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L-Proline catalyzed multicomponent reaction of 3,4-dihydro-(2*H*)-pyran, urea/thiourea, and aldehydes: diastereoselective synthesis of hexahydropyrano pyrimidinones (thiones)

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ABSTRACT

An organocatalytic multicomponent reaction involving 3,4-dihydro-(2*H*)-pyran, aromatic aldehydes, and urea/thiourea as substrates and L-proline/TFA as catalyst afforded hexahydropyrano pyrimidinones (thiones) in good yields. The method is simple, economical, and ecofriendly to generate hexahydropyrano pyrimidinones as precursors for many biologically active molecules and fused oxazines (PA-824), the lead molecules for tuberculosis chemotherapy.

1. Introduction

The small molecules modulating biological functions are of great interest in medicinal chemistry.[1] These molecules with drug-like motifs usually exhibit enhanced bioavailability, especially orally, and can be derived more easily and economically than the biological therapeutics.[2] Nowadays, several of such biologically active compounds are efficiently synthesized by highly elegant multicomponent or domino reactions.[3] Domino or multi-component reactions are the processes that trigger the conversion of three or more starting materials in one pot to a highly functionalized product displaying maximum molecular diversity, complexity, and impressive selectivity. Therefore, these reactions are highly atom economic, ecofriendly, and synthetically efficient in terms of decreasing the time, the number of reaction steps, and the consumption of chemicals and solvents used.[4] Several secondary amines (both chiral and achiral nature), natural and unnatural amino acids have undoubtedly been the most successful catalysts in enamine- and iminium-type transformations. Since the first report of L-proline catalyzed direct asymmetric aldol reaction by List et al.[5a] in 2000 it has been regarded as the simplest 'enzyme' and has been successfully applied to many other reactions in addition to aldol reaction[5] such as Robinson annulation,[6] Mannich reactions,[7] Michael reactions,[8] direct electrophilic α-aminations,[9] Diels–Alder reactions,[10] Baylis–Hillman reactions,[11] aza-Morita–Baylis–Hillman reactions,[12] α-selenenylation,[13] oxidation,[14] chlorination,[15] and others.[16] The rigid ring structure, easy availability, nontoxic nature, economical in cost and simple to use makes this tiny molecule a remarkable organocatalyst in synthesizing small molecules of biological interest. Its organocatalytic activity is mainly due to its Lewis base character, capability for inducing enamine formation and hydrogen bonding with electronegative atoms of other functionalized groups. Noteworthy, among the organocatalytic MCRs several reports by Ramachary et al. are of great significance to develop a series of novel compounds of pharmaceutical importance.[17]

Pyranopyrimidinones and related fused ring pyrimidinones have shown diverse range of biological properties[18] and there is a widespread interest in their synthesis.[19] Such compounds have displayed antitumor, antibacterial, antihypertensive, vasodilator, bronchiodilator, hepatoprotective, cardiotonic, and antiallergic activities. Some of them also exhibit antimalarial, antifungal, analgesics, and herbicidal properties too.[20–27] The synthesis of dihydropyrimidinones using variants of the well established Biginelli reaction is one of the most recognized and often used MCR's for the generation of novel pyrimidine scaffolds.[28] Recently, application of L-proline in Biginelli reaction of aromatic aldehydes, β-keto compounds, and urea/thiourea has been reported by Yadav's group for the synthesis of dihydropyrimidin-2-ones (thiones).[29]

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Modified Biginelli reaction has also been used in accessing fused pyrimidinones or spiro fused pyrimidinones.[30] Wu et al.[31] also reported a TMSCl catalyzed three component diastereoselective reaction of 3,4-dihydro-(2*H*)-pyran with urea/thiourea and aromatic aldehydes to give respective hexahydro-4-phenyl-1*H*-pyrano[2,3-*d*]pyrimidin-2(8*H*)-ones (thiones) in good yields. Very recently, we have used L-proline/TFA as organocatalyst in a five-component reaction to get antimalarial tetrahydropyridines in moderate to good yields.[32] We were interested to synthesize hexahydropyrano pyrimidinones and thiones as precursors of fused oxazine analogues, which have shown potent antitubercular activity and one of such compounds PA-824 is in clinical trial (Fig. 1).

Keeping in view, the above verity we were prompted to synthesize hexahydro-4-phenyl-1*H*-pyrano-[2,3-*d*]pyrimidin-2(8*H*)-ones (thiones) via multicomponent reaction of urea/thiourea, aromatic aldehydes, and 3,4-dihydro-(2*H*)-pyran. The desired compounds were prepared via organocatalyzed (L-proline/TFA), three-component reaction of the above substrates in good to very good yields.

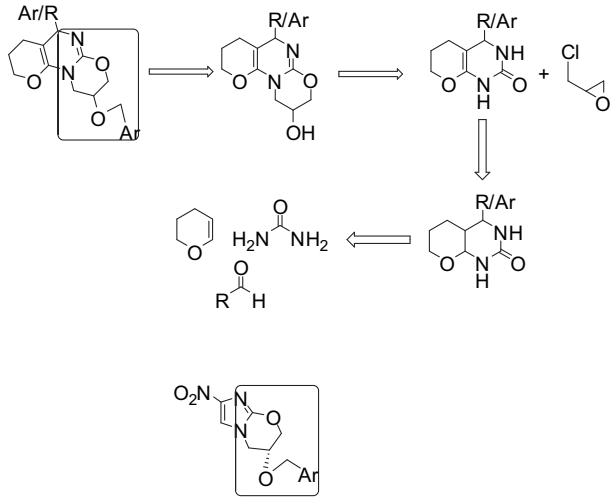


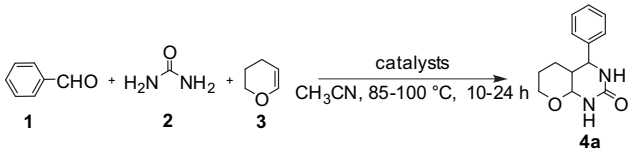
Figure 1. Synthetic strategy for fused oxazines as analogues of potent antitubercular molecules.

2. Results and discussion

Initially we carried out the reaction of benzaldehyde, urea, and 3,4-dihydro-(2*H*)-pyran in the presence of different catalysts to screen a suitable catalyst, for the systematic evaluation of the reaction condition (Table 1, entries 1–7). In many cases, either desired product **4a** was not detected in a complex reaction mixture even on TLC plates (reaction mixture appeared in the form of streak) or the reaction leads to mixture of products including the inseparable desired hexahydropyrimidinones (TLC) after 24 h of refluxing the reaction mixture.

This observation led us to explore the possibility of applying the concept of additives or co-catalysts where the reactions proceed via dual activation route. Several research groups have shown that addition of catalytic amount of very simple achiral compounds as co-catalyst or additive can be beneficial for the reaction in terms of yield and in some cases enantioselectivity.[33,34] Taking this fact into consideration we used TFA as an additive in the above L-proline catalyzed reaction and observed the progress of the reaction (TLC). To our pleasant findings, total benzaldehyde was consumed within 7 h and a solid product was precipitated out on completion of the reaction. The solid separated was filtered and washed with water and crystallized from ethanol to give a pure product, identified as

Table 1
Optimization of reaction condition with different catalysts

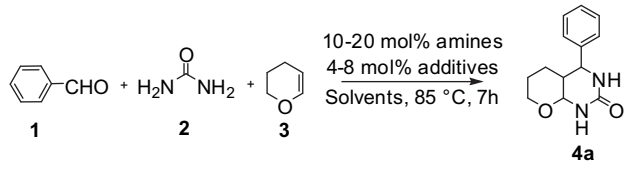


Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Isolated yield (%)
1	TBAHS	CH_3CN	85	10	Complex reaction
2	CuCl	CH_3CN	85	10	mixture[a]
3	$SnCl_4$	CH_3CN	85	10	
4	TMSOTf	CH_3CN	85	10	Complex reaction
5	Silica sulfuric acid	CH_3CN	85	10	mixture with
6	L-Proline	CH_3CN	100	24	desired
7	TFA	CH_3CN	85	10	product[b]

[a] Reaction mixture showed a streak on TLC plate and no desired product was detected.
[b] Several products with very close R_f values were formed and the desired product was detectable (TLC).

4-phenylhexahydro-1*H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one (**4a**) based on the prediction of its spectroscopic data and HRMS. We also observed that both the additives and solvents posed significant impact on the results of the reaction. Use of other acid additives such as acetic acid, benzoic acid, methanesulphonic acid, and *p*-toluenesulphonic acid under similar reaction conditions (Table 2, entries 10–13), proved to be ineffective as they resulted only a complex reaction mixture. The optimum quantity of the catalyst and additive was also screened (Table 2, entries 4–8) and it was found that on increasing the amount of L-proline from 5 mol % to 15 mol %, yield of the reaction increases gradually but on further increment (up to 20 mol %) does not influence the yield of the reaction (Table 2, entries 4–6). Similarly, on increasing the amount of

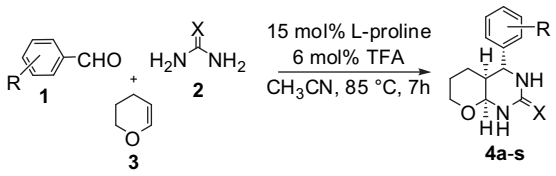
Table 2
Multicomponent reaction catalyzed by dual catalyst system of amines or amino acids and additives in different solvents



Entry	Catalyst (mol %)	Additive (mol %)	Solvent	Isolated yield (%)
1	Pyrrolidine (10)	TFA (4)	CH_3CN	Complex
2	Piperidine (10)	TFA (4)	CH_3CN	reaction mixture[a]
3	Glycine (10)	TFA (4)	CH_3CN	25
4	L-Proline (10)	TFA (4)	CH_3CN	60
5	L-Proline (15)	TFA (4)	CH_3CN	72
6	L-Proline (20)	TFA (4)	CH_3CN	70
7	L-Proline (10)	TFA (6)	CH_3CN	79
8	L-Proline (10)	TFA (8)	CH_3CN	60
9	L-Proline (15)	TFA (6)	CH_3CN	90
10	L-Proline (15)	CH_3COOH (6)	CH_3CN	Complex
11	L-Proline (15)	C_6H_5COOH (6)	CH_3CN	reaction
12	L-Proline (15)	$C_6H_4(4\text{-}CH_3)SO_3H$ (6)	CH_3CN	mixture[b]
13	L-Proline (15)	CH_3SO_3H (6)	CH_3CN	
14	L-Proline (15)	TFA (6)	CH_2Cl_2	
15	L-Proline (15)	TFA (6)	THF	
16	L-Proline (15)	TFA (6)	Toluene	
17	L-Proline (15)	TFA (6)	DMF	
18	L-Proline (15)	TFA (6)	Diethylene glycol	
19	L-Proline (15)	TFA (6)	CH_3CN+DMF	

[a] Reaction mixture showed a streak on TLC plate and no desired product was detected.
[b] Several products with very close R_f values were formed and the desired product was detectable (TLC).

Table 3
Scope of the organocatalyzed multicomponent reaction



Entry	R	X	Product	Isolated yield (%)
1	H	O	**4a**	90
2	H	S	**4b**	87
3	4-Cl	O	**4c**	85
4	4-Cl	S	**4d**	86
5	4-F	O	**4e**	87
6	4-F	S	**4f**	86
7	4-Br	O	**4g**	85
8	4-Br	S	**4h**	83
9	4-NO_2	O	**4i**	85
10	4-NO_2	S	**4j**	86
11	3,4-$(CH_3O)_2$	S	**4k**	78
12	3,4,5-$(CH_3O)_3$	S	**4l**	88
13	3,4,5-$(CH_3O)_3$	O	**4m**	90
14	3-NO_2	O	**4n**	86
15	3-NO_2	S	**4o**	84
16	2-NO_2	O	**4p**	80
17	2-Cl	O	**4q**	79
18	4-$C_6H_5CH_2O$	S	**4r**	85
19	4-$C_6H_5CH_2O$	O	**4s**	90

TFA from 4 mol % to 6 mol %, yield of the reaction increases but get retarded on further addition of TFA (8 mol %) (Table 2, entries 6–8). To check the efficiency of other amines and amino acid we carried out similar reaction and the results are presented in Table 2 (entries 1–4). In case of pyrrolidine and piperidine complex reaction mixture was obtained, whereas in the presence of glycine the yield of the product is very low (25%).

In addition, we also observed the effect of different solvents on the progress of reaction (Table 2, entries 14–19) where acetonitrile was found to be the most appropriate solvent for this MCR. Thus the best suited reaction condition for this type of MCR was the use of L-proline (15%), TFA (6%) in acetonitrile solvent at 85 °C (Table 2, entry 9).

Based on this reaction conditions, MCR with various aromatic aldehydes, urea/thiourea, and dihydropyran investigated and the results are shown in Table 3. All reactions proceeded smoothly to provide corresponding hexahydro-4-phenyl-1*H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-ones or hexahydro-4-phenyl-1*H*-pyrano[2,3-*d*]pyrimidine-2(8a*H*)-thiones in varying yields. As evident from Table 3, neither the nature of substituent nor the positions of substituents on aromatic ring in aromatic aldehydes alter the yield of reaction to any significant extent.

We have proposed a plausible reaction mechanism for the formation of hexahydropyrano pyrimidinones (thiones) based on earlier reports of Wu et al.[31] and Overman and Wolfe,[35] respectively (Fig. 2). It involves the initial formation of the *N*-acyliminium ion intermediate from an aldehyde and urea in presence of an acid. The *N*-acyliminium ion intermediate undergoes complex formation with L-proline via hydrogen bonding to produce *N*-acyliminium

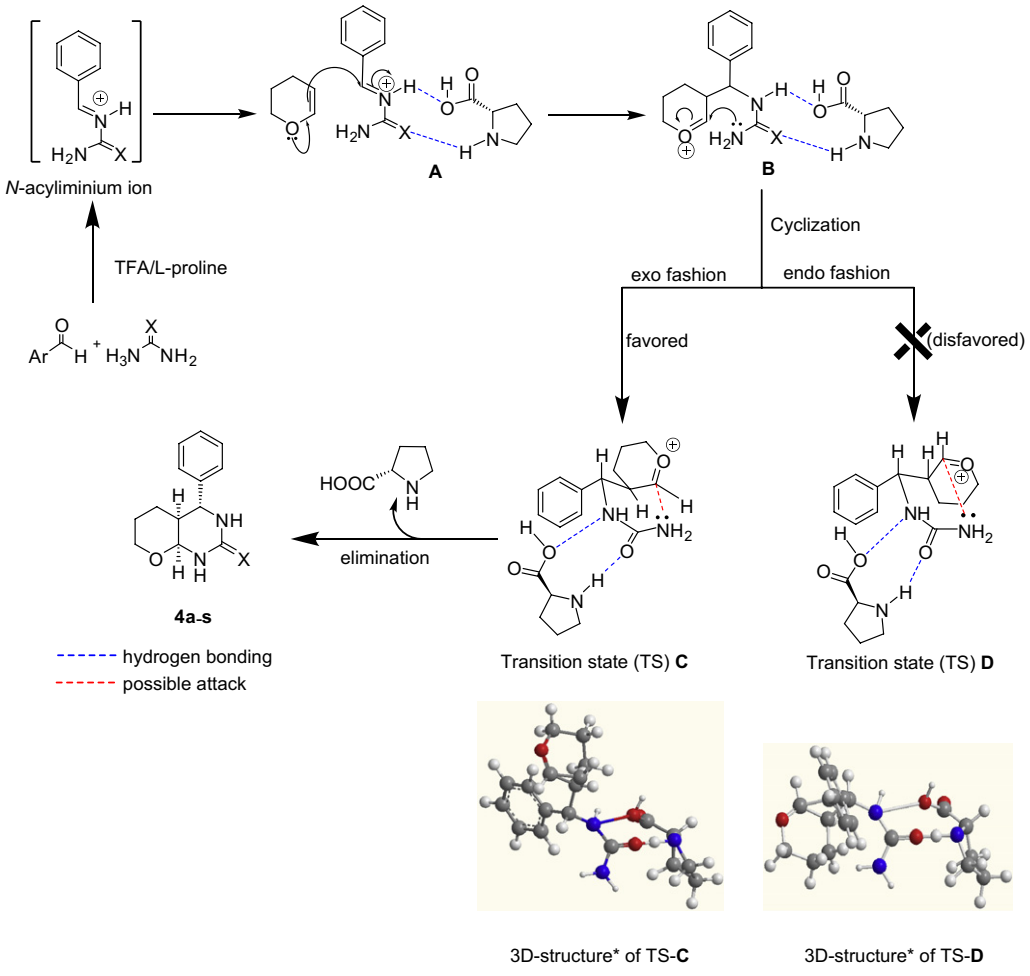


Figure 2. Proposed reaction mechanism. *From ChemBio 3D Ultra 11.0.

ion–proline complex **A**. The formation of hexahydropyrano pyrimidinones is considered to be a Biginelli type reaction of 3,4-dihydro-(2*H*)-pyran (**3**) with the *N*-acyliminium ion–proline complex **A**. The nucleophilic attack of 3,4-dihydro-(2*H*)-pyran (**3**) on complex **A** generates an oxonium ion intermediate **B**, which undergoes cyclization either in an *exo* and/or *endo* fashion as shown in Figure 2, leading to the transition states **C** and **D**. The observed products, hexahydropyrano pyrimidinones arise from the trapping of conformer **C** as the severe steric interaction between the 2,3,4,5-tetrahydropyrylium ring and ureidyl/thioureidyl group is negligible in **C** as compared to the conformer **D**.

The reaction is diastereoselective in nature as only the cis-isomer was observed. Based on NOESY experiment of compound **4b** the cis geometry was established where proton at C-10 shows significant interaction with the proton at C-9 as they are on the same plane (cis relationship) whereas very weak interactions are present between proton at C-10 and the proton at C-4 as they are on the opposite plane (trans relationship) (Fig. 3).

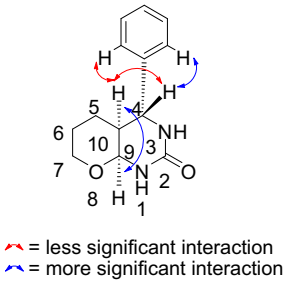


Figure 3. NOESY interactions.

3. Conclusion

We have developed an organocatalyzed multicomponent synthesis of hexahydropyrano pyrimidinones in good to very good yields. Our method is simple as no special apparatus, reagents or chemicals, and work up are required, and the compound formed is filtered and purified by crystallization only. This synthesis is also advantageous in terms of atom economy as well as is devoid of any hazardous chemicals. In near future, these scaffolds may be selectively exploited for further manipulation and diversification to create new class of compounds having great potential in developing of new chemotherapeutics.

4. Experimental section

4.1. General

Commercially available reagent grade chemicals were used as received. TLC was carried out with E. Merck Kieselgel 60 F_{254}. Spots were visualized under UV light and/or visualized by iodine vapors/spraying with a 20% aq $KMnO_4$ or with a Dragondroff spray reagent. Column chromatography was performed on silica gel (230–400 mesh, E. Merck). IR spectra were recorded as thin films or in KBr solution with a Perkin–Elmer RX-1 (4000–450 cm^{-1}) spectrophotometer. The ^1H (200 and 300 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Bruker DRX-300 in $CDCl_3$. Chemical shift values are reported in parts per million relative to TMS as internal reference, unless otherwise stated; s (singlet), d (doublet), t (triplet), m (multiplet); *J* in hertz. Mass spectra were recorded Jeol SX-102 and ESI mass spectra with Quattro II (Micromass). Elemental analyses were performed on a Perkin–Elmer 2400 II elemental analyzer. Optical rotations were determined on a Rudolf Autopol III polarimeter in methanol.

4.2. General procedure for the synthesis of 4a–m

TFA (6 mol %) was added to a solution of aromatic aldehyde **1** (1 equiv), thiourea or urea **2** (1.5 equiv), 3,4-dihydro-(2*H*)-pyran (1 equiv), and L-proline (15 mol %) in CH_3CN (5.0 mL) and the reaction mixture was magnetically stirred and refluxed at 80–85 °C till the reaction was completed (TLC). The products **4a**–**m** were precipitated directly. The crude product was isolated by filtration through a sintered funnel. The residue so obtained was washed with hot water and purified by simple crystallization using ethanol to give pure product.

*4.2.1. 4-Phenylhexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-one (**4a**).* White solid. Mp 218–220 °C; R_f 0.5 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −62.5 (*c* 0.008, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ=1.31–1.84 (m, 4H, $2CH_2$), 1.98–2.01 (m, 1H, H-10), 3.52–3.59 (m, 1H, H-7), 4.01–4.04 (m, 1H, H-7), 4.58–4.74 (m, 2H, H-4 and H-9), 7.38–7.39 (m, 5H, ArH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=20.8 (CH_2), 23.2 (CH_2), 38.0 (CH), 53.5 (CH), 66.8 (CH_2), 80.6 (CH), 127.4, 128.6, 128.9 (ArCH), 139.9 (ArC), 156.3 (C=O); IR (KBr): 3264, 2962, 2913, 2363, 1686, 1509, 1442 cm^{-1}; MS (ESMS): *m*/*z* 233 $[M+H]^+$; HRMS (EI) calcd for $C_{13}H_{16}N_2O_2$ $[M^+]$: 232.1181, found: 232.1212.

*4.2.2. 4-Phenylhexahydro-1H-pyrano [2,3-d]pyrimidine-2(8aH)-thione (**4b**).* White solid. Mp 235–238 °C; R_f 0.3 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ 23.9 (*c* 0.008, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ=1.23–1.27 (m, 2H, CH_2), 1.57–1.76 (m, 2H, CH_2), 1.85–1.88 (m, 1H, H-10), 3.44–3.51 (m, 1H, H-7), 3.89 (d, *J*=11.6 Hz, 1H, H-7), 4.39–4.42 (m, 1H, H-9), 4.52 (d, *J*=10.4 Hz, 1H, H-4), 7.23–7.41 (m, 5H, ArH), 8.36 (br s, 1H, NH), 8.79 (br s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=20.9 (CH_2), 23.0 (CH_2), 36.5 (CH), 54.4 (CH), 65.9 (CH_2), 78.7 (CH), 127.9, 128.3, 128.9, 140.6 (ArCH), 177.0 (ArC), 184.3 (C=S); IR (KBr): 3183, 2973, 2870, 2365, 1615, 1571, 1547, 1465 cm^{-1}; MS (ESMS): *m*/*z* 249 $[M+H]^+$; HRMS (EI) calcd for $C_{13}H_{16}N_2OS$ $[M^+]$: 248.0988, found: 248.0983.

*4.2.3. 4-(4-Chlorophenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-one (**4c**).* White solid. Mp 239–241 °C; R_f 0.3 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ 42.8 (*c* 0.008, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ=1.19–1.44 (m, 2H, CH_2), 1.51–1.73 (m, 2H, CH_2), 1.86 (d, *J*=10.65 Hz, 1H, H-10), 3.46–3.54 (m, 1H, H-7), 4.01–4.04 (d, *J*=11.6 Hz, 1H, H-7), 4.51 (s, 1H, H-9), 4.58 (d, *J*=10.9 Hz, 1H, H-4), 7.20–7.30 (m, 4H, ArH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.0 (CH_2), 23.3 (CH_2), 38.3 (CH), 53.0 (CH), 67.0 (CH_2), 80.7 (CH), 129.1, 129.2 (ArCH), 134.4, 139.1 (ArC), 156.9 (C=O); IR (KBr): 3020, 2362, 1668, 1593, 1481 cm^{-1}; MS (ESMS): *m*/*z* 267 $[M+H]^+$. Anal. Calcd for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.51; H, 5.69; N, 10.48.

*4.2.4. 4-(4-Chlorophenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-thione (**4d**).* White solid. Mp 260–263 °C; R_f 0.3 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −17.6 (*c* 0.008, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ=1.22–1.25 (m, 2H, CH_2), 1.61–1.69 (m, 2H, CH_2), 1.83–1.89 (m, 1H, H-10), 3.11–3.15 (m, 1H, H-7), 3.42–3.50 (m, 1H, H-7), 4.51 (s, 1H, H-9), 4.67 (d, *J*=10.9 Hz, 1H, H-4), 7.27–7.29 (m, 4H, ArH), 7.57 (d, *J*=8.79 Hz, 1H, NH), 8.16 (d, *J*=8.61 Hz, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.2 (CH_2), 23.2 (CH_2), 36.8 (CH), 54.1 (CH), 66.4 (CH_2), 79.1 (CH), 129.2, 130.1 (ArCH), 133.3, 139.8 (ArC), 178.0 (C=O); IR (KBr): 3187, 2964, 2835, 2362, 1668, 1573, 1535 cm^{-1}; MS (ESMS): *m*/*z* 283 $[M+H]^+$. Anal. Calcd for $C_{13}H_{15}ClN_2OS$: C, 55.21; H, 5.35; N, 9.91. Found: C, 55.19; H, 5.39; N, 9.94.

*4.2.5. 4-(4-Fluorophenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-one (**4e**).* White solid. Mp 230–232 °C; R_f 0.3 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −12.6 (*c* 0.008, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6):

δ=1.20–1.46 (m, 2H, CH_2), 1.55–1.75 (m, 2H, CH_2), 1.91 (d, J=9.21 Hz, 1H, H-10), 3.49–3.57 (m, 1H, H-7), 3.97 (d, J=10.4 Hz, 1H, H-7), 4.55 (s, 1H, H-9), 4.63 (d, J=10.8 Hz, 1H, H-4), 7.00–7.05 (m, 2H, ArH), 7.26–7.27 (m, 2H, ArH), 5.92 (br s, 1H, NH), 6.75 (br s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=20.8 (CH_2), 23.2 (CH_2), 38.2 (CH), 52.8 (CH), 67.2 (CH_2), 80.7 (CH), 115.7, 116.0, 129.3, 136.0 (ArCH), 156.6, 161.2 (ArC), 164.5 (C=O); IR (KBr): 3303, 3246, 3073, 2942, 2362, 1692, 1603, 1510, 1446 cm^{-1}; MS (ESMS): m/z 251 [M+H]$^+$; HRMS (EI) calcd for $C_{13}H_{15}FN_2O_2$ [M$^+$]: 250.1116, found: 250.1118.

*4.2.6. 4-(4-Fluorophenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-thione (**4f**).* White solid. Mp 225–230 °C; R_f 0.5 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −15.4 (c 0.008, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.38–1.53 (m, 2H, CH_2), 1.73–1.80 (m, 2H, CH_2), 2.00 (d, J=10.5 Hz, 1H, H-10), 3.62–3.65 (m, 1H, H-7), 4.04 (d, J=11.9 Hz, 1H, H-7), 4.58 (s, 1H, H-9), 4.69 (d, J=10.3 Hz, 1H, H-4), 7.10–7.16 (m, 2H, ArH), 7.35–7.39 (m, 2H, ArH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=20.0 (CH_2), 21.8 (CH_2), 35.8 (CH), 53.2 (CH), 65.2 (CH_2), 79.0 (CH), 114.4, 114.8 (ArCH), 128.2, 128.4 (ArC), 159.4 (C=S); IR (KBr): 3020, 2360, 1665, 1595, 1528, 1481 cm^{-1}; MS (ESMS): m/z 267 [M+H]$^+$; HRMS (EI) calcd for $C_{13}H_{15}FN_2OS$ [M$^+$]: 266.0894, found: 266.0889.

*4.2.7. 4-(4-Bromophenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-one (**4g**).* White solid. Mp 258–262 °C; R_f 0.2 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −25.4 (c 0.008, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.20–1.32 (m, 2H, CH_2), 1.51–1.82 (m, 3H, CH_2 and H-10), 3.42–3.49 (m, 1H, H-7), 3.91 (d, J=9.51 Hz, 1H, H-7), 4.42–4.44 (m, 1H, H-9), 4.57 (d, J=10.8 Hz, 1H, H-4), 7.25–7.29 (m, 2H, ArH), 7.48–7.50 (m, 2H, ArH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=20.8 (CH_2), 23.3 (CH_2), 38.1 (CH), 52.6 (CH), 66.2 (CH_2), 80.7 (CH), 121.4, 130.0, 131.1 (ArCH), 131.6, 141.2 (ArC), 151.1 (C=O); IR (KBr): 3304, 3207, 3096, 2944, 2364, 1700, 1590, 1489 cm^{-1}; MS (ESMS): m/z 311 [M+H]$^+$; HRMS (EI) calcd for $C_{13}H_{15}BrN_2O_2$ [M$^+$]: 310.0315, found: 310.0317.

*4.2.8. 4-(4-Bromophenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-thione (**4h**).* White solid. Mp 255–260 °C; R_f 0.4 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −83.1 (c 0.008, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.20–1.25 (m, 2H, CH_2), 1.58–1.79 (m, 2H, CH_2), 1.87 (d, J=10.2 Hz, 1H, H-10), 3.46–3.50 (m, 1H, H-7), 3.88 (d, J=11.6 Hz, 1H, H-7), 4.32–4.40 (m, 1H, H-9), 4.52 (d, J=10.5 Hz, 1H, H-4), 7.20–7.28 (m, 2H, ArH), 7.49–7.57 (m, 2H, ArH), 8.41 (br s, 1H, NH), 8.82 (br s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=20.8 (CH_2), 22.9 (CH_2), 36.3 (CH), 53.7 (CH), 66.0 (CH_2), 78.6 (CH), 121.3, 130.2 (ArCH), 131.7, 140.2 (ArC), 177.0 (C=S); IR (KBr): 3192, 2970, 2833, 2362, 1783, 1727, 1570, 1533, 1487 cm^{-1}; MS (ESMS): m/z 327 [M+H]$^+$; HRMS (EI) calcd for $C_{13}H_{15}BrN_2OS$ [M$^+$]: 326.0099, found: 326.0088.

*4.2.9. 4-(4-Nitrophenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-one (**4i**).* White solid. Mp 260–265 °C; R_f 0.4 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −48.4 (c 0.005, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.19–1.37 (m, 2H, CH_2), 1.57–1.73 (m, 2H, CH_2), 1.97 (d, J=10.4 Hz, 1H, H-10), 3.45–3.52 (m, 1H, H-7), 3.92 (d, J=11.5 Hz, 1H, H-7), 4.47 (s, 1H, H-9), 4.75 (d, J=10.6 Hz, 1H, H-4), 6.38 (br s, 1H, NH), 7.00 (br s, 1H, NH), 7.55 (d, J=8.64 Hz, 2H, ArH), 8.16 (d, J=8.61 Hz, 2H, ArH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.2 (CH_2), 23.5 (CH_2), 38.3 (CH), 53.2 (CH), 66.7 (CH_2), 80.8 (CH), 124.2, 129.3 (ArCH), 147.9, 149.4 (ArC), 155.9 (C=O); IR (KBr): 3313, 3020, 2930, 2361, 1687, 1599, 1501, 1441 cm^{-1}; MS (ESMS): m/z 278 [M+H]$^+$. Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.49; H, 5.49; N, 15.12.

*4.2.10. 4-(4-Nitrophenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-thione (**4j**).* White solid. Mp 265–270 °C; R_f 0.3 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −56.3 (c 0.005, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.11–1.22 (m, 2H, CH_2), 1.69–1.93 (m, 3H, CH_2 and H-10), 3.43–3.58 (m, 1H, H-7), 3.89 (d, J=17.2 Hz, 1H, H-7), 4.41–4.38 (s, 1H, H-9), 4.70 (d, J=15.6 Hz, 1H, H-4), 7.62 (d, J=13.0 Hz, 2H, ArH), 8.24 (d, J=13.0 Hz, 2H, ArH), 8.59 (br s, 1H, NH), 8.91 (br s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.2 (CH_2), 23.3 (CH_2), 36.8 (CH), 54.2 (CH), 66.4 (CH_2), 79.0 (CH), 124.4, 129.9 (ArCH), 148.0, 148.9 (ArC), 177.5 (C=S); IR (KBr): 3352, 3183, 3056, 2946, 2846, 2362, 1605, 1533, 1517 cm^{-1}; MS (ESMS): m/z 294 [M+H]$^+$. Anal. Calcd for $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.15; N, 14.32. Found: C, 53.20; H, 5.19; N, 14.34.

*4.2.11. 4-(3,4-Dimethoxyphenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-thione (**4k**).* White solid. Mp 220–222 °C; R_f 0.3 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −14.0 (c 0.008, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.31–1.36 (m, 2H, CH_2), 1.51–1.68 (m, 2H, CH_2), 1.93–1.97 (m, 1H, H-10), 3.53–3.57 (m, 1H, H-7), 3.83 (s, 6H, OCH_3), 3.97 (d, J=11.7 Hz, 1H, H-7), 4.47–4.54 (m, 2H, H-4 and H-9), 6.80–6.86 (m, 3H, ArH), 7.55 (br s, 1H, NH), 8.55 (br s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=20.9 (CH_2), 22.9 (CH_2), 36.3 (CH), 54.3 (CH), 55.7 (OCH_3), 65.8 (CH_2), 79.0 (CH), 110.4, 111.3 (ArCH), 119.9, 131.8, 149.2 (ArC), 176.9 (C=S); IR (KBr): 3420, 3020, 2974, 1605, 1516, 1426 cm^{-1}; MS (ESMS): m/z 309 [M+H]$^+$; HRMS (EI) calcd for $C_{15}H_{20}N_2O_3S$ [M$^+$]: 308.1197, found: 308.1195.

*4.2.12. 4-(3,4,5-Trimethoxyphenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-thione (**4l**).* White solid. Mp 241–243 °C; R_f 0.4 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −44.1 (c 0.008, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.19–1.32 (m, 2H, CH_2), 1.60–1.78 (m, 2H, CH_2), 1.92 (d, J=14.9 Hz, 1H, H-10), 3.31 (s, 3H, OCH_3), 3.39–3.63 (m, 1H, H-7), 3.75 (s, 6H, OCH_3), 3.82 (d, J=17.4 Hz, 1H, H-7), 4.37–4.47 (m, 2H, H-4 and H-9), 6.61 (s, 2H, ArH), 8.26 (br s, 1H, NH), 8.78 (br s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.3 (CH_2), 23.6 (CH_2), 36.5 (CH), 54.9 (CH), 56.8, 60.8 (OCH_3), 66.4 (CH_2), 79.2 (CH), 105.7 (ArCH), 136.3, 137.8, 153.6 (ArC), 177.3 (C=S); IR (KBr): 3426, 3020, 2359, 1720, 1601, 1524, 1425 cm^{-1}; MS (ESMS): m/z 339 [M+H]$^+$; HRMS (EI) calcd for $C_{16}H_{22}N_2O_4S$ [M$^+$]: 338.1312, found: 338.1300.

*4.2.13. 4-(3,4,5-Trimethoxyphenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-one (**4m**).* White solid. Mp 218–220 °C; R_f 0.2 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −23.0 (c 0.008, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.29–1.60 (m, 4H, CH_2), 1.89 (d, J=10.3 Hz, 1H, H-10), 3.27 (s, 3H, OCH_3), 3.47–3.55 (m, 1H, H-7), 3.73 and 3.83 (two s, 6H, OCH_3), 3.95 (d, J=9.42 Hz, 1H, H-7), 4.49–4.51 (m, 1H, H-9), 4.55 (d, J=10.7 Hz, 1H, H-4), 6.06 (br s, 1H, NH), 6.57 (s, 2H, ArH), 7.12 (br s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=20.0 (CH_2), 22.6 (CH_2), 37.3 (CH), 52.7 (CH), 55.3, 59.5 (OCH_3), 65.5 (CH_2), 79.9 (CH), 103.7 (ArCH), 136.6, 135.9, 152.4 (ArC), 154.5 (C=O); IR (KBr): 3437, 3020, 2922, 2359, 1669, 1597, 1426 cm^{-1}; MS (ESMS): m/z 323 [M+H]$^+$; HRMS (EI) calcd for $C_{16}H_{22}N_2O_5$ [M$^+$]: 322.1520, found: 322.1529.

*4.2.14. 4-(3-Nitrophenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-one (**4n**).* White solid. Mp 250–255 °C; R_f 0.3 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −58.5 (c 0.005, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.16–1.28 (m, 2H, CH_2), 1.44–1.66 (m, 2H, CH_2), 1.77 (d, J=10.6 Hz, 1H, H-10), 3.30–3.42 (m, 1H, H-7), 3.82 (d, J=9.86 Hz, 1H, H-7), 4.38–4.49 (m, 1H, H-9), 4.61 (d, J=10.8 Hz, 1H, H-4), 6.22 (br s, 1H, NH), 6.90 (br s, 1H, NH), 6.38–7.62 (m, 2H, ArH), 7.93–8.02 (m, 2H, ArH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=20.4 (CH_2), 22.7 (CH_2), 38.7 (CH), 52.5 (CH), 65.8 (CH_2), 80.0 (CH), 121.7, 122.5 (ArCH), 129.3, 133.5 (ArC), 154.7 (C=O); IR (KBr): 3020, 2401, 2361, 2105, 1666, 1596 cm^{-1}; MS (ESMS): m/z 278 [M+H]$^+$; HRMS (EI) calcd for $C_{16}H_{22}N_2O_5$ [M$^+$]: 277.1063, found: 277.1065.

*4.2.15. 4-(3-Nitrophenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-thione (**4o**).* White solid. Mp 270–278 °C; R_f 0.5 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −54.9 (c 0.005, CH_3OH); ^{1}H NMR (300 MHz,

DMSO-d_6): δ=1.25–1.28 (m, 2H, CH_2), 1.60–1.69 (m, 2H, CH_2), 1.79 (d, J=11.5 Hz, 1H, H-10), 3.48–3.52 (m, 1H, H-7), 3.86 (d, J=11.2 Hz, 1H, H-7), 4.41–4.43 (m, 1H, H-9), 4.70 (d, J=10.5 Hz, 1H, H-4), 7.65–7.70 (m, 1H, ArH), 7.82 (d, J=7.71 Hz, 1H, ArH), 8.17–8.20 (m, 2H, ArH), 8.50 (br s, 1H, NH), 8.91 (br s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.2 (CH_2), 23.3 (CH_2), 36.7 (CH), 54.0 (CH), 66.4 (CH_2), 79.0 (CH), 123.2, 123.7, 130.8, 135.4 (ArCH), 143.4, 148.7 (ArC), 177.5 (C=O); IR (KBr): 3385, 3020, 2360, 1665, 1592 cm^{-1}; MS (ESMS): m/z 294 $[M+H]^+$. Anal. Calcd for $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.15; N, 14.32. Found: C, 53.19; H, 5.18; N, 14.35.

*4.2.16. 4-(2-Nitrophenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-one (**4p**).* White solid. Mp 234–237 °C; R_f 0.2 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −26.3 (c 0.008, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.24–1.27 (m, 2H, CH_2), 1.44–1.68 (m, 2H, CH_2), 2.07 (d, J=6.72 Hz, 1H, H-10), 3.38–3.46 (m, 1H, H-7), 3.83 (d, J=11.4 Hz, 1H, H-7), 4.45–4.48 (m, 1H, H-9), 4.94 (d, J=10.1 Hz, 1H, H-4), 6.74 (br s, 1H, NH), 7.30 (br s, 1H, NH), 7.53–7.58 (m, 1H, ArH), 7.68–7.78 (m, 1H, ArH), 7.86 (d, J=7.95 Hz, 1H, ArH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=20.8 (CH_2), 22.9 (CH_2), 36.9 (CH), 47.6 (CH), 65.0 (CH_2), 79.8 (CH), 123.7, 128.9, 129.6, 133.2 (ArCH), 135.0, 149.9 (ArC), 154.4 (C=O); IR (KBr): 3422, 3021, 2359, 1669, 1593 cm^{-1}; MS (ESMS): m/z 278 $[M+H]^+$. Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.29; H, 5.49; N, 15.16.

*4.2.17. 4-(2-Chlorophenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-one (**4q**).* White solid. Mp 242–244 °C; R_f 0.3 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −12.2 (c 0.008, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.12–1.42 (m, 2H, CH_2), 1.52–1.79 (m, 2H, CH_2), 1.92 (d, J=13.4 Hz, 1H, H-10), 3.42–3.47 (m, 1H, H-7), 3.83 (d, J=16.7 Hz, 1H, H-7), 4.43 (br s, 1H, H-9), 4.94 (d, J=15.5 Hz, 1H, H-4), 6.63 (br s, 1H, NH), 7.29–7.49 (m, 5H, ArH and NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=22.1 (CH_2), 23.7 (CH_2), 38.1 (CH), 50.5 (CH), 66.1 (CH_2), 80.9 (CH), 128.6, 130.0, 130.2 (ArCH), 133.7, 139.9 (ArC), 155.4 (C=O); IR (KBr): 3311, 3208, 3095, 2369, 1700, 1574 cm^{-1}; MS (ESMS): m/z 267 $[M+H]^+$. Anal. Calcd for $C_{13}H_{15}N_2O_2Cl$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.52; H, 5.69; N, 10.55.

*4.2.18. 4-(4-Benzyloxyphenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-thione (**4r**).* White solid. Mp 253–255 °C; R_f 0.5 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −31.2 (c 0.008, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.23–1.26 (m, 2H, CH_2), 1.59–1.69 (m, 2H, CH_2), 1.85 (d, J=9.06 Hz, 1H, H-10), 3.42–3.49 (m, 1H, H-7), 3.88 (d, J=11.4 Hz, 1H, H-7), 4.38–4.40 (m, 1H, H-9), 4.47 (d, J=10.6 Hz, 1H, H-4), 5.10 (s, 2H, –OCH_2), 7.02 (d, J=8.61 Hz, 2H, ArH), 7.23 (d, J=8.61 Hz, 2H, ArH), 7.32–7.47 (m, 5H, ArH), 8.20 (br s, 1H, NH), 8.79 (br s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.2 (CH_2), 23.4 (CH_2), 36.9 (CH), 54.1 (CH), 66.5 (CH_2), 70.0 (–OCH_2), 79.2 (CH), 115.5, 128.5, 128.7, 129.3, 129.5 (ArCH), 133.0, 137.9, 158.8 (ArC), 177.2 (C=O); IR (KBr): 3167, 2979, 2938, 2866, 2669, 1608, 1574 cm^{-1}; MS (ESMS): m/z 339 $[M+H]^+$. Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.96; H, 6.59; N, 8.30.

*4.2.19. 4-(4-Benzyloxyphenyl)hexahydro-1H-pyrano[2,3-d]pyrimidin-2(8aH)-one (**4s**).* White solid. Mp 243–245 °C; R_f 0.3 (50:1 $CHCl_3$/MeOH); $[\alpha]_D^{25}$ −63.0 (c 0.008, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.14–1.27 (m, 2H, CH_2), 1.52–1.67 (m, 2H, CH_2), 1.73 (d, J=9.22 Hz, 1H, H-10), 3.42–3.47 (m, 1H, H-7), 3.84 (d, J=8.98 Hz, 1H, H-7), 4.38–4.40 (m, 1H, H-9), 4.45 (d, J=10.7 Hz, 1H, H-4), 5.08 (s, 2H, –OCH_2), 6.43 (br s, 1H, NH), 6.96 (d, J=8.02 Hz, 2H, ArH), 7.21–7.25 (m, 3H, 2ArH and NH), 7.34–7.42 (m, 5H, ArH); ^{13}C NMR (50 MHz, DMSO-d_6): δ=20.7 (CH_2), 23.4 (CH_2), 38.3 (CH), 52.4 (CH), 66.5 (CH_2), 69.7 (–OCH_2), 80.7 (CH), 115.0, 128.0, 128.3, 128.9, 129.0 (ArCH), 137.6, 134.0, 155.1 (ArC), 158.3(C=O); IR (KBr): 3325, 3250, 2927, 2363, 1682, 1609 cm^{-1}; MS (ESMS): m/z 339 $[M+H]^+$. Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.96; H, 6.59; N, 8.30.

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Supplementary data

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