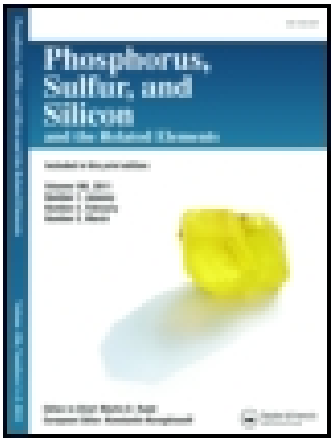

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Synthesis and Pharmacological Evaluation of 1,5-Benzothiazepine Derivatives

Ravindra R. Kamble [a] & Belgur S. Sudha [b]

[a] Post-Graduate Department of Studies and Research in Chemistry , Karnatak University , Dharwad, India

[b] Department of Chemistry and Food Science, Yuvaraja's College , University of Mysore , Mysore, India

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Synthesis and Pharmacological Evaluation of 1,5-Benzothiazepine Derivatives

Ravindra R. Kamble[1] and Belgur S. Sudha[2]
[1]Post-Graduate Department of Studies and Research in Chemistry, Karnatak University, Dharwad, India
[2]Department of Chemistry and Food Science, Yuvaraja's College, University of Mysore, Mysore, India

A simple method for the synthesis of 1,5-benzothiazepines integrated with 5-methyl-2-oxo-3-phenyl-Δ^4-1,3,4-oxadiazoles in 75–95% yield is devised. A comparison of microwave-accelerated reaction with conventional heating is also illustrated. Structures of all the newly synthesised compounds were characterised by physical, analytical and spectral (UV, IR, ^{1}H NMR, and MS) data. Title compounds were screened for their antimicrobial, anticonvulsant, anti-inflammatory, and diuretic activities.

Keywords 1,3-Dipolar cycloaddition; 1,5-benzothiazepine; 4-acetylphenylsydnone; microwave irradiation; thermal method

INTRODUCTION

The use of microwaves in organic synthesis has increased dramatically in last few years, receiving wide spread acceptance and becoming an indispensable tool. The combination of solvents, acids and long reaction time period make conventional synthetic methods environmentally hazardous. The rapid one-pot preparation of heterocyclic compounds from *in situ* generated reactive intermediates and the general application to multi-component reactions, that are adaptable for building a library of compounds has been accomplished using MW technique.[1] The microwaves enhance the rate of chemical reactions and hence they have gained popularity over the usual homogenous and heterogeneous reactions as they can be carried out rapidly, and can provide pure products

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Address correspondence to Ravindra R. Kamble, Department of Chemistry and Food Science, Yuvaraja's College, University of Mysore, Mysore 570 005, India. E-mail: ravichem1234@rediffmail.com

in quantitative yields with minimized by-products.[2] Because of short reaction time requirement, ease of workability and eco-friendliness, microwaves provide an alternative to environmentally unacceptable procedures and expensive reagents.

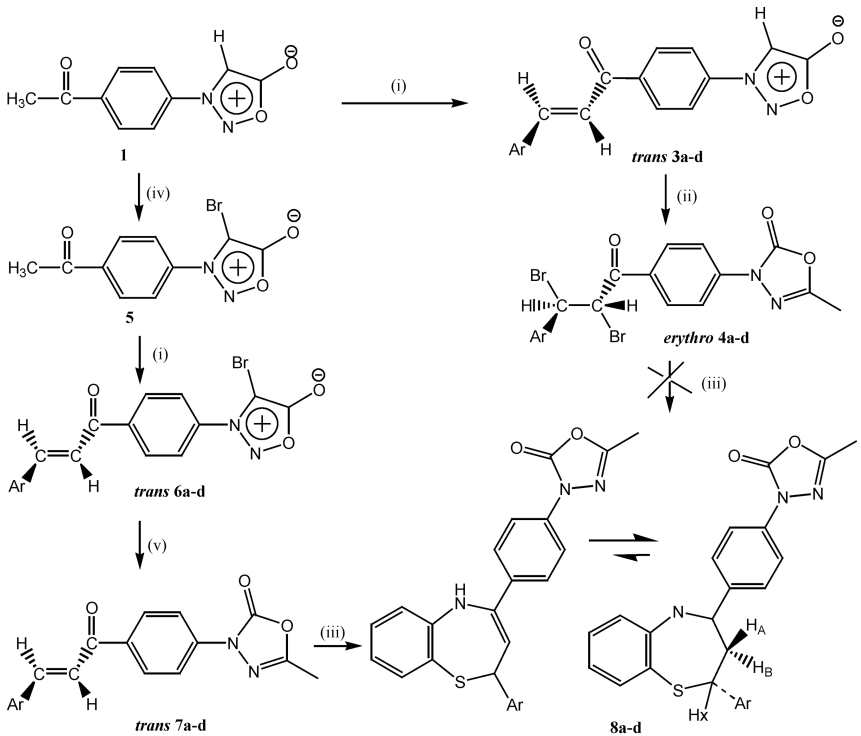
The chemistry of heterocycles has been an interesting branch of the subject in organic chemistry as it offers a challenging task in the development of new synthetic strategies. The 3-arylsydnones, belonging to a class of mesoionic compounds and their derivatives possess diverse chemotherapeutic properties. Hence, sydnone is serendipitous heterocycle as it readily undergoes ring transformation to various heterocycles by 1,3-dipolar cycloaddition reaction.[3] This concept has been adopted to synthesise a number of heterocyclic compounds by one-pot process from 3-arylsydnones.[4–7]

The present work involves incorporation of 1,3,4-oxadiazole, which is 1,3-dipolar cycloaddition product of sydnone with 1,5-benzothiazepine to explore their structure activity relationship (SAR). The attractive bioactivity leading to the immense chemotherapeutic applications of 1,5-benzothiazepines are the treatment of ailments of cardiovascular system such as, hypertension,[8] maintenance of Ca^{+2} ion concentration.[9] A patented report has claimed that integration of additional heterocyclic ring as a pharmacophore in the 1,5-benzothiazepine nucleus has resulted into the compound of useful bioactivity.[10,11] While carrying out drug designing, it was found that the introduction of halogeno groups like *chloro*, *fluoro* in analogous benzodiazepines nucleus lead to the discovery of CNS drugs, chlordiazepoxide.[12] flurazepam,[13] which are currently in use. Thus, it seemed that the halogens might act as potential pharmacophores. The coveted drug 'diltiazem' being used as a calcium channel blocker,[14] calcium channel modulator,[15] calcium channel antagonist,[16] vasodilator,[17] antihypertensive,[18,19] blood platelet aggregation inhibitor,[20] antiarrhythmic,[21] antithrombotic,[22] antianginal,[23] antiischemic,[24] and so on, also possesses a 1,5-benzothiazepine nucleus having an aryl substituent at position 2. In recent years, "clentiazem,"[25] also having this moiety, has been found to be a better drug than diltiazem.

In the light of above observations, we wish to report the use of MORE (Microwave induced Organic Reaction Enhancement) and conventional method of synthesis of 5-methyl-3-[*p*-(2′-aryl-2′,3′-dihydro-benzo[*b*][1′,5′]-thiazepin-4′-yl)-phenyl]-3*H*-2-oxo-Δ^4-1,3,4-oxadiazole **8a–d** herein.

RESULTS

Synthesis of biheterocycles, which is effected sequentially, requires bifunctional precursors, which are not always readily accessible. The



a; Ar = Ph, **b**; Ar = *p*-BrC_6H_4-, **c**; Ar = *p*-$CH_3C_6H_4$, **d**; Ar = *p*-ClC_6H_4

(i) ArCHO (**2a-d**), NaOH/Ethanol (ii) Br_2 in Ac_2O (iii) *o*-Amino thiophenol, Ethanol/H^+

(iv) Br_2 in AcOH (v) Ac_2O

SCHEME 1

4-acetylphenylsydnone **1**, which can be conveniently prepared from *p*-amino acetophenone, serves as an important synthetic precursor for the synthesis of title compounds. As shown in Scheme 1, our initial synthetic strategy involved the preparation of 4-acetyl phenylsydnone[26] **1**. The compound **1** is reacted with an aromatic aldehyde **2a**–**d** in ethanol afforded *trans* 3-[*p*-(3′-aryl acryl-1′-oyl) phenylsydnone **3a**–**d** as a predominant product (*Claisen-Schmidt reaction*). The *trans* isomer is favored, since in the transition state, two large substituents are not eclipsed and there is no interference with coplanarity of the enolate system. Of the two, the later factor is more important.[27] The *trans* **3a–d** on bromination in acetic anhydride sydnone ring underwent 1,3-dipolar cycloaddition to give *meso* 3-[*p*-(2′,3′-dibromo-3′-aryl-propion-1′-yl)-phenyl]-5-methyl-3*H*-2-oxo-Δ^4-1,3,4-oxadiazole **4a–d**. During cycloaddition reaction, chalcone moiety was also brominated. Dibromo

derivative **4a–d** on treatment with *o*-amino thiophenol did not form the target compound **8a–d**. Therefore, this method of ring transformation of sydnone into oxadiazoline and approach for synthesis of the target molecule was not advantageous due to the bromination of chalcone moiety.

Now the strategy of synthesis is changed. The starting material **1** was brominated in presence of acetic acid to 4-bromo-3-(4′-acetyl)-phenylsydnone **5**, which upon treatment with aromatic aldehydes **2a–d** in ethanol afforded *trans* 4-bromo-3-[*p*-(3′-aryl- acryl-1′-oyl)] phenylsydnone **6a–d**. Compound **6a–d** upon heating in the presence of acetic anhydride at 135°C or on microwave irradiation, sydnone ring underwent 1,3-dipolar cycloaddition along with the elimination of bromine as acetyl bromide to afford exclusively *trans* 5-methyl-3- [*p*-(3′-aryl - acryl-1′-oyl)-phenyl]-3*H*-2-oxo- Δ^4-1,3,4-oxadiazole **7a–d**. Nucleophilic addition of sulfhydryl electrons of *o*-amino thiophenol on $C_{2'}$ of **7a–d** is followed by intermolecular dehydrative cyclization afforded the final product **8a–d**.

On comparison, the synthesis by microwave assisted method, with that by conventional method, it is observed that the reaction progressed very fast with excellent yield in the former. Microwave irradiation facilitates polarization of the molecule under irradiation causing rapid reaction to occur. This is consistent with the reaction mechanism, which involves a polar transition state.

Antimicrobial Activity

Antibacterial activity of newly synthesised compounds was determined against *Staphylococcus aureus* and *Pseudomonas aeruginosa* by cup plate method.[28] The test compounds were dissolved in DMF and different aliquots were placed in each cup. Incubation was carried out at 37°C for 24 h. Chloromycetine was used as standard drug. The diameter of zone of inhibition was measured for 100 μg/ml concentration.

The antifungal activity of the compounds was evaluated against *Aspergillus niger* and *Fusarium poa* by adopting the usual cup plate technique and using Griseofulvin as the standard. The diameter of zone of inhibition was measured for 100 μg/ml concentration. The results of antibacterial and antifungal activities were recorded in Table I.

Anti-Inflammatory Activity

Anti-inflammatory activity was measured using the carrageenan-induced paw edema test in rats.[28] Commercially available ibuprofen was used as standard drug. Male swiss rats (150–200 g) were divided

TABLE I Results of in vitro Antimicrobial Activity

Entry no.	Diameter of zone of inhibition (mm)*			
	S. aureus	*P. aeruginosa*	*A. flavus*	*F. oxysporium*
8a	10.0	09.6	11.5	09.0
8b	19.4	23.0	09.8	10.5
8c	11.5	08.5	11.0	14.0
8d	18.3	15.0	13.0	17.0
Chloromycetine	25.0	24.0	—	—
Griseofulvin	—	—	28.0	25.0

Size of the inhibition zone by disk diffusion method, Control (DMF) = No activity. Both test compounds and standards were tested at 100 μg/ml conc.

into control, standard, and test groups—each consisting of six rats. A group of rats was treated with Tween-80 (1%) suspension i.p. (control). Another group was treated with 100 mg/kg of the suspension of the test compounds. After 30 min, the animals were injected with 0.1 ml of carrageenan (1% w/v) in the sub plantar region of left hind paw of the rats. The volume of the paw was measured using the mercury displacement technique with the help of a plethysmograph both in control, as well as in standard animals including the test animals 2 h and 4 h after injection. The initial volume of the paw was measured within 30 sec of the injection. The percent inhibition of the inflammation after 2 hour and 4 hour was calculated using the % inhibition $= (1 - v_t/v_c) \times 100$, where v_t and v_c are the mean relative changes in the volume of paw edema in the test and control respectively. The results are summarized in Table II.

TABLE II Results of Anti-Inflammatory Activity

Entry No.	Dose mg/kg	Edema volume (ml)[x] Different interval (mean ± S. E. M.)		% Inhibition	
		2h	4h	2h	4h
8a	100	0.33 ± 0.02	0.28 ± 0.03	13.0	18.0
8b	100	0.31 ± 0.02	0.28 ± 0.02	18.0	18.0
8c	100	0.29 ± 0.02	0.24 ± 0.03	24.0	30.0
8d	100	0.30 ± 0.02	0.21 ± 0.03	21.0	38.0
Standard (Ibuprofen)	100	0.27 ± 0.03	0.20 ± 0.02	29.0	41.0
Control (Tween)	—	0.38 ± 0.03	0.34 ± 0.02	—	—

x Values = mean ± S.E.M; no.of animals in each group = 06.

Anticonvulsant Activity

The anticonvulsant activity of title compounds was based on maximal electroshock induced convulsions in rats.[28] Male swiss rats were procured from Virus Diagnostic Laboratory, Dharwad and maintained at Department of studies in Botany, Karnatak University Dharwad, were fed with standard diet, water, and *libitum*. All protocols of animal experiments have been approved by the Institutional Animal Ethics Committee (IAEC). Six groups of three rats were selected, and to the first group, saline (control) injected i.p. corneal electrodes were placed on the cornea, and then the prescribed current was applied. The different stages of convulsions were noted and used as control. To the second group, 25 mg/kg of phenytoin sodium (standard) was injected i.p., and after 30 min, they were subjected to electro-convulsions. The same procedure was repeated for remaining four groups using test compounds **8a–d**. Various stages of convulsions were recorded at different intervals. The mean value for each group was calculated and compared with control. The results are summarised in Table III.

Diuretic Activity

Diuretic activity evaluation is based on the effects of drugs on water and electrolytes excretion in rats.[28] The animals were marked, weighed and divided into six groups. To the first group, a water load of 25 ml/kg (control) p.o. was administered orally. To the second group frusemide (standard) was given i.p. along with a water load of 25 ml/kg. To the remaining four groups, suspension of test compounds (100 mg/kg) was administered i.p. along water. The animals were observed for diuresis, and the volume of urine collected was measured periodically. Results

TABLE III Results of Anticonvulsant Activity

Entry no.	Dose[a] mg/kg	Time (sec) in various phases of convulsion				Recovery/ Death
		Flexion	Extensor	Clonus	Stupor	
8a	25	3.3	5.0	2.5	88	Recovery
8b	25	3.1	4.5	2.4	85	Recovery
8c	25	1.6	4.0	2.25	90	Recovery
8d	25	2.5	3.9	2.20	95	Recovery
Control (Saline)	—	4.0	11.0	3.0	120	Recovery
Standard (Phenytoin)	25	1.5	2.0	1.5	100	Recovery

[a]No. of animals in each group = 06.

TABLE IV Results of Diuretic Activity

Compd.	Dose[a] mg/kg	Total amount of urine collected (ml)				
		15′	30′	60′	120′	240′
8a	10	0	0	0	4.0	4.5
8b	10	0	0	0	4.5	3.9
8c	10	0	0	0	4.9	4.4
8d	10	0	0	0	4.8	4.3
Standard (Frusemide)	10	0	0	0	5.4	4.6
Control (Water)	25 ml/kg	0	0	0	3.4	3.2

[a]No. of animals in each group = 06.

were expressed as the mean of six samples and were compared to that of standard frusemide (Table IV).

DISCUSSION

All the newly synthesised compounds were confirmed by spectral characterisation. Ultraviolet spectra of the chalcones **3a–d**, **6a–d,** and **7a–d** have shown a strong band in the range 290–345 nm (Ethanol) due to $\pi \rightarrow \pi^*$ transition indicating the formation of only *trans* chalcone. Absence of this band in **4a–d** indicated the formation. UV spectra of compounds **8a–d** showed a considerable bathochromic shift due to $\pi \rightarrow \pi^*$ (λ_{max} 440–460 nm) as compared to that of $\pi \rightarrow \pi^*$ in **3a–d**, **6a–d**, and **7a–d** (λ_{max} 290–345 nm). A weak band in the range 320–360 nm present in the compounds **3a–d**, **6a–d**, **7a–d** ,and **8a–d** is due to the n$\rightarrow \pi^*$ transition of lone pair of electrons.

In case of IR spectral analyses a band around 1652–1660 cm^{-1} in **3a–d** indicated the presence of the α, β-unsaturated carbonyl function. Another band around 1722–1739 cm^{-1} was observed due to sydnone carbonyl group. A sharp stretching C—H band was observed around 3100–3125 cm^{-1}, which is characteristic of C4, unsubstituted sydnones. Compounds **4a–d** have shown two sharp absorption bands in the functional group region around 1672–1695 cm^{-1} and 1760–1776 cm^{-1} due to saturated keto group and lactone carbonyl function. In case of compound **5**, two carbonyl groups (keto and sydnone) absorptions appeared at 1684 and 1725 cm^{-1}. A band around 3100 cm^{-1}, which is characteristic of sydnone was absent due to C_4-bromo substituent. Compounds **6a–d** have shown IR absorption band in the region 1650–1668 cm^{-1} and 1715–1734 cm^{-1} as in case of **3a–d** due to enone and sydnone carbonyl stretchings. Absorption peaks around 1647–1658 and 1771–1793 cm^{-1} due to enone and lactone carbonyl were observed in **7a–d**. The title

compounds **8a–d** have a stretching band around 1595–1610 cm^{-1} due to C=N group. A band around 1767–1774 cm^{-1} due to lactone carbonyl function was observed.

PMR spectra of **3a–d** have shown a characteristic singlet around δ 6.56–6.94, which was due to C_4 proton. Two doublets in the range δ 8.00–8.45 and 8.15–8.61 appeared due to $C_{2'}$ and $C_{3'}$ vinylic protons with coupling constant around 11–13 Hz. Similar type of observations were made in case of **6a–d** and **7a–d**, each showing two doublets due to $C_{2'}$ and $C_{3'}$ vinylic protons in the range δ 7.63–8.24 ppm. (J = 10-14 Hz) and δ 8.24–8.75 (J = 11–15 Hz), respectively. Compounds **4a–d** have shown two doublets due to $C_{3'}$ and $C_{2'}$ protons in the range δ 5.40–5.66 and 5.54–5.89 ppm, which was up field shift than in case of their precursors **3a–d**. A common singlet due to C_5-methyl protons, which were resonated in the range δ 2.15–2.44 ppm. is exhibited by **4a–d**. Compound **5** showed a singlet at δ 2.19 and two doublets in AA' BB' pattern at δ 7.95–8.05 were observed due to methyl and aromatic protons respectively. The compounds **3a–d**, **6a–d** and **7a–d** showed the J values in the range 11–15 Hz, indicating the *trans* isomers.

The characteristic feature of ^{1}H NMR **8a–d** is the splitting pattern for the H_A, H_B, and H_X protons. H_A and H_B are diastereotopic and also anisochronous as they differ in chemical shifts and since this difference is not large they may be identified as AB protons. The $C_{2'}$- methine proton with larger shift downfield is the H_X proton and all together form the ABX pattern. The H_A and H_B protons appear as doublet of doublet due to geminal and vicinal coupling. The H_A and H_B differ in coupling with H_X; hence, they are also anisogamous.

H_A and H_B experience shielding and deshielding by the adjacent π-electrons differentially. H_B is more shielded as it would be probably in the diamagnetic region of π-cloud of aryl ring present on $C_{2'}$. H_B proton appeared as doublet of doublet in the up field range δ 3.1–3.4 with two coupling constants J_{BA} in the range 16.4–17.6 Hz and J_{BX} in the range 7.85–11.8Hz. The dihedral angle θ is approximately 160° since the H_B and H_X cannot adopt coplanarity in the molecule. H_A proton also appeared as doublet of doublet in the range δ 3.6–4.1 with two coupling constants viz. J_{AB} in the range 17.0–17.65 Hz and J_{AX} in the range 4.0–5.02 Hz. J_{AX} is the *J*ee (i.e., distorted diequatorial) value as the dihedral angle θ is not 90° but 120° due to large aryl ring on $C_{2'}$. H_X appeared as a four line spectrum with J_{XA} in the range δ 4.50–5.0 Hz and J_{XB} in the range 7.87–11.84 Hz. All the compounds **8a–d** has shown a characteristic singlet in the range δ 1.97–2.19 ppm, due to C_5-methyl protons. The above characterised compounds have shown aromatic protons in the expected region either as multiplet in some or as

doublet of doublet in AA'BB' pattern. ^{13}C NMR of all these compounds showed number of signals, which are consistent with the number of carbons in the molecule.

In the electron impact studies, all compounds showed molecular ion peaks at their respective m/z. Compounds **3a**, **3b**, **3c,** and **3d** have shown peaks at 131, 209 (M + 2), 145 and 165 due to aryl substituted cinnamoyl cation. The formed cinnamoyl cations from these **3a–d** inturn lose CO, resulting in the aryl substituted styryl radical cation at 103, 182, 117, and 137 respectively. The formation of this type of ions is typical of the chalcones.[29] All the compounds **3a–d** have shown a base peak commonly at m/z 190 due to prototropic shift from $C_{3'}$ to carbonyl carbon atom attached directly to the phenyl ring and bond fission between same carbonyl carbon and $C_{2'}$.

The dibromo derivatives **4a**, **4c,** and **4d** have shown low abundant molecular ion peaks M^+, M + 2 and M + 4 due to the presence of two bromine atoms in the abundance ratio 1:2:1. This is the typical pattern for two bromine atoms and is in accordance with the literature.[18] Interestingly, the compound **4b** has shown four low abundant peaks at 548 (M + 6), 546 (M + 4), 544 (M + 2), and 542 (M^+) in the ratio 1:3:3:1 which is due to presence of three bromine atoms. All these compounds **4a–d** have shown a base peak at 204 in common. The electron impact mass spectrum of compound **5** shows a molecular ion peak at 284 and 282 (M + 2 and M^+), which agrees with the molecular weight of the compound. Loss of bromine results in the formation of a base peak 203.

The compounds **6a**, **6c** and **6d** exhibited two molecular ion peaks (M + 2 and M^+) due to the presence of bromine in all except for the compound **6b** which has two bromine atoms. Compound **6b** has shown three low abundant molecular ion peaks in 1:2:1 ratio. All these compounds **6a–d** have shown a base peak at 268. The mass spectra of **7a–d** have shown molecular ion peaks at their respective m/z with molecular ion peak at 204. The title compounds **8a–d** have also shown molecular ion peaks at their respective m/z and the base peak is obtained in all compounds due to loss of methyl free radical.

From the antibacterial activity analyses (Table I), it was observed that compounds **8b** and **8d** with *chloro* and *bromo* substituents on $C_{2'}$-phenyl nucleus were more active than methyl substituted **8c** and unsubstituted **8a**. Similar trend was observed in case of antifungal activity data also. Compound **8a** has comparatively good inhibitory activity against *A. flavus*. The anti-inflammatory activity (Table II) also revealed that compounds **8c** (30.0%) and **8d** (38.0%) showed significant activity compared to standard Ibuprofen (41.0%). Amongst the compounds subjected to anticonvulsant activity (Table III), compounds

8c and **8d** were found to possess promising activity compared to that of standard Phenytoin. The diuretic activity (Table IV) results showed that the test compounds produced slight diuresis compared to standard frusemide.

EXPERIMENTAL

Melting points were determined using Thomas Hoover capillary melting point apparatus and are uncorrected. UV and IR spectra were recorded on Specord-50 and Nicolet Impact – 410 FT –IR spectrophotometer, respectively. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz FT-NMR spectrometer at 300 and 75 MHz, respectively. The chemical shifts are in δ units and reported as ppm relative to internal standard TMS. The coupling constants (J) in Hz. Mass spectra were recorded on a EI-70 eV spectrometer. Elemental analyses results are within 0.4% of the calculated value. TLC was performed on preactivated (110°C) silica gel plates using acetone methanol (6:4) as an irrigant, and the plates were visualised with UV light. Microwave irradiations were carried out in a BPL 2300 ET domestic microwave oven. Starting compound **1** was prepared according to literature method.[26]

3-[4′-(3″-Aryl-acryl-1″-oyl)-phenylsydnone (3a–d)

Thermal Method

A mixture of **1** (2.04 g, 10.0 mmol), aromatic aldehyde **2a–d** (10.0 mmol) in ethanol (10 ml) and sodium hydroxide solution (0.5 g in 5 ml of water) was taken in a conical flask (100 ml). The reaction mixture was stirred for 45 min at room temperature. The precipitate formed was immediately collected and washed thoroughly with water. The chalcone derivative **3a–d** obtained was dried and crystallized using methanol: dioxane::1:1 (v/v) to get bright yellow crystals in 80–85% yield (Tables V and VI).

Microwave Method

To a solution of **1**, (2.04 g, 10.0 mmol) and aromatic aldehyde **2a–d** (10.0 mmol) in dry ethanol (20 ml) taken in a borosil beaker (100 ml), sodium hydroxide (0.5 g in 5 ml of water) was added, and the reaction mixture was zapped inside a microwave oven at 55°C (210 W, i.e., 30% microwave power) for 8 min and then cooled in an ice bath; the product formed was filtered and crystallized using methanol: dioxane::1:1 (v/v) to give bright yellow crystals of **3a–d** (Yield 85–92%) (Table V and VI).

TABLE V Comparison of Time Required and Yield

	Thermal		Microwave	
Entry no.	Time (Minutes)	Yield %	Time (Minutes)	Yield %
3a	45	81	8	90
3b	40	80	7	86
3c	40	85	8	92
3d	45	83	7	85
4a	90	74	5	80
4b	85	70	4	84
4c	95	71	5	90
4d	86	70	4	83
5	30	70	—	—
6a	45	65	10	73
6b	50	68	11	90
6c	44	65	13	72
6d	50	64	10	88
7a	120	72	8	95
7b	125	66	11	86
7c	115	70	9	90
7d	115	68	10	89
8a	180	60	9	86
8b	190	49	11	90
8c	175	62	8	84
8d	180	58	10	89

Compound (3a). uv λ_{max}: (Ethanol), 290, 325 (strong) and 355 (weak) nm; IR: enone CO 1660 sydnone CO 1739 and C_4-H 3110 cm^{-1}; ^1H NMR: δ 6.94 (s, 1H, C_4-H), 7.81–7.14 (m, 9H, ArH), 8.45 (d, 1H, *trans*-olefinic $C_{3'}$-H, J = 13 Hz), 8.61 (d, 1H, *trans*-olefinic $C_{2'}$-H, J = 13 Hz); ^{13}C NMR: δ 94.23 (C_4), 119.8 ($C_{2'}$), 126.2–137.0 (ArC), 141.6 ($C_{3'}$), 164.1 ($C_{1'}$), 169.7 (C_5); MS: m/z 292 (M^+, 5%), 262 (33), 234 (20), 207 (45), 190 (100), 160 (72), 132 (61), 131 (80), 105 (11), 103 (17), 90 (40).

Compound (3b). uv λ_{max}: (Ethanol) 253, 310 (strong) and 340 (weak) nm; IR: enone CO 1654 sydnone CO 1727 and C_4-H 3100 cm^{-1}; ^1H NMR: δ 6.56 (s, 1H, C_4-H), 7.19 (d, 2H, $C_{3'}$-ArH, J = 5.0 Hz), 7.38 (d, 2H, $C_{3'}$-ArH, J = 5.0 Hz), 7.63 (d, 2H, N_3-ArH, J = 6.9 Hz), 7.85 (d, 2H, N_3-ArH, J = 6.9 Hz), 8.04 (d, 1H, *trans*-olefinic $C_{3'}$-H, J = 11 Hz), 8.15 (d, 1H, *trans*-olefinic $C_{2'}$-H, J = 11 Hz); ^{13}C NMR: δ 93.85 (C_4), 125.6 ($C_{2'}$), 128.4–138.0 (ArC), 140.7 ($C_{3'}$),162.4 ($C_{1'}$), 170.2 (C_5); MS: m/z 372 (M^{+2}, 4%), 370 (M^+, 5), 342 (21), 340 (23), 314 (15), 312 (15), 287 (40), 285 (41), 211 (75), 209 (71),190 (100), 181 (12), 170 (25),168 (34), 132 (56).

TABLE VI Characterization Data of the Synthesized Compounds

Entry no.	Empirical formula	Found (Calculated) % C	H	N	m.p. °C	R_f
3a	$C_{17}H_{12}N_2O_3$	69.84 (69.86)	4.12 (4.14)	9.55 (9.58)	177–179	0.46
3b	$C_{17}H_{11}BrN_2O_3$	54.96 (55.01)	2.95 (2.99)	7.50 (7.55)	182–184	0.22
3c	$C_{18}H_{14}N_2O_3$	70.55 (70.58)	4.58 (4.61)	9.18 (9.15)	163–165	0.64
3d	$C_{17}H_{11}ClN_2O_3$	62.47 (62.48)	3.33 (3.37)	8.55 (8.57)	220–222	0.34
4a	$C_{18}H_{14}Br_2N_2O_3$	46.34 (46.38)	3.00 (3.03)	5.97 (6.01)	211–213	0.52
4b	$C_{18}H_{13}Br_3N_2O_3$	39.70 (39.67)	2.42 (2.40)	5.13 (5.14)	157–159	0.19
4c	$C_{19}H_{16}Br_2N_2O_3$	47.55 (47.53)	3.39 (3.36)	5.58 (5.83)	204–206	0.34
4d	$C_{18}H_{13}ClBr_2N_2O_3$	43.30 (43.33)	2.60 (2.61)	5.60 (5.62)	157–159	0.50
5	$C_{10}H_7BrN_2O_3$	42.40 (42.43)	2.53 (2.49)	9.90 (9.94)	160–162	0.52
6a	$C_{17}H_{11}BrN_2O_3$	55.05 (55.01)	2.95 (2.99)	7.52 (7.55)	212–214	0.41
6b	$C_{17}H_{10}Br_2N_2O_3$	45.36 (45.37)	2.20 (2.24)	6.19 (6.22)	153–155	0.37
6c	$C_{18}H_{13}BrN_2O_3$	56.10 (56.12)	3.45 (3.40)	7.25 (7.27)	124–126	0.26
6d	$C_{17}H_{10}ClBrN_2O_3$	50.41 (50.43)	2.45 (2.47)	6.94 (6.92)	232–234	0.68
7a	$C_{18}H_{14}N_2O_3$	70.56 (70.58)	4.63 (4.61)	9.17 (9.15)	137–139	0.46
7b	$C_{18}H_{13}BrN_2O_3$	56.10 (56.12)	3.38 (3.40)	7.24 (7.27)	182–184	0.31
7c	$C_{19}H_{16}N_2O_3$	71.29 (71.24)	5.04 (5.03)	8.72 (8.74)	125–127	0.49
7d	$C_{18}H_{13}ClN_2O_3$	63.42 (63.44)	3.84 (3.85)	8.24 (8.22)	196–198	0.40
8a	$C_{24}H_{19}N_3O_2S$	69.68 (69.71)	4.60 (4.63)	10.12 (10.16)	167–169	0.77
8b	$C_{24}H_{18}BrN_3O_2S$	58.50 (58.54)	3.67 (3.68)	8.56 (8.53)	221–223	0.43
8c	$C_{25}H_{21}N_3O_2S$	70.20 (70.23)	4.97 (4.95)	9.85 (9.83)	187–189	0.35
8d	$C_{24}H_{18}ClN_3O_2S$	64.37 (64.35)	4.01 (4.05)	9.40 (9.38)	143–145	0.66

Compound (3c). uv λ_{max}: (Ethanol) 300, 345 (strong), and 360 (weak) nm; IR: enone CO 1663 sydnone CO 1730 and C_4-H 3125 cm^{-1}; ^{1}H NMR: δ 2.35 (s, 3H, CH_3), 6.71 (s, 1H, C_4-H), 7.01 (d, 2H, $C_{3'}$-ArH, $J = 6.2$ Hz), 7.18 (d, 2H, $C_{3'}$-ArH, $J = 6.2$ Hz), 7.42 (d, 2H, N_3-ArH, $J = 7.0$ Hz), 7.80 (d, 2H, N_3-ArH, $J = 7.0$ Hz), 8.31 (d, 1H, *trans* olefinic $C_{3'}$-H, $J = 12$ Hz), 8.54 (d, 1H, *trans* olefinic $C_{2'}$-H, $J = 11.7$ Hz); ^{13}C NMR: δ 20.9 (CH_3), 88.40 (C_4), 112.0 ($C_{2'}$), 122.3–136.6 (ArC), 144.1 ($C_{3'}$), 163.8 ($C_{1'}$), 169.0 (C_5); MS: m/z 326 (M^+, 9%), 300 (16), 272 (23), 245 (32), 190 (100), 160 (61), 145 (90), 132 (50), 117 (12),105 (9),104 (51).

Compound (3d). uv λ_{max}: (Ethanol) 243, 305 (strong), and 340 (weak) nm; IR: enone CO 1652 sydnone CO 1722 and C_4-H 3104 cm^{-1}; ^{1}H NMR: δ 6.65 (s, 1H, C_4-H), 7.10 (d, 2H, $C_{3'}$-ArH, $J = 6.2$ Hz), 7.18 (d, 2H, $C_{3'}$-ArH, $J = 6.2$ Hz), 7.30 (d, 2H, N_3-ArH, $J = 7.0$ Hz), 7.39 (d, 2H, N_3-ArH, $J = 7.0$ Hz), 8.00 (d, 1H, *trans*-olefinic $C_{3'}$-H, $J = 11.5$ Hz), 8.34 (d, 1H, *trans*-olefinic $C_{2'}$-H, $J = 11.5$ Hz); ^{13}C NMR: δ 94.35 (C_4), 118.7 ($C_{2'}$), 122.6–137.0 (ArC), 143.5 ($C_{3'}$), 164.1 ($C_{1'}$), 169.5 (C_5); MS: m/z 326 (M^+, 7%), 300 (16), 272 (23), 245 (31), 190 (100), 160 (54), 165 (91), 137 (10), 132 (50), 124 (47).

3-[*p*-(2′,3′-Dibromo-3′-aryl-propion-1′-yl)-phenyl]-5-methyl-3H-2-oxo-Δ^4-1,3,4-oxadiazole (4a-d)

Thermal Method

To a solution of **3a-d** (5.0 mmol) in acetic anhydride (10 ml) at 0°C was added bromine (10 mmol) in acetic anhydride (10 ml) with constant stirring. After complete addition of bromine solution, the stirring was continued for 30 min. The reaction mixture was then heated to 60°C for 1h until the evolution of carbon dioxide ceased; then the mixture was cooled and poured into water. The solid separated was filtered and dried. Crystallisation of the product from methanol gave **4a–d** in 70–74% yield.

Microwave Method

In a typical method, addition of bromine (10 mmol) in acetic anhydride (10 ml) to **3a–d** (5.0 mmol) was similar to the thermal method at 0°C. The brominated reaction mixture was then introduced into the microwave oven in a conical flask (100 ml) capped with a funnel. The flask was irradiated at 25°C (80 W 12% microwave power) for 5 min. The reaction mixture was cooled, and the solid, thus separated, was filtered and recrystallized from methanol to afford **4a–d** (Yield 80–90%).

Compound (4a). uv λ_{max}: (Ethanol) 243 and 340 nm (weak); IR: C=O 1695 and C_5-C=O 1772 cm^{-1}; ^1H NMR: δ 2.44 (s, 3H, C_5-CH_3), 5.64 (d, 1H, $C_{3'}$-H, $J = 13$ Hz), 5.89 (d, 1H, $C_{2'}$-H, $J = 13$ Hz), 8.21-7.24 (m, 9H, ArH); ^{13}C NMR: δ 14.9 (CH_3), 47.2 ($C_{3'}$), 57.0 ($C_{2'}$), 118.7-138.4 (ArC), 155.0 (C_5), 157.3 (C_2),175.0 ($C_{1'}$); MS: m/z 470 (M + 4, 5%), 468 (M + 2, 11), 466 (M^+, 5), 385 (61), 306 (70), 204 (100), 160 (70), 131 (13), 103 (9), 90 (4).

Compound (4b). uv λ_{max}: (Ethanol) 210 and 326 nm (weak); IR: C=O 1690 and C_5-C=O 1776 cm^{-1}; ^1H NMR: δ 2.33 (s, 3H, C_5-CH_3), 5.40 (d, 1H, $C_{3'}$-H, $J = 12$ Hz), 7.26 (d, 2H, N_3-ArH, $J = 6.7$ Hz), 5.54 (d, 1H, $C_{2'}$-H, $J = 12$ Hz), 6.85 (d, 2H, $C_{3'}$-ArH, $J = 6.2$ Hz), 7.01 (d, 2H, $C_{3'}$-ArH, $J = 6.2$ Hz), 7.91 (d, 2H, N_3-ArH, $J = 6.7$ Hz); ^{13}C NMR: δ 15.04 (CH_3), 45.6 ($C_{3'}$), 57.4 ($C_{2'}$), 113.2-138.0 (ArC), 155.3 (C_5), 157.9 (C_2), 179.0 ($C_{1'}$); MS: m/z 548 (M + 6, 4%), 546 (M + 4,10), 544 (M + 2, 12), 542 (M^+, 4), 467 (9), 465 (17), 463 (9), 386 (13), 384 (15), 204 (100), 160 (61), 131 (17).

Compound (4c). uv λ_{max}: (Ethanol) 225 and 330 (weak); IR: C=O 1687 and C_5-C=O 1769 cm^{-1}; ^1H NMR: δ 2.15 (s, 3H, C_5-CH_3), 2.27 (s, 3H, $ArCH_3$), 5.66 (d, 1H, $C_{3'}$-H, $J = 14$ Hz), 5.73 (d, 1H, $C_{2'}$-H, $J = 14$ Hz), 7.06 (d, 2H, $C_{3'}$-ArH, $J = 6.2$ Hz), 7.30 (d, 2H, $C_{3'}$-ArH, $J = 6.2$

Hz), 7.34 (d, 2H, N_3-ArH, $J = 6.7$ Hz), 7.95 (d, 2H, N_3-ArH, $J = 6.7$ Hz); ^{13}C NMR: δ 14.87 (CH_3), 21.2 ($ArCH_3$), 47.5 ($C_{3'}$), 57.9 ($C_{2'}$), 119.1-137.5 (ArC), 154.2 (C_5), 156.1 (C_2), 174.0 ($C_{1'}$); MS: m/z 482 (M + 4, 5%), 480 (M + 2, 11), 478 (M^+, 5), 401 (8), 399 (9), 320 (21), 204 (100), 160 (80), 145 (43), 131 (78), 117 (31), 104 (45), 43 (21).

Compound (4d). uv λ_{max}: (Ethanol) 210 and 366 (weak) nm; IR: C=O1672 and C_5-C=O 1760 cm^{-1}; ^{1}H NMR: δ 2.24 (s, 3H, C_5-CH_3), 5.51 (d, 1H, $C_{3'}$-H, $J = 12$ Hz,), 5.60 (d, 1H, $C_{2'}$-H, $J = 12$ Hz), 7.10 (d, 2H, $C_{3'}$-ArH, $J = 6.2$ Hz), 7.35 (d, 2H, $C_{3'}$-ArH, $J = 6.2$ Hz), 7.57 (d, 2H, N_3-ArH, $J = 6.7$ Hz), 7.80 (d, 2H, N_3-ArH, $J = 6.7$ Hz); ^{13}C NMR: δ 15.0 (CH_3), 46.8 ($C_{3'}$), 57.4 ($C_{2'}$), 109.2 (C_5), 136.1–151.0 (ArC), 157.9 (C_2), 179.0 ($C_{1'}$); MS: m/z 502 (M + 4, 6), 500 (M + 2, 11), 498 (M^+, 4), 421 (12), 419 (13), 340 (47), 204 (100), 160 (17), 137 (33), 131 (80), 124 (50), 43 (27).

4-Bromo-p-(acetyl)-phenylsydnone (5)

Bromine (0.3 ml) taken in 5 ml of glacial acetic acid was added at room temperature with stirring to a suspension of (2.04 g 10.0 mmol) of **1** in glacial acetic acid (5 ml). After complete addition, stirring was continued for 30 min. The reaction mixture was poured into ice-cold water. The colourless solid separated was filtered and dried. Crystallization of the solid from ethanol yielded white crystalline compound **5** in 70% yield (1.98 g).

uv λ_{max}: (Ethanol) 225 and 374 (weak) nm; IR: sydnone C=O 1725 and C=O 1684 cm^{-1}; ^{1}H NMR: δ 2.19 (s, 3H, CH_3), 7.95 (d, 2H, ArH, $J = 8.04$ Hz), 8.05 (d, 2H, ArH, $J = 8.04$ Hz); ^{13}C NMR: δ 22.8 (CH_3), 100.8 (C_4), 129.6-111.9 (ArC), 170.6 (C_5), 196.5 (CO); MS: m/z 284 (M + 2, 6%), 282 (7), 254 (9), 252 (9), 252 (10), 226 (13), 224 (15), 203 (100%), 177 (80), 43 (21).

4-Bromo 3-[*p*-(3′-aryl-acryl-1′-oyl)] phenylsydnone (6a-d)

Thermal Method

A mixture of **5** (2.82 g, 10.0 mmol), aromatic aldehyde **2a-d** (10.0 mmol) in ethanol (10 ml), and sodium hydroxide solution (0.5 g in 5 ml of water). The reaction mixture was stirred for 45 min at room temperature. Final work up was as in case of **3a–d** to get **6a–d** in 64–68% yield.

Microwave Method

The experimental for preparation of **6a–d** was similar to that of preparation of **3a–d** and time required for completion of the reaction was 10 min. (Yield 73–90%).

Compound (6a). uv λ_{max}: (Ethanol) 280, 305 (strong), and 340 (weak) nm; IR: enone C=O 1653 and sydnone C=O 1729 cm^{-1} ; ^1H NMR: δ 7.74–7.95 (m, 9H, ArH), 8.16 (d, 1H, *trans* olefinic $C_{3'}$-H, J = 12 Hz), 8.24 (d, 1H, *trans* olefinic $C_{2'}$-H, J = 12 Hz); ^{13}C NMR: δ 96.40 (C_4), 119.0 ($C_{2'}$), 121.5–135.0 (ArC), 141.2 ($C_{3'}$), 164.0 ($C_{1'}$), 169.5 (C_5); MS: m/z 372 (M + 2, 8%), 370 (M^+, 9), 342 (15), 340 (17), 314 (19), 312 (21), 270 (97.38), 268 (100), 233 (60), 208 (44), 131 (77), 105 (34), 103 (270), 90 (54).

Compound (6b). uv λ_{max}: (Ethanol) 245, 290 (strong), and 325 (weak) nm; IR: enone C=O1650 and sydnone C=O 1734 cm^{-1}; ^1H NMR: δ 7.10 (d, 2H, $C_{3'}$-ArH, J = 5.0 Hz), 7.22 (d, 2H, $C_{3'}$-ArH, J = 5.0 Hz), 7.59 (d, 2H, N_3-ArH, J = 6.9 Hz), 7.80 (d, 2H, N_3-ArH, J = 6.9 Hz), 7.92 (d, 1H, *trans* olefinic $C_{3'}$-H, J = 13 Hz), 8.00 (d, 1H, *trans* olefinic $C_{2'}$-H, J = 13 Hz); ^{13}C NMR: δ 101.5 (C_4), 116.8 ($C_{2'}$), 120.1–133.9 (ArC), 140.6 ($C_{3'}$), 160.3 ($C_{1'}$), 169.0 (C_5); MS: m/z 453 (M + 4, 7), 451 (M + 2, 13), 449 (M^+, 7), 423 (11), 421 (20), 419 (10), 395 (7), 393 (13), 391 (8), 314 (34), 312 (36), 288 (60), 286 (64), 270 (96), 268 (100), 105 (81).

Compound (6c). uv λ_{max}: (Ethanol) 250, 305 (strong), and 330 (weak) nm; IR: enone C=O 1663 and sydnone C=O 1730 cm^{-1}; ^1H NMR: δ 2.38 (s, 3H, $ArCH_3$), 7.06 (d, 2H, N_3-ArH, J = 5.8 Hz), 7.20 (d, 2H, N_3-ArH, J = 5.8 Hz), 7.43 (d, 2H, $C_{3'}$-ArH, J = 8.4 Hz), 7.62 (d, 2H, $C_{3'}$-ArH, J = 8.4 Hz), 7.91 (d, 1H, *trans* olefinic $C_{3'}$-H, J = 10 Hz), 8.14 (d, 1H, *trans* olefinic $C_{2'}$-H, J = 10 Hz); ^{13}C NMR: δ 25.0 ($ArCH_3$), 106.0 (C_4), 122.3 ($C_{2'}$), 126.1-136.9 (ArC), 140.0 ($C_{3'}$), 165.8 ($C_{1'}$), 168.4 (C_5); MS: m/z 386 (M + 2, 9), 384 (M^+, 11), 356 (17), 354 (19), 328 (28), 326 (30), 270 (97), 268 (100), 247 (65), 221 (46), 145 (38), 117 (20), 105 (80), 104 (66).

Compound (6d). uv λ_{max}: (Ethanol) 250, 347 (strong), and 370 (weak)nm; IR: enone C=O 1668 and sydnone C=O 1715 cm^{-1}; ^1H NMR: δ 7.11 (d, 2H, N_3-ArH, J = 5.8 Hz), 7.35 (d, 2H, N_3-ArH, J = 5.8 Hz), 7.42 (d, 2H, $C_{3'}$-ArH, J = 8.4 Hz), 7.50 (d, 2H, $C_{3'}$-ArH, J = 8.4 Hz), 7.63 (d, 1H, *trans* olefinic $C_{3'}$-H, J = 10 Hz), 7.95 (d, 1H, *trans* olefinic $C_{2'}$-H, J = 10 Hz); ^{13}C NMR: δ 100.5 (C_4), 118 ($C_{2'}$), 119.0-133.0 (ArC), 141.6 ($C_{3'}$), 160.9 ($C_{1'}$), 172.0 (C_5); MS: m/z 406 (M + 2, 8), 404 (M^+, 9), 376 (18), 374 (21), 348 (30), 346 (33), 270 (98), 268 (100), 267 (60), 241 (40), 165 (31), 137 (19), 124 (18), 105 (88).

5-Methyl-3-[*p*-(3′-aryl- acryl-1′-oyl)-phenyl]-3H -2-oxo–Δ^4 -1,3,4-oxadiazole (7a–d)

Thermal Method

Compound **6a-d** (10.0 mmol) was suspended in pure acetic anhydride (5.0 ml) and the mixture was heated on oil bath until the brown fumes of acetyl bromide were removed (2 h). The mixture was poured into water and allowed to stand for 30 min. Colorless solid was filtered and washed with water and recrystallized using methanol-dioxane to get bright yellow crystals of **7a**–**d** in 66–72% yield.

Microwave Method

A mixture of **6a–d** (0.0 mmol) and pure acetic anhydride (3.0 ml) was taken in a borosil beaker (100 ml) was zapped inside a microwave oven at 80°C for a duration of 8 min (280 W, i.e., 40% microwave power). The reaction mixture was cooled and treated with water, dried. Bright yellow crystals of **7a–d** were obtained on recrystallization from methanol-dioxane mixture. (Yield 86–95%).

Compound (7a). uv λ_{max}: (Ethanol) 285, 346 (strong) and 356 (weak)nm; IR: C=O 1652 and C_5-C=O 1772 cm^{-1}; ^{1}H NMR: δ 2.33 (s, 3H, C_5-CH_3), 7.93–8.22 (m, 9H, ArH), 8.67 (d, 1H, *trans* olefinic $C_{3'}$-H, $J = 13$ Hz), 8.71 (d, 1H, *trans* olefinic $C_{2'}$-H, $J = 13$ Hz); ^{13}C NMR: δ 15.4 (CH_3), 120.9 ($C_{2'}$), 123.3-142.8 (ArC), 144.2 ($C_{3'}$),150.1 (C_5), 155.0 (C_2), 187.0 ($C_{1'}$); MS: m/z 306 (M^+, 8%), 204 (100), 160 (75), 131 (61), 103 (33), 90 (45), 43 (21).

Compound (7b). uv λ_{max}: (Ethanol) 256, 341 (strong) and 364 (weak)nm; IR: C=O 1647 and C_5-C=O 1784 cm^{-1} ; ^{1}H NMR: δ 2.14 (s, 3H, C_5-CH_3), 7.07 (d, 2H, N_3-ArH, $J = 7.2$ Hz), 7.27 (d, 2H, N_3-ArH, $J = 6.4$ Hz), 8.01 (d, 2H, $C_{3'}$-ArH, $J = 7.2$ Hz), 8.33 (d, 2H, $C_{3'}$-ArH, $J = 6.4$ Hz), 8.51 (d, 1H, *trans* olefinic $C_{3'}$-H, $J = 15$ Hz), 8.60 (d, 1H, *trans* olefinic $C_{2'}$-H, $J = 15$ Hz); ^{13}C NMR: δ 14.9 (CH_3), 119.4 ($C_{2'}$), 120.8–140.0 (ArC), 144.0 ($C_{3'}$), 155.01 (C_5), 161.7 (C_2), 181.6 ($C_{1'}$); MS: m/z 386 (M + 2, 8%), 384 (M^+, 9), 211 (10), 209 (11), 204 (100), 183 (15), 181 (17), 170 (19), 168 (21), 160 (64), 131 (50), 43 (20).

Compound (7c). uv λ_{max}: (Ethanol), 285, 320 (strong), and 350 (weak) nm; IR: C=O 1658 and C_5-C=O 1793 cm^{-1}; ^{1}H NMR: δ 2.09 (s, 3H, C_5-CH_3), 2.32 (s, 3H, $ArCH_3$), 7.71 (d, 2H, N_3-ArH, $J = 7.0$ Hz), 7.82 (d, 2H, N_3-ArH, $J = 7.0$ Hz), 8.25 (d, 2H, $C_{3'}$-ArH, $J = 5.9$ Hz), 8.44 (d, 2H, $C_{3'}$-ArH, $J = 5.9$ Hz), 8.63 (d, 1H, *trans* olefinic $C_{3'}$-H, $J =$ 11 Hz), 8.75 (d, 1H, *trans* olefinic $C_{2'}$-H, $J = 11$ Hz); ^{13}C NMR: δ 16.7 (CH_3), 16.7 (CH_3), 21.1 ($ArCH_3$), 122.2 ($C_{2'}$), 123.6-145.1 (ArC), 146.8

($C_{3'}$), 151.6 (C_5), 158.1 (C_2), 179.4 ($C_{1'}$); MS: m/z 320 (M^+, 10), 204 (100), 160 (70), 131 (40), 145 (33), 117 (24), 104 (60), 43 (18).

Compound (7d). uv λ_{max}: (Ethanol) 265, 357 (strong), and 370 (weak) nm; IR: C=O1650 and 1771 (C_5-C=O) cm^{-1}; ^1H NMR: δ 2.08 (s, 3H, C_5-CH_3), 7.05 (d, 2H, N_3-ArH, $J = 7.2$ Hz), 7.21 (d, 2H, N_3-ArH, $J = 6.4$ Hz), 7.54 (d, 2H, $C_{3'}$-ArH, $J = 7.2$ Hz), 7.67 (d, 1H, $C_{3'}$-ArH, $J = 6.4$ Hz), 8.24 (d, 1H, *trans* olefinic $C_{3'}$-H, $J = 15$ Hz), 8.35 (d, 1H, *trans* olefinic $C_{2'}$-H, $J = 15$ Hz); ^{13}C NMR 188.7 ($C_{1'}$), 159.3 (C_2), 155.0 (C_5), 145.2 ($C_{3'}$), 144.0-125.7 (ArC), 120.1 ($C_{2'}$), 15.0 (CH_3); MS: m/z 340 (M^+, 11), 204 (100), 160 (63), 131 (34), 165 (28), 137 (20), 124 (54), 43 (22).

5-Methyl-3-[*p*-(2′-aryl-2′,3′-dihydro-benzo[*b*][1′,5′]thiazepin-4′-yl)-phenyl]-3H-2-oxo-Δ^4-1,3,4-oxadiazole (8a-d)

Thermal Method

Compound **7a-d** (10.0 mmol) and *o*-amino thiophenol (10.0 mmol) were taken in absolute ethanol (20.0 ml) and saturated with dry HCl. The reaction mixture was refluxed on a water bath for 3 h, and the solvent was evaporated to obtain **8a–d**. The brown colored crude product on further crystallization from ethanol gave red crystals in 49–62% yield.

Microwave Method

A mixture of chalcone **7a–d** of (10.0 mmol), *o*-amino thiophenol (10.0 mmol) and glacial acetic acid (5.0 ml) in DMF (15 ml) was taken in a conical flask (100 ml) capped with a glass funnel and placed in a microwave oven and irradiated for 9 min at 65°C (250 W, 35% microwave power). The reaction mixture was cooled and treated with cold water. The solid **8a–d** separated was filtered, washed with water, and recrystallized from ethanol. (Yield 84–92%).

Compound (8a). uv λ_{max}: (Ethanol), 245, 350 (weak), 446, and 450 (strong) nm; IR: and C=N 1600 and C_5-C=O 1768 cm^{-1} ; ^1H NMR: δ 2.19 (s, 3H, C_5-CH_3), 3.1 (dd, 1H, $C_{3'}$-H_B, $J_{BA} = 17.6$ Hz, $J_{BX} = 11.8$ Hz), 3.6 (dd, 1H, $C_{3'}$-H_A, $J_{AB} = 17.6$ Hz, $J_{AX} = 4.49$ Hz), 4.91-5.0 (m, 1H, $C_{2'}$-H_X, $J_{XA} = 4.50$ Hz, $J_{XB} = 11.84$ Hz), 7.50-6.31 (m, 13H, ArH); ^{13}C NMR: δ 19.0 (CH_3), 40.1 ($C_{3'}$), 40.8 ($C_{2'}$), 115.3-137.4 (ArC), 154.9 (C_5), 160.0 (C_2), 164.6 ($C_{4'}$); MS m/z 413 (M^+, 5%), 398 (45), 354 (11), 313 (21), 238 (100), 211 (34), 179 (65), 77 (50).

Compound (8b). uv λ_{max}: (Ethanol) 232, 346 (weak), 440, and 448 (strong) nm; IR: C=N 1610 and C_5-C=O 1781 cm^{-1}; ^1H NMR: δ 2.11 (s,

3H, C_5-CH_3), 3.2 (dd, 1H, $C_{3'}$-H_B, $J_{BA} = 17.65$ Hz, $J_{BX} = 11.84$ Hz), 3.9 (dd, 1H, $C_{3'}$-H_A, $J_{AB} = 17.65$ Hz, $J_{AX} = 4.49$ Hz), 5.5–5.6 (m, 1H, $C_{2'}$-H_X, $J_{XA} = 4.50$ Hz, $J_{XB} = 11.80$ Hz), 6.36–6.90 (m, 4H, ArH), 6.92 (d, 2H, $C_{2'}$-ArH, $J = 8.0$ Hz), 7.31 (d, 2H, $C_{2'}$-ArH, $J = 8.0$ Hz), 7.58 (d, 2H, N_3-ArH, $J = 6.4$ Hz), 7.67 (d, 2H, N_3-ArH, $J = 6.4$ Hz); ^{13}C NMR: δ 16.3 (CH_3), 43.7 ($C_{3'}$), 44.0 ($C_{2'}$), 110.0–131.4 (ArC), 151.5 ($C_{4'}$), 155.0 (C_5), 156.5 (C_2); MS m/z 493 (M + 2, 6%), 491 (M^+, 7), 478 (21), 476 (23), 434 (41), 432 (42), 393 (11), 391 (14), 318 (97), 316 (100), 291 (24), 289 (26), 259 (44), 257 (47), 157 (37), 155 (39).

Compound (8c). uv λ_{max}: (Ethanol), 246, 334 (weak) 452 and 460 (strong) nm; IR: C=N 1605 and C_5-C=O 1767 cm^{-1}; ^{1}H NMR: δ 1.97 (s, 3H, C_5-CH_3), 2.25 (s, 3H, $ArCH_3$), 3.4 (dd, 1H, $C_{3'}$-H_B, $J_{BA} = 17.0$ Hz, $J_{BX} = 8.08$ Hz), 4.1 (dd, 1H, $C_{3'}$-H_A, $J_{AB} = 17.65$ Hz, $J_{AX} = 7.02$ Hz), 5.4-5.8 (m, 1H, $C_{2'}$- H_X, $J_{XA} = 6.96$ Hz, $J_{XB} = 7.99$ Hz), 6.57-7.01 (m, 4H, ArH), 7.12 (d, 2H, $C_{2'}$-ArH, $J = 8.0$ Hz), 7.18 (d, 2H, $C_{2'}$-ArH, $J = 8.0$ Hz), 7.60 (d, 2H, N_3-ArH, $J = 5.5$ Hz), 7.69 (d, 2H, N_3-ArH, $J = 5.5$ Hz); ^{13}C NMR: δ 17.0 (CH_3), 24.7 ($ArCH_3$), 40.4 ($C_{3'}$), 41.2 ($C_{2'}$), 112.0–141.2 (ArC), 150.0 (C_5), 156.0 (C_2), 165.7 ($C_{4'}$); MS m/z 427 (M^+, 7%), 412 (40), 368 (10), 327 (19), 252 (100), 225 (30), 193 (61).

Compound (8d). uv λ_{max}: (Ethanol) 236, 337 (weak), 441, and 448 (strong) nm; IR: C=N 1595 and C_5-C=O 1774 cm^{-1}; ^{1}H NMR: δ 2.00 (s, 3H, CH_3), 3.1 (dd, 1H, $C_{3'}$-H_B, $J_{BA} = 16.40$ Hz, $J_{BX} = 7.85$ Hz), 3.6 (dd, 1H, $C_{3'}$-H_A, $J_{AB} = 16.40$ Hz, $J_{AX} = 8.50$ Hz), 4.9 (m, 1H, $C_{2'}$- H_X, $J_{XA} = 8.48$ Hz, $J_{XB} = 7.87$ Hz), 6.59–6.74 (m, 4H, ArH), 4.8–7.04 (d, 2H, $C_{2'}$-ArH, $J = 8.0$ Hz), 7.12 (d, 2H, $C_{2'}$-ArH, $J = 8.0$ Hz), 7.31 (d, 2H, N_3-ArH, $J = 6.4$ Hz), 7.40 (d, 2H, N_3-ArH, $J = 6.4$ Hz); ^{13}C NMR: δ 15.4 (CH_3), 41 ($C_{3'}$), 42 ($C_{2'}$), 116.2-146.0 (ArC), 155 (C_5), 162.9 ($C_{4'}$), 164.0 (C_2); MS m/z: 447 (M^+, 7%), 432 (31), 388 (11), 347 (19), 272 (100), 245 (30), 213 (61), 111 (44).

CONCLUSIONS

In summary, this work demonstrates a rapid, efficient, and environmentally friendly method for the synthesis of 1,5-benzothiazepine derivatives (**8a–d**) under thermal and microwave heating, and the results obtained confirm the superiority of the microwave irradiation method over the classical heating one.

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