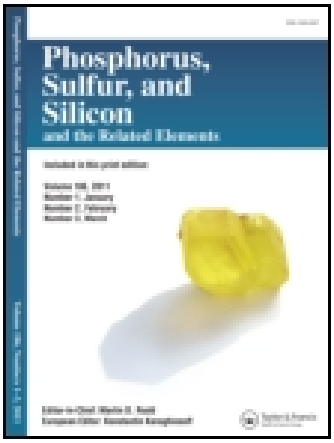

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Activated Fly Ash Catalyzing the Synthesis of Novel Potent 4-Thiazolidinones of 4-Amino Antipyrine Anils Using CEM Discover Microwave Methodology and Their Virtual Screening

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ACTIVATED FLY ASH CATALYZING THE SYNTHESIS OF NOVEL POTENT 4-THIAZOLIDINONES OF 4-AMINO ANTIPYRINE ANILS USING CEM DISCOVER MICROWAVE METHODOLOGY AND THEIR VIRTUAL SCREENING

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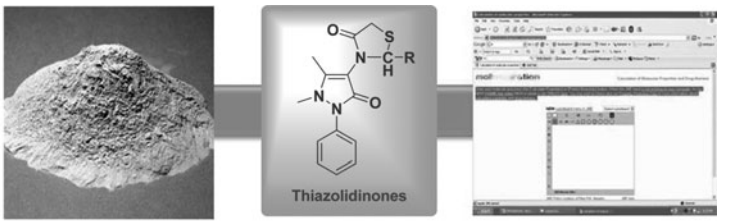
GRAPHICAL ABSTRACT



Fly ash as heterogeneous catalyst. Model of final product synthesized under microwave radiation. Virtual screening

Abstract *Fly ash, an industrial waste, has been used as an efficient and cost-effective activating catalyst for the synthesis of new potent thiazolidinones* ***(4a–n)****, starting from imine* ***(3a–n)*** *and thioacetic acid. The reactions were performed under CEM Discover microwave irradiation in solvent-free conditions. This reaction is scalable to a multigram scale and the methodology has resulted in an efficient synthesis. Herein, a benign, environment friendly, efficient, and extremely fast procedure for the synthesis of thiazolidinones have been demonstrated. The produced thiazolidinone molecules were characterized on the basis of elemental analysis, infrared (IR), mass spectral, and* ^{1}*H NMR spectral data. The synthesized moieties were screened virtually and discussed for their possible biological activity.*

Supplementary materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental files:* Additional text and tables.

Keywords Activated fly ash; thiazolidinones; solvent-free; virtual screening; biological activity

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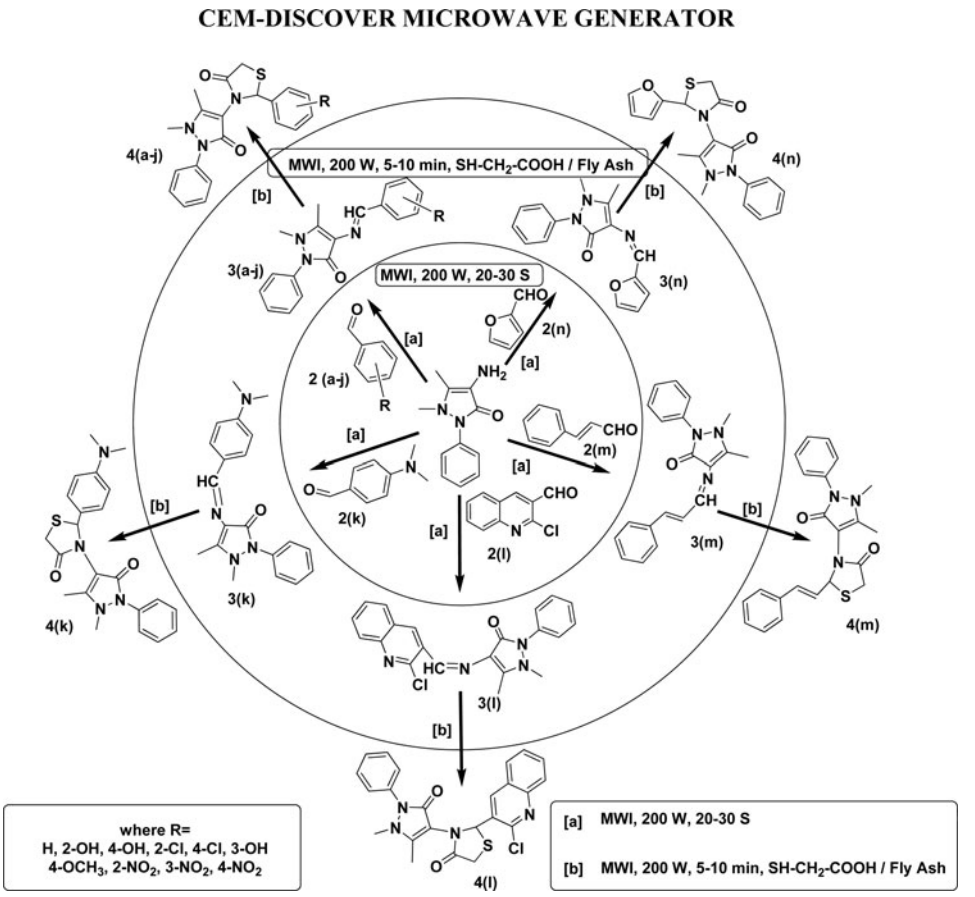
INTRODUCTION

The green chemistry principles include the development of safer chemicals, safer solvents, solvent-free synthetic methods, "atom economy," and inherent safer reaction conditions for accident prevention. Traditionally, thiazolidinones are heterocyclic compounds well known for their broad spectrum of biological activities such as antibacterial, antifungal, antitubercular, anthelmintic, anti-inflammatory, anti-thyroid, local anesthetic, COX-1 inhibitive, antiproliferative, antihistaminic, anti-HIV activities and for monoamine oxidase inhibition.[1–6] In recent years, several new methods for the preparation of thiazolidinone derivatives and reactions have been reported in the literature, using conventional homogeneous acid catalysts such as H_2SO_4, HF, $AlCl_3$, $FeCl_3$ etc.[7] Previously, Wang[8] and Desai and co-workers reported the facile microwave-enhanced synthesis of thiazolidinones using $ZnCl_2$ in dimethylformamide (DMF).[9] However, these reactions suffered from a few shortcomings, such as lengthy reaction times (2–8 h), the use of high-boiling-point solvents [DMF, THF (tetrahydrofuran), dioxane], low yields (50–60%), and the use of reactants with high toxicity, which bound their use for the synthesis of complex molecules. A combination of the mineral-supported and microwave irradiation has been used to carry out a wide range of reactions under solvent-free conditions.[10] Synthesis of organic compounds under solvent-free conditions, especially adopted to microwave irradiation, leads to increased safety and environmental facets.[11]

For this purpose, heterogeneous catalysis plays an elementary role, chiefly due to its economic and environmental advantages (i.e. minimum execution time, low corrosion, waste minimization, recycling of the catalyst, easy transport, and clearance of catalysts).[12] Of course, the combination of heterogeneous catalysis with solvent-free conditions under microwave irradiation represents a suitable way toward the so-called model synthesis.[13] Microwave irradiation facilitates the polarization of the molecule under irradiation, causing a rapid reaction to occur, which increases the yield and the so-called atom economy. The discussed drawbacks were eliminated when the reactions were carried out in the presence of zeolite as an activator under microwave irradiation, which has already been reported.[14] Thus, owing to our interest to use something less costly in comparison with zeolites, we attempted to use activated fly ash as an inexpensive activator for the synthesis of 4-thiazolidinones **4 (a–n)** by the reaction of imine **3 (a–n)** with thioglycolic acid under microwave irradiation to catalyze reactions that have industrial, pharmacological, and therapeutic importance.. Making use of waste and finding something valuable out of it almost makes the synthesis a cost-reductive process. The high synthetic utility and pharmacological importance of thiazolidinone family have prompted us to realize a virtual pharmacological study of the antibacterial activity of the compounds **4 (a–n)** (Scheme 1). Herein, we performed an investigation of compounds **4 (a–n)** because they represent an attractive model for a theoretical and experimental study of the pharmacophore and their medical applications because of the large variability and combination in their substituents. The main interesting tasks of this work are: (i) developing a robust synthetic protocol for the heterocycles, (ii) interpreting the calculated/predicted results for designing of new compounds, (iii) performing pharmacophore modeling based on structures to support the lead optimization process, and (iv) finding the right molecule for the right target.

RESULTS AND DISCUSSION

The emerging interest for the use of solid inorganic acids in organic synthesis in comparison with liquid acids is advantageous due to the simplicity in handling and



Scheme 1 Schematic representation of fly ash-catalyzed microwave production of 4-thiazolidinones.

environmental protection.[15,16] The use of fly ash also reveals some features such as reduction in the thermal degradation, better selectivity, and easy work-up after reaction. The results when compared with known classical laboratory methods show a tremendous decline in the reaction time, from hours to minutes. The idea behind the methodology to use fly ash as an activator arose due to the silica contents of the fly ash and its surface adsorption properties.

Fly ash was collected from BILT Paper Mills, Ashti, Maharashtra, India. The particle size and its composition were recorded accordingly from an analysis by the company. It can adsorb all kinds of molecules smaller than its size.[17] The specific gravity and specific surface area of fly ash were 1.81 and 131 m^2/g, respectively. The chemical compositions of fly ash used for catalysis are reported in Table 1. The chemical compositions vary depending upon the type of coal used. It is rather inconsistent to get fly ash with same amount of ingredients all the time. We just checked for the content of silica and alumina in the provided fly ash.

The high silica content yields high chemical resistance. It is stable above 500–600°C. It can absorb various small molecules such as water, hydrochloric acid, ammonia, methanol, and hydrogen sulfide. It has several advantages, including being environmentally friendly, nontoxic, inexpensive, recoverable, and reusable. Therefore, we decided to explore its

Table 1 Composition of fly ash used in the present study

Constituents	Fly ash (%)	Variation depending upon type of coal used
SiO_2	68.23	70.5 ± 9.6
Fe_2O_3	2.50	7.5 ± 4.3
Al_2O_3	15.53	22.8 ± 5.4
CaO	4.12	4.9 ± 2.9
MgO	0.78	1.3 ± 0.7

suitability in the heterocyclization reaction. Our synthetic approach is very simple and clear. First, Schiff's bases, 1, 2-dihydro-2, 3-dimethyl-4-(4-oxo-2-substituted phenylthiazolidin-3-yl)-1-phenylpyrazol-5-one, were prepared from the reaction of 4-amino-1,2-dihydro-2,3-dimethyl-1-phenylpyrazol-5-one and different aromatic aldehydes using a reported method by the MORE technique.[18,19]. Finally, imines on heterocyclization with mercaptoacetic acid using activated fly ash under microwave irradiation afforded 4-thiazolidinones, as shown in Scheme 1.

Initially, we investigated the microwave-assisted synthesis of 4-(2-hydroxybenzylideneamino)-1,2-dihydro-2,3-dimethyl-1-phenylpyrazol-5-one (imine) by taking salicyaldehyde and 4-amino antipyrine in a 1:1 molar ratio and irradiated the reaction mixture at different temperatures 100, 120, 140, 160°C for a time period ranging from 10 to 40 sec (tabulated in Table 2). The progress of the reaction was monitored by thin-layer chromatography (TLC) using the ethyl acetate:petroleum ether (EtOAc:Pet. ether) (2:8) eluting system, and the completion of the reaction was observed when the reaction mixture was irradiated at 140°C for 20 sec, giving the highest yield.

The resultant imine was then heterocyclized with mercaptoacetic acid in 1:1 proportion with a varying amount of activated fly ash (0.25, 0.5, and 0.75 g) for a period of 5–10 min at different temperatures 160, 170, 180°C. The progress of the reaction was monitered by TLC using the EtOAc:Pet. ether (3:7) eluting system. Best results were obtained with 0.50 g of activated fly ash, irradiation time of 8 min, at 170°C. An optimization chart with fixed amounts of activated fly ash, time, and yield are given in Table 3. This method is very easy and can be used for synthesis of different thiazolidinones **4 (a–n)**, depending on different substituted groups. Structural features of the synthesized azomethine and thiazolidinone were obtained from FTIR, elemental analysis, ^{1}H NMR, ^{13}C NMR(thiazolidinone), and mass spectral studies and they confirmed their structures.

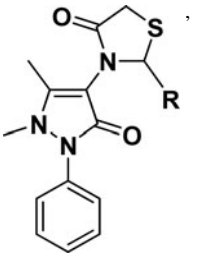
In the infrared (IR) spectra of the 4-amino-1, 2-dihydro-2, 3-dimethyl-1-phenylpyrazol-5-one, the characteristic absorptions around 1620 cm^{-1} and 1750 cm^{-1} are

Table 2 Optimization of microwave-mediated synthesis of imines

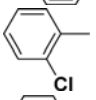
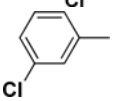
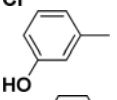
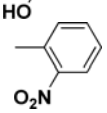
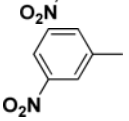
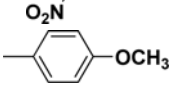
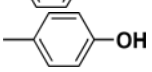
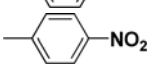
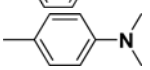
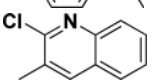
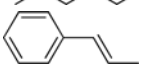
Entry	Temperature (°C)	Time (sec)				Reaction monitoring by TLC [EtOAc: Pet.Ether (2:8)]				% Yield
1	100	10	20	30	40	RNC	RNC	RNC	RC	92
2	120	10	20	30	40	RNC	RNC	RNC	RC	92
3	140	10	20	30	40	RNC	RC	—	—	95
4	160	10	20	30	40	RNC	RC	—	—	95

RNC, reaction not completed; RC, reaction completed

Table 3 Optimization chart for activated fly ash-catalyzed solvent-free synthesis of 4-thiazolidinones under microwave radiation.



General representation of compounds **4(a–n)**

Compound	R	Activated fly ash (g)	Temperature (°C)	Time (min)	Isolated yield (%)
4a		0.50	170	08	90
4b		0.50	170	10	93
4c		0.50	170	07	95
4d		0.50	170	09	95
4e		0.50	170	08	90
4f		0.50	170	08	89
4g		0.50	170	09	92
4h		0.50	170	10	85
4i		0.50	170	10	84
4j		0.50	170	15	85
4k		0.50	170	09	90
4l		0.50	170	10	85
4m		0.50	170	07	91
4n		0.50	170	09	90

assigned to (–C=N) azomethine linkages and (–C=O) carbonyl functionality, respectively, to be present in the imines. The stretching frequencies for –C=N were absent in the IR spectrum, which confirms the cyclization at the hetero atom.

Method for Activation of Fly Ash

The fly ash collected was first sieved in a 100 mesh sieve to remove any coarser and foreign particles and then was mechanically ground in a ball mill to a fine powder. The particle size distribution was found to be between 30 and 80 μm. Finely ground fly ash was kept at a temperature of about 900–1000°C in a muffle furnace for 1 h for activation and was used for investigation. The carbon, sulfur, and other impurities were removed by thermal activation and the resultant fly ash is called activated fly ash. The activated fly ash was then checked for its activity and found to be one of the most efficient microwave absorbers with a very high specificity to microwave heating. This work was conducted in a commercial microwave appartaus (CEM Discover focused MW synthesis system) in a 10-mL crimp-sealed, thick-walled glass tube.

Virtual Screenings and Molecular Properties Calculations

Molinspiration Clculations[23–31]. CLogP is the octanol/water partition coefficient that is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors (Tables S1 and S2). Molecular polar surface area (MPSA) is calculated based on the methodology published by Ertl et al. as a sum of fragment contributions. O- and N-centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption (including intestinal absorption), bioavailability, Caco-2 permeability, and blood–brain barrier penetration, as it is the surface sum of overall polar atoms (usually oxygen and nitrogen), including attached hydrogens also. Prediction results of the molecular properties [TPSA, G-protein coupled receptor (GPCR) ligands, and ion channel modulators (ICMs)] of compounds **4 (a–n)** are presented in Table S2.

It is clear from the tabular data that the compounds **4f** and **4g** have good PSA values comparable with ampicillin and streptomycin. It is predicted that the negative charges of the oxygen and nitrogen atoms of the thiazolidinone group and the partial π-positive charges of sulfur and supplementary arm 2-OH contribute more positively in favor of the antibacterial activity. It has been hypothesized that the difference in charges between two heteroatoms of the same pharmacophore site may facilitate the inhibition of bacteria, more than that of viruses. It has been further found that the activity increases with the increase in the negative charge of one heteroatom of the common pharmacophore fragment of the compounds. Expert system for calculation of the drug likeness score toward GPCR ligands, ICMs, kinase inhibitors, nuclear receptor ligands, and protease inhibitors based on the Molinspiration technology has been tested—the results of which are tabulated in Table S2 and compounds such as **4e**, **4f**, **4g**, **4i**, and **4j** are in good agreement with the reference drugs used.

Osiris Calculations[20–28]. Structure-based design is now fairly routine, but many potential drugs fail to reach the clinic because of ADME-Tox (absorption, distribution, metabolism, excretion, and toxicity) liabilities. The Osiris calculations are tabulated in Table S3. Toxicity risks (mutagenicity, tumorigenicity, irritation, reproduction) and physic-ochemical properties (mi log P, solubility, drug likeness, and drug score) of compounds **4a**

and **4b** are calculated by the methodology developed by Osiris. The toxicity risk predictor locates fragments within a molecule that indicate a potential toxicity risk. Toxicity risk alerts are an indication that the drawn structure may be harmful concerning the risk category specified. The data evaluated in Table S3 indicate that all structures are supposed to be mutagenic, tumorigenic, non-irritating, with no reproductive effects when run through the mutagenicity assessment system, shown with red and green spheres, comparable with standard drugs used. All the compounds **4a–n** have log P values under the acceptable criteria.

Our estimated log S value is a unit stripped logarithm (base 10) of a compound's solubility measured in mol/liter. There are more than 80% of the drugs on the market that have a (estimated) log S value greater than –4. And, to our surprise, we found all the synthesized compounds having a value greater than –4. Further, Table S3 shows drug likeness of compounds **4a** and **4j** that is in the comparable zone with that of standard drugs used for comparison and even greater than them except for the ortho- and the para-nitro derivatives, i.e., **4f** and **4j**. We have calculated the overall drug score for compounds **4a** and **4j** and compared it with that of standard drugs (ampicillin and streptomycin) used, as shown in Table S2. The drug score combines drug likeness, mi log P, log S, molecular weight, and toxicity risks in one handy value that may be used to judge the compound's overall potential to qualify as a drug. This value is calculated by multiplying contributions of the individual properties with Equation (1):

$$\mathrm{DS} = \Pi(1/2 + 1/2S_i)\Pi t_i \tag{1}$$

where, $S = 1/1+e^{ap+b}$, DS is the drug score, S_i is the contributions calculated directly from mi log P, log S, molecular weight, and drug likeness (pi) via the second equation, which describes a spline curve. Parameters a and b are (1, –5), (1, 5), (0.012, –6), and (1, 0) for mi log P, log S, molecular weight, and drug likeness, respectively. t_i is the contributions taken from the four toxicity risk types. The t_i values are 1.0, 0.8, and 0.6 for no risk, medium risk and high risk, respectively. The reported compounds **4a–j** showed moderate to good drug score as compared with standard drugs used, except **4f** and **4j**.

CONCLUSION

In conclusion, we have developed an activated fly ash-catalyzed, simple, solvent-free, cost-effective, and environmentally benign technique for the synthesis of 4-thiazolidinones. This reaction is scalable to multi-gram scale. These compounds have been synthesized in high yield by using fly ash and avoiding the use of any solvent under microwave irradiation. Making use of a waste and carrying out a useful reaction out of it are really inspirational for future research. The astonishing reduction in the rate of reaction invariably made the process efficient from a future perspective to other such acid-catalyzed reactions. Apart from this, the virtual screening results are in good agreement with the standard drugs used for comparison. So, it is worth synthesizing the drug moieties on such a green scale.

EXPERIMENTAL SECTION

General

All reagents, solvents, and the catalyst are of analytical grade from a commercial source and used directly. All the melting points were determined in a SONAR scientific

melting point apparatus and are uncorrected. The purity of compounds was checked routinely by thin-layer chromatography (TLC) (0.5 mm thickness) using silica gel-G coated Al-plates (Merck) and the spots were visualized by exposing the dry plates to iodine vapors. IR spectra (υ_{max} in cm^{-1}) were recorded on a Bruker ALPHA FTIR spectrometer, ^1H NMR spectra on a Bruker WM 400-MHz NMR instrument using $CDCl_3$ and dimethyl sulfoxide (DMSO)-*d*6 as solvents and tetramethylsilane (TMS) as internal reference (chemical shifts in δ, ppm), and mass spectra on a Jeol JMS D-300 spectrometer operating at 75 eV. The elemental analysis (C, H, N, and S) of compounds was performed on a Carlo Erba-1108 elemental analyzer. The results were found to be in good agreement with the calculated values. The microwave-assisted reactions are carried out in a "CEM DISCOVER" manufactured by CEM Technologies Corporation.[29] In this unit, microwaves are generated by a magnetron at a frequency of 2450 MHz, having an output energy range of 100–500 W.

Microwave-Mediated General Synthesis of 4-(2-Hydroxybenzylideneamino)-1,2-dihydro-2,3-dimethyl-1-phenylpyrazol-5-one 3(a). 4-(2-hydroxybenzylideneamino)-1, 2-dihydro-2, 3-dimethyl-1-phenylpyrazol-5-one was obtained by the condensation of 4-amino-1, 2-dihydro-2, 3-dimethyl-1-phenylpyrazol-5-one and salicylaldehyde. This work was conducted in a commercial microwave apparatus (CEM Discover focused microwave synthesis system) in a typical solvent-free approach. A mixture of 4-amino antipyrine(**1**) (2.46 mmol, 1.5 g) and salicylaldehyde (4.92 mmol, 3.0 g) without any solvent was taken in a 10-mL crimp-sealed, thick-walled glass tube and irradiated at 140°C (400 W) for 20 sec. After completion of the reaction, the resultant mixture was allowed to cool down to room temperature. After cooling, the resultant solid was crushed, washed with cold ethanol, filtered, and dried under vacuum to give the crude product. The crude product was recrystallized from methanol.[30,31] The same method was followed for the production of other imines (**3b–n**). The spectral characterization is given in the Supplemental Materials.

Microwave-Mediated Activated Fly Ash-Catalyzed General Synthesis of 1, 2-Dihydro-4-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-2, 3-dimethyl-1-phenylpyrazol-5-one 4(a):. A mixture of 4-(2-hydroxybenzylideneamino)-1, 2-dihydro-2, 3-dimethyl-1-phenylpyrazol-5-one (**3a**) (3.23 mmole, 1.0 g), $SHCH_2COOH$ (thioacetic acid) (3.23 mmole, 0.30 g), and activated fly ash (0.50 g) was taken in a 10-mL crimp-sealed, thick-walled glass tube and irradiated at 170°C (400 W) in a commercial microwave apparatus (CEM Discover focused microwave synthesis system) in a typical solvent-free approach for 8 min. The reaction was monitored by TLC. After completion of the reaction, the pasty solid obtained was allowed to cool. To that, ethanol (15 mL) was added and stirred for 5 min, up to the dissolution of the pasty solid. The fly ash was filtered out of the mother liquor for the other reaction. The mother liquor was poured onto crushed ice and the pH of the solution was set to 10 using 10% $NaHCO_3$ solution. The reaction mass was then stirred, filtered, and washed with cold water. The crude product was recrystallized from methanol. The same process was used for the production of other thiazolidinones **4(b–n)**.

White-yellow solid; yield: 90%. mp 139–141°C. IR (cm^{-1}, KBr): 1295 (−C=O), 3250 (−OH); ^1H NMR (ppm, DMSO-d_6): 1.88 (s, 3H, $-CH_3$), 2.52 (s, 3H, N$-CH_3$), 3.43 (s, 2H, $-CH_2$-thiazolidinone),5.91 (s,1H, N−CH), 6.50–7.45 (m, 9H, aryl), 12.10 (s, H, −OH). ^{13}C NMR (100 MHz) [δ (ppm), $CDCl_3$]: 171.47 (C=O), 170.84 (C=O), 150.12 (C−OH), 136.64 (C), 105.32 (C), 50.52 (CH), 36.26 (N$-CH_3$), 33.12 (CH_2), 16.26 (CH_3), 129.33, 126.77, 123.22, 122.98, 120.50, 117.32, 115.90, 115.70, 111.10 ($C_{aromatic}$); MS (m/z) 404 (M + 23). Anal. Calc. for: $C_{20}H_{19}N_3O_3S$, C, 62.97; H, 5.02; N, 11.02; O, 12.58; S, 8.41%. Found: C, 62.80; H, 5.78; N, 10.80%.

Supplementary Data

Complete spectral characterization data and Tables S1–S3 are provided in the Supplemental Materials.

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