

**HANTZSCH DIHYDROPYRIDINE: AN EFFECTIVE AND
CONVENIENT REGIOSELECTIVE REDUCING AGENT FOR 5-
BENZYLIDENE-2,4-THIAZOLIDINEDIONE DERIVATIVES**

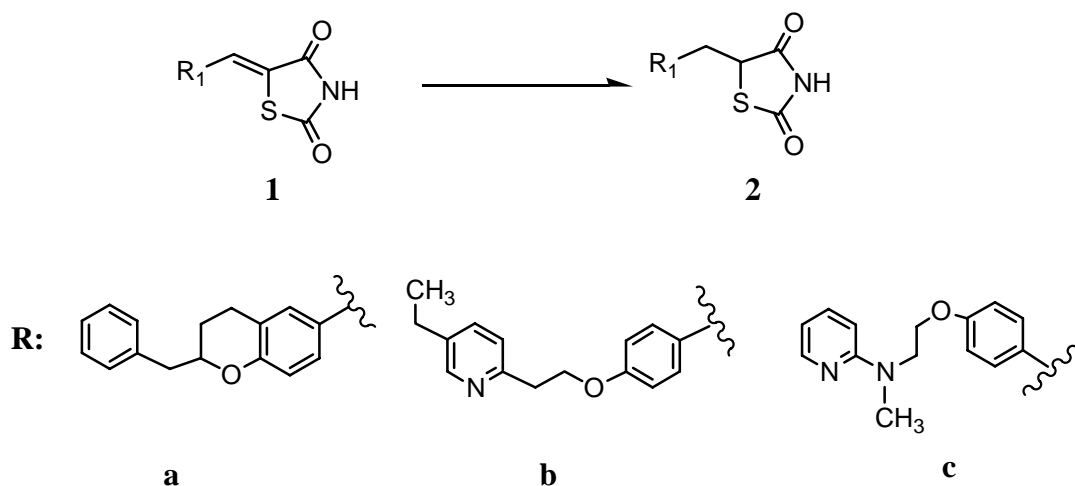
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Abstract-An effective and convenient regioselective reduction of 5-benzylidene-2,4-thiazolidinedione derivatives to the corresponding 5-benzyl 2,4-thiazolidinedione derivatives has been accomplished using 3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine (Hantzsch dihydropyridine ester : HEH) with silica gel as an acid catalyst in a good yield.

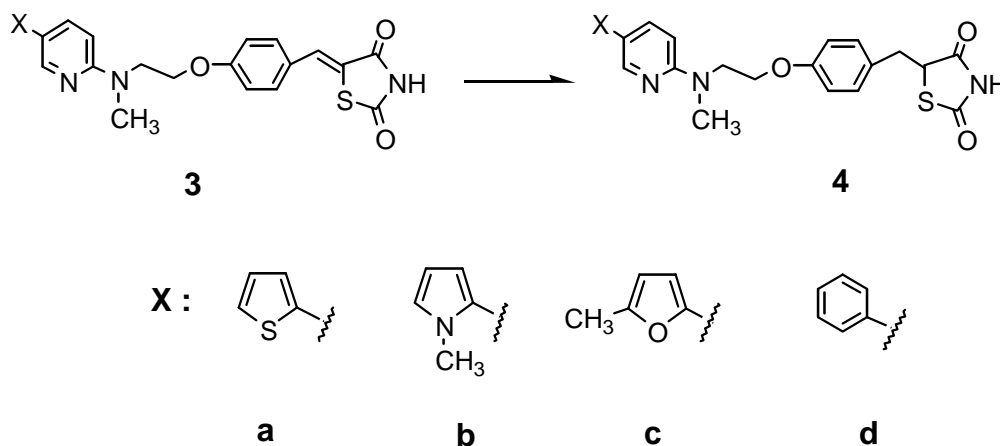
Thiazolidinedione derivatives with a carbonyl group at the 2,4 or 5 position are an important group of heterocyclic compounds with a diverse array of biological activities.¹ The 5-benzylthiazolidine-2,4-dione moiety (**2**) in particular has attracted considerable pharmaceutical interest. The thiazolidinedione derivatives have been extensively studied and their chemistry and biology have been reviewed.^{2,3} The hypoglycemic agent (**2a**) is formed from a catalytic hydrogenation of the corresponding olefin (**1a**),⁴ while cobalt hydride mediated reduction of **1b** gives the corresponding antidiabetic agent pioglitazone (**2b**).⁵ Also rosiglitazone (**2c**) is obtained from a catalytic hydrogenation or lithium borohydride in pyridine as reducing agents of the corresponding benzylidene rosiglitazone (**1c**).⁶ The reduction methods described above are substrate specific which highlight the lack of a general method available

to date (**Scheme 1**).



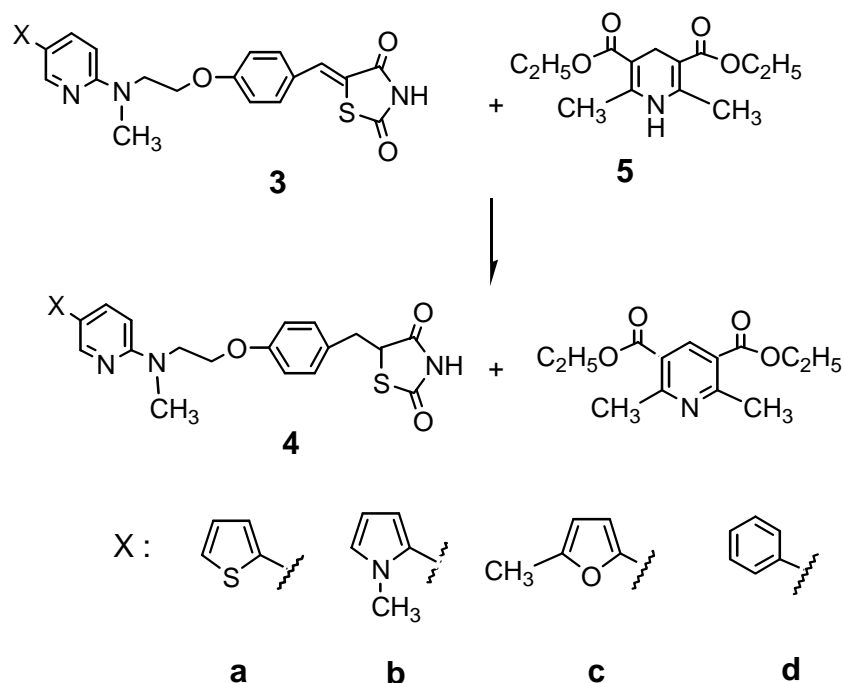
Scheme 1

Recently, our research group has been developing new candidates for the treatment of non-insulin dependent diabetes mellitus (NIDDM). The key step in the synthesis of the candidate materials is the regioselective reduction of the benzylidene derivatives having α,β -unsaturated ketone moiety from **3a-d** to **4a-d**. Use of catalytic hydrogenation to reduce **3a-d** required prolonged reaction time and a large amount of catalysts (**Scheme 2**).



Scheme 2

A range of other reduction conditions including cobalt hydride,⁵ sodium borohydride,⁶ sodium borohydride /cobalt chloride,⁷ zinc/acetic acid,⁸ and palladium on charcoal⁹ was investigated only to give inefficient or unselective results where products derived from both 1,2- and 1,4- reductions were obtained. There are several reports in the literature that the conjugate reduction of unsaturated ketones¹⁰ and bis-activated ketones¹¹ can be effected cleanly by Hantzsch dihydropyridine ester.¹² It has also been reported that direct reductive amination of aldehydes and ketones has been accomplished using a Hantzsch dihydropyridine ester as a reducing agent in the presence of a catalytic amount of Lewis acid.¹³ Therefore, it seemed likely that these conditions could bring about the conversion of **3a-d** to **4a-d**. We found that benzylidene derivatives were reduced regioselectively to the corresponding benzyl derivatives in the presence of silica gel as an acid catalyst. In this paper, we report a convenient and effective methodology for regioselective reduction using Hantzsch dihydropyridine ester (HEH)(**5**).^{14,15}



Reagent and condition: acid catalysts, toluene, reflux, 24 h.

Scheme 3

It should be noted that the present reduction system has synthetic utility in the following points, that is, Hantzsch dihydropyridine ester is stable against light and air, soluble in most organic solvents, commercially available, and inexpensive even in a large scale amount. The results are summarized in **Scheme 3** and **Table 1**.

All condensations from substituted benzaldehydes to **3a-d** as starting materials were carried out using piperidinium acetate as a catalyst in reflux toluene with azeotropic removal of the water. First of all, to explore the scope and limitations of this reduction process, the reductions of benzylidene derivatives (**3a-d**) were carried out by the treatment of various reducing agents. Reduction of the benzylidene derivative (**3a**) with 10% Pd/C, 20% Pd(OH)₂, and platinum oxide under hydrogen atmosphere led to a very slow conversion to the corresponding benzyl derivative (**4a**) in a moderate yield (**Table 1**, Entries 1 to 3). In case of lithium aluminum hydride, sodium borohydride, and lithium borohydride as reducing agents, each of them showed very different results. Reduction of **3a** by lithium aluminum hydride showed several unknown products with no desired product (**4a**) (**Table 1**, Entry 4) and reduction by sodium borohydride did not occur at all (**Table 1**, Entry 6). Reduction by lithium borohydride gave a moderate yield (**Table 1**, Entry 5) in the presence of pyridine/THF as co-solvents.

In the case of zinc in acetic acid with **3a**, no reduction was observed (**Table 1**, Entry 6). The best results were achieved under the Hantzsch dihydropyridine ester with **3a-d** in the presence of silica gel as an acid catalyst (**Table 1**, Entries 8 to 12). In general, the above mentioned reductions proceeded rapidly with complete regioselectivity (**Table 1**, Entries 9 to 12) except for benzene solvent (**Table 1**, Entry 8). All reactions were monitored by TLC and HPLC. Also, the rates of reduction of **3a-d** to **4a-d** were improved from 7 day to 1 day by using Hantzsch's ester and silica gel in an appropriate inert solvent like toluene under reflux conditions.

As shown in **Table 1**, the regioselective products with the best yield were obtained on the condition that 1.3 mol equivalent of Hantzsch's ester and the same weight of silica gel¹⁶ based on the amount of substrate in toluene were stirred at reflux temperature for 24 h under argon atmosphere in the dark.

Table 1. Reduction of the benzylidene derivatives (**3a-d**) to the benzyl derivatives (**4a-d**) by various reducing agents.^{a)}

Entry	Substrate	Reducing agent	Solvents	Reaction condition		Yield ^{e)} (%)
				Temp (°C)	Time	
1	3a	10 % Pd/C, H ₂	CH ₃ OH/DMF	rt	7 day	58
2	3a	20 % Pd(OH) ₂ , H ₂	CH ₃ OH/DMF	rt	5 day	65
3	3a	PtO ₂ , H ₂	CH ₃ OH/DMF	rt	4.5 day	68
4	3a	LiAlH ₄	pyridine/THF	rt	24 h	ND ^{f)}
5	3a	LiBH ₄	pyridine/THF	reflux	4 h	65
6	3a	NaBH ₄	pyridine/THF	reflux	24 h	ND
7	3a	Zn/AcOH	DMF ^{d)}	rt	5 day	ND
8	3a	HEH ^{b)} /SiO ₂ ^{c)}	benzene	reflux	36 h	75
9	3a	HEH/SiO ₂	toluene	reflux	24 h	88
10	3b	HEH/SiO ₂	toluene	reflux	24 h	90
11	3c	HEH/SiO ₂	toluene	reflux	24 h	85
12	3d	HEH/SiO ₂	toluene	reflux	24 h	89

a) Reductions were monitored by HPLC or TLC. b) Hantzsch dihydropyridine ester. c) Silica gel. d) *N,N*-Dimethylformamide. e) The yields are isolated yields. f) Desired product was not detected.

On the basis of these data, we next have applied several reduction conditions varying the ratios of substrate to silica gel and the results are summarized in **Table 2**. The first five Entries show that the reduction is accelerated by increasing the amount of silica gel without side reactions of other reducible functional groups in a good yield. However, when the reduction of the benzylidene compound (**3b**) was carried out in the absence of silica gel as an acid catalyst, desired product (**4b**) was seldom obtained (**Table 2**, Entry 6). Although the silica gel employed for the reduction was commercially available and subjected to the reaction without further treatment, we recommend a dried condition such as an azeotropic condition, because the moisture included in silica gel lowered reaction yields remarkably (**Table 2**, Entries 2 and 8).

Table 2. Reduction of the benzylidene derivatives (**3a-d**) by Hantzsch's ester (**5**) in the presence of the several amounts of silica gel.^{a)}

Entry	Substrate	Substrate vs Silica gel (wt/wt) ratio	Solvent	Reaction condition		Yield (%)
				Temp (°C)	Time	
1	3b	1 : 3	toluene	reflux	12	90
2	3b	1 : 3	toluene ^{b)}	reflux	12	58
3	3b	1 : 1.5	toluene	reflux	24	88
4	3b	1 : 1	toluene	reflux	38	89
5	3b	1 : 0.5	toluene	reflux	60	72
6	3b	-	toluene	reflux	72	ND ^{c)}
7	3b	1 : 1.5	benzene	reflux	30	60
8	3b	1 : 1.5	THF	reflux	48	ND

a) All reaction conditions are carried out : [substrate]=1.0 mmol, [HEH]=1.3 mmol, [silica gel]= wt/wt, at reflux in toluene (5 mL) under nitrogen atmosphere. b) Azeotropic condition was not applied.

c) Not detection.

Although detailed mechanism of the reduction has not yet been clarified, the role of silica gel in the present reduction seems to be as following points; i) To play an important role to set the Hantzsch's ester (HEH) in close proximity to the substrate. ii) To activate the substrate as an acid catalyst and stabilize the resulting enolate anion with a proton from water on the surface of silica gel. The above reaction process was next applied to various Hantzsch dihydropyridine esters and the results are shown in **Scheme 4** and **Table 3**. Unexpectedly, in the present process, the reduction of the benzylidene derivatives (**3a-d**) by methyl or phenyl Hantzsch's esters (**5b-c**) did not occur even at prolonged reaction time as shown in the example (**Table 3**, Entries 2 to 7).

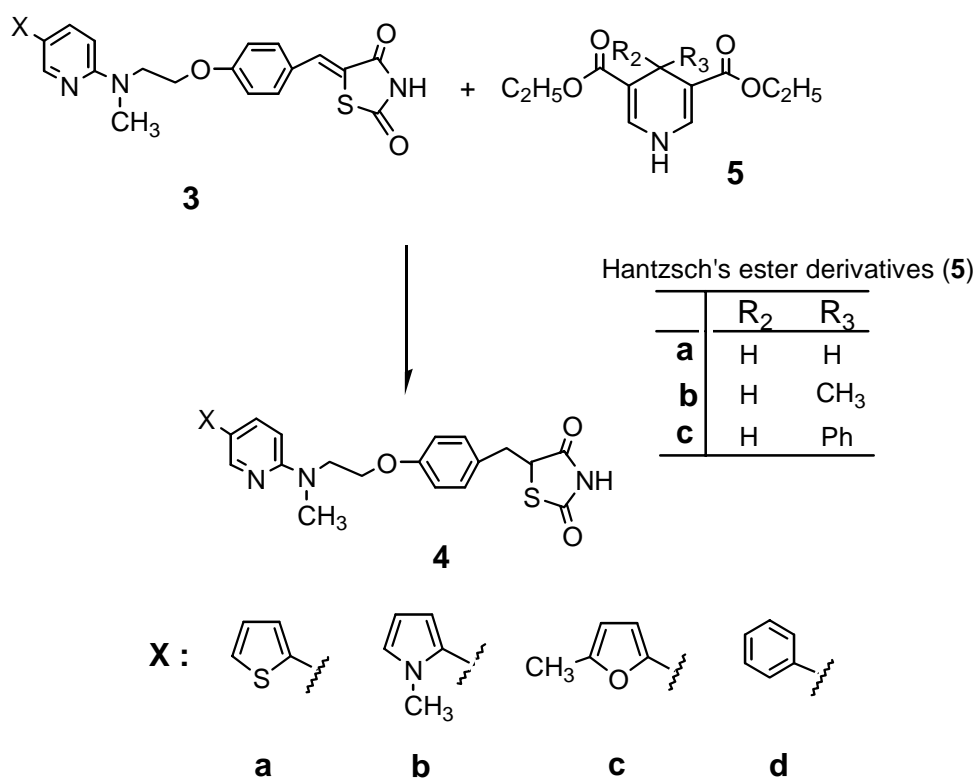
Table 3. Reduction of benzylidene derivatives (**3a-d**) with various Hantzsch's esters (**5a-c**) in the presence of SiO₂ as an acid catalyst.

Entry	Substrate	Hantzsch's ester	Solvent	Reaction condition		Yield ^{a)} (%)
				Temp (°C)	Time	
1	3a	5a	toluene	reflux	24 h	89
2	3a	5b	toluene	reflux	72 h	ND ^{b)}
3	3a	5c	toluene	reflux	72 h	ND
4	3b	5b	toluene	reflux	4 day	ND
5	3b	5c	benzene	reflux	4 day	ND
6	3c	5b	toluene	reflux	4 day	ND
7	3c	5c	benzene	reflux	4 day	ND
8	3d	5b	toluene	reflux	48 h	ND
9	3d	5c	toluene	reflux	48 h	ND

a) All reactions were monitored by TLC and HPLC. b) Not detected.

In conclusion, we have developed a general method for the regioselective reduction of the benzylidene derivatives (**3a-d**) to the corresponding benzyl derivatives (**4a-d**) in a good yield using Hantzsch dihydropyridine ester (**5a**) with silica gel as an acid catalyst in a good yield. This reduction method is also suitable for substrates that cannot be applied to general hydrogenation or whose hydrogenation has been reported to be difficult.

The most remarkable point of the reaction is that the reduction is completely regioselective from α,β -unsaturated ketones to saturated ketones without any by-products.



Scheme 4

EXPERIMENTAL

All reactions were conducted under anhydrous condition in solvents dried over molecular sieves type 4Å under nitrogen atmosphere and performed using oven dried glassware. Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. IR spectra were recorded on a Bruker Vector 22 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker DPX 400 MHz instrument operating at 400 MHz for proton and 100 MHz for carbon NMR and were performed in DMSO-*d*₆ solution using tetramethylsilane as the internal reference and chemical shift (δ) is reported in ppm downfield from internal tetramethylsilane.

The coupling constants (*J*) is reported in Hz. MS spectra were recorded on a HP 5989B instrument. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh) according to the published procedure.¹⁷ TLC was performed on glass backed plates pre-coated with silica (0.2 mm, 60 F₂₅₄) and developed using standard visualizing agents UV fluorescence (254 and 365 nm), potassium permanganate and iodine.

General procedure :

5-[4-(2-[Methyl-[5-(1-methyl-1*H*-pyrrol-2-yl)pyridin-2-yl]amino]ethoxy)benzyl]thiazolidine-2,4-dione (4b): To a stirred suspension of **3b** (100 mg, 0.23 mmol) in toluene (15 mL) are added Hantzsch dihydropyridine (**5a**) (76 mg, 0.3 mmol) and activated silica gel 60 (100 mg, 230-400 mesh). The mixture was heated to reflux with azeotropic apparatus for removal of water for 24 h, and then the heated suspension was filtered. The filter cake was rinsed with ethyl acetate. The combined filtrate and rinse were evaporated to dryness. The evaporation residue was redissolved in ethyl acetate (50 mL) and washed with five portions of 1N HCl. The organic layer was dried over MgSO₄ and evaporated to obtain crude product. The resulting product was purified by recrystallization from methanol to yield 88 mg (90 %) of yellowish crystals, mp 162-164.5 °C. IR (KBr) ν_{\max} cm⁻¹ : 3431, 2924, 1748, 1688. ¹H NMR (DMSO-*d*₆) δ : 3.05 (m, 1H), 3.18 (s, 3H), 3.31 (m, 1H), 3.88 (s, 3H), 3.99 (m, 2H), 4.15 (m, 2H), 4.85 (m, 1H), 6.21 (m, 1H), 6.45 (m, 1H), 6.83 (s, 1H), 6.88 (m, 2H), 7.13 (m, 3H), 7.93 (m, 1H), 8.55 (s, 1H), 12.1 (br, 1H). ¹³C NMR (DMSO-*d*₆) δ : 33.7, 37.0, 38.2, 49.8, 53.8, 65.7, 66.2, 98.8, 107.4, 110.3, 115.1, 127.1, 127.4, 129.5, 131.2, 141.3, 146.7, 147.8, 158.2, 159.2, 172.5, 176.6. HR-MS, *m/z* (M⁺) C₂₃H₂₄N₄O₃S Requires, 436.5267; Found, 436.5261. *Anal.* Calcd for C₂₃H₂₄N₄O₃S: C, 63.28; H, 5.54; N, 12.83. Found: C, 62.99; H, 5.66; N, 12.94.

5-[4-{2-[Methyl-(5-thiophen-2-yl)pyridin-2-yl]amino]ethoxy}benzyl]thiazolidine-2,4-dione (4a) : Yield: 92 mg, 88 %, mp 165-166 °C (ethanol). IR (KBr) ν_{\max} cm⁻¹: 3426, 2944, 1744, 1692. ¹H NMR (DMSO-*d*₆) δ : 3.07 (m, 1H), 3.11 (s, 3H), 3.31 (m, 1H), 3.93 (m, 2H), 4.13 (m, 2H), 4.86 (m, 1H), 6.74 (d, *J* = 8.86 Hz, 1H), 6.88 (d, *J* = 8.61 Hz, 2H), 7.08 (m, 1H) 7.15 (d, *J* = 8.58 Hz, 2H), 7.33 (m, 1H), 7.42 (m, 1H), 7.77 (m, 1H), 8.4 (s, 1H), 12.1 (br, 1H). ¹³C NMR (DMSO-*d*₆) δ : 37.1, 39.0, 49.5, 53.8, 55.7, 60.6, 66.1, 106.7, 115.1, 116.2, 119.1, 122.5, 124.6, 129.1, 129.5, 130.9, 131.2, 132.9, 135.6, 141.9, 145.3, 158.3, 172.5, 176.5. HR-MS *m/z* (M⁺), C₂₂H₂₁N₃O₃S₂ Requires 439.5516 ; Found, 439.5511. *Anal.* Calcd for C₂₂H₂₁N₃O₃S₂: C, 60.11; H, 4.81; N, 9.58. Found: C, 60.18; H, 4.88; N, 9.58.

5-[4-(2-{Methyl-[5-[5-methylfuran-2-yl]pyridin-2-yl]amino}ethoxy)benzyl]thiazolidine-2,4-dione

(4c): Yield: 81 mg, 85 %, mp 181-183 °C (2-propanol-dichloromethane). IR (KBr) ν_{\max} cm^{-1} : 3426, 2921, 1744, 1695. ^1H NMR (DMSO- d_6) δ : 2.31 (s, 3H), 3.05 (m, 1H), 3.11 (s, 3H), 3.30 (m, 1H), 3.91 (m, 2H), 4.13 (m, 2H), 4.85 (m, 1H), 6.13 (m, 1H), 6.56 (d, $J = 3.13$ Hz, 1H), 6.71 (m, 1H), 6.88 (m, 2H), 7.12 (m, 2H), 7.74 (m, 1H), 8.38 (s, 1H). ^{13}C NMR (DMSO- d_6) δ : 37.1, 37.9, 49.4, 53.8, 55.7, 66.1, 104.7, 106.5, 108.6, 115.1, 116.2, 116.3, 129.5, 131.2, 132.9, 133.4, 143.5, 150.9, 151.2, 157.7, 158.3, 172.5, 176.5. HR-MS m/z (M^+), $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_4\text{S}$ Requires 437.5115 ; Found, 437.5127: *Anal.* Calcd for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_4\text{S}$: C, 63.14; H, 5.29; N, 9.60. Found: C, 63.25; H, 5.31; N, 9.63.

5-[4-(2-{Methyl-[5-pyridinphenyl-2-yl]amino}ethoxy)benzyl]thiazolidine-2,4-dione (4d) : Yield:

92 mg, 89 %, mp: 172-173 °C (methanol-dichloromethane). IR (KBr) ν_{\max} cm^{-1} : 3420, 2920, 1742, 1694. ^1H NMR (DMSO- d_6) δ : 3.05 (m, 1H), 3.01 (s, 3H), 3.27 (m, 1H), 3.94 (m, 2H), 4.14 (m, 2H), 4.84 (m, 1H), 6.76 (d, $J = 8.88$ Hz, 1H), 6.92 (d, $J = 8.45$ Hz, 2H), 7.15 (d, $J = 8.44$ Hz, 2H), 7.28 (m, 1H), 7.41 (m, 2H), 7.61 (m, 2H), 7.82 (m, 1H), 8.43 (s, 1H). ^{13}C NMR (DMSO- d_6) δ : 37.1, 38.0, 49.4, 53.9, 66.2, 106.6, 115.1, 124.4, 126.3, 127.2, 129.5, 129.7, 131.2, 136.4, 138.6, 146.3, 158.2, 158.3, 172.6, 176.7. HR-MS m/z (M^+), $\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}_3\text{S}$: Requires 433.5229 ; Found, 433.5249. *Anal.* Calcd for $\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}_3\text{S}$: C, 66.49; H, 5.34; N, 9.69. Found: C, 66.51; H, 5.39; N, 9.71.

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