2.43\left(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.38(\mathrm{~d}, J=$ $\left.17 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.29\left(\mathrm{~d}, J=16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.25(\mathrm{~d}, J=$ $16.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}$ ), 1.64 (quin, $J=7.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}$ ), 1.32 (sextet, $J$ $\left.=7.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 1.10\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.03\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 0.90(\mathrm{t}, J$ $\left.=7.5 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-\mathrm{NMR}\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)(\delta, \mathrm{ppm}): 196.8$, 169.1, 163.7, 156.5, 151.6, 145.3, 126.3, 124.1, 108.7, 91.9, 54.6, 54.3, 50.5, 41.21, 32.7, 30.2, 28.9, 28.3, 27.6, 25.8, 22.3, 13.8; HRMS(+ESI) $446.1946[\mathrm{M}+\mathrm{H}]^{+}$.
3.2.22. 5-(5-Bromothiophen-2-yl)-2,4-dimethoxy-8,8-dimethyl-5,8,9,10-tetrahydropyrimido $[4,5-b]$ quinolin- $6(7 H)$-one (4v). Off white solid, mp $206-208{ }^{\circ} \mathrm{C}$; ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ ( $\delta, \mathrm{ppm}$ ): $8.50(\mathrm{~s}, 1 \mathrm{H}, \mathrm{NH}), 6.76(\mathrm{~d}, J=3.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}), 6.57(\mathrm{dd}$, $J=3.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{ArH}), 5.49(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 3.98\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.94(\mathrm{~s}$, $\left.3 \mathrm{H}, \mathrm{OCH}_{3}\right), 2.48\left(\mathrm{~d}, J=17 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 2.44(\mathrm{~d}, J=17 \mathrm{~Hz}, 1 \mathrm{H}$, $\left.\mathrm{CH}_{2}\right), 2.30\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 1.11\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.09\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}-$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) ( $\delta, \mathrm{ppm}$ ): 195.0, 168.8, 163.4, 156.4, $151.0,150.8,129.3,123.9,110.6,109.8,94.8,54.5,54.2,50.5$, 41.1, 32.5, 29.3, 29.3, 27.5; HRMS(+ESI) 451.0624 [M + $\left.\mathrm{NH}_{4}\right]^{+}\left[-\mathrm{H}_{2} \mathrm{O}\right]$.

### 3.3. Antiproliferative activity

The antiproliferative activity was measured using our implementation of the National Cancer Institute (NCI) screening protocol. ${ }^{37}$ We used the following human solid tumour cell lines: A549 (non-small cell lung), HBL-100 (breast), HeLa (cervix), SW1573 (non-small cell lung), T-47D (breast), and WiDr (colon). Cell seeding densities were 2500 (A549, HBL-100, HeLa, and SW1573) or 5000 (T-47D and WiDr) cells per well. Tested compounds were dissolved in DMSO at an initial concentration of 40 mM . DMSO was used as negative control $(0.25 \% \mathrm{v} / \mathrm{v})$. The results were expressed as $\mathrm{GI}_{50}$, i.e. the dose that causes $50 \%$ growth inhibition after 48 h of exposure.

### 3.4. ADMET prediction

In silico ADMET prediction of potent antiproliferative 2,4-dimethoxy-THPQs $\mathbf{4 h}, \mathbf{4 o}, \mathbf{4 q}$ and $\mathbf{4 v}$ were calculated by web tool SwissADME (http://www.swissadme.ch/). ${ }^{38}$

## 4. Conclusion

In conclusion, we established MWI facilitated green synthetic protocol for a series of 2,4-dimethoxy-THPQs from multicomponent reaction between aldehyde 1, dimedone 2 and 6-amino-2,4-dimethoxypyrimidine 3 using glacial acetic acid. The main features of this green synthetic protocol are the use of commercially available cheap starting materials, metal-free multicomponent synthesis, short reaction time, higher product yield and no need to column chromatography for product purification. Biological screening showed that the compounds are able to inhibit proliferation of human tumour cells at the micromolar range. The SAR study was not able to
provide information for the future design of new analogues. In silico ADMET prediction of antiproliferative 2,4-dimethoxyTHPQs $\mathbf{4 h}, \mathbf{4 o}, \mathbf{4 q}$ and $\mathbf{4 v}$ show good bioavailability radar plot. Furthermore, BOILED-Egg delineation of $\mathbf{4 h}, \mathbf{4 0}, \mathbf{4 q}$ and $\mathbf{4 v}$ show that $\mathbf{4 0}$ have BBB permeability while other show high intestinal absorption. All these also have drug-like properties. Further biological studies will be necessary to identify the cellular targets involved in the biological effects.

## Conflicts of interest

The authors declare no conflict of interest.

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## References

1 V. A. Katzke, R. Kaaks and T. Kühn, Cancer J., 2015, 21.
2 R. M. Vala, M. G. Sharma, D. M. Patel, A. Puerta, J. M. Padrón, V. Ramkumar, R. L. Gardas and H. M. Patel, Arch. Pharm., 2021, 354, 2000466.
3 D. M. Patel, M. G. Sharma, R. M. Vala, I. Lagunes, A. Puerta, J. M. Padrón, D. P. Rajani and H. M. Patel, Bioorg. Chem., 2019, 86, 137-150.
4 B. Jiang, F. Shi and S.-J. Tu, Curr. Org. Chem., 2010, 14, 357378.

5 S. Gorle, S. Maddila, S. N Maddila, K. Naicker, M. Singh, P. Singh and S. B Jonnalagadda, Anticancer Agents Med Chem., 2017, 17, 464-470.
6 S. Moloi, S. Maddila and S. B. Jonnalagadda, Res. Chem. Intermed., 2017, 43, 6233-6243.
7 E. S. H. El Ashry, E. Ramadan, A. A. Kassem and M. Hagar, Adv. Heterocycl. Chem., 2005, 88, 1-110.
8 Y. Gu, Green Chem., 2012, 14, 2091-2128.
9 S. I. Alqasoumi, A. M. Al-Taweel, A. M. Alafeefy, E. Noaman and M. M. Ghorab, Eur. J. Med. Chem., 2010, 45, 738-744.
10 A. A. Abu-Hashem and A. S. Aly, Arch. Pharmacal Res., 2012, 35, 437-445.
11 M. B. El-Ashmawy, M. A. El-Sherbeny and N. S. El-Gohary, Med. Chem. Res., 2013, 22, 2724-2736.
12 M. M. Ghorab, F. A. Ragab, H. I. Heiba and W. M. Ghorab, J. Heterocycl. Chem., 2011, 48, 1269-1279.
13 R. A. Mekheimer, S. M. R. Allam, M. A. Al-Sheikh, M. S. Moustafa, S. M. Al-Mousawi, Y. A. Mostafa, B. G. M. Youssif, H. A. M. Gomaa, A. M. Hayallah,
M. Abdelaziz and K. U. Sadek, Bioorg. Chem., 2022, 121, 105693.

14 M. R. Selim, M. A. Zahran, A. Belal, M. S. Abusaif, S. A. Shedid, A. B. M. Mehany, G. A. M. Elhagali and Y. A. Ammar, Anti-Cancer Agents Med. Chem., 2019, 19, 439-452.
15 E. Tieger, V. Kiss, G. Pokol, Z. Finta, J. Rohlíček, E. Skořepová and M. Dušek, CrystEngComm, 2016, 18, 9260-9274.
16 S. Bedi, S. A. Khan, M. M. AbuKhader, P. Alam, N. A. Siddiqui and A. Husain, Saudi Pharm. J., 2018, 26, 755-763.
17 J. Wan, Y. Qiao, X. Chen, J. Wu, L. Zhou, J. Zhang, S. Fang and H. Wang, Adv. Funct. Mater., 2018, 28, 1804229.
18 K. Montazeri and J. Bellmunt, Expert Rev. Clin. Pharmacol., 2020, 13, 1-6.
19 A. Markham, Drug's, 2020, 80, 1345-1353.
20 A. K. Larsen, C. M. Galmarini and M. D'Incalci, Cancer Chemother. Pharmacol., 2016, 77, 663-671.
21 S. G. Patel, R. M. Vala, P. J. Patel, D. B. Upadhyay, V. Ramkumar, R. L. Gardas and H. M. Patel, RSC Adv., 2022, 12, 18806-18820.
22 A. Sharma, P. Appukkuttan and E. Van der Eycken, Chem. Соттип., 2012, 48, 1623-1637.
23 H. R. Prakash Naik, H. S. Bhojya Naik, T. R. Ravikumar Naik, H. R. Naik, D. S. Lamani and T. Aravinda, J. Sulfur Chem., 2008, 29, 583-592.
24 J. Quiroga, J. Trilleras, B. Insuasty, R. Abonía, M. Nogueras, A. Marchal and J. Cobo, Tetrahedron Lett., 2010, 51, 11071109.

25 M. H. Mosslemin, E. Zarenezhad, N. Shams, M. N. S. Rad, H. Anaraki-Ardakani and R. Fayazipoor, J. Chem. Res., 2014, 38, 169-171.
26 V. Tandon, R. M. Vala, A. Chen, R. L. Sah, H. M. Patel, M. C. Pirrung and S. Banerjee, Biosci. Rep., 2022, 42, BSR20212721.
27 M. G. Sharma, J. Pandya, D. M. Patel, R. M. Vala, V. Ramkumar, R. Subramanian, V. K. Gupta, R. L. Gardas, A. Dhanasekaran and H. M. Patel, Polycyclic Aromat. Compd., 2021, 41, 1495-1505.
28 H. M. Patel, D. P. Rajani, M. G. Sharma and H. G. Bhatt, Lett. Drug Des. Discovery, 2019, 16, 119-126.
29 D. M. Patel, R. M. Vala, M. G. Sharma, D. P. Rajani and H. M. Patel, ChemistrySelect, 2019, 4, 1031-1041.

30 H. M. Patel, Curr. Bioact. Compd., 2018, 14, 278-288.
31 M. G. Sharma, R. M. Vala, D. M. Patel, I. Lagunes, M. X. Fernandes, J. M. Padrón, V. Ramkumar, R. L. Gardas and H. M. Patel, ChemistrySelect, 2018, 3, 12163-12168.
32 H. M. Patel, Green Sustainable Chem., 2015, 5, 137.
33 D. M. Patel, R. M. Vala, M. G. Sharma, D. P. Rajani and H. M. Patel, ChemistrySelect, 2019, 4, 1031-1041.

34 J. Jin, J. Zhang, F. Liu, W. Shang, Y. Xin and S. Zhu, Chin. J. Chem., 2010, 28, 1217-1222.
35 J. A. Mokariya, A. G. Kalola, P. Prasad and M. P. Patel, Mol. Diversity, 2022, 26, 963-979.
36 A. Daina and V. Zoete, ChemMedChem, 2016, 11, 1117-1121. 37 I. Lagunes, E. Martín-Batista, G. Silveira-Dorta, M. X. Fernandes and J. M. Padrón, J. Mol. Clin. Med., 2018, 1, 77-84.
38 A. Daina, O. Michielin and V. Zoete, Sci. Rep., 2017, 7, 42717.


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[^1]:    ${ }^{a}$ Reaction condition: $1 \mathrm{mmol} p$-chlorobenzaldehyde 1a, 1 mmol 6 -amino-2,4-dimethoxypyrimidine 2 and 1 mmol dimedone 3 , 200 W MW. ${ }^{b} 3 \mathrm{~mL}$

[^2]:    ${ }^{a}$ PMI: process mass intensity, E-factor: environmental factor, SI: solvent intensity and WI: water intensity.

