Tetrahedron Letters 53 (2012) 399–402

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient one-pot three-component synthesis of functionalized pyrimido[4,5-*b*]quinolines and indeno fused pyrido[2,3-*d*]pyrimidines in water

Girijesh K. Verma, Keshav Raghuvanshi, Ram Kumar, Maya Shankar Singh *

Department of Chemistry (Centre of Advanced Study), Faculty of Science, Banaras Hindu University, Varanasi 221 005, India

ARTICLE INFO

Article history:
Received 18 October 2011
Revised 7 November 2011
Accepted 10 November 2011
Available online 18 November 2011

Keywords:
One-pot three-component coupling
Pyrimido[4,5-*b*]quinolines
Indeno fused pyrido[2,3-*d*]pyrimidines
PTSA

ABSTRACT

A simple, efficient, and high yielding one-pot protocol for the synthesis of pyrimido[4,5-*b*]quinolines and indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidines has been developed by three-component domino coupling of 6-amino-1,3-dimethyluracil, aldehydes, and cyclic 1,3-diketones in ecofriendly solvent water promoted by PTSA. The protocol avoids the use of expensive catalysts, toxic solvents, and chromatographic separation. The generality and functional tolerance of this convergent and environmentally benign method is demonstrated.

In recent years, the key constraints for the synthetic chemists are the use of hazardous solvents, expensive, and toxic reagents, multistep protocols, and generation of unwanted side-products.[1] Now a days, green chemistry has attained the status of a major scientific discipline, and it now encompasses wide areas of chemical enterprise and is an alternative way to reduce drastic requirements for reactions.[2] To find new alternatives for simple and eco-compatible protocols, chemists have adopted water as the solvent of choice in organic synthesis.[3] Water offers several practical advantages over conventional organic solvents[4] such as easy availability, cheap, non-toxic, non-corrosive, non-flammable, and environmentally acceptable.[5] Furthermore, besides having a unique reactivity and selectivity, water also offers an easy separation.[6] The above advantages have been attributed to many factors, including the hydrophobic effect,[7] enhanced hydrogen bonding in the transition state,[8] and the high cohesive energy density of water.[9,10]

Due to growing environmental concerns, carrying out organic reactions in water has become highly desirable, and several reports of organic synthesis in water have appeared during the past decade.[11] Recently, a variety of organic transformations such as aldol reaction, allylation reaction, Diels–Alder reaction, Henry reaction, Michael reaction, Mannich reaction, and Pd-catalyzed coupling reactions have been reported in aqueous media.[12] Indeed, industry prefers to use water as a solvent rather than organic solvents. In the past decade there have been tremendous development in multi-component reactions and great efforts are being made to develop new multicomponent reactions[13] (MCRs) in water. They have become an increasingly powerful tool[14] in organic, combinatorial, and medicinal chemistry because of their convergence, atom-economy, multiple bond forming efficiency,[15] and other suitable characteristics from the green chemistry point of view.[16] These features make MCRs well-suited for the easy construction of diversified heterocyclic scaffolds.[17]

Organic compounds containing pyrimidine scaffold as a core unit are important targets and are known to exhibit various biological and pharmaceutical activities.[18] 6-Amino-1,3-dimethyluracil and its fused derivatives[19] are versatile building blocks for the synthesis of several bioactive heterocycles.[20] Pyrido[2,3-*d*]pyrimidines are a class of naturally occurring fused uracils occupying a special place in synthetic and medicinal chemistry due to their wide range of pharmacological activities.[21] 5-(3-Bromophenyl)-1,3-dimethyl-5,11-dihydro-1*H*-indeno [2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione (BPIPP) was identified as new potent inhibitor of STa induced cyclic nucleotide synthesis, and as a promising lead for the treatment of acute diarrhea.[22a,b] Moreover, appropriately functionalized pyrido[2,3-*d*]pyrimidines have also been identified as a new class of fibroblast growth factor receptor (FGFR3) tyrosine kinase inhibitors.[22c,d] Quinolines an important class of heterocyclic alkaloids, are important synthetic targets both in pharmaceutical industries and in academic laboratories displaying rich chemistry and various useful biological activities.[23] They are widely present as key structural motifs in a large number of bioactive drugs such as Quinine, Chloroquine, Luotonine-A, and Camptothecin. Furthermore, quinoline derivatives find applications in flavoring agents[24a] and in luminescence chemistry.[24b] In addition quinolines are valuable synthons for the preparation of nano-and meso-structures with enhanced electronic as well as photonic functions.[25]

* Corresponding author. Fax: +91 542 2368127.
E-mail address: mssinghbhu@yahoo.co.in (M.S. Singh).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.11.047

In view of the immense biological significance of these heterocycles, many synthetic protocols involving multicomponent strategies have been developed.[26,27] However, despite the potential utility of the methods published so far, they exhibit varying degrees of successes as well as limitations such as harsh reaction conditions, expensive catalysts/reagents, toxic organic solvents, cumbersome experimental procedures, and long reaction time. Therefore, to overcome these problems development of more general, efficient, eco-compatible, and viable protocols are highly desirable. In this context, in recent years, much attention has been focused on acid catalyzed organic reactions in water. *p*-Toluenesulfonic acid (PTSA) is environmentally benign, inexpensive, and economically feasible catalyst that offers several advantages.[28] Therefore, organic reactions that exploit PTSA catalyst in water could prove ideal for industrial synthetic organic chemistry applications provided that the catalyst shows high catalytic activity in water. In continuation of our efforts for the development of one-pot three-component protocols[29] under solvent-free conditions to synthesize biologically important heterocycles, we have explored a straightforward convergent one-pot synthesis of pyrimido[4,5-*b*]quinoline-2,4,6-triones and indeno fused pyrido[2,3-*d*] pyrimidine-2,4,6-triones in water promoted by PTSA.[30]

Our literature survey at this stage revealed that, there is no report yet available on the synthesis of pyrimido[4,5-*b*]quinolines and indeno fused pyrido[2,3-*d*]pyrimidines in one-pot via three-component coupling of 6-amino-1,3-dimethyluracil, aldehydes, and cyclic-1,3-diketones in water promoted by PTSA. The utility of multicomponent reactions has been significantly expanded if they are conducted in water or under solvent-free conditions. The aim of this present protocol is to highlight the synergistic effect of the combined use of MCRs and water for the development of new eco-compatible strategy for heterocyclic synthesis.

Initially, the three-component coupling reaction of 6-amino-1,3-dimethyluracil **1**, 4-nitrobenzaldehyde **2a**, and dimedone **3a** under solvent-free conditions and in water, separately was examined without any catalyst. It was found that only trace amount of the desired product **4a** was observed on TLC plate even after 14 h of reflux, while undesired Knoevenagel condensation product was formed as a major one (Table 1, entries 1 and 2) under above two conditions. Subsequently, various acidic catalysts such as SiO_2–H_2SO_4, SiO_2–$HClO_4$, $InCl_3$, P_2O_5, and PTSA were tested in water and under solvent-free conditions, separately. SiO_2–H_2SO_4 and SiO_2–$HClO_4$ could trigger the reaction providing only trace amount of the product after 12 h of heating, while $InCl_3$ and P_2O_5 gave the desired product in low yield along with octahydroxanthene-1,8-dione as a side product (Table 1, entries 3–10). To our delight, PTSA gave the desired product in good yield under above two conditions. However, the reaction in water showed superiority over the solvent-free conditions in terms of yield (Table 1, entries 11 and 12). PTSA loading was subsequently examined and it was found that 20 mol % of PTSA provided the maximum yield in minimum time (Table 1, entry 13). We immediately undertook a study to examine the effect of temperature on this transformation, and the results demonstrated that 90 °C appeared to be the optimum temperature. Thus, the best yield, cleanest reaction, and most facile work-up was achieved employing 20 mol % of PTSA in water at 90 °C. The starting materials were completely consumed to afford the desired product that was highly visible on TLC under UV light.[30] Furthermore, simple work-up in water opened the route for an entirely green and highly efficient one-pot reaction in water.

Table 1
Optimization of reaction conditions[a]

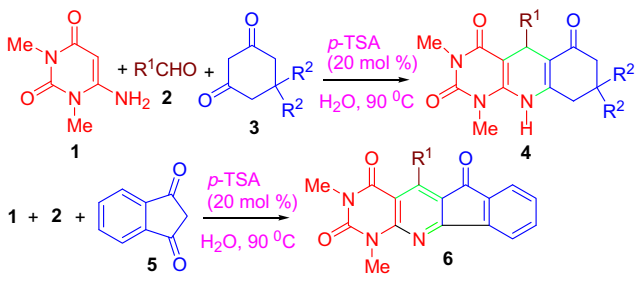
Entry	Catalyst (mol %)	Solvent	Time (h)	Temp (°C)	Yield[b] (%)
1	None	None	14	90	Trace[c]
2	None	H_2O	14	90	Trace[c]
3	SiO_2–H_2SO_4 (10)	None	12	90	Trace[c]
4	SiO_2–H_2SO_4 (10)	H_2O	12	90	Trace[c]
5	SiO_2–$HClO_4$ (10)	None	12	90	Trace[c]
6	SiO_2–$HClO_4$ (10)	H_2O	12	90	Trace[c]
7	$InCl_3$ (10)	None	4	90	55[d]
8	$InCl_3$ (10)	H_2O	4	90	46[d]
9	P_2O_5 (10)	None	4	90	25[d]
10	P_2O_5 (10)	H_2O	4	90	40[d]
11	*p*-TSA (10)	None	3	90	62
12	*p*-TSA (10)	H_2O	3	90	77
13	*p*-TSA (20)	H_2O	2.5	90	94
14	*p*-TSA (30)	H_2O	2.5	90	90
15	*p*-TSA (20)	H_2O	4	80	80
16	*p*-TSA (20)	H_2O	6	70	72

[a] All the reactions were carried out using 6-amino-1,3-dimethyluracil **1** (1.0 mmol), 4-nitrobenzaldehyde **2a** (1.0 mmol), and dimedone **3a** (1.0 mmol).
[b] Isolated pure yields.
[c] Knoevenagel condensation product was obtained as a major one.
[d] Xanthene as side product was formed.

Encouraged by the remarkable results obtained with the above reaction conditions, and in order to show the generality and scope of this new protocol, we used various aldehydes and cyclic 1,3-diketones (Scheme 1). Notably, a wide range of aldehydes (aromatic, heteroaromatic, and aliphatic) were well tolerated under the reaction conditions (Table 2). However, in comparison to aromatic aldehydes, heteroaromatic, and aliphatic aldehydes gave somewhat lower yields. In order to further investigate the scope of this reaction with indane-1,3-dione, the reaction of **1** and **2** with **5** was examined under the above optimized conditions, and found to produce tetracyclic indeno fused pyrido[2,3-*d*]pyrimidines **6a**–**h** in good yields (Table 2). This is particularly attractive because compounds with indeno fused pyrido[2,3-*d*]pyrimidine motif show a wide range of biological activities. Table 2 clearly demonstrates that PTSA is an excellent catalyst for this one-pot three-component reaction in water. Notably, the reactions were clean and all the products were easily isolated simply by filtration and washing with water. The structures of compounds **4** and **6** were established by their satisfactory elemental analyses and spectral (^1H, ^{13}C NMR, IR, and Mass) studies,[30] and by comparison with known compounds reported in the literature.[26,27]

A probable mechanistic rationale portraying sequence of events for this domino coupling is postulated in Scheme 2. The first step is believed to be the acid-catalyzed Knoevenagel condensation between the aldehyde and cyclic 1,3-diketone to generate adduct **A**, which acts as Michael acceptor. The 6-amino-1,3-dimethyl uracil **1** attacks to adduct **A** in a Michael-type fashion to produce an open chain intermediate **B**. Intermediate **B** undergoes intramolecular cyclization by the reaction of nucleophilic amino function to carbonyl group followed by dehydration to form pyrimido[4,5-*b*]quinoline **4**.

In conclusion, we have developed a simple one-pot three-component synthesis of pyrimido[4,5-*b*]quinoline-2,4,6-triones and indeno fused pyrido[2,3-*d*]pyrimidines by the coupling of 6-amino-1,3-dimethyluracil, aldehydes, and cyclic 1,3-dicarbonyl compounds in water promoted by PTSA. This protocol is endowed with several advantages such as convergent nature, improved

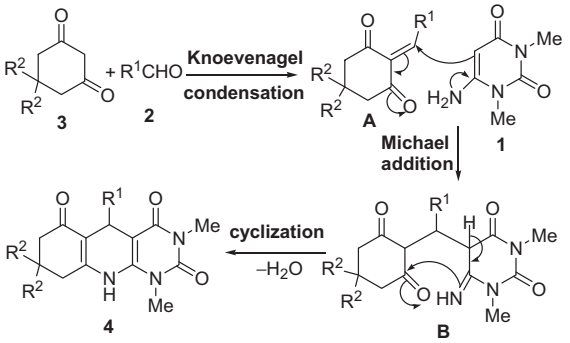


Scheme 1. Synthesis of pyrimido[4,5-*b*]quinolines **4a**–**t** and indeno fused pyrido[2,3-*d*]pyrimidines **6a**–**h**.

Table 2
Exploration of the substrate scope for the synthesis of **4** and **6**

Products[a] **4**,**6**	Aldehyde **2** (R^1)	Diketones **3**,**5**	Time (h)	Yield[b] (%)
4a	4-$NO_2C_6H_4$ (**2a**)	R^2 = CH_3 (**3a**)	2.5	94
4b[27a]	4-BrC_6H_4 (**2b**)	**3a**	3.0	91
4c[27a]	4-ClC_6H_4 (**2c**)	**3a**	2.5	89
4d[27a]	4-$CH_3C_6H_4$ (**2d**)	**3a**	2.5	85
4e	3-OHC_6H_4 (**2e**)	**3a**	3.0	86
4f[27a]	4-$OMeC_6H_4$ (**2f**)	**3a**	3.0	84
4g	2-$NO_2C_6H_4$ (**2g**)	**3a**	3.0	90
4h	3-$NO_2C_6H_4$ (**2h**)	**3a**	3.0	86
4i[27e]	C_6H_5 (**2i**)	**3a**	3.0	85
4j[27a]	2-Thienyl (**2j**)	**3a**	3.0	82
4k	*i*-Propyl (**2k**)	**3a**	3.5	66
4l	Cyclohexyl (**2l**)	**3a**	3.5	62
4m[26b]	4-$NO_2C_6H_4$ (**2a**)	R^2 = H (**3b**)	2.5	95
4n	3-$NO_2C_6H_4$ (**2h**)	**3b**	2.0	87
4o	2,4-$Cl_2C_6H_3$ (**2m**)	**3b**	2.5	90
4p[26b]	4-$CH_3C_6H_4$ (**2d**)	**3b**	2.5	88
4q	C_6H_5 (**2i**)	**3b**	2.5	86
4r[26b]	4-FC_6H_4 (**2n**)	**3b**	2.5	86
4s	2-ClC_6H_4 (**2o**)	**3b**	3.0	87
4t	2-$OMeC_6H_4$ (**2p**)	**3b**	3.0	84
6a[27a]	4-BrC_6H_4 (**2b**)	**5**	3.0	88
6b[27a]	4-ClC_6H_4 (**2c**)	**5**	2.5	86
6c[27a]	4-FC_6H_4 (**2n**)	**5**	2.5	90
6d[27a]	3-$NO_2C_6H_4$ (**2h**)	**5**	3.0	82
6e[27a]	4-$CH_3C_6H_4$ (**2d**)	**5**	3.0	86
6f	5-Br-2-OHC_6H_3 (**2q**)	**5**	3.0	76
6g	2-Thienyl (**2j**)	**5**	3.5	72
6h	*i*-Propyl (**2k**)	**5**	3.5	60

[a] Literature reference.
[b] Isolated yields.



Scheme 2. Plausible mechanism for the formation of **4**.

yields, clean reaction, easy operation, and simple purification. Furthermore, it can be considered as environmental friendly, since it uses water as the reaction medium, and purification is done by simple filtration and washing, avoiding the use of organic solvents at any point of the experimental procedure. No extraction or separation by column chromatography is necessary.

Acknowledgements

We are grateful to the Council of Scientific and Industrial Research (CSIR) and the Department of Science and Technology (DST), New Delhi for the financial support. G.K.V. is thankful to the University Grant Commission (UGC), New Delhi, for Junior Research Fellowship. We also thank Professor H. Ila (JNCASR, Bangalore) for her timely valuable advice and suggestions.

References and notes

1. (a) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239; (b) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901; (c) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.
2. (a) Clark, J. H.; Macquarrie, D. In *Handbook of Green Chemistry and Technology*; Blackwell Publishers: Oxford, 2002; (b) Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301; (c) Anastas, P. T.; Warner, J. C. In *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998; (d) Leitner, W. *Green Chem.* **2009**, *11*, 603.
3. (a) Breslow, R. In *Green Chemistry*; Anastas, P. T., Williamson, T. C., Eds.; Oxford Press: New York, 1998. Chapter 13; (b) DeSimone, J. M. *Science* **2002**, *297*, 799; (c) Horvath, I. T.; Anastas, P. T. *Chem. Rev.* **2007**, *107*, 2167; (d) Kumar, B. S. P. A.; Madhav, B.; Reddy, K. H. V.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2011**, *52*, 2862.
4. (a) Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365; (b) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275; (c) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725.
5. (a) Aplander, K.; Hidestal, O.; Katebzadeh, K.; Lindstorm, U. M. *Green Chem.* **2006**, *8*, 22; (b) Liu, R.; Dong, C.; Liang, X.; Wang, X.; Hu, X. *J. Org. Chem.* **2005**, *70*, 729; (c) Stavber, G.; Zupan, M.; Jereb, M.; Stavber, S. *Org. Lett.* **2004**, *6*, 4973; (d) Lindstrom, U. M. In *Organic Reactions in Water: Principles, Strategies and Applications*; Wiley-Blackwell: Oxford, UK, 2007; (e) Hailes, H. C. *Org. Process Res. Dev.* **2007**, *11*, 114.
6. (a) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751; (b) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302; (c) Polshettiwar, V.; Varma, R. S. *Green Chem.* **2010**, *12*, 743; (d) Khatik, G. L.; Kumar, R.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 2433; (e) Azizi, N.; Aryanasab, F.; Torkiyan, L.; Ziyaei, A.; Saidi, M. R. *J. Org. Chem.* **2006**, *71*, 3634.
7. (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159; (b) Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809; (c) Lindstrom, U. M.; Andersson, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 548.
8. Chandrasekhar, J.; Shariffskul, S.; Jorgensen, W. L. *J. Phys. Chem. B* **2002**, *106*, 8078.
9. (a) Lubineau, A.; Auge, J. *Top. Curr. Chem.* **1999**, *206*, 1; (b) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741.
10. Sheldon, R. A. *J. Mol. Catal. A* **1996**, *107*, 75.
11. (a) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095; (b) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Org. Lett.* **2005**, *7*, 4411; (c) Pirrung, M. C.; Das Sarma, K. *J. Am. Chem. Soc.* **2004**, *126*, 444; (d) Azoulay, S.; Manabe, K.; Kobayashi, S. *Org. Lett.* **2005**, *7*, 4593; (e) Manabe, K.; Limura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971; (f)*Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998; (g) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68; (h) Breslow, R. *Acc. Chem. Res.* **2004**, *37*, 471; (i) Pirrung, M. C. *Chem. -Eur. J.* **2006**, *12*, 1312.
12. (a) Virkutyte, J.; Baruwati, B.; Varma, R. S. *Nano Scale* **2010**, *2*, 1109; (b) Polshettiwar, V.; Varma, R. S. *Tetrahedron* **2010**, *66*, 1091; (c) Liu, X.-L.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron Lett.* **2011**, *52*, 903; (d) Azizi, N.; Torkiyan, L.; Saidi, M. R. *Org. Lett.* **2006**, *8*, 2079; (e) Wu, H.; Lin, W.; Wan, Y.; Xin, H.-Q.; Shi, D.-Q.; Shi, Y.-H.; Yuan, R.; Bo, R.-C.; Yin, W. *J. Comb. Chem.* **2010**, *12*, 31; (f) Krasovskaya, V.; Krasovskiy, A.; Bhattacharjya, A.; Lipshutz, B. H. *Chem. Commun.* **2011**, *47*, 5717.
13. (a) Gogoi, S.; Dutta, M.; Gogoi, J.; Boruah, R. C. *Tetrahedron Lett.* **2011**, *52*, 813; (b) Kumar, D.; Kumar, N. M.; Patel, G.; Gupta, S.; Varma, R. S. *Tetrahedron Lett.* **2011**, *52*, 1983; (c) Xie, J.-W.; Li, P.; Wang, T.; Zhou, F.-T. *Tetrahedron Lett.* **2011**, *52*, 2379; (d) Ramesh, K.; Murthy, S. N.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2011**, *52*, 2362; (e) El Kaïm, L.; Grimaud, L.; Purumandla, S. R. *Tetrahedron Lett.* **2010**, *51*, 4962; (f) Palasz, A. *Synthesis* **2010**, 4021; (g) Kolla, S. R.; Lee, Y. R. *Tetrahedron* **2010**, *66*, 8938; (h) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. *Org. Lett.* **2004**, *6*, 1001; (i) Ma, N.; Jiang, B.; Zhang, G.; Tu, S.-J.; Wever, W.; Li, G. *Green Chem.* **2010**, *12*, 1357; (j) Adib, M.; Sheikhi, E.; Kavoosi, A.; Bijanzadeh, H. R. *Tetrahedron* **2010**, *66*, 9263.
14. (a) Zhu, J.; Bienayme, H. In *Multicomponent Reactions*; Wiley-VCH Weinheim: Germany, 2005; (b) Malacria, M. *Chem. Rev.* **1996**, *96*, 289; (c) Schwier, T.; Sromek, A. W.; Yap, D. M.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868; (d) Barluenga, J.; Jimenez-Aquino, A.; Valdes, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1529; (e) Waldmann, H.; Kuhn, M.; Liu, W.; Kumar, K. *Chem. Commun.* **2008**, 1211; (f) de Meijere, A.; von Zezschwitz, P.; Braese, S. *Acc. Chem. Res.* **2005**, *38*, 413; (g) Tietze, L. F.; Brasche, G.; Gericke, K. In *Domino Reactions in Organic Synthesis*; Wiley-VCH Weinheim: Germany, 2006; (h) Diguez-Vzquez, A.; Tzschucke, C. C.; Lam, W. Y.; Ley, S. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 209; (i) Arya, A. K.; Kumar, M. *Green Chem.* **2011**, *13*, 1332.
15. (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695; (c) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40.
16. (a) Döemling, A. *Chem. Rev.* **2006**, *106*, 17; (b) D'Souza, D. M.; Mueller, T. J. *J. Chem. Soc. Rev.* **2007**, *36*, 1095; (c) Polshettiwar, V.; Varma, R. S. *Chem. Soc. Rev.* **2008**, *37*, 1546; (d) Shore, G.; Yoo, W.-J.; Li, C.-J.; Organ, M. G. *Chem. -Eur. J.* **2010**, *16*, 126; (e) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463; (f) Padwa, A. *Chem. Soc. Rev.* **2009**, *38*, 3072.
17. (a) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133; (b) Willy, B.; Mueller, T. J. J. *Curr. Org. Chem.* **2009**, *13*, 1777; (c) Bello, D.; Ramon, R.; Lavilla, R. *Curr. Org. Chem.* **2010**, *14*, 332; (d) Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G. *Chem. Asian J.* **2010**, *5*, 2318.
18. (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937; (b) Ibrahim, D. A.; El-Metwally, A. M. *Eur. J. Med. Chem.* **2010**, *45*, 1158; (c) Deshmukh, M. B.; Salunkhe, S. M.; Patil, D. R.; Anbhule, P. V. *Eur. J. Med. Chem.* **2009**, *44*, 2651; (d) Gasse, C.; Douguet, D.; Huteau, V.; Marchal, G.; Munier-Lehmann, H.; Pochet, S. *Bioorg. Med. Chem.* **2008**, *16*, 6075; (e) Lin, R.; Johnson, S. G.; Connolly, P. J.; Wetter, S. K.; Binnun, E.; Hughes, T. V.; Murray, W. V.; Pandey, N. B.; Moreno-Mazza, S. J.; Adams, M.; Fuentes-Pesquera, A. R.; Middleton, S. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2333; (f) Falcao, E. P. S.; Melo, S. J.; Srivastava, R. M.; Catanho, M. T. J. A.; Do

Nascimento, S. C. *Eur. J. Med. Chem.* **2006**, *41*, 276; (g) Chen, Q.; Zhu, X.-L.; Jiang, L.-L.; Liu, Z.-M.; Yang, G.-F. *Eur. J. Med. Chem.* **2008**, *43*, 595; (h) Hassan Hilmy, K. M.; Khalifa, M. M. A.; Allah Hawata, M. A.; AboAlzeen Keshk, R. M.; El-Torgman, A. A. *Eur. J. Med. Chem.* **2010**, *45*, 5243; (i) Aliaga, M. J.; Ramon, D. J.; Yus, M. *Org. Biomol. Chem.* **2010**, *8*, 43.

19. (a) Hirota, K.; Kuki, H.; Maki, Y. *Heterocycles* **1994**, *37*, 563; (b) Griengl, H.; Wanek, E.; Schwarz, W.; Streicher, W.; Rosenwirth, B.; De Clercq, E. *J. Med. Chem.* **1987**, *30*, 1199; (c) Srivastava, P.; Saxena, A. S.; Ram, V. J. *Synthesis* **2000**, 541; (d) Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533; (e) Pontikis, R.; Monneret, C. *Tetrahedron Lett.* **1994**, *35*, 4351; (f) Wamhoff, H.; Schupp, W. *J. Org. Chem.* **1986**, *51*, 2787; (g) Walsh, E. B.; Wamhoff, H. *Chem. Ber.* **1989**, *122*, 1673.
20. (a) Lunt, E.; Newton, C. G. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Boulton, A. J., Mckillop, A., Eds.; Permgamon Press: Oxford, 1984; Vol. 3, p 199–232, 260–262; (b) Bradshaw, T. K.; Hutchinson, D. W. *Chem. Soc. Rev.* **1977**, *6*, 43.
21. (a) Kanth, S. R.; Reddy, G. V.; Kishore, K. H.; Rao, P. S.; Narsaiah, B.; Murthy, U. S. N. *Eur. J. Med. Chem.* **2006**, *41*, 1011; (b) Grivsky, E. M.; Lee, S.; Sigel, C. W.; Duch, D. S.; Nichol, C. A. *J. Med. Chem.* **1980**, *23*, 327; (c) Bennett, L. R.; Blankley, C. J.; Fleming, R. W.; Smith, R. D.; Tessman, D. K. *J. Med. Chem.* **1981**, *24*, 382.
22. (a) Hughes, J. M.; Murad, F.; Chang, B.; Guerrant, R. L. *Nature* **1978**, *271*, 755; (b) Kots, A. Y.; Choi, B.-K.; Estrella-Jimenez, M. E.; Warren, C. A.; Gilbertson, S. R.; Guerrant, R. L.; Murad, F. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 8440; (c) Le Corre, L.; Girard, A.-L.; Aubertin, J.; Radvanyi, F.; Benoist-Lasselin, C.; Jonquoy, A.; Mugniery, E.; Legeai-Mallet, L.; Busca, P.; Le Merrer, Y. *Org. Biomol. Chem.* **2010**, *8*, 2164; (d) Kammasud, N.; Boonyarat, C.; Sanphanya, K.; Utsintong, M.; Tsunoda, S.; Sakurai, H.; Saiki, I.; André, I.; Grierson, D. S.; Vajragupta, O. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 745.
23. (a) Perzyna, A.; Klupsch, F.; Houssin, R.; Pommery, N.; Lemoine, A.; Henichart, J.-P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2363; (b) Joshi, A. A.; Viswanathan, C. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2613; (c) Klingenstein, R. M. P.; Leliveld, S. R.; Ryckebusch, A.; Korth, C. *J. Med. Chem.* **2006**, *49*, 5300; (d) Benkovic, S. J.; Baker, S. J.; Alley, M. R. K.; Woo, Y.-H.; Zhang, Y.-K.; Akama, T.; Mao, W.; Baboval, J.; Rajagopalan, P. T. R.; Wall, M.; Kahng, L. S.; Tavassoli, A.; Shapiro, L. *J. Med. Chem.* **2005**, *48*, 7468; (e) El-Gazzar, A. B. A.; Youssef, M. M.; Youssef, A. M. S.; Abu-Hashem, A. A.; Badria, F. A. *Eur. J. Med. Chem.* **2009**, *44*, 609; (f) Benedetti, P.; Mannhold, R.; Cruciani, G.; Ottaviani, G. *Bioorg. Med. Chem.* **2004**, *12*, 3607.
24. (a) Holla, B. S.; Mahalinga, M.; Karthikeyan, M. S.; Akberali, P. M.; Shetty, N. S. *Bioorg. Med. Chem.* **2006**, *14*, 2040; (b) Całus, S.; Gondek, E.; Danel, A.; Jarosz, B.; Pokładko, M.; Kityk, A. V. *Mater. Lett.* **2007**, *61*, 3292.
25. (a) Agarwal, A. K.; Jenekhe, S. A. *Macromolecules* **1991**, *24*, 6806; (b) Zhang, X.; Shetty, A. S.; Jenekhe, S. A. *Macromolecules* **1999**, *32*, 7422; (c) Jenekhe, S. A.; Lu, L.; Alam, M. M. *Macromolecules* **2001**, *34*, 7315; (d) Kim, J. I.; Shin, I.-S.; Kim, H.; Lee, J.-K. *J. Am. Chem. Soc.* **2005**, *127*, 1614.
26. (a) Quiroga, J.; Insuasty, B.; Insuasty, H.; Abonia, R.; Ortiz, A.; Sanchez, A.; Nogueras, M. *J. Heterocycl. Chem.* **2001**, *38*, 339; (b) Hassan, N. A.; Hegab, M. I.; Hashem, A. I.; Abdel-Motti, F. M.; Hebah, S. H. A.; Abdel-Megeid, F. M. E. *J. Heterocycl. Chem.* **2007**, *44*, 775; (c) Jiang, B.; Cao, L.-J.; Tu, S.-J.; Zheng, W.-R.; Yu, H.-Z. *J. Comb. Chem.* **2009**, *11*, 612; (d) Quiroga, J.; Acosta, P. A.; Cruz, S.; Abonia, R.; Insuasty, B.; Nogueras, M.; Cobo, J. *Tetrahedron Lett.* **2010**, *51*, 5443; (e) Aknin, K.; Desbene-Finck, S.; Helissey, P.; Giorgi-Renault, S. *Mol. Divers.* **2010**, *14*, 123.
27. (a) Shi, D.-Q.; Ni, S.-N.; Yang, F.; Shi, J.-W.; Dou, G.-L.; Li, X.-Y.; Wang, X.-S.; Ji, S.-J. *J. Heterocycl. Chem.* **2008**, *45*, 693; (b) Quiroga, J.; Trilleras, J.; Insuasty, B.; Abonia, R.; Nogueras, M.; Marchal, A.; Cobo, J. *Tetrahedron Lett.* **2010**, *51*, 1107; (c) Kumar, A.; Maurya, R. A. *Tetrahedron* **2007**, *63*, 1946; (d) Tanifum, E. A.; Kots, A. Y.; Choi, B.-K.; Murad, F.; Gilbertson, S. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3067; (e) Mosslemin, M. H.; Nateghi, M. R. *Ultrasonics Sonochem.* **2010**, *17*, 162.
28. (a) Quiroga, J.; Portillo, S.; Pérez, A.; Gálvez, J.; Abonia, R.; Insuasty, B. *Tetrahedron Lett.* **2011**, *52*, 2664; (b) Ghahremanzadeh, R.; Sayyafi, M.; Ahadi, S.; Bazgir, A. *J. Comb. Chem.* **2009**, *11*, 393; (c) Ahadi, S.; Mirzaei, P.; Bazgir, A. *Synth. Commun.* **2010**, *40*, 1224; (d) Ghahremanzadeh, R.; Shakibaei, G. I.; Ahadi, S.; Bazgir, A. *J. Comb. Chem.* **2010**, *12*, 191.
29. (a) Nandi, G. C.; Samai, S.; Kumar, R.; Singh, M. S. *Tetrahedron* **2009**, *65*, 7129; (b) Nandi, G. C.; Samai, S.; Kumar, R.; Singh, M. S. *Tetrahedron Lett.* **2009**, *50*, 7220; (c) Samai, S.; Nandi, G. C.; Kumar, R.; Singh, M. S. *Tetrahedron Lett.* **2009**, *50*, 7096; (d) Kumar, R.; Raghuvanshi, K.; Verma, R. K.; Singh, M. S. *Tetrahedron Lett.* **2010**, *51*, 5933; (e) Nandi, G. C.; Samai, S.; Singh, M. S. *Synlett* **2010**, 1133; (f) Nandi, G. C.; Samai, S.; Singh, M. S. *J. Org. Chem.* **2010**, *75*, 7785; (g) Verma, G. K.; Raghuvanshi, K.; Verma, R. K.; Dwivedi, P.; Singh, M. S. *Tetrahedron* **2011**, *67*, 3698; (h) Verma, R. K.; Verma, G. K.; Raghuvanshi, K.; Singh, M. S. *Tetrahedron* **2011**, *67*, 584; (i) Chowdhury, S.; Nandi, G. C.; Samai, S.; Singh, M. S. *Org. Lett.* **2011**, *13*, 3762; (j) Shukla, G.; Verma, R. K.; Verma, G. K.; Singh, M. S. *Tetrahedron Lett.* **2011**, *52*, 7195.
30. *General procedure for the synthesis of compounds* ***4*** *and* ***6***: To a mixture of 6-amino-1,3-dimethyluracil (1.0 mmol), aldehyde (1.0 mmol), and cyclic 1,3-diketone (1.0 mmol) in distilled water (10 mL) 20 mol % of PTSA was added. The reaction mixture was heated at 90 °C for the stipulated period of time till the full consumption of the starting materials (monitored by TLC). After completion of the reaction, the reaction mixture was allowed to cool to room temperature. The solid obtained was filtered and washed with water to get the pure product in good yield. However, in some cases they were recrystallized from ethanol. *Data of some selected new compounds: 5-(4-Nitrophenyl)-1,3,8,8-tetramethyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-trione* (***4a***): ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.12 (s, 1H, NH, D_2O exchangeable), 8.07 (d, J = 8.7 Hz, 2H, ArH), 7.46 (d, J = 8.7 Hz, 2H, ArH), 4.97 (s, 1H, CH), 3.45 (s, 3H, NCH_3), 3.07 (s, 3H, NCH_3), 2.59 (d, J = 6.9 Hz, 2H, CH_2), 2.23 (d, J = 16.2 Hz, 1H, CH), 2.03 (d, J = 15.9 Hz, 1H, CH), 1.07 (s, 3H, CH_3), 0.87 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 194.5, 160.6, 153.7, 150.4, 150.2, 145.7, 144.1, 129.0, 122.9, 110.5, 89.0, 56.0, 49.8, 34.6, 32.0, 30.2, 28.9, 27.6, 26.4, 18.5. IR (KBr): ν = 3468, 3272, 3095, 2960, 1700, 1644, 1511, 1378, 1244, 1081 cm^{-1}. ESI MS (m/z): 411 (M^++1); Anal. Calcd for $C_{21}H_{22}N_4O_5$: C, 61.45; H, 5.40; N, 13.65%. Found C, 61.13; H, 5.62; N, 13.80%. *5-(3-hydroxyphenyl)-1,3,8,8-tetramethyl-7,8,9,10-tetrahydropyrimido [4,5-b]quinoline-2,4,6-trione* (***4e***): ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.09 (s, 1H, NH, D_2O exchangeable), 8.97 (s, 1H, OH, D_2O exchangeable), 7.42–7.35 (m, 2H, ArH), 7.18–7.10 (m, 2H, ArH), 4.83 (s, 1H, CH), 3.44 (s, 3H, NCH_3), 3.08 (s, 3H, NCH_3), 2.56 (d, J = 6.9 Hz, 2H, CH_2), 2.21 (d, J = 15.6 Hz, 1H, CH), 2.03 (d, J = 16.2 Hz, 1H, CH), 1.03 (s, 3H, CH_3), 0.89 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 198.5, 165.3, 161.0, 156.2, 154.2, 148.0, 149.9, 133.2, 121.0, 118.5, 96.4, 55.6, 45.3, 38.9, 35.1, 34.0, 33.6, 18.7. IR (KBr): ν = 3397, 3279, 3220, 3098, 2963, 1701, 1658, 1623, 1495, 1455, 1382, 1246, 1213, 1147, 1052, 962, 869, 785 cm^{-1}. ESI MS (m/z): 382 (M^++1); Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02%. Found C, 66.30; H, 6.26; N, 11.34%. *5-(3-Nitrophenyl)-1,3-dimethyl-7,8,9,10-tetrahydropyrimido[4,5-b] quinoline-2,4,6-trione* (***4n***): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00–7.93 (m, 3H, ArH), 7.42 (t, J = 8.4 Hz, 1H, ArH), 6.30 (s, 1H, NH, D_2O exchangeable), 5.24 (s, 1H, CH), 3.56 (s, 3H, NCH_3), 3.25 (s, 3H, NCH_3), 2.62 (m, 2H, CH_2), 2.39 (m, 2H, CH_2), 2.07 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 194.2, 160.9, 151.4, 150.8, 148.2, 147.8, 144.5, 135.2, 128.7, 122.4, 121.8, 113.5, 91.2, 36.3, 34.3, 27.4, 26.4, 20.4. IR (KBr): ν = 3451, 3275, 3219, 3087, 2960, 2875, 1691, 1666, 1643, 1498, 1379, 1348, 1257, 1198, 1168, 1134, 1084, 1050, 946, 873, 817, 745 cm^{-1}. ESI MS (m/z): 383 (M^++1); Anal. Calcd for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65%. Found: C, 59.87; H, 4.85; N, 14.78%. *5-(2-Methoxyphenyl)-1,3-dimethyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-trione* (***4t***): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (s, 1H, NH, D_2O exchangeable), 7.22–6.75 (m, 4H, ArH), 4.95 (s, 1H, CH), 3.68 (s, 3H, NCH_3), 3.46 (s, 3H, NCH_3), 3.04 (s, 3H, OCH_3), 2.68–2.66 (m, 2H, CH_2), 2.46–2.43 (m, 2H, CH_2), 2.17–2.14 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.8, 160.7, 150.9, 150.4, 147.8, 147.5, 143.2, 134.5, 128.0, 121.9, 120.7, 112.6, 90.2, 56.4, 39.3, 38.3, 28.2, 27.6, 21.4. IR (KBr): ν = 3245, 3159, 2972, 1698, 1668, 1656, 1349, 1247, 1178, 1064, 986, 867, 765 cm^{-1}. ESI MS (m/z): 368 (M^++1); Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44%. Found: C, 65.51; H, 5.52; N, 11.60%. *1,3-Dimethyl-5-(5-bromo-2-hydroxyphenyl)indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6-trione* (***6f***): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.03 (s, 1H, OH, D_2O exchangeable), 7.95 (d, J = 7.5 Hz, 1H, ArH), 7.68–7.64 (m, 2H, ArH), 7.56–7.52 (m, 1H, ArH), 7.44 (d, J = 8.7 Hz, 1H, ArH), 7.18(s, 1H, ArH), 6.84 (d, J = 8.7 Hz, 1H, ArH), 3.90 (s, 3H, NCH_3), 3.38 (s, 3H, NCH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 185.3, 172.5, 170.3, 160.4, 158.4, 151.7, 132.5, 131.6, 130.4, 129.9, 128.1, 128.0, 125.7, 119.5, 118.7, 113.0, 35.2, 30.0. IR (KBr): ν = 3409, 3063, 2965, 1730, 1670, 1578, 1436, 1362, 1245, 1160, 1089. cm^{-1}. ESI MS (m/z): 465 (M^++1); Anal. Calcd for $C_{22}H_{14}BrN_3O_4$: C, 56.91; H, 3.04; N, 9.05%. Found C, 57.23; H, 2.85; N, 9.23%. *1,3-Dimethyl-5-(iso-propyl)indeno[2′,1′:5,6] pyrido[2,3-d] pyrimidine-2,4,6-trione* (***6h***): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, J = 7.2 Hz, 1H, ArH), 7.80 (d, J = 7.2 Hz, 1H, ArH), 7.67 (t, J = 7.5 Hz, 1H, ArH), 7.56 (t, J = 7.5 Hz, 1H, ArH), 3.86 (s, 3H, NCH_3), 3.50 (s, 3H, NCH_3), 2.49–2.38 (m, 1H, CH), 0.87 (s, 6H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 180.2168.5, 165.3, 164.6, 159.4, 155.3, 146.2, 130.7, 129.1, 128.5, 125.3, 122.6, 107.5, 37.5, 30.4, 28.3, 28.2, 22.4. IR (KBr): ν = 2987, 1755, 1700, 1555, 1510, 1400, 1398, 1330, 1250, 1185, 1040 cm^{-1}. ESI MS (m/z) 365(M^+ + 1); Anal. Calcd for $C_{19}H_{17}N_3O_3$: c, 68.05; H, 5.11; N, 12.53%. Found C, 68.26; H, 5.43; N, 12.29%.