KI-VO(acac)$_2$-H_2O_2-AcOH, A New Iodinating System for Selective Iodination at C-5 Position of Activated Pyrimidinediones: A Combined Experimental and Density Functional Study

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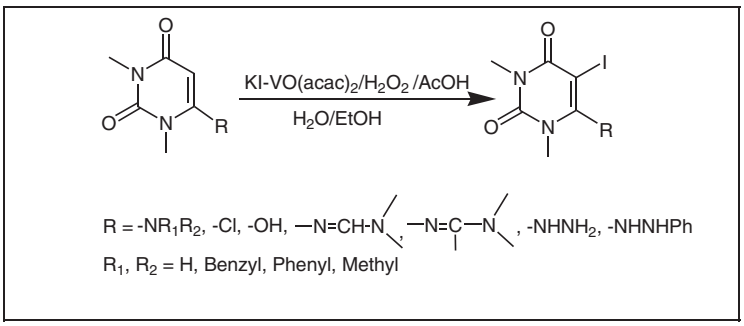

KI-VO(acac)$_2$-H_2O_2 in aqueous ethanolic medium with acetic acid as additive has been found to iodinate pyrimidinediones and aromatic amines. The methodology is mild, efficient, and environmentally benign. Density functional theory-based reactivity parameters support the experimentally observed reactivity of pyrimidinedione derivatives.

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INTRODUCTION

The halogenation reaction has been getting much attention as the halogenated species are very useful in the preparation of organometallic compounds, metal-catalyzed cross coupling, and C-C and/or C-N bond-forming reactions [1]. Halogenation of pyrimidines is particularly important because of the potent activity of 5-halogenated pyrimidines as anticancer and antiviral agents [2] as well as their usefulness as intermediates for further synthetic manipulation [3]. However, halogenation reactions are associated with environmental hazards with respect to transport, handling, and storage [4]. So, efforts are on to minimize the hazards as well as the risk by replacing the halogens with halide salts as the later are comparatively safer commodities and can be oxidized to the corresponding positive halogen/hypohalous acids. Among the halogenation reactions, iodination is somewhat difficult because of the poor electrophilic nature of iodine compared with that of molecular bromine or chlorine and requires an oxidizing agent in to produce electrophilic I^+ species. Among various oxidizing agents, hydrogen peroxide is considered to be the most preferable one because of its strong oxidizing ability and environment-friendly nature [5]. Iodination using hydrogen peroxide [6] or other oxidizing agents [7] to generate I^+ *in situ* is reported. Iodination of pyrimidines bears additional importance as the iodinated species are excellent precursors for radical reactions. Only few reports [8] described iodination of pyrimidine ring as compared with aromatic counterpart. To the best our knowledge, there has not been found any generalized procedure for iodination of pyrimidines. However, reports are available, which are limited to some selective pyrimidines only. That is why the search for an effective and generalized novel methodology for iodination is still relevant.

Meanwhile, peroxo complexes of vanadium, molybdenum, and tungsten have established their role as excellent oxidant *in situ* [9], especially in bromination reactions of organic compounds [10].

RESULTS AND DISCUSSION

Continuing our interest in the synthesis of pyrimidine derivative [11] and iodine-mediated reactions [11], herein, we want to divulge that KI-VO(acac)$_2$-H_2O_2 is an effective reagent protocol for mono-iodination of activated pyrimidinediones **1** at C-5 (Scheme 1)

Scheme 1. Selective iodination of pyrimidinediones **1** using KI-VO(acac)$_2$-O_2-AcOH.

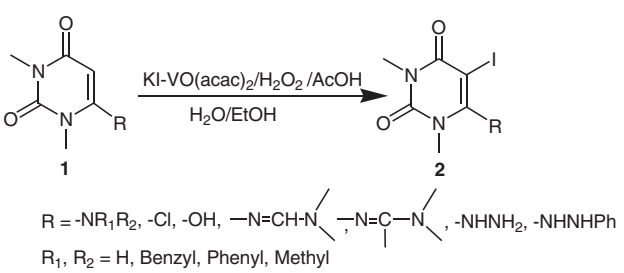
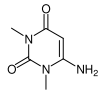
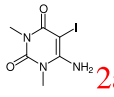
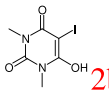
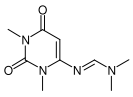
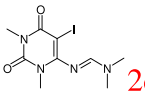
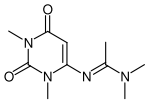
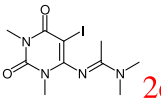
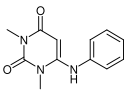
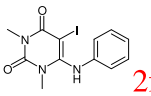
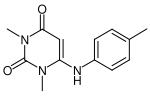
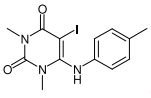
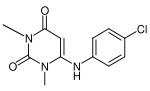
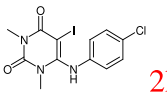
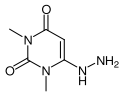
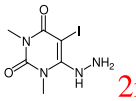
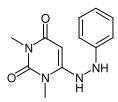
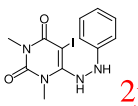
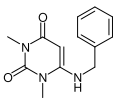
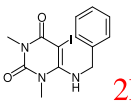


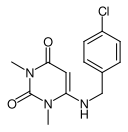
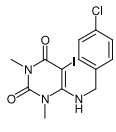
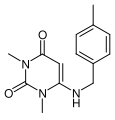
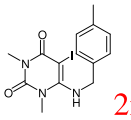
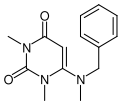
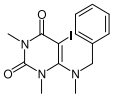
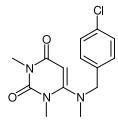
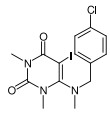
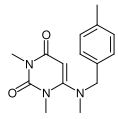
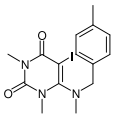
Table 1

Iodination of pyrimidinediones **1a–p** according to Scheme 1.

Entry	Substrate	Product	Time	Yield (%)[a]
1	 1a	 2a	10 min	98 [8a]
2	 1b	 2b	6 h	23
3	 1c	—	6 h	—[b]
4	 1d	 2d	20 min	94 [8d]
5	 1e	 2e	15 min	96 [12]
6	 1f	 2f	35 min	93
7	 1g	 2g	32 min	94
8	 1h	 2h	40 min	92
9	 1i	 2i	10 min	95
10	 1j	 2j	15 min	90
11	 1k	 2k	30 min	92

(*Continued*)

Table 1.
(Continued)

Entry	Substrate	Product	Time	Yield (%)[a]
12	 1l	 2l	35 min	88
13	 1m	 2m	30 min	89
14	 1n	 2n	25 min	92
15	 1o	 2o	25 min	90
16	 1p	 2p	25 min	92

[a]Isolated yield.
[b]No product found.

position selectively. A small amount of acetic acid as additive promotes the reaction. Here, potassium iodide is the iodine source, and hydrogen peroxide is the oxidant. DFT-based reactivity parameters were derived for some selected pyrimidines to support the experimentally observed reactivity.

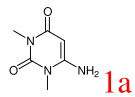
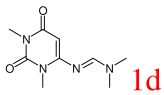
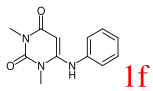
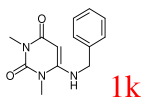
The methodology is based on the activation of dioxygen by *in situ* generated peroxocomplex that oxidizes I^- to I^+ in acidic medium. As a test experiment, we examined the iodination reaction with pyrimidinedione **1a** (Table 1), and to our delight, we found complete conversion to provide the product **2a** in 98% isolated yield within 10 min. The amino group was found to be compatible.

To examine the regioselectivity of our methodology, we have applied the same procedure on pyrimidinediones **1d**,**f**,**k**, and it has been found that our iodination protocol is exclusively regioselective at C-5 position. Encouraged by this result, we extended the reaction to other differently substituted at 6-position of pyrimidinediones, which were urgently required as precursors in one of our ongoing projects on intramolecular radical cyclisation reaction. The results are summarized in Table 1 (entries 1–16).

From Table 1, it is evident that our methodology is very selective for mono-iodination at C-5 position of pyrimidinedione ring irrespective of the presence of double bond in the side chain or aromatic ring in the substrate. Dissolution of vanadyl acetylacetonate in hydrogen peroxide makes the system acidic, and so, the reaction can also be conducted without using extra acid; however, conversion to product is rather slow and low yielding. In Table 2, we have made a comparison between the methodologies with and without using acetic acid as an additive with different catalyst loading. Table 2 clearly reveals that acetic acid promotes the catalytic activity of peroxovanadium complex formed *in situ*. Various conditions were examined and concluded that 1:0.05:1.2:5:0.5 (substrate : vanadyl acetylacetonate : potassium iodide : hydrogen peroxide : acetic acid) stoichiometry was the optimal. Notably, increase in potassium iodide amount did not lead to any loss in regioselectivity of the product. However, use of mineral acids such as hydrochloric acid, sulphuric acid, etc.

Table 2

Comparision of the iodination methodology (Scheme 1) using and without using the additive (AcOH).

		Without additive[a,b]		With additive[a,c]	
Entry	Substrate	Time (catalyst %)	Yield (%)	Time (catalyst %)	Yield (%)
1	 1a	2.5 h (5)	87	—	—
		30 min (10)	92	—	—
		30 min (15)	92	10 min (5)	98
		30 min (20)	94	—	—
2	 1d	4 h (5)	56	—	—
		2 h (10)	62	—	—
		2 h (15)	64	20 min (5)	94
		2 h (15)	65	—	—
3	 1f	6 h (5)	48	—	—
		4.5 h (10)	50	—	—
		4.5 h (15)	52	35 min (5)	93
		4.5 h (20)	52	—	—
4	 1k	4 h (5)	40	—	—
		4 h (10)	52	—	—
		4 h (15)	54	—	—
		4 h (20)	55	30 min (5)	92

[a]Catalyst % was in comparison with substrate.
[b]Substrate to H_2O_2 ratio was taken as 1:10.
[c]Substrate to H_2O_2 ratio was taken as 1:5.

affects the selectivity, leading to more than one product. In a controlled experiment, no product formation was noticed in the absence of vanadyl acetylacetonate, thereby confirming the importance of it.

From Table 1, it can easily be seen that the presence of the group at C-6 position that can activate the C-5 position (electron rich) via +M, +I, or conjugation facilitates the reaction, whereas the case is found to be reversed when the groups at C-6 deactivate the C-5 position. The point that C-5 position is the activated one is clear from our recent work [11]. When the group at C-6 position is electron-withdrawing, for example, -Cl (**1c**, Table 1), it deactivates the C-5 position by its strong -I effect and so gives negative result toward the iodination reaction. In entries 1 and 4–16 (Table 1), the C-5 position is activated because of the presence of enaminone moiety involving C-6 position.

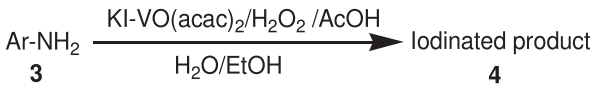
The same protocol was applied for iodination of aromatic amines **3**, and the results are summarized in Table 3. Table 3 reflects that the activated amine **3b** undergoes iodination more easily than the nonactivated **3a** or deactivated amines **3c** and **3d**. 4-Nitroaniline **3e** is found to be inert to the reaction condition as obvious. Diphenyl amine **3f** also shows tolerance to the reaction condition. The iodination generally occurs at the *para* position where available otherwise, results its *ortho* isomer. The protocol is found to be less effective for phenol resulting only 42% yield after overnight reaction, whereas attempts for iodination of benzamide, *N*-phenylbenzamide, and benzoic acid failed.

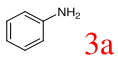
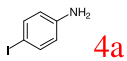
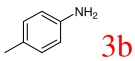
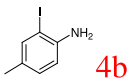
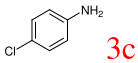
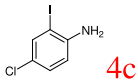
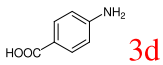
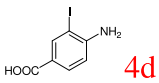
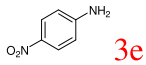
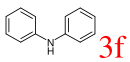
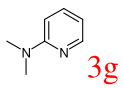
We propose that the active catalyst that actually takes part is the *in situ* generated peroxovanadium complex that oxidizes I^- to I^+. Activated pyrimidinediones have nucleophilic C-5 position that reacts with the active species, I^+, to give the iodinated products. The formation of peroxovanadium complexes is an exothermic process, hence needs to be carried out at low temperature. To maintain the homogeneity of the solution, potassium iodide was made soluble in water, whereas the organic substrates were taken in ethanol.

From Table 1, it is seen that **1a** is the most reactive, and the barbituric acid **1b** is the least reactive compound. Therefore, we performed DFT calculations on these two molecules. The reactivity of the molecules was derived by calculating local reactivity descriptors, the Fukui functions ($f(\boldsymbol{r})$) [17], which have attracted considerable interests to describe the relative reactivity and site selectivity in chemical reactions. It is seen that the C-5 carbon is the more reactive one in **1a** than **1b** as indicated by respective f^- values (0.077 and 0.037, respectively) (Table 4). Hence, an incoming electrophile can easily attack the C-5 position in **1a**. The reactivity of these two molecules can also be compared from the relative electrophilicity values [18] (f^-/f^+) of C-5 atoms which are 1.974 and 1.135 for **1a** and **1b**, respectively, which also supports the experimentally observed results.

Table 3

Iodination of aromatic amines **3**.



Entry	Substrate	Product	Time (h)	Yield (%)[a]
1	 3a	 4a	2	92 [13]
2	 3b	 4b	1.5	96 [14]
3	 3c	 4c	2.5	92 [14]
4	 3d	 4d	3	91 [15]
5	 3e	—	12	—
6	 3f	—	12	—
7	 3g	 4g	2	96 [16]

[a]Isolated yield.

CONCLUSIONS

In conclusion, we have developed a very simple, selective, mild, environment-friendly, and effective method for mono-iodination of activated pyrimidinediones using KI-VO(acac)$_2$-H_2O_2–AcOH. The methodology is also equally useful for iodination of amines. Vanadyl acetylacetonate can be easily prepared [10], whereas potassium iodide and hydrogen peroxide are easily available and hence cost effective.

The Fukui function and relative electrophilicity values are in good agreement with the experimentally observed highest reactivity of **1a** and least reactivity of **1b**.

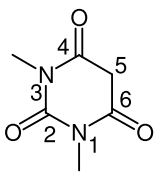
EXPERIMENTAL

Ethanol required to dissolve the organic starting materials was distilled prior to use. Ethyl acetate and hexane for column chromatography were distilled before use. Strength of hydrogen peroxide was determined freshly by titration method prior to experiment. Melting points were determined on a Büchi 504 apparatus (Flawil, Switzerland). IR spectra were recorded in potassium bromide pallets on a Nicolet (Impact 410) FTIR spectrophotometer (Wisconsin, USA). ^{1}H and ^{13}C NMR spectra were recorded on a JNM ECS 400 MHz (JEOL) (Tokyo, Japan) NMR spectrophotometer with tetramethylsilane as the internal standard. All the chemicals were used as received without further purification. Mass spectra were recorded on a Waters Q-TOF Premier & Aquity UPLC spectrometer (Connecticut, USA). Reaction progress was monitored by TLC using Merck silica gel 60F_{254} (0.25 mm) (Mumbai, India) with detection by UV or iodine. Elemental analyses were carried out on a PerkinElmer 2400 (Massachusetts, USA) automatic carbon, hydrogen, nitrogen, and sulfur analyser. Column chromatography was performed on Silica (60–120 mesh).

Typical procedure for iodination. Vanadyl acetylacetonate (0.05 mmol) was added to an ice-cooled solution of 30% hydrogen peroxide (5 mmol). The solution became light green colored because of formation of peroxovanadium complex. Acetic acid (0.5 mmol) was added dropwise to the solution. A solution of potassium iodide (1.1 mmol) in 2 mL of water was added to the cooled solution followed by the substrate (1 mmol) in 2 mL of

Table 4

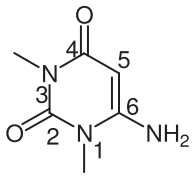
Fukui functions and relative nucleophilicity values calculated using Mulliken population scheme for each atom of barbituric acid **1b** and 6-aminouracil **1a**.



barbituric acid **1b**

Barbituric acid **1b**

Atom number	ƒ+	ƒ−	ƒ−/ƒ+
N(1)	0.032	0.025	1.280
C(2)	0.036	0.095	0.379
N(3)	0.032	0.025	1.280
C(4)	0.052	0.082	0.634
C(5)	0.042	0.037	1.135
O(6)	0.188	0.117	1.607
C(7)	0.023	0.020	1.150
O(8)	0.125	0.129	0.969
C(9)	0.022	0.020	1.100
O(10)	0.191	0.117	1.632
H(11)	0.033	0.063	0.524
H(12)	0.032	0.053	0.604
H(13)	0.024	0.021	1.143
H(14)	0.025	0.024	1.042
H(15)	0.022	0.022	1.000
H(16)	0.023	0.023	1.000
H(17)	0.024	0.024	1.000
H(18)	0.023	0.020	1.150
C(19)	0.051	0.083	0.614



6-aminouracil **1a**

6-Aminouracil **1a**

Atom number	ƒ+	ƒ−	ƒ−/ƒ+
N(1)	0.02	0.035	0.571
C(2)	0.028	0.029	0.966
N(3)	0.048	0.035	1.371
C(4)	0.063	0.13	0.485
C(5)	0.152	0.077	1.974
O(6)	0.152	0.124	1.226
O(7)	0.093	0.073	1.274
N(8)	0.078	0.078	1.000
C(9)	0.021	0.024	0.875
C(10)	0.024	0.022	1.091
H(11)	0.034	0.042	0.810
H(12)	0.039	0.05	0.780
H(13)	0.024	0.029	0.828
H(14)	0.019	0.02	0.950
H(15)	0.023	0.026	0.885
H(16)	0.026	0.024	1.083
H(17)	0.023	0.024	0.958
H(18)	0.027	0.025	1.080
H(19)	0.055	0.044	1.250
C(20)	0.049	0.092	0.533

ethanol. Then, the reaction mixture was allowed to stir at RT for the required period of time. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was treated with sodium thiosulphate solution and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and finally, column chromatography was performed to afford the pure product.

Synthetic procedure for the compounds 1a–p. Compounds **1a**,[19] 1b,[20] **1c**,**i**,**j**,[21] **1d** (using DMF–DMA), **1e** (using DMA–DMA),[22] **1f–h**, and **1k–p**[23] are synthesized as per literature procedures.

Spectral and physical data of selected compounds

5-Iodo-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (2b). Sticky solid; MS: *m/z* $[M]^+$ Calcd for $C_6H_7IN_2O_3$: 281.95; found 281.90. IR: 1710, 1640 cm^{-1}. ^1H NMR (400 MHz, deuteriochloroform): δ = 3.20 (s, 3H, CH_3), 3.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, deuteriochloroform): δ 31.34, 34.97, 45.01, 152.09, 159.21, 165.21. *Anal*. Calcd for $C_6H_7IN_2O_3$: C, 25.55; H, 2.50; N, 9.93. Found: C, 25.58; H, 2.57; N, 9.96.

5-Iodo-1,3-dimethyl-6-(phenylamino)pyrimidine-2,4(1H,3H)-dione (2f). Sticky solid; MS: *m/z* $[M]^+$ Calcd for $C_{12}H_{12}IN_3O_2$: 357.15; found 357.22. IR: 3464, 3300, 2926, 2376, 2279, 1701, 1633, 1538, 1458 cm^{-1}. ^1H NMR (400 MHz, deuteriochloroform): δ = 3.23 (s, 3H, CH_3), 3.45 (s, 3H, CH_3), 6.21 (b, s, 1H, NH), 6.91–7.38 (m, 5H, Ph); ^{13}C NMR (100 MHz, deuteriochloroform): δ 31.39, 35.17, 61.21, 119.01, 120.07, 124.97, 129.54, 130.07, 139.93, 151.18, 152.15, 160.22. *Anal*. Calcd for $C_{12}H_{12}IN_3O_2$: C, 40.36; H, 3.39; N, 11.77. Found: C, 40.38; H, 3.37; N, 11.78.

5-Iodo-1,3-dimethyl-6-(4-iodo-phenylamino)pyrimidine-2,4(1H,3H)-dione (2g). Sticky solid; MS: *m/z* $[M]^+$ Calcd for $C_{13}H_{14}IN_3O_2$: 371.01; found 371.2. IR: 3460, 3297, 2922, 2371, 2280, 1706, 1636, 1450 cm^{-1}. ^1H NMR (400 MHz, deuteriochloroform): δ = 1.45 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 6.31 (b, s, 1H, NH), 6.37–7.02 (m, 4H, Ph); ^{13}C NMR (100 MHz, deuteriochloroform): δ 24.56, 31.46, 35.47, 61.18, 117.19, 121.10, 124.87, 129.34, 129.97, 140.03, 151.69, 152.32, 160.10. *Anal*. Calcd for $C_{13}H_{14}IN_3O_2$: C, 42.07; H, 3.80; N, 11.32. Found: C, 42.04; H, 3.84; N, 11.38.

5-Iodo-1,3-dimethyl-6-(4-chloro-phenylamino)pyrimidine-2,4(1H,3H)-dione (2h). Sticky solid; MS: *m/z* $[M]^+$ Calcd for $C_{12}H_{11}ClIN_3O_2$: 390.96; found 390.98. IR: 3470, 3311, 2920, 2380, 2290, 1715, 1639, 1542, 1450 cm^{-1}. ^1H NMR (400 MHz, deuteriochloroform): δ = 3.34 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 6.03 (b, s, 1H, NH), 6.41–7.89 (m, 4H, Ph); ^{13}C NMR (100 MHz, deuteriochloroform): δ 31.32, 35.19, 61.42, 118.97, 120.12, 125.02, 129.32, 130.00, 140.01, 151.21, 152.19, 160.00. *Anal*. Calcd for $C_{12}H_{11}ClIN_3O_2$: C, 36.81; H, 2.83; N, 10.73. Found: C, 36.84; H, 2.87; N, 10.77.

***5-Iodo-1,3-dimethyl-6-(hydrazino)pyrimidine-2,4(1H,3H)*-dione (2i).** Sticky solid; MS: *m/z* $[M]^+$ Calcd for $C_9H_9IN_4O_2$: 295.98; found 296.02. IR: 3452, 3302, 2928, 2385, 2278, 1706, 1626, 1548, 1447 cm^{-1}. ^1H NMR (400 MHz, deuteriochloroform): δ = 3.07 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 3.43 (b, s, 2H, NH_2), 4.33 (b, s, 1H, NH); ^{13}C NMR (100 MHz, deuteriodimethylsulphoxide): δ 27.32, 29.80, 52.21, 152.10, 156.90, 162.2. *Anal*. Calcd for $C_9H_9IN_4O_2$: C, 24.34; H, 3.06; N, 18.92. Found: C, 24.38; H, 3.07; N, 19.98.

6-(2-Phenylhydrazinyl)-5-iodo-1,3-dimethylpyrimidine-2,4 (1H,3H)-dione (2j). Sticky solid; MS: *m/z* $[M]^+$ Calcd for $C_{12}H_{13}IN_4O_2$: 372.16; found 372.10. IR: 3419, 3371, 3037, 2957, 1672, 1618, 1532, 1431 cm^{-1} ^1H NMR (400 MHz, deuteriochloroform): δ = 1.24 (b, s, 1H, NH), 3.48 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 6.9–7.5 (m, 5H, Ph), 8.24 (b, s, 1H, NH). ^{13}C NMR (100 MHz, deuteriochloroform): δ 27.68, 30.75, 55.24, 111.24, 119.57, 121.97, 122.44, 123.91, 134.75, 145.07, 151.58, 159.07. *Anal*. Calcd for $C_{12}H_{13}IN_4O_2$: C, 38.73; H, 3.52; N, 15.05. Found: C, 38.75; H, 3.50; N, 15.03.

6-(Benzylamino)-5-iodo-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (2k). Sticky solid; MS: *m/z* $[M]^+$ Calcd for $C_{13}H_{14}IN_3O_2$: 371.17; found 371.15. IR: 3421, 3389, 3112, 2987, 1682, 1650, 1557, 1442 cm^{-1} ^1H NMR (400 MHz, deuteriochloroform): δ = 3.23 (s, 3H, CH_3), 3.45 (s, 3H, CH_3), 4.13 (s, 2H, CH_2), 4.73 (b, s, 1H, NH), 6.91–7.38 (m, 5H, Ph). ^{13}C NMR (100 MHz, deuteriochloroform): δ 27.87, 28.79, 47.40, 127.63, 128.36, 129.15, 136.02, 151.94, 152.88, 163.07. *Anal*. Calcd for $C_{13}H_{14}IN_3O_2$: C, 42.07; H, 3.80; N, 11.32. Found: C, 42.05; H, 3.82; N, 11.35.

***6-(4-Chlorobenzylamino)-5-iodo-1,3-dimethylpyrimidine-2,4 (1H,3H)*-dione (2l).** Sticky solid; MS: *m/z* $[M]^+$ Calcd for $C_{13}H_{13}ClN_3O_2$: 404.97; found 404.99. IR: 3460, 3307, 2930, 2372, 2279, 1710, 1635, 1541, 1452 cm^{-1}. ^1H NMR (400 MHz, deuteriochloroform): δ = 3.33 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 4.16 (s, 2H, CH_2), 4.70 (b, s, 1H, NH), 6.88–7.41 (m, 4H, Ph). ^{13}C NMR (100 MHz, deuteriochloroform): δ 27.72, 28.81, 47.37, 127.56, 128.30, 129.22, 136.10, 151.88, 152.93, 167.12. *Anal*. Calcd for $C_{13}H_{13}ClN_3O_2$: C, 38.49; H, 3.23; N, 10.36. Found: C, 38.45; H, 3.21; N, 10.32.

6-(4-Methylbenzylamino)-5-iodo-1,3-dimethylpyrimidine-2,4 (1H,3H)-dione (2m). Sticky solid; MS: *m/z* $[M]^+$ Calcd for $C_{14}H_{16}IN_3O_2$: 385.03; found 385.03. IR: 3421, 3389, 3112, 2987, 1682, 1650, 1557, 1442 cm^{-1} ^1H NMR (400 MHz, deuteriochloroform): δ = 1.35 (s, 3H, CH_3), 3.28 (s, 3H, CH_3), 3.39 (s, 3H, CH_3), 4.68 (b, s, 1H, NH), 6.86–7.42 (m, 4H, Ph). ^{13}C NMR (100 MHz, deuteriochloroform): δ 27.69, 28.84, 47.64, 127.71, 128.31, 129.23, 136.10, 152.01, 153.10, 158.11. *Anal*. Calcd for $C_{14}H_{16}IN_3O_2$: C, 43.65; H, 4.19; N, 10.91. Found: C, 43.62; H, 4.17; N, 10.95.

6-(N-Benzyl-N-methylamino)-5-iodo-1,3-dimethylpyrimidine-2,4 (1H,3H)-dione (2n). Sticky solid; MS: *m/z* $[M]^+$ Calcd for $C_{13}H_{14}IN_3O_2$: 385.03; found 385.06. IR: 3425, 3388, 3118, 2989, 1685, 1653, 1559, 1444 cm^{-1}. ^1H NMR (400 MHz, deuteriochloroform): δ = 2.86 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 3.48 (s, 3H, CH_3), 4.11 (s, 2H, CH_2), 6.871–7.40 (m, 5H, Ph). ^{13}C NMR (100 MHz, deuteriochloroform): δ 27.06, 27.76, 28.58, 46.98, 128.63, 128.976, 129.07, 136.29, 152.04, 152.56, 163.11. *Anal.* Calcd for $C_{14}H_{16}IN_3O_2$: C, 43.65; H, 4.19; N, 10.91. Found: C, 43.61; H, 4.22; N, 10.95.

6-(N-(4-Chlorobenzyl)-N-methylamino)-5-iodo-1,3-dimethyl-pyrimidine-2,4(1H,3H)-dione (2o). Sticky solid; MS: *m/z* $[M]^+$ Calcd for $C_{14}H_{15}ClIN_3O_2$: 418.99; found 419.01. IR: 3460, 3309, 2931, 2372, 2279, 1706, 1635, 1532, 1454 cm^{-1}. ^1H NMR (400 MHz, deuteriochloroform): δ = 3.16 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 6.96–7.45 (m, 4H, Ph); ^{13}C NMR (100 MHz, deuteriochloroform): δ 31.45, 32.34, 34.74, 61.42, 119.14, 120.17, 125.03, 129.57, 129.11, 140.05, 151.10, 152.09, 164.05. *Anal*. Calcd for $C_{14}H_{15}ClIN_3O_2$: C, 40.07; H, 3.60; N, 10.01. Found: C, 40.08; H, 3.56; N, 10.04.

6-(N-(4-Methylbenzyl)-N-methylamino)-5-iodo-1,3-dimethylpy-rimidine-2,4(1H,3H)-dione (2p). Sticky solid; MS: *m/z* $[M]^+$ Calcd for $C_{15}H_{18}IN_3O_2$: 399.04; found 399.09. IR: 3457, 3304, 2930, 2382, 2279, 1718, 1642, 1546, 1468 cm^{-1}. ^1H NMR (400 MHz, deuteriochloroform): δ = 1.96 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 3.49 (s, 3H, CH_3), 6.99–7.50 (m, 4H, Ph); ^{13}C NMR (100 MHz, deuteriochloroform): δ 24.35, 31.47, 32.89, 34.93, 60.89, 119.25, 120.10, 125.04, 129.29, 130.00, 140.02, 151.12, 152.19, 159.78. *Anal*. Calcd for $C_{15}H_{18}IN_3O_2$: C, 45.13; H, 4.54; N, 10.53. Found: C, 45.09; H, 4.50; N, 10.55.

Computational details. All the density functional calculations were carried out using the DMol^3 program (California, USA) [24]. The selected molecules were subjected to full geometry optimization using double numerical with polarization basis set [25] in combination with three generalized gradient approximation exchange-correlation functionals BLYP. The double numerical with polarization basis is comparable with Gaussian 6–31G** basis set. We calculated local reactivity descriptors such as Fukui functions and relative nucleophilicity values of each atom using Mulliken population scheme, details of which are discussed elsewhere [26,27].

The condensed Fukui functions (FF) are calculated as follows:

$$f_k^+ = \frac{1}{\Delta N}[q_k(N_0 + \Delta N) - q_k(N_0)](\text{for nucleophilic attack})$$

$$f_k^- = \frac{1}{\Delta N}[q_k(N_0) - q_k(N_0 - \Delta N)](\text{for electrophilic attack})$$

where q_k is the electronic population of atom k in a molecule. In conventional FF computations, a value of 1.0 is used for ΔN. In this case, calculations on the cationic and anionic species are required. In the present study, we have used a value of 0.1 for ΔN.

The stationary points are characterized by calculating vibrational frequencies for all the molecules. No imaginary vibrational frequency was found for any of the compound. Absence of imaginary frequency indicates that the optimized compounds are at their local or global minimum energy states.

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