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ONE-POT TWO-STEP SYNTHESIS OF *N*3-FUNCTIONALIZED 3,4-DIHYDROPYRIMIDINONES IN THE PRESENCE OF TMSCl

Zheng-Jun Quan,* Rong-Guo Ren, Yu-Xia Da, Zhang Zhang, Xiao-Dong Jia, Cai-Xia Yang, and Xi-Cun Wang*

Key Laboratory of Eco-Environment-Related Polymer Materials, Ministry of Education, China, Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Anning East Road 967#, Lanzhou, Gansu 730070, China
Tel./Fax: +86-931-7971971
E-mail: wangxicun@nwnu.edu.cn, quanzj@nwnu.edu.cn

Abstract – Novel 3,4-dihydropyrimidinones modified with *N*3-alkyloxymethyl, aminomethyl, arylsulfonylmethyl, and azidomethyl groups can be regioselectively obtained over their isomeric *N*1 compounds in good yields by reaction of 3,4-dihydropyrimidinones with paraformaldehyde and alcohol, amine, sodium benzenesulfinate, and sodium azide, respectively, by a one-pot two-step strategy in the presence of chlorotrimethylsilane. The advantages of this method are the simple procedure, the high regioselectivity of the products, no requirement for a base catalyst, and the mild reaction conditions.

INTRODUCTION

In past decades, dihydropyrimidinones (DHPMs) and their derivatives have attracted considerable interest due to their heterocyclic scaffold[1-8] and interesting pharmacological properties. They form the underlying structure for many clinically important substances, such as calcium channel modulators, antihypertensives, α_{1a} adrenergic agonists, mitotic kinesin inhibitors, and hepatitis B virus replication suppressors.[9-11] Among DHPM derivatives, most of the pharmacologically attractive forms are *N3*-substituted analogues.[3] The *N*-alkylation of dihydropyrimidin-2-ones is one way of functionalizing the ring to achieve important

bioactive properties. Most *N*-alkylated pyrimidin-2-ones are obtained from S_N2 displacement of an electrophile, such as a diazoalkane,[12] alkyl halide,[13-15] alkyl sulfate, and alkyl phosphate,[16] with the pyrimidine reacting as the nucleophile. Generally, most nucleophilic reactions[17] involving *N*-alkylation of pyrimidinones yield *N*1-alkylated products.[18]

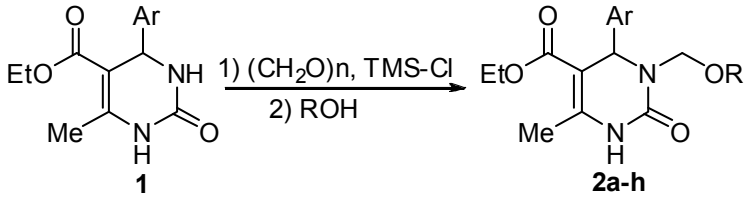
The classical method for the preparation of *N3*-substituted DHPMs, which employs a base-mediated alkylation of *S*-alkylated or *O*-alkylated pyrimidinones, results in protected *N3*-alkylated dihydropyrimidines.[19] An alternative for this reaction is the "Atwal modification" of the Biginelli condensation.[20, 21] Kappe et al. have reported the synthesis of *N*3-acylated DHPMs by acylation of DHPMs with ethyl chloroformate and *N,N*-dimethylcarbamoyl chloride[22] or with anhydrides.[23] Reaction of DHPMs with a base (LDA or *n*-BuLi) followed by quenching with electrophiles, resulted in a mixture of *N*1 and *N*3 position products.[24, 25] *N*3-Acetoxymethyl[26] DHPM has also been synthesized by standard acylation reaction of acetyl chloride with *N*3-hydroxylmethylated DHPM, which was produced by treating DHPM with aqueous formaldehyde and potassium carbonate at reflux temperature for 48 h.[27] The *N*-alkyl-pyrimidin-2-ones were also generated by the cyclocondensation of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones with methyl and allylureas and the *N*-alkylation of 4-(trihalomethyl)-pyrimidin-2-ones with methyl iodide and allyl bromide.[28] DHPMs could be regioselectively substituted at the *N*3 position by aza-Michael addition reactions of DHPMs to *α,β*-ethylenic compounds.[29,30] *N*3,*S*-Dimethylated 1,6-dihydropyrimidine has also been prepared by the reaction of 3,4-dihydropyrimidine-2-thiones with dimethyl carbonate.[31]

Unfortunately, these strategies suffer from the disadvantage that the procedures need to be carried out in harsh conditions such as high temperature with long reaction time and/or in the presence of strong base. Sometimes unexplained low selectivity in the position of *N*3 to *N*1 also occurs. To the best of our knowledge, a comparative study on the synthesis of DHPM derivatives, including addition of alkyloxymethyl, arylsulfonylmethyl, and azidomethyl groups at the *N*3 position of the pyrimidine ring by a one-pot multi-component reaction, has not yet been carried out. In this article, we present a convenient approach for the preparation of *N*3 functionalized DHPM derivatives that involves addition of alkyloxymethyl, aminomethyl, arylsulfonylmethyl, and azidomethyl groups under mild conditions and in the absence of a base catalyst. This was performed by treatment of DHPMs with paraformaldehyde and chlorotrimethylsilane (TMSCl), followed by reactions with various substrates such as alcohols, morpholine, sodium benzenesulfinate, and sodium azide.

RESUSTS AND DISCUSSIONS

Initially, experiments were carried out for the optimal reaction conditions using the reaction for **2a** as a typical reaction. A mixture of DHPM (**1a**) with TMSCl and paraformaldehyde in dichloromethane was stirred for 24 h. The mixture subsequently was added to methanol for another 4 h to give *N*3-methoxymethyl DHPM (**2a**). The catalysts, solvents, and reaction temperature greatly influenced the product yield. Use of 2.0 equiv of TMSCl with 5 equiv of paraformaldehyde in CH_2Cl_2 at 35 ^oC afforded **2a** in 73% yield; however, in the case of 2.5 equiv of TMSCl, the yield of **2a** increased to 82%. Increasing the amount of TMSCl to 3 equiv led to isolation of **2a** in a lower yield (60 %). Different solvents also influenced the reaction yield, as the reaction worked well in CH_2Cl_2 and THF; however, the product **2a** was not detected when MeCN, TFA, *p*-TSA, HCl, acetic acid, $FeCl_3$, and $CuCl_2$ were used as catalysts. Thus, we decided to use 2.5 equiv of TMSCl and 5 equiv of paraformaldehyde in CH_2Cl_2 at 35 ^oC as the optimal reaction conditions for the preparation of *N*3 substituted DHPMs.

Table 1. Reactions of DHPMs with TMSCl, paraformaldehyde and alcohols[a]



1 **2a-h**

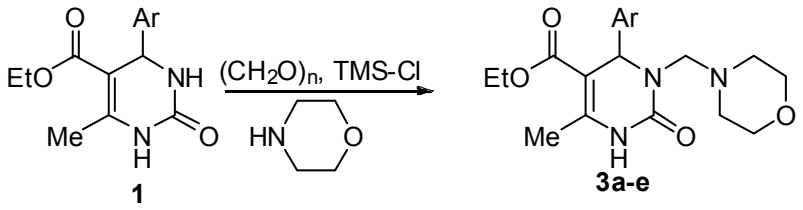
Entry	Ar	R	Product	Isolated Yield(%)
1	C_6H_5	Me	**2a**	82
2	*p*-MeO-C_6H_4	Me	**2b**	85
3	*p*-Cl-C_6H_4	Me	**2c**	75
4	C_6H_5	Et	**2d**	88
5	*p*-MeO-C_6H_4	Et	**2e**	90
6	*p*-Cl-C_6H_4	Et	**2f**	84
7	C_6H_5	*i*-Pr	**2g**	71
8	C_6H_5	Me_3C	**2h**	65

[a] Reaction conditions: (1) DHPM (1 mmol), $(CH_2O)_n$ (5 mmol), TMS-Cl (2.5 mmol), CH_2Cl_2 (5 mL), 35 ^oC, 24 h; (2) ROH (3 mmol), 35 ^oC, 4 h.

Under optimal conditions, other *N*3-methoxymethyl DHPMs (**2b-c**) were prepared in good yields (Table 1,

entries 1-3). We then investigated other alcohols, such as ethanol, isopropanol, and tert-butyl alcohol as substrates and the corresponding *N*3-alkyloxymethyl DHPMs were obtained (Table 2, entries 4-8). In general, *N*3-substituted DHPMs were generated with primary, secondary and tertiary aliphatic alcohol substrates. In fact, when using tert-butyl alcohol as a nucleophile substrate, a lower yield of product **2 h** resulted (entry 8).

Table 2. Reaction of DHPM with paraformaldehyde and morpholine[a]



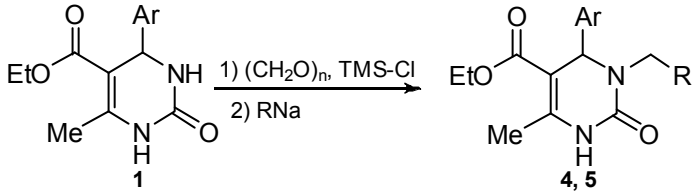
Entry	Ar	Product	Isolated Yield(%)		
			Method A	Method B	Method C
1	C_6H_5	**3a**	90	94	89
2	*p*-MeO-C_6H_4	**3b**	88	90	85
3	*p*-Me-C_6H_4	**3c**	85	87	80
4	*p*-Cl-C_6H_4	**3d**	86	87	87
5	*p*-Br-C_6H_4	**3e**	92	92	86

[a] Reaction conditions: Method A: (1) DHPM (1 mmol), $(CH_2O)_n$ (5 mmol), TMS-Cl (2.5 mmol), CH_2Cl_2 (5 mL), 35 ^oC, 24 h; (2) morpholine (2 mmol), 35 ^oC, 4 h. Method B: DHPM (1 mmol), $(CH_2O)_n$ (5 mmol), TMS-Cl (0.5 mmol), morpholine (1 mmol), MeOH (3 mmol), 80 ^oC, 8 h. Method C: DHPM (1 mmol), $(CH_2O)_n$ (5 mmol), AcOH (0.5 mmol), morpholine (3 mmol), MeOH (5 mL), 80 ^oC, 8 h.

To expand the scope and limitation of this one-pot reaction, we then investigated amine, sodium benzenesulfinate, and sodium azide as substrates in the reaction. The reaction between DHPM, paraformaldehyde, and morpholine in the presence of TMSCl was studied and good yields of DHPM derivatives **3a-e** were obtained (Method A) (Table 2). Reactions for **3a-e** were more efficient than alcohols and gave higher yields. We postulated that this reaction was performed by the three-component reaction of DHPMs, formaldehyde, and morpholine in the presence of TMSCl. As expected, the direct treatment of DHPMs **1** and formaldehyde with morpholine in methanol in the presence of TMSCl (Method B) or acetic acid (Method C), with refluxing for 8 h, resulted in the formation of compounds **3a-**

e with higher yields than those of the two-step reactions (Method A). However, *N*3-alkyloxymethyl DHPM (2) could not be obtained by method B or C. Therefore, we could presumably assume that the reaction for compounds **3a-e** was performed via the Mannich reaction[32] that started with the dehydration of the amine with formaldehyde to give an imine ion, which reacted with DHPMs to afford the products **3a-e**.

Table 3. Reactions of DHPMs with TMSCl, paraformaldehyde and sodium salts[a]



Entry	Ar	R	Product	Yield(%)[b]
1	C_6H_5	$C_6H_5SO_2$	**4a**	76
2	C_6H_5	*p*-Me-$C_6H_4SO_2$	**4b**	85
3	*p*-MeO-C_6H_4	$C_6H_5SO_2$	**4c**	80
4	*p*-MeO-C_6H_4	*p*-Me-$C_6H_4SO_2$	**4d**	70
5	*p*-Me-C_6H_4	$C_6H_5SO_2$	**4e**	79
6	*p*-Me-C_6H_4	*p*-Me-$C_6H_4SO_2$	**4f**	86
7	*p*-NO_2-C_6H_4	$C_6H_5SO_2$	**4g**	70
8	*p*-NO_2-C_6H_4	*p*-Me-$C_6H_4SO_2$	**4h**	72
9	C_6H_5	N_3	**5a**	72
10	*p*-MeO-C_6H_4	N_3	**5b**	70
11	*p*-Me-C_6H_4	N_3	**5c**	74
12	*p*-Cl-C_6H_4	N_3	**5d**	75

[a] Reaction conditions: (1) DHPM (1 mmol), $(CH_2O)_n$ (5 mmol), TMS-Cl (2.5 mmol), CH_2Cl_2 (5 mL), 35 ^oC, 24 h; (2) NaR (3 mmol), 35 ^oC, 8-12 h.

[b] Isolated yields based on DHPMs.

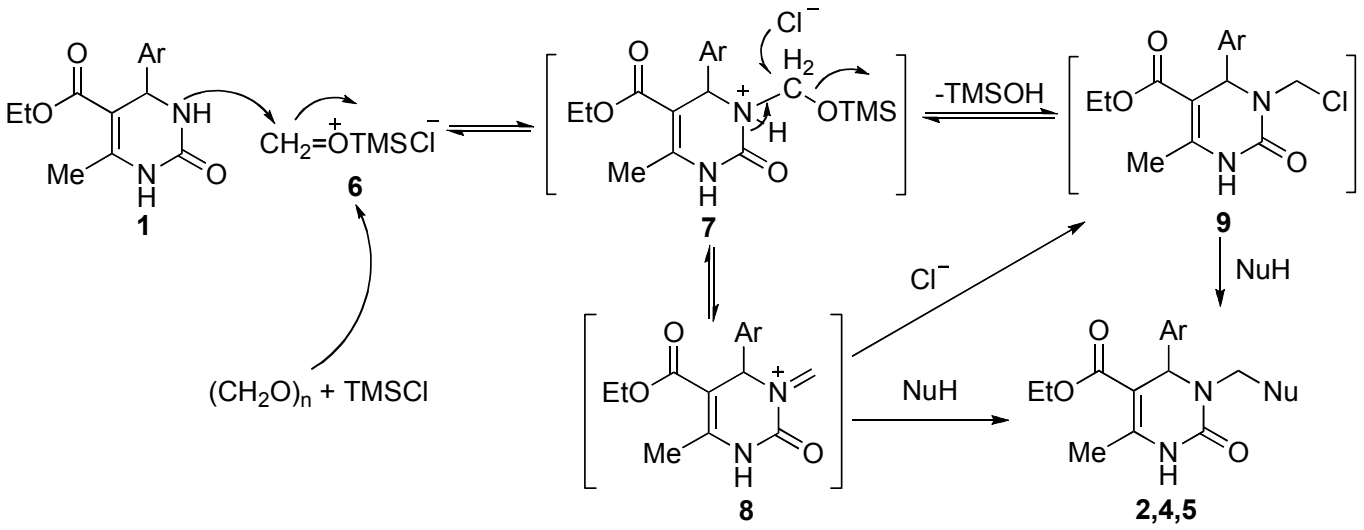
Consistent with previous studies, replacing alcohol with sodium benzenesulfinate or 4-methylphenylsulfinic acid sodium salt allowed the reactions to proceed smoothly and afforded the desired

products **4a-h** in high yields (Table 3). However, this reaction needed a longer reaction time (second step with 12 h), which was probably due to the poor solubility of sodium benzenesulfinate in CH_2Cl_2. The electronic effects of the substituents on the aromatic rings of DHPMs **1** are not important. In the presence of a nitro group at the aromatic rings of DHPMs **1**, the yields such as **4g** and **4h** were not apparently lower (Table 2, entries 7 and 8).

Finally, we observed that the readily available and stable DHPMs offered themselves for introduction of an azido group at the *N*3 position of pyrimidine ring. The reactions for the synthesis of compounds **5a-d** were smoothly carried out by the procedures described above, using sodium azide as substrate instead of alcohol (Table 3, entries 9-12). However, the yields of **5a–d** were moderate to good with longer reaction time (second step with 8 h), which perhaps due to the poor reactivity of sodium azide.

The structures of the *N*3-functionalized dihydropyrimidinones were determined by ^{1}H NMR, H,H-COSY, and two-dimensional HMBC NMR experiments, using **2a** as a model compound. The structures of compounds **2g** and **5b** were unambiguously confirmed by X-ray crystallography, revealing the *N*3 selectivity products *N*3-(isopropylmethyl)-3, 4-dihydropyrimidine-2-ones (**2g**), *N*3-(morpholinomethyl)-3, 4-dihydropyrimidine-2-ones (**3c**) and *N*3-(azidomethyl)-3, 4-dihydropyrimidine-2-ones (**5b**), which confirmed the structures of the obtained products.[33]

Scheme 1. Plausible reaction mechanism



We postulate that the reaction starts with the reaction of paraformaldehyde with TMSCl to give **6**, which then reacts with DHPM to afford the crucial intermediate *N*3-chloromethylation DHPM (**9**) by two

possible pathways forming ammonium ion (**7**) or iminium ion (**8**). Subsequently, **9** reacts with the various nucleophiles (alcohols, benzenesulfinic acid sodium salt, and sodium azide) to give the *N*3-functionalization DHPMs **2,4,5** (Scheme 1). Although neither of the intermediates **6** or **9** was isolated, intermediate **9** was detected by LC-MS; the other intermediate was not detected.

In conclusion, a variety of *N*3-substituted DHPMs were regioselectively prepared through a one-pot two-step reaction between of 3,4-dihydropyrimidinones, paraformaldehyde, chlorotrimethylsilane, and various substrates. To the best of our knowledge, the methodology described herein affording the novel functionalized DHPM products has not been reported previously. Furthermore, the desired compounds contain N_3CH_2- group, which increases the diversity of the molecule and can allow preparation of other interesting libraries. Synthesis and screening of desired compounds based on DHPM scaffolds may lead to the discovery of interesting biological activities.

EXPERIMENTAL

All reagents were obtained commercially and used without further purification. Melting points were determined on an XT-4 electrothermal micromelting point apparatus and uncorrected. NMR spectra were recorded at 400 (^{1}H) and 100 (^{13}C) MHz, respectively, on a Varian Mercury plus-400 instrument using $CDCl_3$ as solvent and TMS as internal standard. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analysis instrument. Mass-spectra were recorded on a TRACE DSQ instrument. Compounds **1** were prepared following the reported methods.[34]

General procedure for compounds 2a-h. To a suspension of 3,4-dihydropyrimidinone (1.0 mmol), paraformaldehyde (5.0 mmol), and CH_2Cl_2 (5 mL), TMSCl (2.5 mmol) were added and the reaction mixture was stirred at 35 ^{o}C for 24 h. Alcohol (3 mmol) was then added and the reaction mixture was stirred for an additional 4 h until the reaction was complete (monitored by TLC). After reaction completion, the solid was filtered and the filtrate was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (15 mL) and the combined organic phase was washed with brine (15 mL), dried over Na_2SO_4, and concentrated. Purification by crystallization from aq. EtOH (EtOH: H_2O = 4:1) afforded *N3*-substituted 3,4-dihydropyrimidinone (**2a-h**).

2a: Yield 82%; mp 157-159 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.05 (bs, 1H, NH), 7.38-7.26 (m, 5H, H_{Ar}), 5.33 (s, 1H, 4-CH), 5.19 (d, J = 10.4 Hz, 1H, NCH*H*), 4.22 (d, J = 10.4 Hz, 1H, NCH*H*), 4.12-4.07 (m, 2H, OC*H*$_2$CH$_3$), 3.32 (s, 3H, OCH_3), 2.37 (s, 3H, 6-CH_3), 1.22-1.18 (m, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 153.6, 146.3, 144.7, 128.5, 127.9, 127.4, 102.1, 75.6, 59.9, 57.9, 55.9, 18.3,

14.1. MS: *m/z* = 304 (M^+). Anal. Calcd for $C_{16}H_{20}N_2O_4$ (304.14): C 63.14, H 6.62, N 9.20. Found: C 63.30, H 6.72, N 9.08.

2b: Yield 85%; mp 150-152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (bs, 1H, NH), 7.30-7.26 (m, 2H, H_{Ar}), 6.84-7.80 (m, 2H, H_{Ar}), 5.43 (s, 1H, 4-CH), 5.15 (d, *J* = 10.4 Hz, 1H, NC*H*H), 4.18 (d, *J* = 10.4 Hz, 1H, NCH*H*), 4.14-4.05 (m, 2H, OCH_2CH$_3$), 3.77 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 2.36 (s, 3H, 6-CH_3), 1.26-1.18 (m, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 159.2, 153.4, 145.8, 133.9, 128.6, 113.8, 102.4, 75.4, 59.9, 57.3, 55.9, 55.2, 18.9, 14.1. MS: *m/z* = 334 (M^+). Anal. Calcd for $C_{17}H_{22}N_2O_5$ (334.15): C 61.07, H 6.63, N 8.38. Found: C 61.25, H, 6.54, N 8.51.

2c: Yield 75%; mp 144-146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (bs, 1H, NH), 7.32-7.28 (m, 2H, H_{Ar}), 7.27-7.7.25 (m, 2H, H_{Ar}), 5.45 (s, 1H, 4-CH), 5.14 (d, *J* = 10.4 Hz, 1H, NC*H*H), 4.32 (d, *J* = 10.4 Hz, 1H, NCH*H*), 4.12-4.06 (m, 2H, OCH_2CH$_3$), 3.28 (s, 3H, OCH_3), 2.36 (s, 3H, 6-CH_3), 1.23-1.16 (m, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 153.1 146.1, 140.2, 133.8, 128.8, 128.7, 102.0, 75.7, 60.2, 57.4, 56.0, 18.5, 14.2, MS: *m/z* = 338 (M^+). Anal. Calcd for $C_{16}H_{19}ClN_2O_4$ (338.10): C 56.72, H 5.65, N 8.27. Found: C 56.91, H, 5.74, N 8.13.

2d: Yield 88%; mp 172-174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (bs, 1H, NH), 7.35-7.27 (m, 5H, H_{Ar}), 5.93 (d, *J* = 10.0 Hz, 1H, NC*H*H), 5.68 (s, 1H, 4-CH), 4.66 (d, *J* = 10.0 Hz, 1H, NC*H*H), 4.19-4.12 (m, 2H, OCH_2CH$_3$), 3.68-3.64 (m, 1H, OCH_2CH$_3$), 3.56-3.52 (m, 1H, OCH_2CH$_3$), 2.36 (s, 3H, 6-CH_3), 1.27-1.23 (m, 3H, OCH_2CH_3), 1.19-1.15 (m, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 165.2, 142.3, 140.5, 128.7, 128.3, 127.1, 103.7, 79.2, 64.6, 60.4, 57.2, 18.1, 14.9, 14.2. MS: *m/z* = 318 (M^+). Anal. Calcd for $C_{17}H_{22}N_2O_4$ (318.16): C 64.13, H 6.97, N 8.80. Found: C 63.95, H 6.88, N 8.91.

2e: Yield 90%; mp 134-136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (bs, 1H, NH), 7.30-7.27 (m, 2H, H_{Ar}), 6.83-6.81 (m, 2H, H_{Ar}), 5.45 (s, 1H, 4-CH), 5.34 (d, *J* = 10.4 Hz, 1H, NC*H*H), 4.35 (d, *J* = 10.4 Hz, 1H, NC*H*H), 4.11-4.05 (m, 2H, OCH_2CH$_3$), 3.80 (s, 3H, OCH_3), 3.61-3.57 (m, 1H, OCH_2CH$_3$), 3.52-3.42 (m, 1H, OCH_2CH$_3$), 2.37 (s, 3H, CH_3), 1.24-1.16 (m, 6H, OCH_2CH_3×2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 153.3, 145.9, 138.9, 137.7, 129.1, 127.3, 102.4, 73.9, 63.8, 60.0, 57.6, 21.1, 18.4, 14.9, 14.2. MS: *m/z* = 348 (M^+). Anal. Calcd for $C_{18}H_{24}N_2O_5$ (348.17): C 62.05, H 6.94, N 8.04. Found: C 62.21, H 6.88, N 8.25.

2f: Yield 84%; mp 175-177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (bs, 1H, NH), 7.33-7.26 (m, 4H, H_{Ar}), 5.48 (s, 1H, C4-CH), 5.19 (d, *J* = 10.8 Hz, 1H, NC*H*H), 4.37 (d, *J* = 10.8 Hz, 1H, NC*H*H), 4.15-4.06 (m, 2H, OCH_2CH$_3$), 3.59-3.53 (m, 1H, OCH_2CH$_3$), 3.43-3.39 (m, 1H, OCH_2CH$_3$), 2.36 (s, 3H, 6-CH_3), 1.26-1.20 (m, 3H, OCH_2CH_3), 1.18-1.12 (m, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 153.2, 146.3, 140.4, 133.7, 128.8, 128.6, 101.9, 74.2, 63.8, 60.1, 57.4, 18.4, 14.8, 14.2. MS: *m/z* = 352 (M^+), 354 (M+2). Anal. Calcd for $C_{17}H_{21}ClN_2O_4$ (352.12): C 57.87, H 6.00, N 7.94. Found: C 58.01,

H 6.08, N 7.81.

2g: Yield 71%; mp 127-129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (bs, 1H, NH), 7.39-7.32 (m, 3H, H_{Ar}), 7.31-7.32 (m, 2H, H_{Ar}), 5.53 (s, 1H, 4-CH), 5.26 (d, J = 10.4 Hz, 1H, NC*H*H), 4.34 (d, J = 10.4 Hz, 1H, NC*H*H), 4.13-4.07 (m, 2H, OC*H*$_2$CH$_3$), 3.74-3.68 (m, 1H, OC*H*CH$_3$CH$_3$), 2.35 (s, 3H, 6-CH$_3$), 1.26-1.18 (m, 6H, CH(C*H*$_3$)$_2$), 1.07-1.05 (m, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 153.3, 146.1, 141.9, 128.5, 127.9, 127.4, 102.2, 71.9, 68.8, 59.9, 57.7, 22.7, 21.4, 18.4, 14.2. MS: *m/z* = 332 (M^+). Anal. Calcd for $C_{18}H_{24}N_2O_4$ (332.17): C 65.04, H 7.28, N 8.43. Found: C 65.21, H 7.40, N 8.32.

2h: yield 65%; mp 142-144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (bs, 1H, NH), 7.38-7.24 (m, 5H, H_{Ar}), 5.60 (s, 1H, 4-CH), 5.40 (d, J = 10.0 Hz, 1H, NC*H*H), 4.12 (d, J = 10.0 Hz, 1H, NC*H*H), 4.10-4.06 (m, 2H, OC*H*$_2$CH$_3$), 2.32(s, 3H, CH$_3$), 1.29-1.19 (m, 9H, CH$_3$), 1.18-1.14 (m, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 152.7, 146.3, 141.8, 128.4, 127.9, 127.5, 102.0, 74.1, 67.9, 59.9, 57.0, 28.0, 18.4, 14.2. MS: *m/z* = 346 (M^+), 348 (M+2). Anal. Calcd for $C_{19}H_{26}N_2O_4$ (346.19): C 65.87, H 7.56, N 8.09. Found: C 65.91, H 7.50, N 8.21.

General procedure compounds 3a-e. Method A: To a suspension of 3,4-dihydropyrimidinone (1.0 mmol), paraformaldehyde (5.0 mmol), and CH_2Cl_2 (5 mL), TMSCl (2.5 mmol) was added and the reaction mixture was stirred at 35 °C for 24 h. Morpholine (3 mmol) was then added and the reaction mixture was stirred for an additional 4 h until the reaction was complete (monitored by TLC). After reaction completion, the solid was filtered and the filtrate was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was then extracted with CH_2Cl_2 (15 mL) and the combined organic phase was washed with brine (15 mL), dried over Na_2SO_4, and concentrated. Purification by crystallization from aq. EtOH (EtOH: H_2O = 6:1) afforded *N3*-morpholinomethyl 3,4-dihydropyrimidinone (**3a-e**).

Method B: A mixture of 3,4-dihydropyrimidinone (1.0 mmol), paraformaldehyde (5.0 mmol), TMSCl (0.5 mmol), and morpholine (3.0 mmol) in MeOH (5 mL) was refluxed under stirring for 8 h. The work-up was same as mentioned in Method A, giving compounds **3a-d**.

Method C: A mixture of 3,4-dihydropyrimidinone (1.0 mmol), paraformaldehyde (5.0 mmol), AcOH (0.5 mmol), and morpholine (3.0 mmol) in MeOH (5 mL) was refluxed under stirring for 8 h. The work-up was same as mentioned in Method A, giving compounds **3a-d**.

3a: Yield 90%; mp 176-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (bs, 1H, NH), 7.35-7.24 (m, 5H, H_{Ar}), 5.59 (s, 1H, 4-CH), 4.24 (d, J = 12.0 Hz, 1H, NCH*H*), 4.17-4.08 (m, 2H, OC*H*$_2$CH$_3$), 3.72-3.66 (m, 4H, $H_{morpholino}$), 3.42 (d, J = 12.0 Hz, 1H, NC*H*H), 2.62-2.57 (m, 2H, $H_{morpholino}$), 2.49-2.44 (m, 2H, $H_{morpholino}$), 2.35 (s, 3H, 6-CH$_3$), 1.26-1.20 (m, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 153.9,

146.3, 141.7, 128.5, 127.8, 127.2, 101.9, 66.8, 65.7, 60.0, 58.2, 50.8, 18.4, 14.2. MS: *m/z* = 359 (M^+). Anal. Calcd for $C_{19}H_{25}N_3O_4$ (359.18): C 63.49, H 7.01, N 11.69. Found: C 63.33, H 7.10, N 11.82.

3b: Yield 88%; mp 198-200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (bs, 1H, NH), 7.25 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 6.82 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 5.54 (s, 1H, 4-CH), 4.51 (d, *J* = 12 Hz, 1H, NCH*H*), 4.14-4.09 (m, 2H, OC*H*$_2$CH$_3$), 3.78 (s, 3H, CH_3O), 3.74-3.69 (m, 4H, $H_{morpholino}$), 3.39 (d, *J* = 12 Hz, 1H, NC*H*H), 2.61-2.56 (m, 2H, $H_{morpholino}$), 2.49-2.44 (m, 2H, $H_{morpholino}$), 2.33 (s, 3H, 6-CH_3), 1.26-1.21 (m, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 159.2, 153.3, 145.5, 133.8, 128.4, 113.8, 102.5, 66.9, 65.6, 60.1, 57.6, 55.2, 50.9, 18.7, 14.2. MS: *m/z* = 389 (M^+). Anal. Calcd for $C_{20}H_{27}N_3O_5$ (389.20): C 61.68, H 6.99, N 10.79. Found: C 61.85, H 7.10, N 10.92.

3c: Yield 85%, mp 202-204 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (bs, 1H, NH), 7.25 (m, 2H, H_{Ar}), 7.10 (m, 2H, H_{Ar}), 5.55 (s, 1H, 4-CH), 4.52 (d, *J* = 12.0 Hz, 1H, NCH*H*), 4.14-4.11 (m, 2H, OC*H*$_2$CH$_3$), 3.70-3.68 (m, 4H, $H_{morpholino}$), 3.40 (d, *J* = 12.0 Hz, 1H, NC*H*H), 2.57 (m, 2H, $H_{morpholino}$), 2.48 (m, 2H, $H_{morpholino}$), 2.35 (s, 3H, 6-CH_3), 2.32 (s, 3H, CH_3), 1.25-1.18 (m, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.7, 153.9, 146.4, 140.9, 137.5, 129.2, 127.1, 101.6, 66.8, 65.6, 59.9, 57.9, 50.9, 21.1, 18.5, 14.2. MS: *m/z* = 373 (M^+). Anal. Calcd for $C_{20}H_{27}N_3O_4$ (373.20): C 64.32, H7.29, N 11.25. Found: C 64.45, H 7.40, N 11.12.

3d: Yield 86%; mp 197-199 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (bs, 1H, NH), 7.30-7.21 (m, 4H, H_{Ar}), 5.58 (s, 1H, 4-CH), 4.49 (d, *J* = 12 Hz, 1H, NCH*H*), 4.15-4.10 (m, 2H, OC*H*$_2$CH$_3$), 3.67-3.66 (m, 4H, $H_{morpholino}$), 3.37 (d, *J* = 12 Hz, 1H, NC*H*H), 2.59-2.56 (m, 2H, $H_{morpholino}$), 2.46-2.43 (m, 2H, $H_{morpholino}$), 2.27 (s, 3H, 6-CH_3), 1.25-1.18 (m, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 153.2, 146.0, 140.1., 133.7, 128.7, 128.6, 101.9, 66.9, 65.8, 60.2, 57.5, 50.8, 18.7, 14.2. MS: *m/z* = 393 (M^+). Anal. Calcd for $C_{19}H_{24}ClN_3O_4$ (393.15): C 57.94, H 6.14, N 10.67. Found: C 57.61, H 6.20, N 10.43.

3e: Yield 92%; mp 212-214 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (bs, 1H, NH), 7.44-7.42 (m, 2H, H_{Ar}), 7.27-7.21 (m, 2H, H_{Ar}), 5.57 (s, 1H, 4-CH), 4.50 (d, *J* = 12.0 Hz, 1H, NCH*H*), 4.15-4.12 (m, 2H, OC*H*$_2$CH$_3$), 3.70-3.67 (m, 4H, $H_{morpholino}$), 3.39 (d, *J* = 12 Hz, 1H, NC*H*H), 2.60-2.56 (m, 2H, $H_{morpholino}$), 2.47-2.44 (m, 2H, $H_{morpholino}$), 2.33(s, 3H, 6-CH_3), 1.26-1.22 (m, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 153.6, 146.4, 140.7, 131.6, 129.0, 121.8, 101.6, 66.8, 65.7, 60.2, 57.6, 50.8, 18.5, 14.2. MS: *m/z* = 437 (M^+). Anal. Calcd for $C_{19}H_{24}BrN_3O_4$ (437.10): C 52.06, H 5.52, N 9.59. Found: C 52.20, H 5.63, N 9.50.

General procedure compounds 4a-h: To a suspension of 3,4-dihydropyrimidinone (**1**, 1.0 mmol), paraformaldehyde (5.0 mmol, 5.0 equiv), and CH_2Cl_2 (5 mL), TMSCl (2.5 mmol, 2.5 equiv) were added and the reaction mixture was stirred at 35 °C for 24 h. Sodium benzenesulfinate (3 mmol) was then added

and the reaction mixture was stirred for an additional 12 h. The work-up was same as mentioned in above processes, giving compounds **4a-h**.

4a: Yield 76%; mp 193-194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96-7.94 (m, 2H, H_{Ar}), 7.68-7.55 (m, 3H, H_{Ar}), 7.35-7.27 (m, 5H, H_{Ar}), 5.67 (s, 1H, 4-CH), 5.30 (d, *J* = 14.4 Hz, 1H, NCH*H*), 4.14-4.05 (m, 2H, OC*H*$_2$CH$_3$), 3.95 (d, *J* = 14.4 Hz, 1H, NC*H*H), 2.27 (s, 3H, 6-CH_3), 1.24-1.12 (m, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 151.8, 145.2, 139.9, 137.5, 134.2, 129.2, 128.9, 128.8, 128.7, 128.5, 127.6, 127.3, 102.2, 64.0, 60.5, 60.3, 18.3, 14.1. MS: *m/z* = 414 (M^+). Anal. Calcd for $C_{21}H_{22}N_2O_5S$ (414.12): C 60.85, H 5.35, N 6.76. Found: C 61.00, H 5.43, N 6.88.

4b: Yield 85%; mp 206-207 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85-7.81 (m, 3H, H_{Ar}), 7.36-7.26 (m, 6H, H_{Ar}), 5.65 (s, 1H, 4-CH), 5.28 (d, *J* = 14.4 Hz, 1H, NCH*H*), 4.14-4.04 (m, 2H, OC*H*$_2$CH$_3$), 3.93 (d, *J* = 14.4 Hz, 1H, NC*H*H), 2.44 (s, 3H, CH_3), 2.26 (s, 3H, 6-CH_3), 1.26-1.18 (m, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 151.9, 145.4, 145.3, 140.0, 134.6, 129.9, 128.9, 128.8, 128.7, 127.6, 102.2, 64.0, 60.5, 60.2, 21.7, 18.3, 14.1. MS: *m/z* = 428 (M^+). Anal. Calcd for $C_{22}H_{24}N_2O_5S$ (428.14): C 61.67, H 5.65, N 6.54. Found: C 61.52, H 5.57, N 6.41.

4c: Yield 80%; mp 195-197 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (br, 1H, NH), 7.95-7.93 (m, 2H, H_{Ar}) 7.67-7.65 (m, 1H, H_{Ar}), 7.58-7.54 (m, 2H, H_{Ar}), 7.27-7.18 (m, 2H, H_{Ar}), 6.85-6.83 (m, 2H, H_{Ar}), 5.58 (s, 1H, 4-CH), 5.28 (d, *J* = 14.4 Hz, 1H, NCH*H*), 4.11-4.06 (m, 2H, OC*H*$_2$CH$_3$), 3.96 (d, *J* = 14.4 Hz, 1H, NCH*H*), 3.78 (s, 3H, OCH_3), 2.22 (s, 3H, CH_3), 1.22-1.18 (m, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 159.7, 152.3, 145.2, 137.6, 134.1, 132.1, 129.2, 128.8, 128.7, 114.0, 102.2, 63.9, 60.1, 59.9, 55.2, 18.1, 14.1. MS: *m/z* = 444 (M^+). Anal. Calcd for $C_{22}H_{24}N_2O_6S$ (444.14): C 59.45, H 5.44, N 6.30; Found: C 61.61, H 5.52, N 6.42.

4d: Yield 70%; mp 194-196 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (br, 1H, NH), 7.82-7.80 (m, 2H, H_{Ar}) 7.36-7.34 (m, 2H, H_{Ar}), 7.20-7.17 (m, 2H, H_{Ar}), 6.84-6.82 (m, 2H, H_{Ar}), 5.56 (s, 1H, 4-CH), 5.27 (d, *J* = 14.4 Hz, 1H, NCH*H*), 4.13-4.03 (m, 2H, OC*H*$_2$CH$_3$), 3.99 (d, *J* = 14.4 Hz, 1H, NC*H*H) 3.78 (s, 3H, OCH_3), 2.44 (s, 3H, CH_3), 2.23 (s, 3H, CH_3) 1.25-1.18 (m, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 159.7, 152.2, 145.3, 145.1, 134.7, 132.1, 129.9, 128.9, 128.7, 127.6, 114.1, 102.2, 67.0, 63.9, 60.0, 55.2, 21.7, 18.1, 14.1. MS: *m/z* = 458 (M^+). Anal. Calcd for $C_{23}H_{26}N_2O_6S$ (458.15): C 60.25, H 5.72, N 6.11. Found: C 60.37, H 5.81, N 6.02.

4e: Yield 79%; mp 197-199 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95-7.93 (m, 2H, H_{Ar}), 7.92 (br, 1H, NH), 7.69-7.65 (m, 1H, H_{Ar}), 7.58-7.54 (m, 2H, H_{Ar}), 7.16-7.11 (m, 4H, H_{Ar}), 5.60 (s, 1H, 4-CH), 5.28 (d, *J* = 14.4 Hz, 1H, NCH*H*), 4.13-4.04 (m, 2H, OC*H*$_2$CH$_3$), 3.96 (d, *J* = 14.4 Hz, 1H, NC*H*H), 2.33 (s, 3H, CH_3), 2.23 (s, 3H, 6-CH_3), 1.22-1.19 (m, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 151.9,

145.1, 138.5, 137.6, 136.9, 134.2, 129.5, 129.2, 128.8, 127.5, 102.3, 64.0, 60.2, 21.1, 18.3, 14.1. MS: *m/z* = 428 (M^+). Anal. Calcd for $C_{22}H_{24}N_2O_5S$ (428.14): C 61.67, H 5.65, N 6.54. Found: C 61.80, H 5.58, N 6.43.

4f: Yield 86%; mp 196-198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82-7.80 (m, 1H, H_{Ar}), 7.36-7.26 (m, 6H, H_{Ar}), 7.17-7.10 (m, 1H, H_{Ar}), 5.60 (s, 1H, 4-CH), 5.29 (d, *J* = 14.4 Hz, 1H, NCH*H*), 4.13-4.04 (m, 2H, OC*H*$_2$CH$_3$), 3.93 (d, *J* = 14.4 Hz, 1H, NC*H*H), 2.44 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.26 (s, 3H, 6-CH_3), 1.24-1.18 (m, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 151.7, 145.4, 145.1, 138.5, 137.0, 136.9, 134.6, 129.9, 129.5, 128.9, 127.6, 102.3, 64.0, 60.5, 21.8, 21.7, 18.3, 14.1. MS: *m/z* = 442 (M^+). Anal. Calcd for $C_{23}H_{26}N_2O_5S$ (442.16): C 62.42, H 5.92, N 6.33. Found: C 62.60, H 5.83, N 6.45.

4g: Yield 70%; mp 166-168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.94 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.70 (br, 1H, NH), 7.60-7.57 (m, 3H, H_{Ar}), 7.26-7.24 (m, 2H, H_{Ar}), 5.87 (s, 1H, 4-CH), 5.34 (d, *J* = 14.4 Hz, 1H, NCH*H*), 4.17-4.11 (m, 2H, OC*H*$_2$CH$_3$), 3.85 (d, *J* = 14.4 Hz, 1H, NC*H*H), 2.29 (s, 3H, 6-CH_3), 1.26-1.22 (m, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4, 151.5, 148.0, 147.0, 146.1, 137.2, 134.5, 129.4, 128.8, 128.5, 124.2, 101.5, 64.1, 60.7, 59.9. 18,6, 14.2. MS: *m/z* = 459 (M^+). Anal. Calcd for $C_{21}H_{21}N_3O_7S$ (459.11): C 54.89, H 4.61, N 9.15. Found: C 54.99, H 4.72, N 9.02.

4h: Yield 72%; mp 208-210 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.80 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.50-7.48 (m, 2H, H_{Ar}), 7.38-7.30 (m, 2H, H_{Ar}), 7.27 (br, 1H, NH), 5.88 (s, 1H, 4-CH), 5.32 (d, *J* = 14.4 Hz, 1H, NCH*H*), 4.15-4.11 (m, 2H, OC*H*$_2$CH$_3$), 3.83 (d, *J* = 14.4 Hz, 1H, NC*H*H), 2.46 (s, 3H, CH_3), 2.31 (s, 3H, 6-CH_3), 1.25-1.21 (m, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4 151.6 147.9 147.0 146.2 145.7 134.3 130.0 128.7 128.5 124.2 101.4 64.1 60.6 59.8 21.8 18.5 14.1 MS: *m/z* = 473 (M^+). Anal. Calcd for $C_{22}H_{23}N_3O_7S$ (473.13): C 55.80, H 4.90, N 8.87. Found: C 55.92, H 4.99, N 8.75.

General procedure compounds 5a-d: To a suspension of 3,4-dihydropyrimidinone (1.0 mmol), paraformaldehyde (5.0 mmol), and CH_2Cl_2 (5 mL), TMSCl (2.5 mmol) were added and the reaction mixture was stirred at 35 °C for 24 h. Sodium azide (3 mmol) was then added and the reaction mixture was stirred for an additional 8 h. The work-up was same as mentioned in above processes, giving compounds **5a-d**.

5a: Yield 72%; mp 136-138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (br, 1H, NH), 7.35-7.26 (m, 5H, H_{Ar}), 5.54 (s, 1H, 4-CH), 5.17 (d, *J* = 12.0Hz, 1H, NCH*H*), 4.26 (d, *J* = 12.0Hz, 1H, NC*H*H), 4.11-4.08 (m, 2H, OC*H*$_2$CH$_3$), 2.37 (s, 3H, 6-CH_3), 1.23-1.19 (m, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ

= 165.2, 152.9, 145.5, 141.2, 128.8, 128.4, 127.3, 102.4, 60.9, 60.3, 60.2, 18.5, 14.1. MS: *m/z* = 315 (M^+). Anal. Calcd for $C_{15}H_{17}N_5O_3$ (315.13): C 57.13, H 5.43, N 22.21. Found: C 57.25, H 5.25, N 22.07.

5b: Yield 74%; mp 184-186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (br, 1H, NH), 7.28-7.25 (m, 2H, H_{Ar}), 6.86-6.83 (m, 2H, H_{Ar}), 5.39 (s, 1H, 4-CH), 5.16 (d, *J* = 12.4Hz, 1H, NCH*H*), 4.24 (d, *J* = 12.4Hz, 1H, NC*H*H), 4.22-4.06 (m, 2H, O*CH*$_2$CH$_3$), 3.78 (s, 3H, OCH_3), 2.36 (s, 3H, 6-CH_3), 1.26-1.120 (m, 3H, OCH_2*CH*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2 159.5, 153.0, 145.2, 133.4, 128.6, 114.0, 102.5, 60.8, 60.2, 59.7, 55.2, 18.5, 14.2. MS: m/z = 345 (M+). Anal. Calcd for $C_{16}H_{19}N_5O_4$ (345.14): C 55.64, H 5.55, N 20.28. Found: C 55.50, H 5.41, N 20.39.

5c: Yield 70%; mp 176-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (br, 1H, NH), 7.26-7.23 (m, 2H, H_{Ar}), 7.14-7.12 (m, 2H, H_{Ar}), 5.40 (s, 1H, 4-CH), 5.16 (d, *J* = 12.4Hz, 1H, NCH*H*), 4.17 (d, *J* = 12.4Hz, 1H, NC*H*H), 4.09-4.05 (m, 2H, O*CH*$_2$CH$_3$), 2.35 (s, 3H, CH_3), 2.33 (s, 3H, 6-CH_3), 1.26-1.120 (m, 3H, OCH_2*CH*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 153.3, 145.6, 138.3, 138.2, 129.4, 127.2, 102.3, 60.9, 60.1, 60.0, 21.1, 18.4, 14.1. MS: m/z = 329 (M+). Anal. Calcd for $C_{16}H_{19}N_5O_3$ (329.15): C 58.35, H 5.81, N 21.26. Found: C 58.25, H 5.69, N 21.39.

5d: Yield 75%; mp 180-182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (br, 1H, NH), 7.30-7.26 (m, 4H, H_{Ar}), H_{Ar}), 5.42 (s, 1H, 4-CH), 5.10 (d, *J* = 12.8Hz, 1H, NCH*H*), 4.30 (d, *J* = 12.8Hz, 1H, NC*H*H),4.13-4.07 (m, 2H, O*CH*$_2$CH$_3$), 2.35 (s, 3H, 6-CH_3), 1.25-1.120 (m, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 153.0, 145.9, 139.9, 134.2, 128.9, 128.7, 102.0, 61.1, 60.3, 59.8, 18.5, 14.2. MS: *m/z* = 349 (M^+). Anal. Calcd for $C_{15}H_{16}ClN_5O_3$ (349.09): C 51.51, H 4.61, N 20.01. Found: C 51.42, H 4.53, N 20.17.

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