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$FeCl_3$-catalyzed three-component reaction: a novel synthesis of tetrahydro-2,6-dioxopyrimidin-4-yl-2,3-dihydrophthalazine-1,4-dione derivatives under solvent-free conditions

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ABSTRACT

Three-component coupling of phthalhydrazide, aldehydes, and barbituric acid has been accomplished in the presence of 15 mol % $FeCl_3$ under solvent-free conditions to afford the corresponding tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives in excellent yields. This method provides high yields, shorter reaction time, and mild reaction conditions. This is the first example of the condensation of phthalhydrazide, aldehydes, and barbituric acid to provide a novel series of phthalhydrazide derivatives.

1. Introduction

Heterocyclic compounds have allured extensive great comprehensive due to their therapeutic properties in natural product and medicinal chemistry.[1] Nitrogen-containing heterocycles have wide range of biologically activities such as antibiotics, fungicides, anti-HIV protease, plant growth regulators, anti-thrombotic agents, anti-cancer, anti-inflammatory, anti-allergic, analgesic, glucagon receptor antagonism, herbicides, and insecticides.[2] Phthalazine derivatives have attracted much attention owing to their biological activities such as anticonvulsant, cardiotonic, vasorelaxant, pharmacological properties, and many other applications are well documented.[2,3] Due to their importance, some methods have been reported for synthesis of phthalazine derivatives.[4] Although, a number of adapted methods under enhanced conditions have been reported, many of them suffer from one or more drawbacks, such as unsatisfactory yields, high temperature, long reaction times, and the use of toxic organic solvents and catalysts. Thus, it is essential to further develop an efficient and suitable method to build this type of heterocyclic compounds.

Herein multi-component reactions (MCRs) are gaining more importance in the synthesis of biologically active heterocyclic compounds.[5] MCRs offer superior potential for molecular diversity per step with a minimum of synthetic time and under solvent-free conditions have concerned more attention from chemists principally from the viewpoint of green chemistry aspects due to formation of carbon–heteroatom bond.[6] Therefore, research on the MCR for the synthesis of heterocyclic compounds under solvent-free conditions is an interesting challenge.

$FeCl_3$ is a 'green' and efficient Lewis acid catalyst is potentially attractive in current organic synthesis by forming carbon–carbon and carbon–heteroatom bonds.[7] In recent years there have been many reports unraveling the utility of $FeCl_3$ in a wide variety of organic transformations.[8] Moreover, $FeCl_3$ is inexpensive, easy to handle, and are environmentally friendly. However, there have been no previous reports on the direct synthesis of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives (**4a**–**t**) using $FeCl_3$ as a catalyst.

As part of our continuing effort for accessing heterocyclic compounds, the development of an efficient green methodologies and Lewis acid-catalyzed organic transformations,[9] herein, we report a new and simple synthesis of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives (**4a**–**t**) promoted by $FeCl_3$ via condensation of phthalhydrazide, aldehydes, and barbituric acid under neat condition at 60 °C (Scheme 1).

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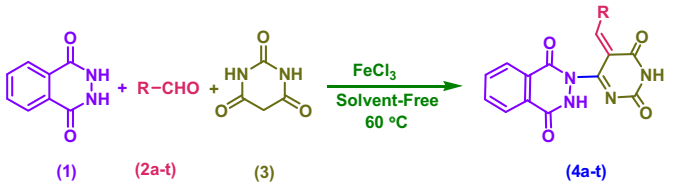
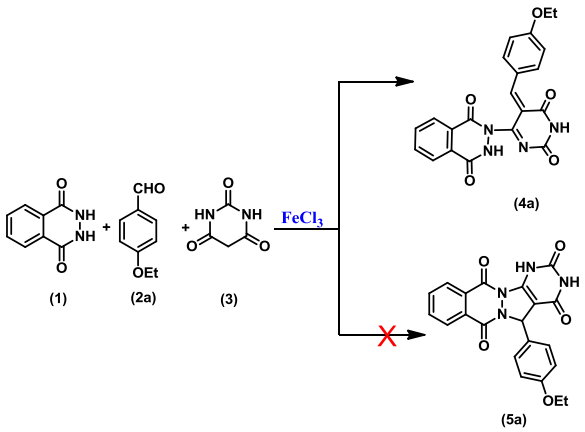


Scheme 1. Synthesis of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives (**4a**–**t**) catalyzed by $FeCl_3$ under solvent-free condition.

2. Results and discussion

At beginning we performed three-component condensation reaction of phthalhydrazide (**1**), 4-ethoxybenzaldehyde (**2a**), and barbituric acid (**3**) in the presence of $FeCl_3$ (15 mol %) at 60 °C. Curiously, the product 2-((5*Z*)-5-(4-ethoxybenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4a**) was found in 94% yield instead of the cyclization product, 5-(4-ethoxyphenyl)-1*H*-pyrimido[4′,5′:3,4]pyrazolo[1,2-*b*]phthalazine-2,4,7,12(3*H*,5*H*)-tetraone (**5a**) (Scheme 2)which was confirmed by NMR and HRMS. Probably lower selectivity of $FeCl_3$ and extended conjugation of the double bonds are the reasons for the inability of the formation of **5a**.



Scheme 2. Condensation of phthalhydrazide (1 mmol), 4-ethoxybenzaldehyde (1 mmol), and barbituric acid (1 mmol).

Encouraged by this result, we chosen this reaction as a model reaction to study the reaction conditions further for the synthesis of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives (**4a**–**t**). At first investigated the effect of solvent on model reaction in the presence of $FeCl_3$ catalyst at 60 °C. The results are summarized in Table 1. It was observed that, among all solvents ethanol shown good product yield (Table 1, entry 4), but even better result was obtained under solvent-free condition and gave excellent product yield in less reaction time and high purity of product (Table 1, entry 5).

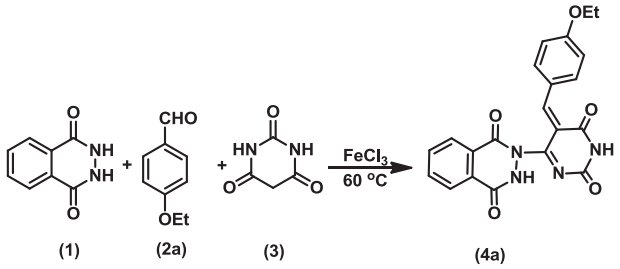
The catalyst plays an important role in the success of the reaction in terms of rate of the reaction and yields. After determined the optimized solvent conditions, we performed the scope of the catalyst. To find the best catalyst, we screened the model reaction in the presence and absence of different Lewis acid catalysts. In all cases the catalysts were taken as 15 mol % and reaction was done under solvent-free conditions at 60 °C (Table 2). In absence of the catalyst, the model reaction could be carried out but the product was obtained in very low yield after prolonged reaction time (Table 2, entry 1). But in the presence of the catalysts showed good results and in them found that, $FeCl_3$ proved to be the most efficient catalyst for the model reaction (Table 2, entry 8).

In order to optimize the suitable reaction conditions for preparation of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives (**4a**–**t**) via this novel green chemical approach, quantity of the catalyst required was determined. Initially, 5 mol % $FeCl_3$was used to perform the reaction. But it requires slightly long reaction time. Therefore, the loading of the catalyst was gradually increased from 5 mol % to 30 mol % (Table 2, entries 8–11). It was found that 15 mol % of $FeCl_3$ is optimal to carry out the reactions in a short duration (Table 2, entry 8). The use of excess of catalyst did not alter either reaction time or yield of the product. Thus, the use of 15 mol % $FeCl_3$ at 60 °C is ideal to achieve the desired product in good yields.

We also investigated different temperatures for the model reaction (Table 3). It was observed that fast reaction occurred on raising the temperature from 30 °C to reflux and the yield of preferred product increased significantly. We were satisfied to find that the reaction proceeded smoothly and almost complete conversion of reactants was observed at 60 °C to afford the desired product (**4a**) in 94% yield within 15 min (Table 3, entry 3). Further increase in the temperature did not affect the product yield.

Having optimized reaction conditions for the synthesis of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione

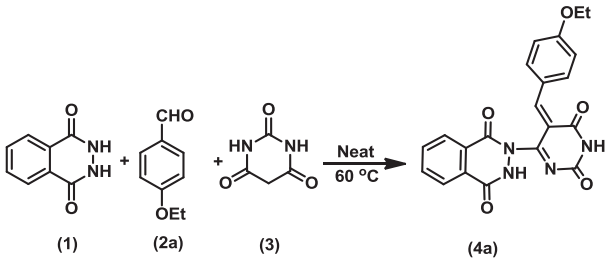
Table 1
Influence of the solvent on the synthesis of (**4a**)[a]



Entry	Solvent (5 mL)	Time (min)	Yield[b] (%)
1	Toluene	80	55
2	Acetonitrile	180	40
3	Tetrahydrofuran	130	35
4	Ethanol	60	75
5	Neat	15	94

[a] Reaction of phthalhydrazide(1 mmol), 4-ethoxybenzaldehyde (1 mmol), and barbituric acid (1 mmol) catalyzed by 15 mol % of $FeCl_3$ at 60 °C.
[b] Isolated yield.

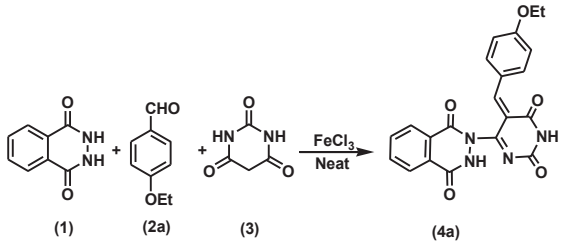
Table 2
Influence of the catalyst on the synthesis of (**4a**)[a]



Entry	Catalyst	Catalyst (mol %)	Time (min)	Yield[b] (%)
1	Free	—	110	30
2	$ZnCl_2$	15	60	40
3	FeF_3	15	45	60
4	InF_3	15	40	70
5	$GaCl_3$	15	70	55
6	$Y(OAc)_3 \cdot H_2O$	15	100	40
7	$Cd(ClO_4)_2 \cdot H_2O$	15	55	40
8	$FeCl_3$	15	15	94
9	$FeCl_3$	5	40	50
10	$FeCl_3$	10	15	75
11	$FeCl_3$	30	15	94

[a] Reaction of phthalhydrazide(1 mmol), 4-ethoxybenzaldehyde (1 mmol), and barbituric acid (1 mmol) under solvent-free conditions at 60 °C.
[b] Isolated yield.

Table 3
Effect of temperature for the synthesis of (**4a**)[a]



Entry	Temp (°C)	Time (min)	Yield[b] (%)
1	30	150	10
2	40	80	40
3	60	15	94
4	100	15	94
5	Reflux	15	94

[a] Reaction of phthalhydrazide(1 mmol), 4-ethoxybenzaldehyde (1 mmol), and barbituric acid (1 mmol) catalyzed by $FeCl_3$ under solvent-free conditions.
[b] Isolated yield.

derivatives (**4a**–**t**) using 15 mol % $FeCl_3$ as the catalyst under solvent-free conditions at 60 °C we subsequently applied for a variety of aldehydes including *ortho*-, *meta*-, and *para*-substituted arylaldehydes (Table 4). Notably, sterically hindered *ortho*-substituted

Table 4
$FeCl_3$-catalyzed multi-component synthesis of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives[a]

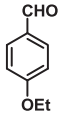
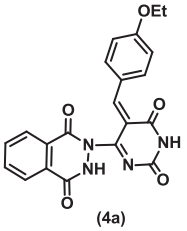
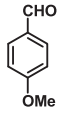
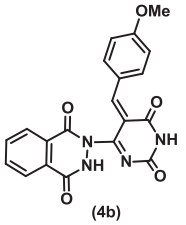
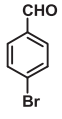
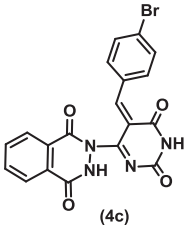
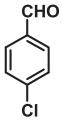
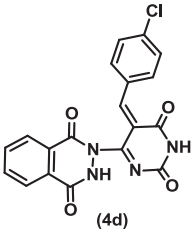
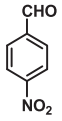
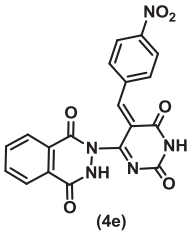
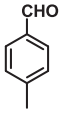
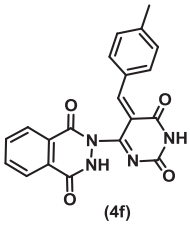
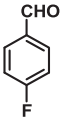
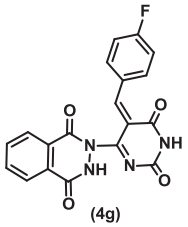
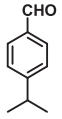
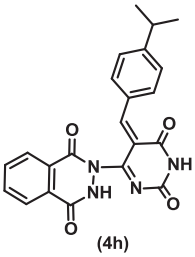
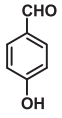
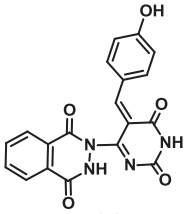
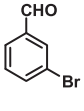
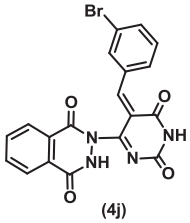
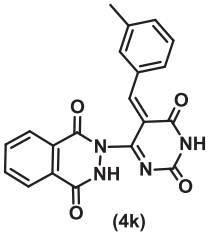
Entry	Aldehydes (R)	Product	Time (min)	Yield[b] (%)	Mp (°C)
1		 (4a)	15	94	268–270
2		 (4b)	16	93	255–257
3		 (4c)	20	90	270–272
4		 (4d)	18	91	262–264

Table 4 (*continued*)

Entry	Aldehydes (R)	Product	Time (min)	Yield[b] (%)	Mp (°C)
5		 (4e)	21	90	274–276
6		 (4f)	16	93	258–260
7		 (4g)	18	91	290–292
8		 (4h)	20	94	248–250
9		 (4i)	16	92	330–332
10		 (4j)	19	90	248–250
11		 (4k)	17	91	232–234

(*continued on next page*)

Table 4 (*continued*)

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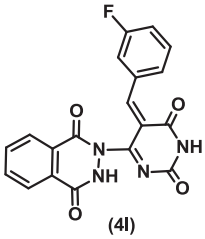
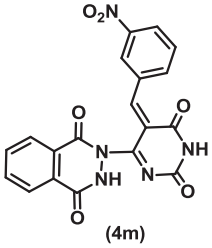
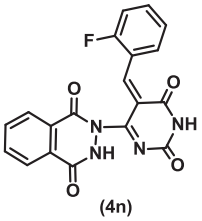
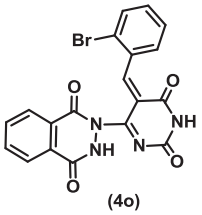
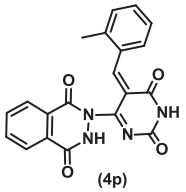
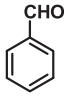
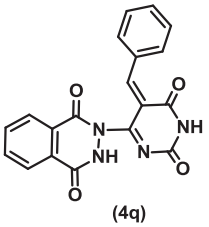
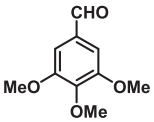
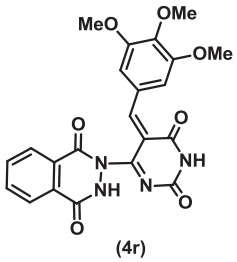
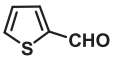
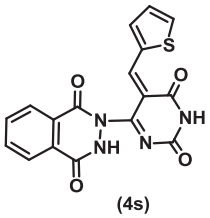
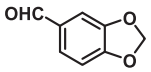
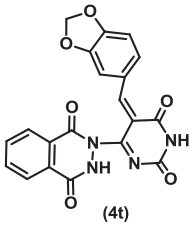
12		 (4l)	22	90	258–260
13		 (4m)	25	89	280–282
14		 (4n)	21	90	276–278
15		 (4o)	17	91	238–240
16		 (4p)	19	90	256–258
17		 (4q)	20	91	230–232
18		 (4r)	18	94	268–270

Table 4 (*continued*)

Entry	Aldehydes (R)	Product	Time (min)	Yield[b] (%)	Mp (°C)
19		 (4s)	22	90	272–274
20		 (4t)	20	90	280–282

[a] Reaction of aldehydes (1 mmol), phthalhydrazide(1 mmol), and barbituric acid (1 mmol) catalyzed by $FeCl_3$ under solvent-free microwave irradiation at 60 °C.
[b] Isolated yield.

aldehydes (Table 4, entries 14–16) also participated effectively in this reaction. Both the electron rich (Table 4, entries 1–4, 6, 8, 9 and 17–20) as well as electron deficient substrates (Table 4, entries 5 and 7) are found to be equally effective for this conversion. The acid-sensitive heterocyclic aldehyde, thiophene-2-carbaldehyde was also obtained in good yield (Table 4, entry 19). But the *meta*-substituted aldehydes resulted little bit lesser product yields (Table 4, entries 10–13). All of the new structures were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS.

2.1. Spectral analysis of (*Z*)-2-(5-(2-methylbenzylidene)-2,6-dioxo-1,2,5,6-tetrahydropyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (4p)

Compound **4p** showed absorption bands in IR spectrum (Fig. 1) at 3070 and 1922 cm^{-1} indicating that the presence of unsaturation, which is as internal double bond and it clearly observed as *Z*-configuration at C=C due to appearance of a strong absorption band at 746 cm^{-1}. The carbonyl groups of this compound showed an absorption band at 1691 cm^{-1} indicating that the C=O is in an amide function.

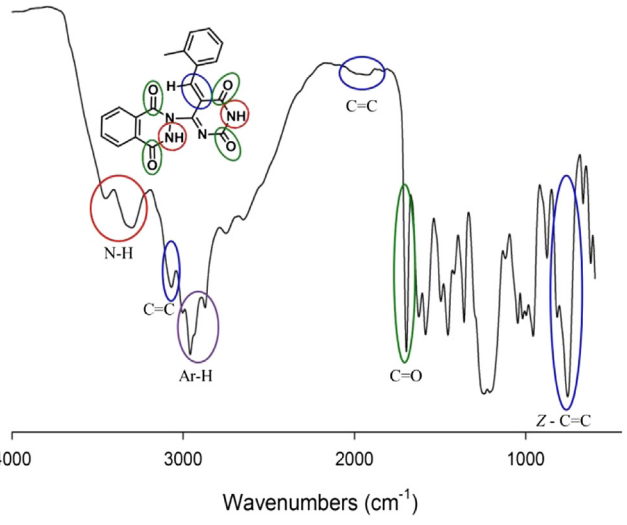


Fig. 1. FTIR spectrum of compound **4p**.

In PMR spectrum (Fig. 2) of this compound the basic protons (N–H), olefinic proton (C=C–H), and methyl protons appear as singlet at δ 11.40, 11.17, 8.40, and 2.27 ppm, respectively. All the aromatic protons appear in the region of δ 8.08–7.15 ppm. All these protons are correlating to each other in their corresponding correlation spectroscopy (COSY) (Fig. 3). At the inset of the COSY spectrum shows a part of nuclear Overhauser exchange spectroscopy (NOESY) spectrum indicating that a much weaker correlation through-space appears between N–H and C=C–H protons at 8.40 ppm. It indicates that the compound exists in *Z*-configuration at the double bond.

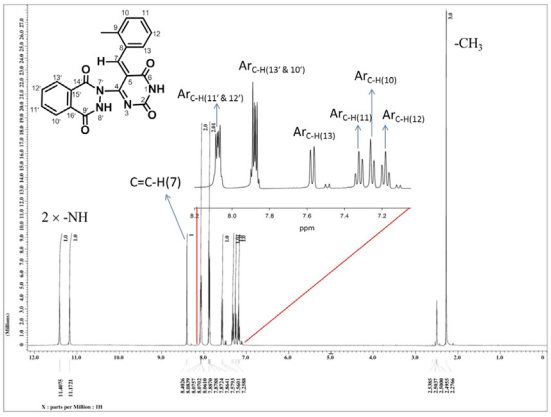


Fig. 2. 1D-PMR spectrum of compound **4p**.

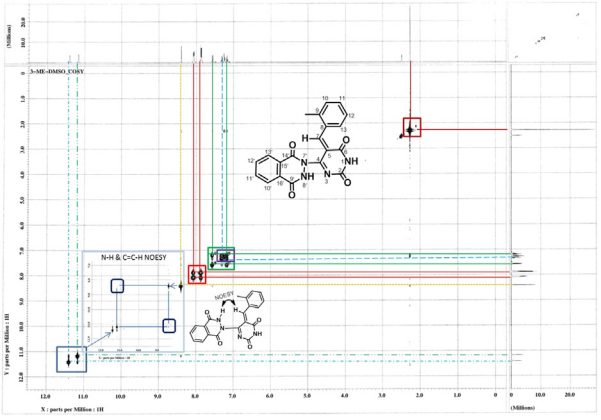


Fig. 3. H–H COSY (inset: part of NOESY of N–H & C=C–H) spectrum of compound **4p**.

The CMR spectrum (Fig. 4) shows that the amide carbonyl carbons and the olefinic carbon appear at high frequency region. And also the aromatic carbons appear at lower field region. The olefinic carbon and its corresponding protons are in correlation in their heteronuclear single quantum correlation (HSQC) spectrum (Fig. 5). And all the remaining protons are also correlating with corresponding carbons in their single quantum correlation spectrum. The carbons, which have no protons are not correlating with any other proton nuclei.

The role of $FeCl_3$ as catalyst in titled compounds (**4a**–**t**) synthesis should be postulated as shown in Scheme 3. The multicomponent reaction should be proceeding in a stepwise manner. At first, the reaction occurs via Knoevenagel condensation between enolic form of barbituric acid (**3**) and aldehyde (**2**) in the presence of $FeCl_3$ catalyst to form the intermediate, **6a**. This is enolising as **6b** to stabilize by extending conjugation in presence of catalyst. After that it transforms immediately into one more intermediate, **7**, by Michael addition of 2,3-dihydrophthalazine-1,4-dione (**1**) at

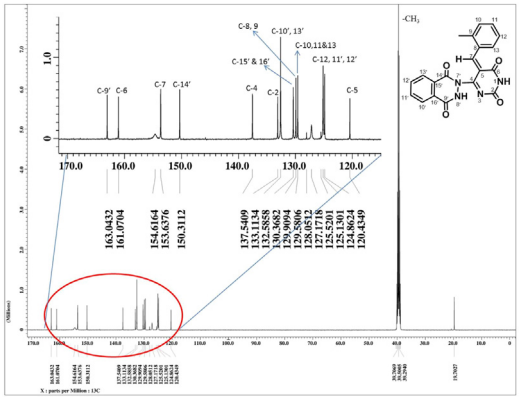


Fig. 4. 1D-CMR spectrum of compound **4p**.

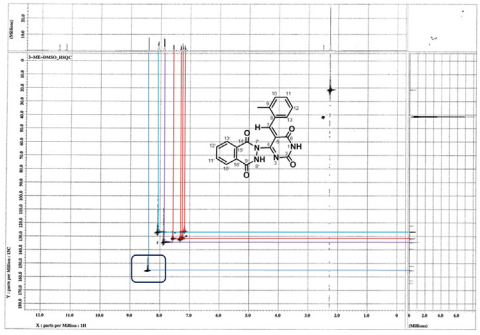
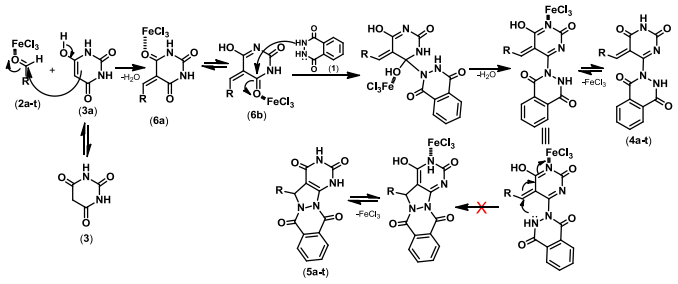


Fig. 5. HSQC spectrum of compound **4p**.

conjugated C=O bond of **6b**. Finally, the products (**4a**–**t**) obtained by elimination of water molecule in good yields rather than the cyclization products (**5a**–**t**).



Scheme 3. Schematic presentation of the possible mechanism for products **4a**–**t** formation.

3. Conclusion

In summary, we have successfully developed a green and facile method for the synthesis of tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione derivatives from easily available starting materials using $FeCl_3$ as a catalyst under solvent-free conditions. The mild reaction conditions, simple work-up without column chromatographic purification, neat condition, operational simplicity, and high yields are the advantages of this protocol.

4. Experimental

4.1. General

Chemicals were purchased from Aldrich and Alfaaesar Chemical Companies. NMR spectra were recorded in parts per million (ppm)

in DMSO-d_6 on a Jeol JNM ECP 400 NMR instrument using TMS as internal standard. Mass spectra were recorded on a Jeol JMS-700 mass spectrometer. All melting points were determined using open capillaries on an Electrothermal-9100 (Japan) instrument.

4.2. Synthesis of 2-((13*Z*)-5-(4-ethoxybenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (4a)

A mixture of phthalhydrazide (**1**, 1 mmol), 4-ethoxtbenzaldehyde (**2a**, 1 mmol), barbituric acid (**3**, 1 mmol), and $FeCl_3$ (15 mol %) was stirred at 60 °C under solvent-free condition for 15 min (Table 4, entry 1). The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was washed with water and ethanol and residue recrystallized from ethanol to afford the pure product **4a** (94%).

*4.2.1. 2-((13Z)-5-(4-Ethoxybenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4a**).* Yield 94%; yellow solid; mp 268–270 °C. IR (KBr): ν=3350, 3196, 2853, 1740, 1695, 1664, 1591, 708 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.29 (s, 1H), 11.17 (s, 1H), 8.35 (d, J=8.8 Hz, 2H), 8.24 (s, 1H), 8.07–8.05 (m, 2H), 7.88–7.86 (m, 2H), 7.02 (d, J=9.1 Hz, 2H), 4.15–4.11 (q, 2H), 1.34 (t, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 162.8, 162.2, 155.1, 150.2, 137.6, 132.6, 127.2, 125.1, 125.0, 115.3, 114.3, 63.7, 14.4; HRMS (ESI, m/z): calcd for $C_{21}H_{16}N_4O_5$ ($M+H^+$) 404.1121, found: 404.1120.

*4.2.2. 2-((13Z)-5-(4-Methoxybenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4b**).* Yield 93%; yellow solid; mp 255–257 °C. IR (KBr): ν=3370, 3042, 2847, 1745, 1693, 1646, 1545, 710 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.31 (s, 1H), 11.18 (s, 1H), 8.36 (d, J=9.1 Hz, 2H), 8.24 (s, 1H), 8.07–8.05 (m, 2H), 7.88–7.86 (m, 2H), 7.04 (d, J=8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 163.4, 162.2, 154.9, 150.2, 137.5, 132.6, 128.0, 127.1, 125.1, 115.5, 113.9, 55.6; HRMS (ESI, m/z): calcd for $C_{20}H_{14}N_4O_5$ ($M+H^+$) 390.0964, found: 390.0960.

*4.2.3. 2-((13Z)-5-(4-Bromobenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4c**).* Yield 90%; yellow solid; mp 270–272 °C. IR (KBr): ν=3203, 3092, 2850, 1726, 1660, 1654, 1598, 711 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 11.28 (s, 1H), 8.21 (s, 1H), 8.07–8.04 (m, 2H), 7.97 (d, J=8.8 Hz, 2H), 7.86 (dd, J=2.1, 10.2 Hz, 2H), 7.66–7.62 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.2, 161.6, 153.1, 150.2, 134.7, 132.6, 131.9, 131.0, 128.1, 127.1, 125.8, 125.5, 125.1, 119.7; HRMS (ESI, m/z): calcd for $C_{19}H_{11}BrN_4O_4$ ($M+H^+$) 439.219, found: 439.215.

*4.2.4. 2-((13Z)-5-(4-Chlorobenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4d**).* Yield 91%; yellow solid; mp 262–264 °C. IR (KBr): ν=3309, 3012, 2850, 1761, 1662, 1644, 1559, 718 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 11.21 (s, 1H), 8.24 (s, 1H), 8.07 (d, J=8.8 Hz, 3H), 7.89–7.85 (m, 2H), 7.51 (d, J=8.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.2, 161.5, 153.0, 150.1, 136.7, 134.7, 132.5, 131.5, 128.0, 127.1, 125.1, 119.6; HRMS (ESI, m/z): calcd for $C_{19}H_{11}ClN_4O_4$ ($M+H^+$) 394.768, found: 394.764.

*4.2.5. 2-((13Z)-5-(4-Nitrobenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4e**).* Yield 90%; yellow solid; mp 274–276 °C. IR (KBr): ν=3350, 3017, 2853, 1740, 1657, 1634, 1596, 717 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.52 (s, 1H), 11.34 (s, 1H), 8.31 (s, 1H), 8.27–8.20 (m, 2H), 8.07–8.04 (m, 2H), 8.00 (d, J=7.2 Hz, 2H), 7.87–7.83 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7, 161.5, 151.2, 150.3, 148.0, 140.0, 132.6, 132.3, 127.2, 125.2, 122.7, 122.3; HRMS (ESI, m/z): calcd for $C_{19}H_{11}N_5O_6$ ($M+H^+$) 405.0709, found: 405.0704.

*4.2.6. 2-((13Z)-5-(4-Methylbenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4f**).* Yield 93%; yellow solid; mp 258–260 °C. IR (KBr): ν=3290, 3096, 2840, 1749, 1665, 1621, 1581, 712 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.38 (s, 1H), 11.23 (s, 1H), 8.23 (s, 1H), 8.08–8.05 (m, 4H), 7.88–7.85 (m, 2H), 7.26 (d, J=8.0 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.6, 161.8, 155.0, 150.2, 143.5, 134.0, 132.6, 129.9, 128.8, 127.2, 125.1, 117.8, 21.4; HRMS (ESI, m/z): calcd for $C_{20}H_{14}N_4O_4$ ($M+H^+$) 374.1015, found: 374.1015.

*4.2.7. 2-((13Z)-5-(4-Fluorobenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4g**).* Yield 92%; yellow solid; mp 290–292 °C. IR (KBr): ν=3390, 3096, 2851, 1761, 1679, 1659, 1588, 695 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.41 (s, 1H), 11.27 (s, 1H), 8.26 (s, 1H), 8.23–8.20 (m, 2H), 8.07–8.05 (m, 2H), 7.87–7.85 (m, 2H), 7.28 (t, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.2 (C–F, d, J=252.2 Hz), 163.4, 161.8, 153.5, 150.2, 136.4, 136.3, 132.6, 129.2, 127.2, 125.1, 118.7, 115.3, 115.1; HRMS (ESI, m/z): calcd for $C_{19}H_{11}FN_4O_4$ ($M+H^+$) 378.0764, found: 378.0760.

*4.2.8. 2-((13Z)-5-(4-Isopropylbenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4h**).* Yield 90%; yellow solid; mp 248–250 °C. IR (KBr): ν=3351, 3086, 2853, 1740, 1693, 1660, 1581, 712 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.37 (s, 1H), 11.22 (s, 1H), 8.25 (s, 1H), 8.07–8.05 (m, 3H), 7.88–7.86 (m, 3H), 7.34 (d, J=8.4 Hz, 2H), 2.95–2.90 (m, 1H), 1.20 (d, J=6.9 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.6, 161.8, 154.9, 153.8, 150.2, 134.1, 132.6, 130.2, 128.1, 127.1, 126.1, 125.5, 125.1, 117.9, 33.6, 23.4; HRMS (ESI, m/z): calcd for $C_{22}H_{18}N_4O_4$ ($M+H^+$) 402.1328, found: 402.1325.

*4.2.9. 2-((13Z)-5-(4-Hydroxybenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4i**).* Yield 92%; yellow solid; mp 330–332 °C. IR (KBr): ν=3350, 3100, 2858, 1748, 1695, 1664, 1590, 710 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.27 (s, 1H), 11.14 (s, 1H), 10.82 (s, 1H), 8.32 (d, J=7.6 Hz, 2H), 8.21 (s, 1H), 8.08–8.05 (m, 2H), 7.87 (t, J=5.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.1, 163.0, 162.3, 155.5, 150.3, 138.3, 132.6, 127.2, 125.2, 123.8, 115.5, 114.2; HRMS (ESI, m/z): calcd for $C_{19}H_{12}N_4O_5$ ($M+H^+$) 376.0808, found: 376.0810.

*4.2.10. 2-((13Z)-5-(3-Bromobenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4j**).* Yield 89%; yellow solid; mp 248–250 °C. IR (KBr): ν=3290, 3096, 2863, 1760, 1685, 1654, 1586, 715 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.46 (s, 1H), 11.30 (s, 1H), 8.27 (s, 1H), 8.21 (s, 1H), 8.08–8.05 (m, 2H), 7.88–7.85 (m, 3H), 7.66 (d, J=7.6 Hz, 1H), 7.39 (t, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.1, 161.5, 152.5, 150.2, 135.1, 134.3, 134.1, 132.6, 131.7, 130.0, 127.2, 125.2, 121.0, 120.6; HRMS (ESI, m/z): calcd for $C_{19}H_{11}BrN_4O_4$ ($M+H^+$) 439.219, found: 439.214.

*4.2.11. 2-((13Z)-5-(3-Methylbenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4k**).* Yield 92%; yellow solid; mp 232–234 °C. IR (KBr): ν=3352, 3086, 2857, 1751, 1678, 1639, 1588, 709 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.40 (s, 1H), 11.24 (s, 1H), 8.23 (s, 1H), 8.08–8.05 (m, 3H), 7.88–7.85 (m, 3H), 7.33 (d, J=7.2 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.4, 161.6, 154.9, 150.3, 137.2, 133.6, 133.0, 132.6, 130.3, 128.0, 127.1, 125.1, 118.9, 20.9; HRMS (ESI, m/z): calcd for $C_{20}H_{14}N_4O_4$ ($M+H^+$) 374.1015, found: 374.1010.

*4.2.12. 2-((13Z)-5-(3-Fluorobenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4l**).* Yield

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90%; yellow solid; mp 258–260 °C. IR (KBr): ν=3299, 3076, 2850, 1749, 1690, 1650, 1598, 705 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.46 (s, 1H), 11.31 (s, 1H), 8.24 (s, 1H), 8.08–8.05 (m, 2H), 8.02–7.99 (m, 1H), 7.88–7.85 (m, 2H), 7.75 (d, J=7.7 Hz, 1H), 7.51–7.46 (m, 1H), 7.37–7.33 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.1, 161.5, 160.3 (C–F, d, J=240.0 Hz), 152.7, 150.2, 134.9, 132.6, 130.0, 129.9, 129.4, 127.2, 125.1, 120.4, 118.8–118.4; HRMS (ESI, m/z): calcd for $C_{19}H_{11}FN_4O_4$ ($M+H^+$) 378.0764, found: 378.0758.

*4.2.13. 2-((13Z)-5-(3-Nitrobenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4m**).* Yield 89%; yellow solid; mp 280–282 °C. IR (KBr): ν=3300, 3056, 2831, 1726, 1670, 1689, 1598, 715 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 11.35 (s, 1H), 8.90 (s, 1H), 8.31–8.29 (m, 1H), 8.21 (d, J=7.6 Hz, 1H), 8.07–8.05 (m, 2H), 7.89–7.85 (m, 3H), 7.72 (t, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 161.5, 151.2, 150.3, 147.1, 138.4, 134.5, 132.6, 129.4, 126.1, 125.5, 125.1, 121.6; HRMS (ESI, m/z): calcd for $C_{19}H_{11}N_5O_6$ ($M+H^+$) 405.0709, found: 405.0702.

*4.2.14. 2-((13Z)-5-(2-Fluorobenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4n**).* Yield 90%; yellow solid; mp 276–278 °C. IR (KBr): ν=3310, 3096, 2851, 1741, 1670, 1650, 1594, 713 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.47 (s, 1H), 11.29 (s, 1H), 8.27 (s, 1H), 8.08–8.05 (m, 2H), 7.94–7.86 (m, 3H), 7.55–7.51 (m, 1H), 7.30–7.22 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7, 161.8, 160.5 (C–F, d, J=200.0 Hz), 150.2, 145.5, 133.5, 132.6, 132.2, 125.1, 123.8, 121.6, 121.5, 121.3, 115.3, 115.1; HRMS (ESI, m/z): calcd for $C_{19}H_{11}FN_4O_4$ ($M+H^+$) 378.0764, found: 378.0761.

*4.2.15. 2-((13Z)-5-(2-Bromobenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4o**).* Yield 91%; yellow solid; mp 238–240 °C. IR (KBr): ν=3290, 3088, 2850, 1761, 1666, 1633, 1580, 712 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.48 (s, 1H), 11.25 (s, 1H), 8.22 (s, 1H), 8.08–8.06 (m, 2H), 7.89–7.86 (m, 2H), 7.70 (dd, J=2.2, 9.1 Hz, 2H), 7.39–7.36 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.6, 160.8, 151.8, 150.2, 134.2, 132.5, 131.9, 127.1, 126.7, 125.1, 123.3, 121.3; HRMS (ESI, m/z): calcd for $C_{19}H_{11}BrN_4O_4$ ($M+H^+$) 439.219, found: 439.216.

*4.2.16. 2-((13Z)-5-(2-Methylbenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4p**).* Yield 90%; yellow solid; mp 256–258 °C. IR (KBr): ν=3452, 3314, 3070, 2959, 2872, 1691, 1615, 1569, 1226, 746 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 11.19 (s, 1H), 8.40 (s, 1H), 8.09–8.06 (m, 2H), 7.89–7.86 (m, 2H), 7.57 (d, J=7.6 Hz, 1H), 7.31 (t, J=7.3 Hz, 1H), 7.24 (d, J=7.3 Hz, 1H), 7.17 (t, J=7.6 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.1, 161.1, 153.7, 150.3, 137.6, 133.1, 132.6, 130.4, 129.9, 129.6, 127.2, 125.1, 124.9, 120.4, 19.7; (ESI, m/z): calcd for $C_{20}H_{14}N_4O_4$ ($M+H^+$) 374.1015, found: 374.1013.

*4.2.17. 2-((13Z)-5-Benzylidene-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4q**).* Yield 91%; yellow solid; mp 230–232 °C. IR (KBr): ν=3390, 3017, 2853, 1761, 1657, 1639, 1596, 713 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.41 (s, 1H), 11.25 (s, 1H), 8.27 (s, 1H), 8.09–8.05 (m, 4H), 7.88–7.85 (m, 2H), 7.51–7.49 (m, 1H), 7.45–7.43 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.4, 161.6, 154.7, 150.2, 133.1, 132.7, 132.6, 132.2, 128.1, 128.0, 127.2, 125.5, 125.1, 119.1; HRMS (ESI, m/z): calcd for $C_{19}H_{12}N_4O_4$ ($M+H^+$) 360.0859, found: 360.0856.

*4.2.18. 2-((13Z)-5-(3,4,5-Trimethoxybenzylidene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4r**).* Yield 93%; yellow solid; mp 268–270 °C. IR (KBr): ν=3370, 3042, 2847, 1744, 1690, 1646, 1578, 716 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.37 (s, 1H), 11.24 (s, 1H), 8.25 (s, 1H), 8.07–8.05 (m, 2H), 7.89–7.86 (m, 2H), 7.83 (s, 2H), 3.81 (s, 6H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.7, 162.1, 155.2, 151.9, 150.1, 141.9, 132.5, 127.5, 125.1, 117.2, 112.6, 60.3, 56.0; HRMS (ESI, m/z): calcd for $C_{22}H_{18}N_4O_7$ ($M+H^+$) 450.1175, found: 450.1172.

*4.2.19. 2,3-Dihydro-2-((13Z)-1,2,5,6-tetrahydro-2,6-dioxo-5-((thiophen-2-yl)methylene)pyrimidin-4-yl)phthalazine-1,4-dione (**4s**).* Yield 88%; yellow solid; mp 272–274 °C. IR (KBr): ν=3390, 3022, 2852, 1751, 1679, 1659, 1597, 700 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.32 (s, 1H), 11.28 (s, 1H), 8.56 (s, 1H), 8.27–8.25 (m, 1H), 8.16–8.15 (m, 1H), 8.08–8.05 (m, 2H), 7.88–7.7.85 (m, 2H), 7.33–7.32 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.5, 163.0, 150.0, 145.8, 145.7, 142.1, 136.6, 132.6, 128.4, 127.1, 125.1, 111.6; HRMS (ESI, m/z): calcd for $C_{17}H_{10}N_4O_4S$ ($M+H^+$) 366.0423, found: 366.0420.

*4.2.20. 2-((5Z)-5-((Benzo[d][1,3]dioxol-5-yl)methylene)-1,2,5,6-tetrahydro-2,6-dioxopyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-dione (**4t**).* Yield 90%; yellow solid; mp 280–282 °C. IR (KBr): ν=3370, 3016, 2841, 1755, 1679, 1648, 1593, 698 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.33 (s, 1H), 11.21 (s, 1H), 8.25 (d, J=7.0 Hz, 1H), 8.19 (s, 1H), 8.07–8.05 (m, 2H), 7.88–7.86 (m, 2H), 7.72 (dd, J=2.2, 8.8 Hz, 1H), 7.06 (d, J=8.3 Hz, 1H), 6.17 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.8, 162.2, 154.9, 151.9, 150.1, 147.3, 133.7, 132.6, 126.7, 125.1, 115.9, 112.4, 108.2, 102.3; HRMS (ESI, m/z): calcd for $C_{20}H_{12}N_4O_6$ ($M+H^+$) 404.0757, found: 404.0755.

Supplementary data

NMR spectra of all compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.04.044.

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