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An Efficient Synthesis of New Pyrazolines and Isoxazolines Bearing Thiazolyl and Etheral Pharmacophores

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A convenient synthetic route has been developed to synthesize 5-(4-((2-phenylthiazol-4-yl) methoxy)phenyl)-3-(4-sustituted phenyl)pyrazolines (**5a-f**) and 5-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-3-(4-substituted phenyl)isoxazolines (**6a-f**) starting from 2-phenyl-4-chloromethylthiazole (**1**). The chloromethylthiazole (**1**) was first condensed with 4-hydroxy benzaldehyde (**2**) for obtaining 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde (**3**). Claisen-Smidth condensation of 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde (**3**) and acetophenones has been carried in alkaline alcohol and obtained 3-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-1-(4-substituted phenyl)prop-2-en-1-ones (**4a-f**). The cyclocondensation of 2-propen-1-ones has been first time carried separately with hydrazine hydrate and hydroxylamine hydrochloride in aqueous micellar tetradecyltrimethylammonium bromide (TTAB) medium for getting the titled heterocycles with good to excellent yields.

Key Words : Surfactants, Pyrazoline, Isoxazolines, Aqueous micellar tetradecyltrimethylammonium bromide (TTAB)

Introduction

Derivatives of pyrazolines and isoxazolines have played crucial role in the history of heterocyclic chemistry and have been used extensively as an important pharmacophores and synthones in the field of organic chemistry.[1] Many classes of chemotherapeutic agents containing pyrazolines and isoxazolines are in clinical use as antibacterial,[2] anticancer,[3] antiproliferative,[4] antifungal,[5] antiamoebic[6] and anti-inflammatory[7] agents. They also exhibit analgesic,[8] antimicrobial,[9] antitumor,[10] and antidepressant[11] activities.

Pyrazoline and isoxazoline scaffolds have been also found in various antidiabetics.[12] Ethereal linkage is necessary component in the molecular framework of various antidiabetic agents[13] like rosiglitazone and pioglitazone.

The thiazole ring unit is a common structural feature in various bioactive molecules. This heterocyclic system has been employed in the preparation of different important drugs required for the treatment of inflammation, bacterial infections and hypertension.[14] When the thiazole nucleus is coupled to other biologically active heterocycles, the resulting molecules have displayed an increased spectrum of biological activities.[15]

In view of pharmacological importance of pyrazolines, isoxazolines, thiazoles and ethereal linkages, here it was thought worthwhile to construct some new pyrazolines and isoxazolines having thiazolyl and ethereal pharmacophores in a molecular framework with the hope to obtain the compounds with intensified activities.

A literature survey reveals that pyrazolines and isoxazolines have been usually prepared by the separate cyclocondensation of α,β-unsaturated aldehydes and ketones with bidentate nucleophiles, hydrazines and hydroxylamines, respectively. Several methods have been developed to enhance the rate of the cyclocondensation leading to the heterocycles, which includes use of sodium acetate-acetic acid aqueous solution and ultrasound irradiation,[16] microwave assisted synthesis,[17] K_2CO_3 mediated microwave irradiation[18] and $H_3PW_{12}O_{40}$ as heterogeneous catalyst.[19] However these reported methods still suffered from one or more limitations such as, use of hazardous/flammable solvents, long reaction time, and tedious workup procedures. Therefore, the new, concise and efficient synthetic routes for these important classes of compounds using easily accessible reagents and catalysts are very much needed.

With an increasing environmental consciousness in chemical research and industry, more attention is found to be directed to design and development of sustainable, clean chemical procedures.[20] To minimize use of expensive, toxic, flammable, not recyclable organic solvents in chemical processes, water is becoming safe alternative chemical medium.[21] Water is cheap, abundant, non-toxic, non-flammable and relatively green solvent.[22] On the other hand, water with its chemical and physical properties imposes selectivity and reactivity in reactions, conducted in aqueous media which cannot be gained using organic solvents.[23] However, dissolving many organic compounds in water is difficult and for this reason, most of the reactions cannot proceed easily in aqueous media.[24] One way to improve the solubility of substrates in water is the incorporation of surface active agents (surfactants) in aqueous media that has been found to enhance the rate of water mediated reactions through the generated micelles or vesicular cavities and also acting as phase transfer catalyst.[25] The use of micellar and vesicle

forming surfactants as catalysts in water has been well explored for a number of different synthetic transformations.[26]

Considering the significance of surfactants and in continuation of our earlier interests in providing new and convenient synthetic protocols for the construction of bioactive heterocycles,[27] herein we wish to report a convenient synthetic route for pyrazolines and isoxazolines bearing thiazolyl methoxy phenyl pharmacophore using aqueous tetradecyltrimethylammonium bromide (TTAB) as medium.

Results and Discussion

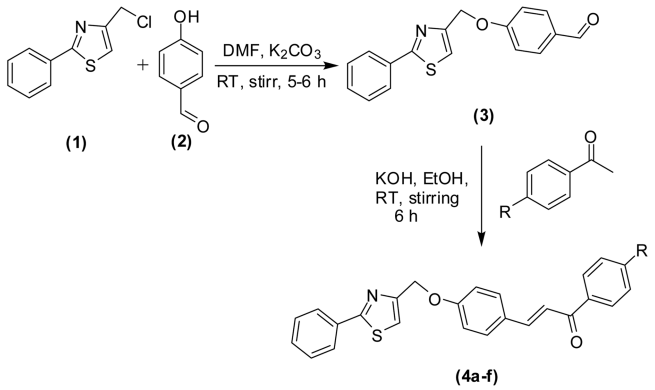
In the present work the syntheses of thiazolyl methoxy phenyl pyrazolines and isoxazolines have been carried using 3-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-1-(4-substituted phenyl)prop-2-en-1-ones (**4a-f**) (Scheme 2). The required precursors 2-propen-1-ones (**4a-f**) were freshly prepared by following the reaction sequences presented in Scheme 1, starting from known reactant chloromethylthiazole (**1**).[28] Chloromethylthiazole on alkylation with 4-hydroxybenzyldehyde in the presence of K_2CO_3 in *N,N*-dimethylformamide at room temperature gave the required precursor 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde (**3**) in quantitative yield (97%). The Claisen-Smith condensation of the aldehyde (**3**) and various acetophenones when carried in ethanol in presence of KOH at room temperature gave 3-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-1-(4-fluorophenyl)-prop-2-en-1-ones (**4a-f**) with good to excellent yields.

Considering the need of safer medium like water and importance of surfactants, we separately attempted the cyclocondensation of 2-propen-1-ones (**4a-f**) with hydrazine hydrate and hydroxylamine hydrochloride using aqueous emulsion of cationic, CTAB, TTAB and anionic, SDS surfactants. It was observed that the condensation has been found to run successfully and gave the titled pyrazolines and isoxazolines in aqueous emulsion of the surfactants at 80 °C (Table 1).

In order to establish the best experimental conditions, we have considered the reaction of 3-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-1-(4-fluorophenyl)prop-2-en-1-one (**4d**) and hydrazine hydrate in water as a standard model reaction (Scheme 2). In the initial optimization studies, the synthesis of pyrazolines was carried using 3-(4-((2-phenylthiazol-4-yl)methoxy) phenyl)-1-(4-fluorophenyl)prop-2-en-1-one (**4d**) with hydrazine hydrate in ethanol under reflux for more than 2 h and obtained less than 50% yield of the titled compounds (**5d**). Therefore we have carried the synthesis of pyrazolines in aqueous emulsion of surfactants.

During this investigation, it was found that aqueous micellar cationic surfactants, tetradecyltrimethylammonium bromide (TTAB) and cetyltrimethylammonium bromide (CTAB) were served as best media than the other aqueous micellar cationic methyltriphenylphosphonium bromide (MTPPB) and anionic surfactant like sodium dodecylsulfate (SDS). When the aq. micellar medium of MTPPB and SDS was used the yields of the desired products were found to be low *i.e.* 59% and 52%, respectively (Table 1, entries-1, 2). In contrast cationic surfactant CTAB was found to accelerate the model reaction resulting in to high yield, 87% (Table 1, entry-6). From this it was concluded that cationic surfactants, particularly with quaternary ammonium bromides, are far superior to other surfactants for carrying the model reaction.

Encouraged by these results, we then investigated the role of some more cationic surfactants, particularly quaternary ammonium bromides. For this purpose, we used tetraethylammonium bromide (TEAB), tetrabutylammonium bromide (TBAB), and TTAB in the model reaction. It was noted that the product yields were increased with increasing alkyl chain



Scheme 1

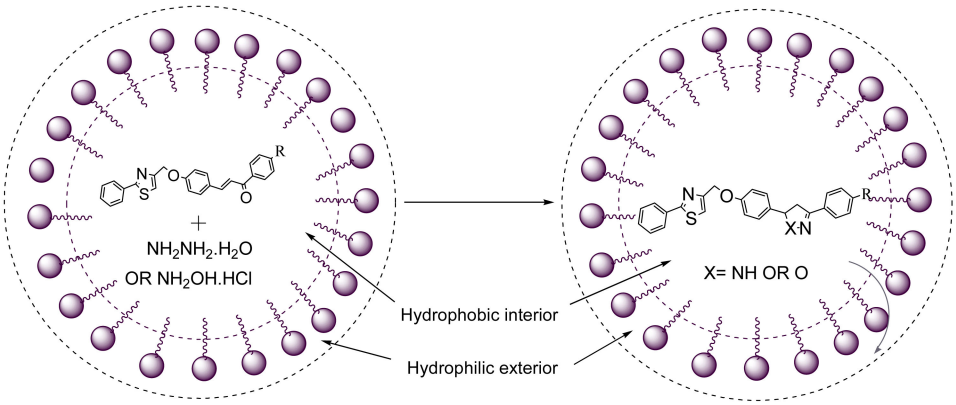
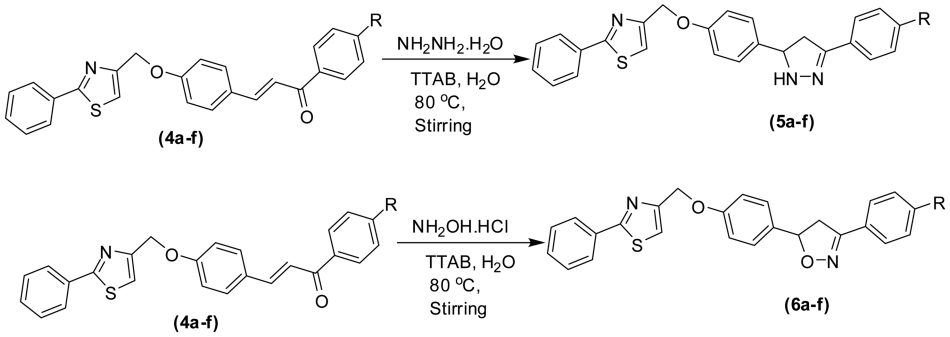


Figure 1. Schematic diagram representing the role of TTAB.



Scheme 2

Table 1. Screening of surfactant for the synthesis of 5-(4-((2-phenylthiazol-4-yl)methoxy) phenyl)-3-(4-fluorophenyl)pyrazoline (**5d**)[a]

Entry	Surfactant	Yield (%)[b]
1	SDS	52
2	MTPPB	59
3	TEAB	57
4	TBAB	69
5	TTAB (5, 10, **15**, 20 mol %)	70, 82, **89**, 90
6	CTAB	87

[a]Reaction conditions: **4d** (2 mmol), hydrazine hydrate (4 mmol), surfactant in water (10 mL), at 80 °C. [b]Isolated yields. [c]In absence of surfactant

length of the surfactant up to C14. Longer than C14 alkyl chains led to a decrease in product yields. TEAB and TBAB gave 57% and 69% yield (Table 1, entries-3, 4), respectively. However, TTAB gave the product in excellent yield of 88% (Table 1, entry-5) within 30 min of reaction time and proved to be better medium and catalyst than CTAB. The success of TTAB as an efficient catalyst could be related to the number of carbon atoms in its hydrophobic chain reaching to saturation. In absence of surfactants the cyclocondensation/ model reaction could not be run in water even at reflux.

We next turned our attention to optimize the reaction temperature. The reaction was carried out at different temperatures, ranging from room temperature to 100 °C. We found that at room temperature the rate of reaction was too slow; yield of the product was improved when it was run at 60 °C to 80 °C. When the reaction was carried at above 80 °C there was no improvement in the product yield. Therefore, the most suitable/optimized reaction temperature was found to be 80 °C.

The optimization of amount of the surfactant, required for the transformation has also been attempted. It was noted that the yield of product was found to be increased (70-90%) with increasing concentration of the surfactant (5-20 mol %) in its aqueous emulsion (Table 1, entry-5). From the results it was clear that the optimized concentration of surfactant required is 15 mol %.

After optimization of cyclocondensation conditions, to expand the scope of the reaction the other 2-propen-1-ones (**4a-f**) have also been separately cyclocondensed with hydrazine hydrate under optimized conditions to give pyrazolines (**5a-f**) in good to excellent yields.

Table 2. Physical data of 2-propen-1-ones (**4a-f**), pyrazolines (**5a-f**) and isoxazolines (**6a-f**)

Entry	Compound	R	Yield (%)a	Time	Melting Point
1	**4a**	-H	95	6 h	120-121 °C
2	**4b**	$-CH_3$	92	6 h	115-117 °C
3	**4c**	$-OCH_3$	86	6 h	76-78 °C
4	**4d**	-F	90	6 h	148-150 °C
5	**4e**	-Br	82	6 h	185-187 °C
6	**4f**	$-NO_2$	91	6 h	190-191 °C
7	**5a**	-H	95	30 min	136-138 °C
8	**5b**	$-CH_3$	90	30 min	214-215 °C
9	**5c**	$-OCH_3$	92	30 min	82-84 °C
10	**5d**	-F	89	30 min	126-128 °C
11	**5e**	-Br	87	30 min	118-120 °C
12	**5f**	$-NO_2$	85	30 min	168-170 °C
13	**6a**	-H	77	3 h	123-124 °C
14	**6b**	$-CH_3$	72	3 h	176-178 °C
15	**6c**	$-OCH_3$	75	3 h	138-140 °C
16	**6d**	-F	78	3 h	150-152 °C
17	**6e**	-Br	68	3 h	98-100 °C
18	**6f**	$-NO_2$	60	3 h	140-142 °C

[a]Isolated yield

In another attempt, we have noticed that hydroxyl amine hydrochloride when condensed with 2-propen-1-ones (**4a-f**) in the presence of stoichiometric KOH in aqueous emulsion of TTAB under the above optimized conditions gave the titled isoxazolines (**6a-f**) in good yields.

The role of aqueous emulsion of surfactant in rate acceleration of organic transformations is well established.[29] The rate acceleration and yield enhancement in these cyclocondensations leading to the titled heterocycles could be accounted for solubilisation of 2-propen-1-ones in micellar cavities and the reagents, hydrazine hydrate and hydroxylamine hydrochloride in hydrophobic interface of micelles, in water layer generated because of aqueous emulsion of the surfactant. Localized concentrations of the reactants in micellar cavity would be responsible for accelerating the rate of cyclocondensations. The initial cyclocondensed products would have rapidly proceeded towards

elimination of water resulting into the desired heterocycles, pyrazolines and isoxazolines.

Summary

In summary, we have developed a simple, mild and clean synthetic protocol for the synthesis of new pyrazolines and isoxazolines. The use of aqueous TTAB for cyclocondensation leading to new pyrazolines and isoxazolines has been attempted for the first time. Aqueous TTAB not only shortens reaction time, but also provides simple environmentally friendly workup procedure. The outcome of these reactions demonstrates that reactions, being historically performed in organic solvents, can have facile and more convenient aqueous counterparts.

Experimental

General. The chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance 400 spectrometer operating at 400 MHz, 200 MHz and 75 MHz using DMSO-d_6 or $CDCl_3$ solvent and tetramethylsilane (TMS) as the internal standard and chemical shift in δ ppm. Mass spectra were recorded on a Sciex, Model; API 3000 LCMS/MS Instrument. The purity of each compound was checked by TLC using silica-gel, $60F_{254}$ aluminum sheets as adsorbent and visualization was accomplished by iodine/ultraviolet light.

Synthesis of 4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde (3). A mixture of chloromethylthiazole **1** (10 mmol), potassium carbonate (20 mmol), and 4-hydroxy benzaldehyde **2** (10 mmol) was added to *N,N*-dimethylformamide (20-30 mL). The reaction mixture was then stirred for 5-6 h. After completion of the reaction, the reaction mixture was poured on crushed ice. Thus obtained solid was filtered, washed with water, and crystallized from ethanol. Yield: 97%, mp 87 °C.

General Procedure for the Synthesis of 3-(4-((2-Phenylthiazol-4-yl)methoxy)phenyl)-1-(4-sustituted phenyl) prop-2-en-1-ones (4a-f). To the stirred alcoholic solution of 4-substituted acetophenones (10 mmol in 20 mL ethanol), potassium hydroxide (15 mmol) and 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde (10 mmol) were added in portions and the resulting mixture was further stirred at room temperature. The progress of the reaction was monitored by TLC using ethyl acetate: hexane as a solvent system. After 6 h of stirring the reaction mass was poured on crushed ice and neutralized with hydrochloric acid. Thus obtained solid was filtered, dried and crystallized from ethanol.

General Procedure for the Synthesis of 5-(4-((2-Phenylthiazol-4-yl)methoxy)phenyl)-3-(4-sustituted phenyl)-pyrazolines (5a-f). A mixture of 3-(4-((2-phenylthiazol-4-yl) methoxy) phenyl)-1-(4-sustituted phenyl) prop-2-en-1-ones (2 mmol) and hydrazine hydrate (4 mmol) was added to aqueous TTAB (15 mol % in 10 mL water). The reaction mixture was allowed to stir vigorously at 80 °C. Progress of the reaction was monitored by TLC (ethyl acetate: hexane). After 30 min of stirring, the solid obtained was seperated by filtration and washed successively with hot water. The crude product was crystallized from ethanol to get the pure products. Yields and melting points of the products are recorded in Table 2.

General Procedure for the Synthesis of 5-(4-((2-Phenylthiazol-4-yl)methoxy)phenyl)-3-(4-substituted phenyl) isoxazolines (6a-f). A mixture of 3-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-1-(4-sustituted phenyl) prop-2-en-1-ones **4a-f** (2 mmol), hydroxylamine hydrochloride (2 mmol) and KOH (2 mmol) was added to aqueous TTAB (15 mol % in 10 mL water). The reaction mixture was allowed to stir vigorously at 80 °C. Progress of the reaction was monitored by TLC (ethyl acetate: hexane). After 3 h of stirring, the solid obtained was separated by filtration and washed successively with hot water. The crude products were crystallized from ethanol to afford the pure products. Yields and melting points of the products are recorded in Table 2.

Spectral and Elemental Analyses of the Representative Compounds.

4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde (3): MS, *m/z* (% intensity): 295 (M^+ 100), ^{1}H NMR ($CDCl_3$) δ 5.33 (s, 2H, CH_2), 7.14-7.42 (m, 6H, overlap, Ar-H, thiazolyl-H), 7.42-7.82 (m, 4H, Ar-H) and 9.89 (s, 1H, -CHO).

3-(4-((2-Phenylthiazol-4-yl)methoxy)phenyl)-1-phenyl) prop-2-en-1-one (4a): MS (*m/z*) (% intensity): 398.1 (M^+, 100) and 173.9 (3). ^{1}H NMR ($CDCl_3$) δ 5.32 (s, 2H, CH_2), 7.05-7.15 (d, 2H, olefinic), 7.24-7.44 (m, 11H, Ar-H and thiazolyl-H) and 7.95-8.05 (m, 4H, Ar-H).

5-(4-((2-Phenylthiazol-4-yl)methoxy)phenyl)-3-phenyl)-pyrazoline (5a): MS, (*m/z*) (% intensity): 411 (M^+ 100). ^{1}H NMR (DMSO) δ 3.00-3.06 (dd, 1H, J = 7.8 and 2.8 Hz), 3.40-3.5 (dd, 1H, J = 8.0 and 2.8 Hz), 4.81-4.90 (t, 1H, J = 8.0 Hz), 5.31 (s, 2H, CH_2), 7.10-7.52 (m, 13H, Ar-H and thiazolyl-H) and 7.71-7.73 (d, 2H, Ar-H). ^{13}C NMR (DMSO) δ 41.23, 63.73, 66.43, 115.07, 115.94, 125.94, 126.54, 127.08, 127.53, 128.12, 128.93, 130.13, 132.81, 133.39, 135.40, 151.29, 153.36, 158.01 and 168.65. Anal. Calcd for ($C_{25}H_{21}N_3OS$) C, 72.97; H, 5.14; N, 10.21; S, 7.79 found C, 72.99; H, 5.12; N, 10.25 and S, 7.75.

5-(4-((2-Phenylthiazol-4-yl)methoxy)phenyl)-3-(4-fluro-phenyl)-pyrazoline (5d): MS (*m/z*) (% intensity): 430 (M^+ 100). ^{1}H NMR (DMSO) δ 2.99-3.01 (dd, 1H, J = 7.9 and 2.7 Hz), 3.33-3.40 (dd, 1H, J = 8.1 and 2.8 Hz), 4.83-4.88 (t, 1H, J = 8.0 Hz), 5.23 (s, 2H, CH_2), 6.95-7.26 (m, 13H, Ar-H and thiazolyl-H) and 7.60-7.61(d, 2H, Ar-H).

5-(4-((2-Phenylthiazol-4-yl)methoxy)phenyl)-3-(4-bromo-phenyl)-pyrazoline (5e): MS (*m/z*) (% intensity): 491 (M^+ 100), 489 (78), 477 (15.53), 357 (15.5), 338 (3), 296 (3) and 241 (2). ^{1}H NMR (DMSO) δ 2.97-3.01 (dd, 1H, J = 7.8 and 2.8 Hz), 3.35-3.40 (dd, 1H, J = 8.0 and 2.7 Hz), 4.85-4.87 (t, 1H, J = 8.1 Hz), 5.25 (s, 2H, CH_2), 7.28-7.93 (m, 14H and Ar-H, thiazolyl-H).

5-(4-((2-Phenylthiazol-4-yl)methoxy)phenyl)-3-(4-nitro-phenyl)-pyrazoline (5f): MS (*m/z*) (% intensity): 457 (M^+

100), 427 (4.3), 356.9 (6) and 338 (4). ^{1}H NMR (DMSO) δ 3.03-3.07 (dd, 1H, *J* = 7.9 and 2.8 Hz), 3.43-3.47 (dd, 1H, *J* = 8.0 and 2.7 Hz), 4.95-4.98 (t, 1H, *J* = 8.0 Hz), 5.25 (s, 2H, CH_2), 7.27-7.44 (m, 8H, Ar-H and thiazolyl-H), 7.76-7.78 (d, 2H, Ar-H), and 8.21-8.23 (m, 4H, Ar-H). ^{13}C NMR (DMSO) δ 40.65, 64.38, 66.45, 115.12, 115.22, 115.99, 123.87, 126.54, 127.48, 128.95, 130.18, 133.37, 134.59, 148.16, 153.27, 158.25 and 168.70; Anal. Calcd for ($C_{25}H_{20}N_4O_3S$) C, 65.77; H, 4.42; N, 12.27; S, 7.02 found C, 65.80; H, 4.41; N, 12.55 and S, 7.00.

5-(4-((2-Phenylthiazol-4-yl)methoxy)phenyl)-3-phenyl) isoxazoline (6a): MS (*m/z*) (% intensity): 413 (M^+ 100) and 412 (6). ^{1}H NMR (DMSO) δ 3.81-3.87 (dd, 1H, *J* = 7.8 and 2.9 Hz), 4.20-4.23 (dd, 1H, *J* = 8.0 and 2.8 Hz), 5.12 (s, 2H, CH_2), 5.6 (t, 1H, *J* = 8.0 Hz), 6.90-6.95 (m, 15H, Ar-H and thiazolyl-H) and 7.3-8.0 (d, 2H, Ar-H). ^{13}C NMR (DMSO) δ 40.14, 65.43, 78.74, 114.61, 117.36, 125.91, 126.31, 127.56, 128.71, 129.86, 130.21, 131.42, 132.81, 133.35, 147.22, 152.53, 158.77 and 167.39. Anal. Calcd for ($C_{25}H_{20}N_2O_2S$) C, 72.79; H, 4.89; N, 6.79; S, 7.77 found C, 72.88; H, 4.87; N, 6.79 and S, 7.65.

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