A Novel Biginelli-Like Reaction: An Efficient One-pot Synthesis of Spiro[oxindole-quinazoline/pyrimidine]ones

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Received May 13, 2009: Revised February 18, 2010: Accepted February 22, 2010

Abstract: Some new spiro[oxindole-quinazoline/pyrimidine]ones were synthesized *via* a novel three-component Biginelli-like reaction between isatin, cyclic or acyclic 1,3-dicarbonyl compounds, and urea, *N*-methyl urea or thiourea in one pot and good yields.

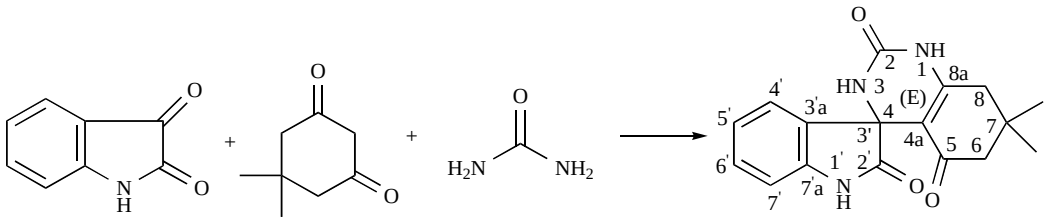
Keywords: Quinazolinone, pyrimidinone, spiro oxindole, multi-component reaction, Biginelli-like reaction, isatin.

INTRODUCTION

Indole nucleus is probably one of the most studied heterocycles, a common and important feature of a variety of natural products and medicinal agents [1]. Compounds carrying the indole moiety exhibit antibacterial and antifungal activities [2]. Synthesis and high throughput screening of indoles have revealed that sharing of indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances their biological activities [3-5].

Recently, 3,4-dihydropyrimidine-2(1H)-ones have attracted great attention of synthetic organic chemists due to their anti-hypertensive activities as well behaving as calcium channel blockers, α-1a-antagonists and neuropeptides-Y antagonists [6-8]. The Biginelli reaction is one of the well established multicomponent reactions (MCRs) which frequently was employed for synthesis of 3,4-dihydropyrimidine-2(1H)-ones (DHPMs). The traditional Biginelli reactions are referred to the one-pot condensations between a *β*-dicarbonyl compound, an aldehyde, and urea under strongly acidic conditions [9]. There are a wealth of reports on improvements and extending of this reaction using new techniques, variety of catalysts and various reactants [10-25]. In recent years, several synthetic procedures for preparation of DHPMs *via* Biginelli-like reactions have been reported, which remarkably have broadened the scope of Biginelli reactions [26-29]. In spite of their potential utility, all of the so far reported synthetic methods on Biginelli and Biginelli-like reactions start from substrates which are limited to aromatic aldehydes, acetophenone or *β*-dicarbonyl compounds, and urea or thiourea.

As a finding of a research project in continuation of our previous work on the Biginelli-like reaction [30], herein we report, for the first time, a simple approach to novel spiro[oxindole-quinazoline/pyrimidine]ones *via* a new Biginelli-like reaction consisting of a three-component cyclocondensation of cyclic or acyclic dicarbonyl compounds, urea or *N*-methyl urea and isatin derivatives instead of aromatic aldehydes.



1a **2a** **3a** **4a**

Scheme 1.

RESULT AND DISCUSSION

Our preliminary experiment using isatin instead of aldehydes in the traditional condition of Biginelli reaction was successful as a mixture of isatin **1a** (5 mmol), dimedone **2a** (7.5 mmol) and urea **3a** (5 mmol) in the presence of a catalytic amount of acetic acid afforded the spiro[oxindole-quinazolin]dione **4a** in low yield (Scheme **1**). Delighted by this result we set out to improve the yield by screening some possible catalysts, so we chose the condensation of dimedone, isatin, and urea as the model reaction being performed in the presence of various protic and Lewis acids. As is indicated in Table **1**, the best yields were obtained in the presence of HCl.

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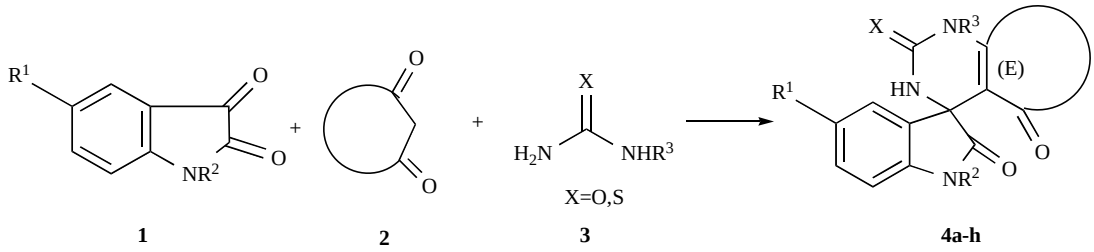
Table 1. Three-Component Reaction of Isatin, Urea and Dimedone in the Presence of 10% mmol of Different Catalysts*

Entry	Catalyst	Yield (%)
1	CH_3COOH	52
2	HCl	86
3	NH_4Cl	60
4	$NaHSO_4$	55
5	$FeCl_3$	47
6	$AlCl_3$	45

*Isatin (5 mmol), urea (5 mmol) and dimedone (7.5 mmol) in absolute ethanol.

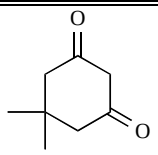
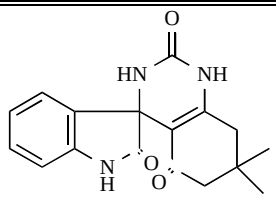
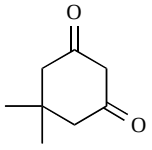
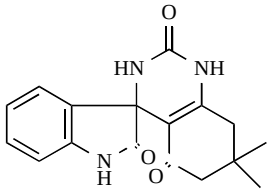
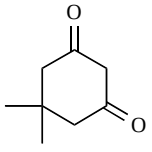
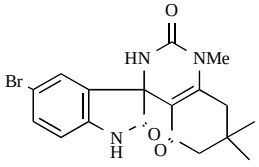
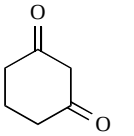
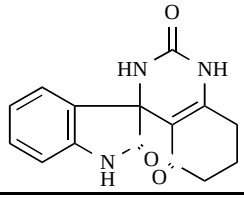
Also, to verify the scope of substrates in this synthetic method, a set of reactions of isatin derivatives and urea with some other cyclic 1,3-dicarbonyl compounds such as 1,3-cyclohexadione and barbituric acid were examined under the same conditions (Scheme **2**). As was shown in Table **2**, the results account for the viability of the reactions with all the selected substrates [31, 32].

However, we have not determined the mechanism of reaction. A reasonable and more accepted one for formation of the spiro products **4a-h** is depicted in Scheme **3**. The process represents a typical cascade reaction in which the isatin **1** first condenses with urea **3** to afford the intermediate **5**. Then, the iminium intermediate **5** subjects to the 1,2-addition of cyclic 1,3-dicarbonyl compound **2** to give the compound **6** followed by cyclocondensation of the amidic

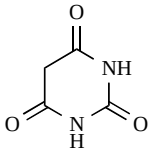
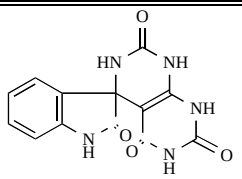
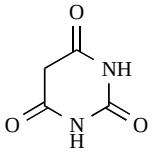
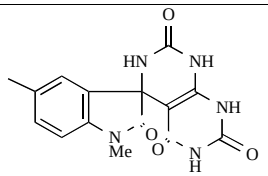
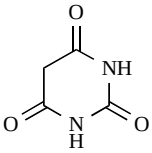
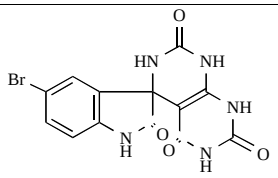
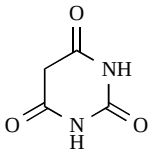
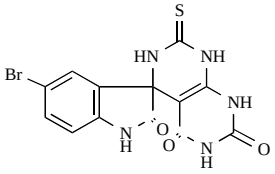


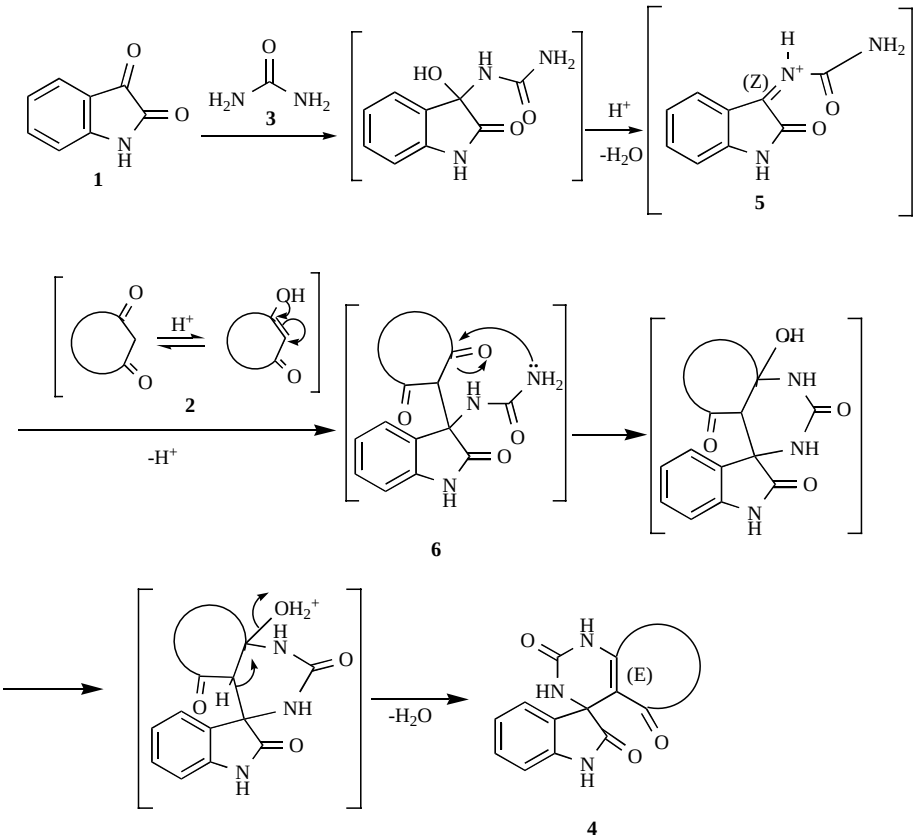
Scheme 2.

Table 2. Synthesis of Spiro[oxindole-quinazoline/pyrrimidine]ones by the Reaction of Isatin Derivatives, Urea or *N*-methyl Urea or Thiourea and Cyclic 1,3-dicarbonyl Compounds in the Presence of a Catalytic Amount of HCl

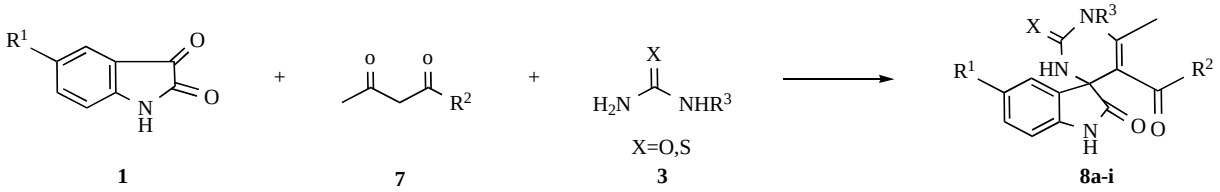
Products	R^1	R^2	R^3	Cyclic-1,3-dicarbonyl	Time (h)	Structure of Products	Mp(^{0}C)	Yield (%)
4a	H	H	H		3:30		350-352	82
4b	H	H	Me		3		336-338	78
4c	Br	H	Me		1		344-346	77
4d	H	H	H		2		345-347	72

(Table 2). Contd…..

Products	R^1	R^2	R^3	Cyclic-1,3-dicarbonyl	Time (h)	Structure of Products	Mp(^{0}C)	Yield (%)
4e	H	H	H		1:40		270-272	96
4f	H	Me	H		3		328-330	92
4g	Br	H	H		2		238-240	85
4h	Br	H	H		3:20		365-367	72



Scheme 3.



1 **7** **3** **8a-i**

Scheme 4.

Table 3. Synthesis of Spiro[oxindole-pyrrimidine]-2-ones by the Reaction of Isatin Derivatives, Urea or *N*-methyl Urea and Acyclic 1,3-dicarbonyl Compounds in the Presence of a Catalytic Amount of HCl

Products	R^1	R^2	R^3	X	Time (h)	Yield (%)	Mp (^{0}C)
8a	H	OCH_2CH_3	H	O	6	90	297-299
8b	Br	OCH_2CH_3	H	O	5:30	87	293-295
8c	H	OCH_2CH_3	CH_3	O	5:30	85	248-250
8d	Br	OCH_2CH_3	CH_3	O	5	81	175-178
8e	H	HNC_6H_5	H	O	7	80	298-300
8f	H	HNC_6H_5	CH_3	O	6	88	265-268
8g	Br	HNC_6H_5	H	O	6:30	86	295-297
8h	Br	OCH_2CH_3	H	S	7	68	323-325
8i	H	HNC_6H_5	H	S	8:20	69	331-333

function, with a carbonyl group of the 1,3-dicarbonyl moiety to form the desired products **4a-h** (Scheme **3**) [33]. Also, there is another frequently suggested mechanism which was based on Knoevenagel condensation between 1,3-dicarbonyl compounds and isatin, followed by Michael addition of urea to form an α,β-unsaturated carbonyl transient. The process entails with a cyclocondensation of the final intermediate to afford the spiro products.

In the course of further exploring the scope of substrates, applicable to this synthesis, we used of ethyl acetoacetate as an acyclic 1,3-dicarbonyl compound (Scheme **4**). Refluxing a solution of 5 mmol isatin **1** with 7.5 mmol ethyl acetoacetate **7** and 5 mmol urea **3** in ethanol, afforded spiro[oxindole-pyrimidine]one **8a**, but the yield was not so high (37%) (Scheme **4**). In order to increase the yield, we examined the effects of amount of urea and catalyst on the formation of **8a**. Fortunately, we found that, with increasing the amount of urea from 5 mmol to 10 mmol and HCl from 10% mmol to 15% mmol the yield of **8a** is also increases to 90%.

Similarly, under the above optimized condition, the reaction with other acyclic 1,3-dicarbonyl compounds proceeded well and a variety of the desired spiro oxindole products **8b-i** were obtained in good yields [34] (Scheme **4**, Table **3**).

In summary, a new class of three-component Biginelli-like reactions based on using isatin derivatives instead of aldehydes was introduced here. These reactions were successfully devised as an efficient and convenient means for synthesis of some novel spiro[oxindole-pyrimidine/quinazoline]ones. This method has shown the ability to tolerate a reasonable variety of substituents in all three components; therefore we anticipate that it will be adopted in combinatorial chemistry to synthesize the related spiro oxindoles of potent biological importance for screening.

ACKNOWLEDGEMENT

We are grateful to the research council of Islamic Azad University of Rasht Branch for financial support of this project.

REFERENCES AND NOTES

[1] Houlihan, W.J.; Remers, W.A.; Brown, R.K. *Indoles*: Part I, Wiley: New York, **1992**.

[2] Sundberg, R.J. *The Chemistry of Indoles*, Academic: New York, **1996**.

[3] Da-Silva, J.F.M.; Garden, S.J.; Pinto, A.C. The chemistry of isatins: a review from 1975 to 1999. *J. Braz. Chem. Soc.*, **2001**, *12*, 273.

[4] Joshi, K.C.; Jain, R.; Sharma, K. Synthesis of some fluorine containing spiro[3H-indole-3,4'(4H)-pyrano[2,3-d]pyrimidine]-2,5', 7'(1H)-triones as CNS agents. *J. Indian Chem. Soc*., **1998**, *115*, 202.

[5] Abdel-Rahman, A.H.; Keshk, E.M.; Hanna, M.A. Synthesis and evaluation of some new spiro indoline-based heterocycles as potentially active antimicrobial agents. *Bioorg. Med. Chem.*, **2004**, *12*, 2483.

[6] Zorkun, I.S.; Sarac, S.; Celebi, S.; Erol, K. Synthesis of 4-aryl-3,4-dihydropyrimidin-2(1H)-thione derivatives as potential calcium channel blockers. *Bioorg. Med. Chem.*, **2006**, *14*, 8582.

[7] Kappe, C.O. Biologically active dihydropyrimidones of the Biginelli-type. *Eur. J. Med. Chem.*, **2000**, *35*, 1043.

[8] Kappe, C.O.; Fabian, W.M.F.; Semones, M.A. Conformational analysis of 4-aryl-dihydropyrimidine calcium channel modulators: a comparison of ab initio, semiempirical and X-ray crystallographic studies. *Tetrahedron*, **1997**, *53*, 2803.

[9] Biginelli, P. Derivati aldeiduredici degli eteri acetil-e dossal-acetico. *Gazz. Chim. Ital.*, **1893**, *23*, 360.

[10] Stadler, A.; Kappe, C.O. Automated library generation using sequential microwave-assisted chemistry: application toward the Biginelli multicomponent condensation. *J. Comb. Chem.,* **2001**, *3*, 624.

[11] Yadav, J.S.; Reddy, B.V.S.; Reddy, K.B.; Raj, K.S.; Prasad, A.R. Ultrasound-accelerated synthesis of 3,4-dihydropyrimidin-2(1H)-ones with ceric ammonium nitrate. *J. Chem. Soc., Perkin Trans. 1,* **2001**, 1939.

[12] Alessandro, D.; Alessandro, M. Parallel synthesis of dihydropyrimidinones using Yb(III)-resin and polymer-supported scavengers under solvent-free conditions: a green chemistry approach to the Biginelli reaction. *Tetrahedron Lett.,* **2001**, *42*, 7975.

[13] Kappe, C.O.; Falsone, S.F. Polyphosphate ester-mediated synthesis of dihydropyrimidines. Improved conditions for the Biginelli reaction. *Synlett,* **1998**, 718.

[14] Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. A revision of the Biginelli reaction under solid acid catalysis: solvent-free synthesis of dihydropyrimidines over montmorillonite KSF. *Tetrahedron Lett.,* **1999**, *40*, 3465.

[15] Ranu, B.C.; Hajra, A.; Jana, U. Indium(III) chloride-catalyzed one-pot synthesis of dihydropyrimidinones by a three-component coupling of 1,3-dicarbonyl compounds, aldehydes, and urea: an improved procedure for the Biginelli reaction. *J. Org. Chem.,* **2000**, *65*, 6270.

[16] Ma, Y.; Qian, C.; Wang, L.; Yang, M. Lanthanide triflate catalyzed Biginelli reaction: one-pot synthesis of dihydropyrimidinones under solvent-free conditions**.** *J. Org. Chem.,* **2000**, *65*, 3864.

[17] Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T.N.B. Bismuth(III)-catalyzed synthesis of dihydropyrimidinones: Improved protocol conditions for the Biginelli reaction. *Synlett,* **2001**, 863.

[18] Yadav, J.S.; Reddy, B.V.S.; Srinivas, R.; Venugopal, C.; Ramalingam, T. $LiClO_4$-catalyzed one-pot synthesis of dihydropyrimidinones: an improved protocol for Biginelli reaction. *Synthesis,* **2001**, 1341.

[19] Lu, J.; Bai, Y. Catalysis of the Biginelli reaction by ferric and nickel chloride hexahydrates: one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. *Synthesis,* **2002**, 466.

[20] Pani, A.S.; Arjun, M.; Sridhar, D.; Srinivas, K;. Raviprasad, T. N-Substituted benzoxazolyl ureas and thioureas in Biginelli reaction promoted by trifluoromethane sulfonic acid: An efficient and convenient synthesis of substituted benzoxazolyl 3,4-dihydropyrimidine (1H)-(thio)-ones. *Chinese Chem. Lett.,* **2009**, *20*, 909.

[21] Ryabukhin, S.V.; Plaskon, A.S.; Ostapchuk, E.N.; Volochnyuk, D.M.; Tolmachev, A.A. N-Substituted ureas and thioureas in Biginelli reaction promoted by chlorotrimethylsilane: convenient synthesis of N1-alkyl-, N1-aryl-, and N1,N3-dialkyl-3,4-dihydropyrimidin-2(1H)-(thi)ones. *Synthesis-Stuttgart,* **2007**, 417.

[22] Dwivedi, N.; Mishra, R.C.; Tripathi, R.P. Tetrabutylammonium hydrogensulphate catalyzed efficient synthesis of glycosyl(aryl) dihydropyrimidinones. *Lett. Org. Chem.,* **2005**, *2*, 450.

[23] Zhu, Y.L.; Huang, S.L.; Pan, Y.J. Highly chemoselective multicomponent Biginelli-type condensations of cycloalkanones, urea or thiourea and aldehydes. *Eur. J. Org. Chem.,* **2005**, 2354.

[24] Zhu, Y.L.; Pan, Y.J.; Huan, S.L. Chemoselective multicomponent condensation of 1,3-cyclohexanedione, urea or thiourea with aldehydes: one-pot synthesis of two families of fused heterobicyclic and spiro-fused heterobicyclic aliphatic rings. *Heterocycles,* **2005**, *65*, 133.

[25] Shaabani, A.; Sarvary, A.; Rahmati, A.; Rezayan, A.H. Ionic liquid/silica sulfuric acid promoted fast synthesis of a Biginelli-like scaffold reaction. *Lett. Org. Chem.,* **2007**, *4*, 68

[26] Kumar, S.; Saini, A.; Sandhu, J.S. Cobalt(II) chloride or manganese(II) chloride or tin(II) chloride promoted one pot synthesis of dihydropyrimidin-2(1H)-ones using microwave irradiation. *Ind. J. Chem. Sect. B Org. Chem. Includ. Med. Chem.,* **2005**, *44B*, 762.

[27] Wang, Z.T.; Xu, L.W.; Xia, C.G.; Wang, H.Q. Novel Biginelli-like three-component cyclocondensation reaction: efficient synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2(1H)-ones. *Tetrahedron Lett.,* **2004**, *45*, 7951.

[28] Sabitha, G.; Reddy, K.B.; Srinivas, R.; Yadav, J.S. Iodotrimethylsilane-accelerated one-pot synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2(1H)-ones: A novel procedure for the Biginelli-like cyclocondensation reaction at room temperature. *Helv. Chim. Acta,* **2005**, *11*, 2996.

[29] Liang, B.; Wang, X.T; Wang, J.X.; Zhengyin, D. New three-component cyclocondensation reaction: microwave-assisted one-pot synthesis of 5-unsubstituted-3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions. *Tetrahedron,* **2007**, *63*, 1981.

[30] Kefayati, H.; Fakhriyannejad, M.; Mohammadi, A.A. An efficient synthesis of new 3,4-dihydropyrimidin-2(1H)-ones incorporating a phenyl moiety at C-5 and C-6 catalyzed by $Co(OAc)_2.4H_2O$ and TMSCl. *Phosphorus Sulfur Silicon Relat. Elem.,* **2009**, 1796.

[31] All chemicals were purchased from Merck and Fluka. Melting points were obtained in open capillary tubes and were measured on an Electro-thermal IA 9100 apparatus. IR spectra were recorded on KBr pellets on a Shimadzu FT-IR 8600 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 and 75 MHz, respectively. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. Elemental analysis were carried out on a Thermo Finnigan Flash EA 1112 series instrument.

[32] General procedure for the synthesis of spiro[oxindole-quinazoline/pyrrimidine]ones **4a-h**: A mixture of isatin derivatives **1** (5 mmol), cyclic 1,3-dicarbonyl compound **2** (7.5 mmol), urea or *N*-methyl urea or thiourea **3** (5mmol) and HCl (10% mmol) in absolute ethanol (5 mL) refluxed for appropriate time according to Table **2** (Scheme **2**). Upon completion, as monitored by TLC on silica gel using ethyl acetate as eluent, the reaction mixture was allowed to cool to room temperature. The solid was filtered off and washed with cold ethanol (3×0.5 ml) to give white powders of **4a-h**.

Spiro[4.3′]oxindole-3,4,7,8-tetrahydro-7,7-dimethylquinazoline-2, 5-(1H,6H)-dione **(4a)**: Mp 350-352 ˚C, IR (KBr) (υ_{max} cm^{-1}): 3367, 3258, 3165, 1722, 1689, 1635; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.95 (s, 3H, CH_3), 1.00 (s, 3H, CH_3),1.93 (d, *J*=16.0 Hz, 1H, H-8a), 2.08 (d, *J*=16.0 Hz, 1H, H-8b), 2.31 (d, *J*=17.1 Hz, 1H, H-6a), 2.43 (d, *J*=17.1 Hz, 1H, H-6b), 6.74-7.14 (m, 4H, H-aromatic), 7.87 (s, 1H, NH), 9.69 (s, 1H, NH), 10.27 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 26.7, 26.8, 28.0, 32.2, 49.7, 61.7, 105.2, 109.2, 121.4, 122.9, 129.6, 133.5, 141.9, 150.2, 153.9, 176.4, 191.9 ppm. *Anal.* Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.62; H, 5.53; N, 13.35.

Spiro[4.3′]oxindole-3,4,7,8-tetrahydro-1,7,7-trimethylquinazoline-2,5-(1H,6H)-dione **(4b)**: Mp 336-338 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3220, 3200, 3082, 2935, 1732, 1685; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.97 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.93 (d, *J*=15.9 Hz, 1H, H-8a), 2.01 (d, *J*=15.9 Hz, 1H, H-8b), 2.47 (d, *J*=3.0 Hz, 1H, H-6a), 2.50 (d, *J*=3.0 Hz, 1H, H-6b), 3.31 (s, 3H, CH_3), 6.73-7.13 (m, 4H, H-aromatic), 8.04 (s, 1H, NH), 10.22 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 27.1, 27.1, 28.2, 29.2, 32.0, 48.9, 61.0, 107.4, 109.3, 121.4, 123.0, 128.7, 133.6, 142.0, 150.7, 155.3, 176.5, 192.3 ppm; MS (70 eV): m/z (%): 325 (5, M^+), 295 (5.5), 280 (50), 241 (100), 212 (22).

5′-Bromo-spiro[4.3′]oxindole-3,4,7,8-tetrahydro-1,7,7-trimethylquinazoline-2,5-(1H,6H)-dione **(4c)**: Mp 344-346 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3207, 3089, 2947, 1728, 1689; ^{1}H NMR (300 MHz, DMSO-d_6) δ:1.01 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.99 (d, *J*=9.5 Hz, 1H, H-8a), 2.01 (d, *J*=9.5 Hz, 1H, H-8b), 2.62 (d, *J*=9.5 Hz, 1H, H-6a), 2.65 (d, *J*=9.5 Hz, 1H, H-6b), 3.32 (s, 3H, CH_3), 6.72-7.33 (m, 3H, H-aromatic), 8.11 (s, 1H, NH), 10.39 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 28.4, 28.7, 30.2, 32.9, 49.1, 56.8, 62.1, 107.6, 112.1, 113.8, 126.8, 132.2, 136.8, 142.3, 151.40, 156.8, 177.1, 193.3 ppm.

Spiro[4.3′]oxindole-3,4,7,8-tetrahydro quinazoline-2,5-(1H,6H)-dione **(4d)**: Mp 345-347 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3311, 3228, 3118, 1712, 1695, 1631; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.86-2.15 (m, 4H, H-7,8), 2.50 (m, 2H, H-6), 6.74-7.14 (m, 4H, H-aromatic), 7.83 (s, 1H, NH), 9.68 (s, 1H, NH), 10.25 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.6, 27.0, 37.2, 62.8, 107.5, 110.1, 122.3, 124.1, 129.5, 134.5, 142.9, 151.0, 156.9, 177.5, 193.0 ppm. *Anal.* Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.66; H, 4.69; N, 14.76.

Spiro[5.3′]oxindole-5,6-dihydropyrimido[4,5-b]pyrimidine-2,4,7-(1H,3H,8H)-trione **(4e)**: Mp 270-272 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3367, 3301, 3265, 1762, 1749, 1712, 1690; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.67-7.13 (m, 4H, H-aromatic), 10.54 (s, 1H, NH), 11.17 (m, 4H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 53.4, 109.4, 121.4, 124.2, 128.0, 128.7, 143.1, 150.2, 167.4, 175.6 ppm. *Anal.* Calcd. for $C_{13}H_9N_5O_4$: C, 52.18; H, 3.03; N, 23.40. Found: C, 52.23; H, 2.99; N, 23.44.

Spiro[5.3′]-1′-N-Methyl-oxindole-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7-(1H,3H,8H)-trione **(4f)**: Mp 228-230 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3380, 3184, 3097, 2981, 1740, 1710, 1690; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.03 (s, 3H, CH_3), 6.91-7.28 (m, 4H, H-aromatic), 11.2 (m, 4H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 53.5, 56.9, 109.2, 123.0, 124.7, 128.4, 129.8, 145.4, 151.0, 168.6, 175.1 ppm.

5′-Bromo-spiro[5,3′]oxindole-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7-(1H,3H,8H)- trione **(4g)**: Mp 238-240 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3334, 3211, 3093, 1731, 1689; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.68-7.35 (m, 3H, H-aromatic), 10.74 (s, 1H, NH), 11.25 (m, 4H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 56.9, 112.1, 113.8, 128.1, 131.6, 132.3, 143.6, 151.0, 168.0, 176.3 ppm.

5′-Bromo-spiro[5,3′]oxindole-5,6,7,8-tetrahydro-7-thioxopyrimido [4,5-d]pyrimidine-2,4-(1H,3H)-dione **(4h)**: Mp 365-367 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3328, 3151, 3098, 1710, 1681; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.73-8.27 (m, 3H, H-aromatic), 10.63 (s, 1H, NH), 11.20 (m, 2H, NH), 11.32 (m, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 57.3, 112.8, 112.9, 128.6, 132.1, 132.7, 143.9, 168.3, 176.7, 178.1 ppm.

[33] Kappe, C.O. A reexamination of the mechanism of the Biginelli dihydropyrimidine synthesis. Support for an N-acyliminium ion intermediate. *J. Org. Chem.* **1997**, *62*, 7201.

[34] General procedure for the synthesis of spiro[oxindole-pyrrimidine]ones **8a-i**: A mixture of isatin derivative **1** (5 mmol), acyclic 1,3-dicarbonyl compound **7** (7.5 mmol), urea or *N*-methyl urea or thiourea **3** (10 mmol), HCl (15% mmol) and ethanol (5 mL) refluxed for appropriate time according to Table **3** (Scheme **4**). The reaction after completion, as monitored by TLC on silica gel using ethyl acetate as eluent, was allowed to cool to room temperature. Then 30 mL distilled water was added to the beaker and stirred for 10 minute. The precipitate thus obtained was filtered off. The crude product was purified by recrystallization from ethanol 95.5% and dried.

Spiro[4.3']oxindole-ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-pyrimidine-5-carboxylate **(8a)**: Mp 297-299 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3436, 3201, 3089, 2970, 1716, 1664; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.80 (t, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.72 (m, 2H, CH_2), 6.75-7.19 (m, 4H, H-aromatic), 7.80 (s, 1H, NH), 9.37 (s, 1H, NH), 10.23 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.0, 19.0, 19.4, 63.9, 97.86, 110.2, 122.5, 124.1, 129.7, 135.1, 143.0, 150.8, 151.3, 165.4, 178.2 ppm; MS (70 eV): m/z (%): 301 (10, M^+), 272 (64), 228 (100), 200 (34), 131 (7), 103 (10), 91 (8), 77 (8), 56 (7), 42 (17). *Anal.* Calcd. for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95. Found: C, 59.85; H, 4.86; N, 14.00.

5′-Bromo-spiro[4.3']oxindole-ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-pyrimidine-5-carboxylate **(8b)**: Mp 293-295 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3420, 3310, 3145, 1730, 1705, 1640; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.85 (t, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.76 (m, 2H, CH_2), 6.71-7.37 (m, 3H, H-aromatic), 7.87 (s, 1H, NH), 9.44 (s, 1H, NH), 10.39 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.0, 19.0, 19.1, 64.0, 97.0, 112.2, 113.9, 126.9, 132.4, 142.3, 151.0, 151.7, 165.2, 177.9 ppm; MS (70 eV): m/z (%): 379 (14, M^+), 350 (75), 306 (100), 278 (19), 263 (12), 210 (11), 131 (12), 103 (14), 91 (10), 77 (9), 42 (43).

Spiro[4.3']oxindole-ethyl-1,2,3,4-tetrahydro-1,6-dimethyl-2-oxo-pyrimidine-5-arboxylate **(8c)**: Mp 248-250 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3320, 3259, 1735, 1710, 1664; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.78 (t, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 3.69 (m, 2H, CH_2), 6.75-7.20 (m, 4H, H-aromatic), 7.93 (s, 1H, NH), 10.25 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.8, 17.3, 30.2, 60.2, 62.8, 101.0, 110.3, 122.5, 124.1, 129.9, 134.4, 143.0, 151.7, 152.3, 165.8, 178.0 ppm; MS (70 eV): m/z (%): 315 (16, M^+), 286 (90), 242 (100), 214 (35), 199 (13), 103 (9), 91 (7), 77 (9), 56 (70), 42 (8).

5′-Bromo-spiro[4.3']oxindole-ethyl-1,2,3,4-tetrahydro-1,6-dimethyl-2-oxo-pyrimidine-5-carboxylate **(8d)**: Mp 175-178 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3452, 3217, 1740, 1712, 1649. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.64 (t, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.01 (s, 3H, CH_3), 3.59 (m, 2H, CH_2), 6.46-7.13 (m, 3H, H-aromatic), 7.29 (s, 1H, NH), 9.80 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.5, 14.4, 17.3, 60.3, 63.0, 100.2, 111.8, 114.5, 126.9, 132.2, 135.9, 141.3, 151.9, 152.0, 165.3, 177.9 ppm. MS (70 eV): m/z (%): 393 (6, M^+), 364 (40), 320 (38), 292 (12), 277 (8), 103(8), 91 (7), 77 (7), 56 (100), 42 (15).

Spiro[4.3']oxindole-N-Phenyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-pyrimidine-5-carboxamide **(8e)**: Mp 298-300 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3400, 3298, 1722, 1700. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.01 (s, 3H, CH_3), 6.69-7.38 (m, 9H, H-aromatic), 7.56 (s, 1H, NH), 8.92 (s, 1H, NH), 9.69 (s, 1H, NH), 10.13 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 18.3, 64.2, 105.3, 110.3, 120.0, 122.3, 123.9, 124.7, 129.3, 133.2, 139.7, 139.8, 143.3, 152.8, 165.0, 178.3 ppm. *Anal.* Calcd. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.46; H, 4.55; N, 16.12.

Spiro[4.3']oxindole-N-Phenyl-1,2,3,4-tetrahydro-1,6-dimethyl-2-oxo-pyrimidine-5-carboxamide **(8f)**: Mp 265-268 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3410, 3298, 1718, 1700. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.16 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 6.69-7.36 (m, 9H, H-aromatic), 7.72 (s, 1H, NH), 9.91 (s, 1H, NH), 10.16 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 18.3, 30.0, 63.1, 107.8, 110.3, 120.2, 122.3, 124.0, 125.0, 129.3, 130.0, 132.4, 139.6, 140.5, 143.2, 153.6, 165.3, 178.0 ppm.

5′-Bromo-spiro[4.3']oxindole-N-Phenyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-pyrimidine-5-carboxamide **(8g)**: Mp 295-297 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3405, 3220, 1712, 1690. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.02 (s, 3H, CH_3), 6.67-7.39 (m , 8H, H-aromatic), 7.67 (s, 1H, NH), 9.01 (s, 1H, NH), 9.74 (s, 1H, NH), 10.30 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 18.4, 64.3, 104.6, 112.3, 113.7, 120.0, 120.2, 124.0, 127.5, 129.4, 132.6, 135.8, 139.6, 140.5, 142.6, 152.5, 164.9, 177.8 ppm.

5′-Bromo-spiro[4.3']oxindole-ethyl-1,2,3,4-tetrahydro-6-methyl-2-thio-pyrimidine-5-carboxylate **(8h)**: Mp 323-325 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3407, 3315, 3132, 1715, 1709; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.88 (t, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.78 (m, 2H, CH_2), 6.46-7.13 (m, 3H, H-aromatic), 7.76 (s, 1H, NH), 9.54 (s, 1H, NH), 10.48 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 15.1, 20.4, 20.9, 69.7, 100.6, 114.1, 115.8, 127.6, 132.1, 141.9, 151.3, 165.4, 174.7, 178.1 ppm.

Spiro[4.3']oxindole-N-Phenyl-1,2,3,4-tetrahydro-6-methyl-2-thio-pyrimidine-5-carboxamide **(8i)**: Mp 331-333 ˚C; IR (KBr) (υ_{max} cm^{-1}): 3408, 3301, 1718, 1703. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.08 (s, 3H, CH_3), 6.72-7.43 (m, 9H, H-aromatic), 7.50 (s, 1H, NH), 9.01 (s, 1H, NH), 9.73 (s, 1H, NH), 10.53 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 19.3, 64.8, 106.3, 111.2, 119.8, 122.7, 124.1, 124.9, 130.2, 133.1, 139.9, 140.0, 143.9, 165.9, 175.6, 177.1 ppm.