Solvent-Free Synthesis of Monastrol Derivatives Catalyzed by $NaHSO_4$

Qingfang Cheng,[a,b]* Qifa Wang,[b] Xingyou Xu,[b] Mingjie Ruan,[b] Hailun Yao,[b] and Xujie Yang[b]

[a]Materials Chemistry Laboratory, Nanjing University of Science and Technology, Nanjing, Jiangsu 210094, China
[b]Department of Chemical Technology, Huaihai Institute of Technology, Lianyungang, Jiangsu 222005, China
*E-mail: cheng_qingfang@yahoo.com.cn

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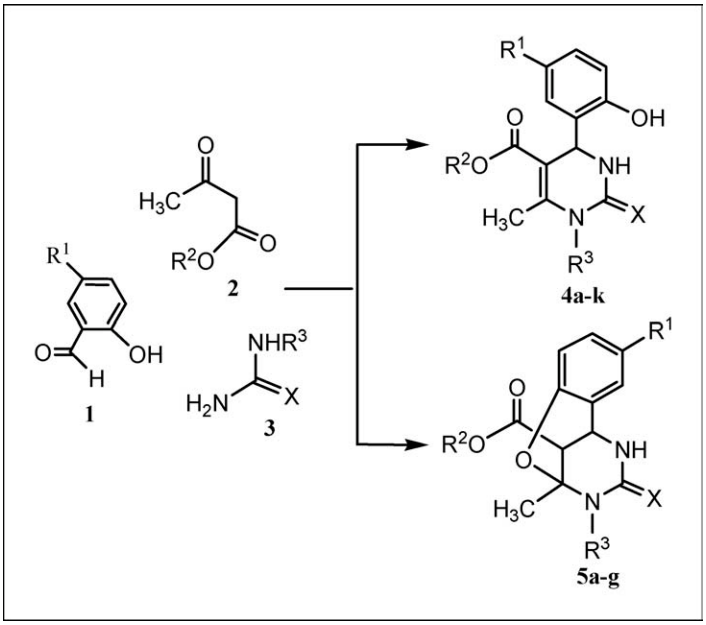

Monastrol derivatives were synthesized by environment-friendly three component condensation reaction of salicylaldehyde analogues, β-ketoester, and urea or thiourea under solvent-free conditions with $NaHSO_4$ as catalyst in high yields. The reactions formed two different monastrol products, 4-(2-hydroxyphenyl)pyrimidines **4** and 9- methyl- 11-oxo(or thioxo)-8-oxa-10,12-diazatricyclotrideca derivatives **5**.

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INTRODUCTION

It is well known that 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) and their derivatives are an important class of heterocyclic compounds having important biological activities, pharmaceutical and therapeutic properties, such as antiviral [1], antitumour [2], antibacterial, anti-inflammatory, and antihypertensive [3]. Therefore, the preparation of this heterocyclic nucleus has gained great importance in organic synthesis. One of the simple and direct method for the synthesis of this class of compounds is known as Biginelli reaction involving one-pot condensation of aldehyde, β-ketoester, and urea under strong acidic conditions, which was first reported by Biginelli in 1893 [4]. In this class of compounds, Monastrol, ethyl 6-methyl-4-(3-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, is a recently highlighted Biginelli compound [5,6], which showed promise in a new strategic approach to cancer research [7] and has been found to affect the function of mitotic kinesin Eg5, a motor protein responsible for spindle bipolarity [8]. Thus, kinesin spindle protein represents an attractive target for biochemical studies because human Eg5 inhibitors induce cell death *via* apoptosis [9]. Owing to the versatile biological activity of Monastrol derivatives, development of an alternative synthetic methodology is of paramount importance. This has led to the development of several new synthetic strategies involving combinations of Lewis acids and transition metal salts, e.g. $Sr(OTf)_2$ [10], *p*-TsOH [11,12], HPA [13], NiCl2.6H2O [14], $LaCl_3$ [15], $InBr_3$ [16] and Bakers' yeast [17]. Obviously, most of these catalysts

Table 1

NaHSO4 mediated synthesis of monastrol derivatives.

Products[a]	R^1	R^2	R^3	X	Time (h)	Yield[b] (%)	Mp (°C)
4a	H	Et	H	O	3	91	201–202
4b	H	Et	H	S	3	86	162–164
4c	H	Et	Ph	O	4	83	98–100
4d	Cl	Et	H	O	3.5	88	228–230
4e	Br	Et	H	O	3.5	86	231–233
4f	Cl	Et	Ph	O	4.5	82	102–104
4g	Br	Et	Ph	O	4.5	81	111–113
4h	Cl	Me	H	O	3.5	84	257–259
4i	Br	Me	H	O	3.5	82	215–217
4j	Cl	Me	Ph	O	4.5	82	107–109
4k	Br	Me	Ph	O	4.5	81	114–116
5a	H	Me	H	O	3	92	197–200
5b	H	Me	Ph	O	3.5	89	118–120
5c	H	Me	H	S	3	90	148–150
5d	Cl	Me	H	S	4	86	238–240
5e	Cl	Et	H	S	3.5	84	216–218
5f	Br	Me	H	S	4	85	157–159
5g	Br	Et	H	S	3.5	83	127–129

[a] Products were characterized by ^1H, ^{13}C NMR, IR, MS, and elemental analyses.
[b] Isolated yield.

and solvents are not acceptable in the context of green synthesis. Thus, as a part of our program towards green synthesis [18], and continuing our studies on the Multi-Component reactions (MCRs) [19], we report herein, a simple, facile, and efficient MCRs for the preparation of some new Monastrol analogues with NaHSO4 as a non-toxic, inexpensive, and easily available reagent.

Herein we wish to report the utilization of NaHSO4 as a catalyst in Biginelli's reaction of substitued salicylaldehydes, β-ketoester and urea or thiourea for the synthesis of some new Monastrol derivatives under solvent-free conditions.

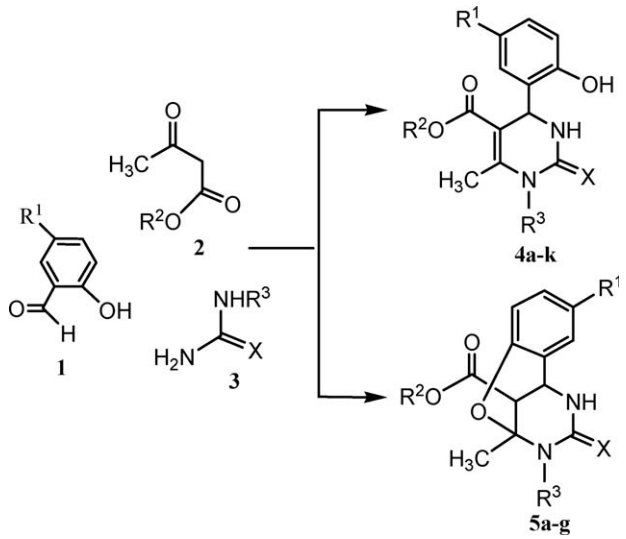
The three-component cyclocondensation reaction was performed under relatively simple reaction conditions by heating together the three components, salicylaldehyde, β-ketoester, and urea or thiourea, in the ratio of 1:1:1.5 and NaHSO4 (20 mol %), to 90°C with stirring. After the completion of the reaction, as indicated by TLC, the reaction mixture was poured onto crushed ice. From which the Monastrol derivatives were isolated by filtration and recrystallized from ethanol as indicated in Table 1.

Reactions of salicylaldehyde, methyl acetoacetate with urea (or thiourea, phenylurea) as well as reactions of 5-chloro or 5-bromo salicylaldehyde, methyl (or ethyl) acetoacetate with thiourea did not give the expected free hydroxyl compounds **4,** however, the product is the 9-methyl-11-oxo(or thioxo)-8-oxa-10,12-diazatricyclo [7.3.1.$0^{2,7}$]trideca-2,4,6-triene **5a-g** (Scheme 1).

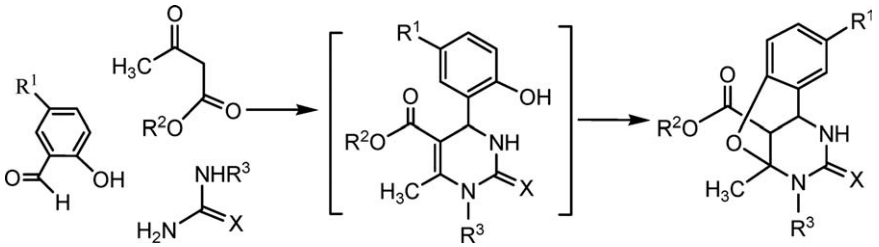
The results presented in the Table 1 indicate the scope and generality of the method, which is efficient, not only for urea or thiourea, but also for salicylaldehydes as well as 5-chloro and 5-bromo salicylaldehydes. In most cases, the reactions proceeded smoothly to produce the corresponding Monastrol derivatives in high yields.

In the course of our work, we have observed that the product from reactions involving salicylaldehyde, methyl acetoacetate with urea (or thiourea, phenylurea) is in fact the 9-methyl-11-oxo(or thioxo)-8-oxa-10, 12-diazatricyclo [7.3.1.$0^{2,7}$]trideca-2,4,6-triene **5a-c** rather than a free hydroxyl compounds, 4-(2-

Scheme 1



Scheme 2



hydroxyphenyl)pyrimidines **4**. However, this oxygen-bridged pyrimidine structures were not discussed in several recent reports [13–15,20,21], but were supported by others [12,16,17]. The product from reactions involving 5-chloro or 5-bromosalicylaldehyde, methyl (or ethyl) acetoacetate with thiourea is also an oxygen-bridged compounds **5d-g** rather than the corresponding 4-(2-hydroxyphenyl)pyrimidines.

The production of compounds **5a-g** can be explained by the isomerization reaction of the 4-(2-hydroxyphenyl) pyrimidines, **4** which were initially formed (Scheme 2).

In summary, we have described a convenient, environment-friendly method for the preparation of some new Monastrol derivatives by the Biginelli cyclocondensation reaction of salicylaldehyde analogues, β-ketoester with urea or thiourea using nontoxic, cheap $NaHSO_4$ catalyst. Additionally, when using salicylaldehyde as the aldehyde reagent, methyl acetoacetate as the active methylene compound, urea (or thiourea, phenylurea) as the condensation reagent, as well as using 5-chloro or 5-bromo salicylaldehyde as the aldehyde reagent, methyl (or ethyl) acetoacetate as the active methylene compound, thiourea as the condensation reagent, the Biginelli product will be an oxygen-bridged compound, 9-methyl-11-oxo(or thioxo)-8-oxa-10,12-diazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene **5** rather than 4-(2-hydroxyphenyl)pyrimidines **4**.

EXPERIMENTAL

IR spectra were recorded on a Nicolet FTIR-500 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer at 400 MHz and 75 MHz. Elemental analysis was performed on an Elementar Vario EL III analyzer. Melting points were determined on a XT-5A digital melting-points apparatus and are uncorrected.

General procedure for the synthesis of Monastrol derivatives 4a-k and 5a-g. A mixture of the appropriate salicylaldehyde (2 mmol), β-ketoester (2 mmol), urea or thiourea (3 mmol), and NaHSO4 (0.4 mmol) was heated with stirring at 90°C for the time period as indicated in Table 1. After completion of the reaction (TLC analysis), ice water was added to the mixture, and the crude products collected by filtration were recrystallized from EtOH, to give the products **4a-k** or **5a-g** (Table 1). All products were characterized by ^{1}H, ^{13}C NMR, IR, MS spectral, and by elemental analyses.

Ethyl 6-methyl-2-oxo-4-(2-hydroxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a). Yellow powder, yield 91%, mp 201–202°C, IR(KBr), (ν_{max}/cm^{-1}): 3355, 3267, 1683, 1597. ^{1}H NMR (DMSO-*d*6) δ_H : 9.6 (s, 1H, NH), 9.10 (s, 1H, NH), 6.68–7.16 (m, 5H, arom, OH), 5.45 (s, 1H, H-4), 3.93 (q, J = 6.8 Hz, 2H, CH_2), 2.26 (s, 3H, CH_3), 1.01 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 14.9, 18.6, 44.7, 59.8, 98.6, 116.1, 119.6, 121.3, 128.1, 129.5, 149.4, 151.5, 155.5, 169.3. MS(ESI) *m*/*z*: 277.0 (M+H). Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found : C, 60.89; H, 5.88; N, 10.17.

Ethyl 6-methyl-2-thioxo-4-(2-hydroxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b). Yellow powder, yield 86%, mp 162–164°C, IR(KBr), (ν_{max}/cm^{-1}): 3359, 3279, 1689. ^{1}H NMR (DMSO-*d*6) δ_H : 9.72 (s, 1H, NH), 9.10 (s, 1H, NH), 6.83–7.31 (m, 5H, arom, OH), 5.51 (s, 1H, H-4), 4.14 (q, J = 7.3 Hz, 2H, CH_2), 2.21 (s, 3H, CH_3), 1.13 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 14.4, 18.9, 44.2, 58.6, 102.5, 118.7, 120.9, 127.2, 129.1, 130.1, 148.3, 150.5, 169.2, 177.5. MS(ESI) *m*/*z*: 293.1 (M+H). Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.51; H, 5.52; N, 9.58. Found : C, 57.46; H, 5.44; N, 9.65.

Ethyl 1-phenyl-6-methyl-2-oxo-4-(2-hydroxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c). Green powder, yield 83%, mp 98–100°C, IR (KBr), (ν_{max}/cm^{-1}): 3347, 3268, 1681, 1589. ^{1}H NMR (DMSO-*d*6) δ_H : 7.50 (s, 1H, NH), 6.83–7.45 (m, 10H, arom, OH), 5.58 (s, 1H, H-4), 4.22 (q, J = 6.9 Hz, 2H, CH_2), 2.29 (s, 3H, CH_3), 1.28 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 14.7, 18.9, 44.9, 59.2, 99.3, 113.1, 117.5, 119.3, 121.5, 127.6, 129.1, 129.8, 130.7, 149.6, 150.1, 152.2, 155.9, 169.7. MS(ESI) *m*/*z*: 353.1 (M+H). Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found : C, 68.22; H, 5.75; N, 7.87.

Ethyl 6-methyl-2-oxo-4-(2-hydroxy-5-chlorphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d). Yellow powder, yield 88%, mp 228–230°C, IR(KBr), (ν_{max}/cm^{-1}): 3344, 3249, 1679, 1605. ^{1}H NMR (DMSO-*d*6) δ_H : 9.93 (s, 1H, NH), 9.17 (s, 1H, NH), 6.80 (t, J = 6.8 Hz, 1H, ArH), 6.92 (s, 1H, ArH), 7.19 (t, J = 6.8 Hz, 1H, ArH), 7.28 (s, 1H, OH), 5.41 (s, 1H, H-4), 3.92 (q, J = 7.0 Hz, 2H, CH_2), 2.27 (s, 3H, CH_3), 1.04 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 14.4, 18.2, 51.2, 59.5, 97.7, 117.6, 122.5, 127.6, 128.4, 132.5, 149.4, 152.5, 154.2, 165.8. MS (ESI) *m*/*z*: 309.0 (M-H). Anal. Calcd. for $C_{14}H_{15}N_2O_4Cl$: C, 54.11; H, 4.87; N, 9.02. Found : C, 54.16; H, 4.92; N, 9.07.

Ethyl 6-methyl-2-oxo-4-(2-hydroxy-5-bromophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e). Gray powder, yield 86%, mp 231–233°C, IR(KBr), (ν_{max}/cm^{-1}): 3339, 3252, 1677, 1609. ^{1}H NMR (DMSO-*d*6) δ_H : 9.91 (s, 1H, NH), 9.19 (s, 1H, NH), 6.77 (t, J = 6.9 Hz, 1H, ArH), 6.95 (s, 1H, ArH),

7.23 (t, J = 6.9 Hz, 1H, ArH), 7.31 (s, 1H, OH), 5.42 (s, 1H, H-4), 5.42 (s, 1H, H-4), 3.90 (q, J = 7.1 Hz, 2H, CH_2), 2.29 (s, 3H, CH_3), 1.07 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 14.5, 18.6, 51.1, 59.3, 97.5, 110.2, 118.2, 129.7, 132.0, 132.5, 149.7, 152.8, 154.5, 166.8. MS(ESI) *m*/*z*: 356.9 (M+H). Anal. Calcd. for $C_{14}H_{15}N_2O_4Br$: C, 47.34; H, 4.26; N,7.89. Found: C, 47.38; H, 4.22; N, 7.83.

Ethyl 6-methyl-1-phenyl-2-oxo-4-(2-hydroxy-5-chlorphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f). Yellow powder, yield 82%, mp 102–104°C, IR(KBr), (ν_{max}/cm^{-1}): 3355, 3269, 1688, 1611. ^{1}H NMR (DMSO-*d*6) δ_H : 9.06 (s, 1H, NH), 6.86–7.45 (m, 9H, arom, OH), 5.48 (s, 1H, H-4), 4.12 (q, J = 7.1 Hz, 2H, CH_2), 2.27 (s, 3H, CH_3), 1.25 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 14.9, 18.6, 50.3, 59.4, 99.8, 113.1, 117.3, 118.1, 122.1, 127.9, 129.1, 129.9, 132.4, 149.5, 150.3, 152.6, 154.9, 167.4. MS(ESI) *m*/*z*: 385.1 (M-H). Anal. Calcd. for $C_{20}H_{19}N_2O_4Cl$: C, 62.11; H, 4.95; N, 7.24. Found: C, 62.07; H, 4.88; N, 7.29.

Ethyl 6-methyl-1-phenyl-2-oxo-4-(2-hydroxy-5-bromophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g). Yellow powder, yield 81%, mp 111–113°C, IR(KBr), (ν_{max}/cm^{-1}): 3349, 3257, 1678, 1599. ^{1}H NMR (DMSO-*d*6) δ_H : 9.09 (s, 1H, NH), 6.73–7.32 (m, 9H, arom, OH), 5.49 (s, 1H, H-4), 4.12 (q, J = 6.9 Hz, 2H, CH_2), 2.29 (s, 3H, CH_3), 1.26 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 14.4, 18.2, 50.9, 58.9, 98.4, 110.5, 117.8, 118.4, 122.6, 129.4, 129.9, 132.8, 133.3, 149.6, 150.8, 152.7, 154.8, 168.1. MS(ESI) *m*/*z*: 432.9 (M+H). Anal. Calcd. for $C_{20}H_{19}N_2O_4Br$: C, 55.70; H, 4.44; N, 6.50. Found : C, 55.66; H, 4.41; N, 6.57.

Methyl 6-methyl-2-oxo-4-(2-hydroxy-5-chlorphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h). Yellow powder, yield 84%, mp 257–259°C, IR(KBr), (ν_{max}/cm^{-1}): 3346, 3261, 1688, 1592. ^{1}H NMR (DMSO-*d*6) δ_H : 9.96 (s, 1H, NH), 9.22 (s, 1H, NH), 6.78 (t, J = 7.0 Hz, 1H, ArH), 7.05 (s, 1H, ArH), 7.24 (t, J = 7.0 Hz, 1H, ArH), 7.29 (s, 1H, OH), 5.41 (s, 1H, H-4), −7.24 (m, 4H, arom, OH), 5.37 (s, 1H, H-4), 3.41 (s, 3H, CH_3), 2.19 (s, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 18.4, 48.9, 50.8, 98.3, 110.1, 118.1, 129.1, 130.7, 132.2, 147.9, 151.2, 154.3, 164.9. MS(ESI) *m*/*z*: 297.1. Anal. Calcd. for $C_{13}H_{13}N_2O_4Cl$: C, 52.62; H, 4.42; N, 9.44. Found : C, 52.67; H, 4.38; N, 9.48.

Methyl 6-methyl-2-oxo-4-(2-hydroxy-5-bromophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i). Yellow powder, yield 82%, mp 215–217°C, IR(KBr), (ν_{max}/cm^{-1}): 3339, 3254, 1676, 1599. ^{1}H NMR (DMSO-*d*6) δ_H : 10.03 (s, 1H, NH), 9.21 (s, 1H, NH), 6.77 (t, J = 7.2 Hz, 1H, ArH), 7.02 (s, 1H, ArH), 7.22 (t, J = 7.2 Hz, 1H, ArH), 7.27 (s, 1H, OH), 5.41 (s, 1H, H-4), 5.41 (s, 1H, H-4), 3.50 (s, 3H, CH_3), 2.29 (s, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 18.3, 49.6, 51.2, 97.5, 110.3, 118.3, 130.0, 131.4, 132.8, 149.8, 152.6, 154.7, 166.2. MS(ESI) *m*/*z*: 342.9 (M+H). Anal. Calcd. for $C_{13}H_{13}N_2O_4Br$: C, 45.77; H, 3.84; N, 8.21. Found: C, 45.73; H, 3.89; N, 8.26.

Methyl 6-methyl-1-phenyl-2-oxo-4-(2-hydroxy-5-chlorphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j). Brown powder, yield 82%, mp 107–109°C, IR(KBr), (ν_{max}/cm^{-1}): 3341, 3269, 1682, 1603. ^{1}H NMR (DMSO-*d*6) δ_H : 9.11 (s, 1H, NH), 6.71–7.39 (m, 9H, arom, OH), 5.44 (s, 1H, H-4), 3.45 (s, 3H, CH_3), 2.24 (s, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 18.1, 48.4, 51.3, 99.6, 112.1, 117.4, 118.5, 122.3, 128.1, 129.5, 130.1, 132.6, 148.4, 150.2, 152.8, 154.2, 166.9. MS(ESI) *m*/*z*: 373.1. Anal. Calcd. for $C_{19}H_{17}N_2O_4Cl$: C, 61.21; H, 4.60; N, 7.53. Found : C, 61.16; H, 4.53; N, 7.56.

Methyl 6-methyl-1-phenyl-2-oxo-4-(2-hydroxy-5-bromophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k). Yellow powder, yield 81%, mp 114–116°C, IR(KBr), (ν_{max}/cm^{-1}): 3336, 3258, 1671, 1589. ^{1}H NMR (DMSO-*d*6) δ_H : 9.15 (s, 1H, NH), 6.69–7.37 (m, 9H, arom, OH), 5.49 (s, 1H, H-4), 3.52 (s, 3H, CH_3), 2.26 (s, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 18.2, 49.1, 51.7, 98.6, 111.3, 115.7, 118.3, 120.4, 128.3, 129.1, 130.6, 131.5, 149.1, 151.9, 153.7, 154.2, 167.1. MS(ESI) *m*/*z*: 418.9 (M+H). Anal. Calcd. for $C_{19}H_{17}N_2O_4Br$: C, 54.69; H, 4.11; N, 6.72. Found : C, 54.62; H, 4.06; N, 6.78.

13-Methoxycarbonyl-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene (5a). Yellow powder, yield 92%, mp 117–120°C, IR(KBr), (ν_{max}/cm^{-1}): 3308, 3075, 1683, 1643. ^{1}H NMR (DMSO-*d*6) δ_H : 7.19 (s, 1H, NH), 6.78–7.18 (m, 5H, arom, NH), 4.61 (dd, J = 2.8, 2.8 Hz, 1H, H-1), 3.69 (s, 3H, CH_3), 3.49–3.52 (m, 1H, H-13), 1.78 (s, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 24.7, 44.0, 48.9, 51.8, 82.1, 116.4, 121.7, 124.6, 128.5, 130.1, 151.3, 155.8, 169.1. MS(ESI) *m*/*z*: 262.9 (M+H). Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found : C, 59.58; H, 5.35; N, 10.62.

13-Methoxycarbonyl-9-methyl-10-phenyl-11-oxo-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene (5b). Green powder, yield 89%, mp 118–120°C, IR(KBr), (ν_{max}/cm^{-1}): 3316, 3089, 1675, 1653. ^{1}H NMR (DMSO-*d*6) δ_H : 8.51 (s, 1H, NH), 6.78–7.68 (m, 9H, arom), 4.38 (dd, J = 2.9, 2.9 Hz, 1H, H-1), 3.70 (s, 3H, CH_3), 3.43–3.58 (m, 1H, H-13), 1.85 (s, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 25.1, 47.2, 49.1, 51.8, 83.1, 112.3, 116.5, 117.8, 120.9, 123.5, 128.3, 129.7, 130.4, 150.6, 151.7, 156.4, 167.3. MS(ESI) *m*/*z*: 339.1 (M+H). Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found : C, 67.48; H, 5.31; N, 8.25.

13-Methoxycarbonyl-9-methyl-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene (5c). Yellow powder, yield 90%, mp 148–150°C, IR(KBr), (ν_{max}/cm^{-1}): 3307, 3073, 1670. ^{1}H NMR (DMSO-*d*6) δ_H : 9.17 (s, 1H, NH), 6.81–7.22 (m, 4H, ArH), 4.58 (dd, J = 3.1, 2.4 Hz, 1H, H-1), 3.69 (s, 3H, CH_3), 3.34–3.37 (m, 1H, H-13), 1.77 (s, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 24.2, 43.0, 48.8, 53.0, 82.2, 117.3, 121.7, 124.6, 129.6, 130.6, 151.3, 169.2, 177.2. MS(ESI) *m*/*z*: 279.0 (M+H). Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.09; H, 5.07; N, 10.07. Found : C, 56.13; H, 5.13; N, 10.02.

13-Methoxycarbonyl-9-methyl-4-chlor-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene (5d). Gray powder, yield 86%, mp 238–240°C, IR(KBr), (ν_{max}/cm^{-1}): 3298, 3079, 1689. ^{1}H NMR (DMSO-*d*6) δ_H : 10.01 (s, 1H, NH), 9.22 (s, 1H, NH), 6.80 (t, J = 6.7 Hz, 1H, ArH), 6.90 (s, 1H, ArH), 7.13 (t, J = 6.7Hz, 1H, ArH), 5.41 (s, 1H, H-4), 4.55 (dd, J = 3.2, 2.4 Hz, 1H, H-1), 3.56 (s, 3H, CH_3), 3.35–3.41 (m, 1H, H-13), 1.82 (s, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 24.5, 43.5, 47.2, 52.5, 82.1, 117.8, 122.7, 125.0, 129.4, 131.3, 150.2, 168.1, 177.2. MS(ESI) *m*/*z*: 313.0 (M+H). Anal. Calcd. for $C_{13}H_{13}N_2O_3SCl$: C, 49.92; H, 4.19; N, 8.96. Found : C, 49.88; H, 5.15; N, 8.93.

13-Ethoxycarbonyl-9-methyl-4-chlor-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene (5e). Yellow powder, yield 84%, mp 216–218°C, IR(KBr), (ν_{max}/cm^{-1}): 3315, 3091, 1689. ^{1}H NMR (DMSO-*d*6) δ_H : 10.06 (s, 1H, NH), 9.23 (s, 1H, NH), 6.82 (t, J = 7.1 Hz, 1H, ArH), 6.94 (s, 1H, ArH), 7.18 (t, J = 7.1 Hz, 1H, ArH), 5.41 (s, 1H, H-4), 4.58 (dd, J = 3.0, 2.6 Hz, 1H, H-1), 4.03 (q, J = 7.1 Hz, 2H, CH_2), 3.34–3.44 (m, 1H, H-13), 1.80 (s, 3H, CH_3), 1.24 (t, J

= 7.1 Hz, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 14.9, 24.4, 43.1, 47.3, 57.5, 82.2, 117.9, 123.3, 125.6, 130.4, 133.5, 152.2, 167.1, 177.1. MS(ESI) *m*/*z*: 328.5 (M+H). Anal. Calcd. for $C_{14}H_{15}N_2O_3SCl$: C, 51.45; H, 4.63; N, 8.57. Found : C, 51.48; H, 4.67; N, 8.53.

13-Methoxycarbonyl-9-methyl-4-bromo-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene (5f). Gray powder, yield 85%, mp 157–159°C, IR(KBr), (ν_{max}/cm^{-1}): 3295, 3077, 1681. ^1H NMR (DMSO-*d*6) δ_H : 10.04 (s, 1H, NH), 9.25 (s, 1H, NH), 6.77 (t, *J* = 6.8 Hz, 1H, ArH), 6.95 (s, 1H, ArH), 7.27 (t, *J* = 6.8 Hz, 1H, ArH), 5.41 (s, 1H, H-4), 4.57 (dd, *J* = 3.0, 2.4 Hz, 1H, H-1), 3.61 (s, 3H, CH_3), 3.41 (m, 1H, H-13), 1.75 (s, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 24.3, 43.2, 47.6, 52.3, 82.3, 113.5, 120.4, 124.5, 130.8, 131.7, 149.9, 168.8, 177.5. MS(ESI) *m*/*z*: 358.9 (M+H). Anal. Calcd. for $C_{13}H_{13}N_2O_3SBr$: C, 43.71; H, 3.67; N, 7.84. Found : C, 43.78; H, 3.72; N, 7.81.

13-Ethoxycarbonyl-9-methyl-4-bromo-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene (5g). Gray powder, yield 83%, mp 127–129°C, IR(KBr), (ν_{max}/cm^{-1}): 3309, 3091, 1673. ^1H NMR (DMSO-*d*6) δ_H : 10.04 (s, 1H, NH), 9.21 (s, 1H, NH), 6.75 (t, *J* = 7.0 Hz, 1H, ArH), 7.04 (s, 1H, ArH), 7.24 (t, *J* = 7.0 Hz, 1H, ArH), 5.41 (s, 1H, H-4), 4.54 (dd, *J* = 3.2, 2.2 Hz, 1H, H-1), 3.92 (q, *J* = 7.1 Hz, 2H, CH_2), 3.35∼3.42 (m, 1H, H-13), 1.78 (s, 3H, CH_3), 1.23 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (DMSO-*d*6) δ_C: 14.3, 24.5, 43.4, 47.2, 61.2, 82.1, 112.6, 119.2, 125.6, 131.8, 132.2, 150.7, 167.5, 177.2. MS(ESI) *m*/*z*: 372.9 (M+H). Anal. Calcd. for $C_{14}H_{15}N_2O_3SBr$: C, 45.29; H, 4.07; N, 7.55. Found : C, 45.23; H, 4.04; N, 7.52.

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