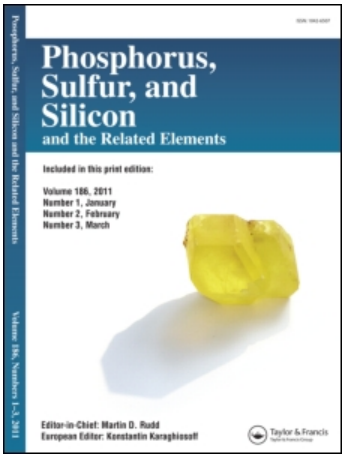

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis and Biological Screening of Novel Thiadiazoles, Selenadiazoles, and Spirocyclic Benzopyran by Ultrasonic and Microwave Irradiation

A. D. Shinde[a]; S. S. Sonar[a]; B. B. Shingate[a]; M. S. Shingare[a]
[a] Department of Chemistry, Dr. Babasheb Ambedkar Marathwada University, Aurangabad, India

Online publication date: 02 August 2010

To cite this Article Shinde, A. D. , Sonar, S. S. , Shingate, B. B. and Shingare, M. S.(2010) 'Synthesis and Biological Screening of Novel Thiadiazoles, Selenadiazoles, and Spirocyclic Benzopyran by Ultrasonic and Microwave Irradiation', Phosphorus, Sulfur, and Silicon and the Related Elements, 185: 8, 1594 — 1603
To link to this Article: DOI: 10.1080/10426500903136913
URL: http://dx.doi.org/10.1080/10426500903136913

Phosphorus, Sulfur, and Silicon, 185:1594–1603, 2010

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500903136913

Taylor & Francis
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SYNTHESIS AND BIOLOGICAL SCREENING OF NOVEL THIADIAZOLES, SELENADIAZOLES, AND SPIROCYCLIC BENZOPYRAN BY ULTRASONIC AND MICROWAVE IRRADIATION

A. D. Shinde, S. S. Sonar, B. B. Shingate, and M. S. Shingare
Department of Chemistry, Dr. Babasheb Ambedkar Marathwada University, Aurangabad, India

We describe the synthesis of novel thiadiazole, selenadiazole, and spirocyclic benzopyrans via the semicarbazides 3 and thiosemicarbazides 3 of 2-ethyl-2-methyl-4H-chromen-4-ones 1 by conventional and nonconventional methods. The microwave and ultrasonic irradiation methods form the respective products in excellent yields in very short reaction time as compared to the conventional method. The synthesized compounds were tested for antimicrobial screening against bacteria and fungi show moderate activity.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Biological activities; microwave and ultrasonic irradiation; selenadiazole; spirocyclic benzopyran; thiadiazole

INTRODUCTION

4*H*-Chromen-4-ones, a class of two oxygen heterocyclic systems, have a widespread existence among the plant kingdom.[1] Many natural and synthetic 4*H*-chromen-4-ones derivatives exhibit various types of biological activities[2,3] such as antiallergenic,[2a] anticancer,[2b] antifungal,[2c] and protein kinase C inhibitor,[2a] and are also used as substrates in the preparation of a variety of rearranged products and new heterocyclic systems.[3]

Thiadiazole derivatives are highly potent inhibitors of HIV-1[4a] and useful as anti-inflammatory[4b] and anti-arrhythmic agents.[4c] In addition, it is a common structural feature in many biologically active molecules that are used clinically in the treatment of some forms of epilepsy.[4d] The complexes of thiadiazole derivatives show antifungal[5a] and antibacterial,[5c] as well as carbonic anhydrase inhibitory activities.[5b] In particular, 1,2,3-thiadiazoles are useful pharmacophore and biologically active agents.[6] The compounds with the 1,2,3-thiadiazole nucleus are antibacterial, antipsychotic, platelet-activating factors and antagonistic[7] agents.

Received 24 February 2009; accepted 18 June 2009.
Address correspondence to M. S. Shingare, Department of Chemistry, Dr. Babasheb Ambedkar Marathwada University, Aurangabad- 431 004, MS, India. E-mail: prof_msshingare@rediffmail.com

1,2,4-Selenadiazole derivatives have potential biological activities and are important intermediates in medicinal chemistry.[8] The pair of sulfur and selenium are considered to be isosteric,[9] and the medicinal application of isosterism has been reviewed.[10] Selenium compounds have been found to be bactericides and their chemotherapeutic activities are reported.[11] Moreover, some bicyclic annelated 1,2,3-selenadiazoles are potent bioactive agents.[12] Recently, the synthesis of some fused selenadiazoles and thiodiazoles has been reported.[13]

Spirocyclic compounds have attracted considerable attention of organic chemists due to their unique structural and reactivity patterns. The spiro-1,3,4-thiadiazolines exhibit a broad spectrum of biological activities such as fungi-toxic, CNS stimulant, anticholinergic, hypoglycemic, and anticonvulsant.[14] They are used in industry as oxidation inhibitors, coloring agents, and complexing agents with metals.

The resistance of pathogenic bacteria toward available antibiotics is rapidly becoming a major worldwide problem, and it is known that antifungal drugs do not have selective activity because of the biochemical similarity between human cell and fungi forms. Therefore, the synthesis of new compounds to deal with antibacterial and antifungal activity is of growing interest.[15]

The science of green chemistry was developed to meet the increasing demand for environmentally benign chemical processes. Microwave[16] and ultrasonic[17] irradiation techniques are important in the search for green synthesis because of their use as an efficient alternative heating source for organic reactions. The main advantage of microwave and ultrasonically assisted organic synthesis is the shorter reaction time, simple experimental procedure, very high yields, and clean reaction of many microwave and ultrasonically induced transformations, which offer additional convenience in the field of organic synthesis. Thus, in this article, we describe syntheses of some new 4*H*-chromen-4-ones containing some 1,2,3-thiadiazole, 1,2,3-selenadiazole, and spiro-1,3,4-thiadiazoline moieties by modern techniques and their antimicrobial activities.

RESULTS AND DISCUSSION

In continuation of our work in synthetic organic chemistry,[18] a number of 2-ethyl-2-methyl-4*H*-chromen-4-ones **1** were synthesized by reacting ortho hydroxy acetophenone with 2-butanone in presence of pyrrolidine in 78–90% yield. Compound **1** was converted into semicarbazones **2** and thiosemicarbazones **3** by the treatment of semicarbazide hydrochloride and thiosemicarbazides, respectively, in presence of sodium acetate in good yields.

Semicarbazones **2** upon treatment with SeO_2 in acetic anhydride at 60°C for 2–3 h gave selenadiazoles **4** in 68–73% yield. The same selenadiazoles were obtained under ultrasound and microwave irradiation with 78–84% and 86–95% yields, respectively. The same semicarbazones **2** upon treatment with $SOCl_2$ under conventional, ultrasonic, and microwave irradiation afforded the 1,2,3-thiadiazoles **5** in 69–74%, 80–88%, and 89–97% yields, respectively. Similarly, thiosemicarbazide **3,** upon reaction with acetic anhydride at 60°C for 6 h, resulted in thiadizolines **6** in 62–71% yield. The same compounds **6** were obtained under ultrasound and microwave irradiation with 70–89% and 76–98% yields, respectively. The formation of compounds **1–6** was confirmed by physical and spectroscopic analysis (Tables I and II). In all cases, due to super heating, the time required to complete the reaction under microwave irradiation is lower than the ultrasonic irradiation (cavitation) and than conventional heating. Also, the formation of product using nonconventional energy

Table I Characterization data of the synthesized compounds

Entry	Compound no.	R_1	R_2	Yield (%)[a]	Mp (°C)
1	**1a**	H	H	90	56
2	**1b**	F	H	89	40
3	**1c**	Cl	Cl	85	39
4	**1d**	F	F	78	56
5	**1e**	OCH_3	H	81	40
6	**2a**	H	H	91	120
7	**2b**	F	H	88	145
8	**2c**	Cl	Cl	92	140
9	**2d**	F	F	87	155
10	**2e**	OCH_3	H	89	160
11	**3a**	H	H	93	139
12	**3b**	F	H	90	148
13	**3c**	Cl	Cl	88	144
14	**3d**	F	F	86	137
15	**3e**	OCH_3	H	91	140

[a]Isolated yields.

(microwave and ultrasonic irradiation) takes place in greater percentage as compared with the conventional heating.

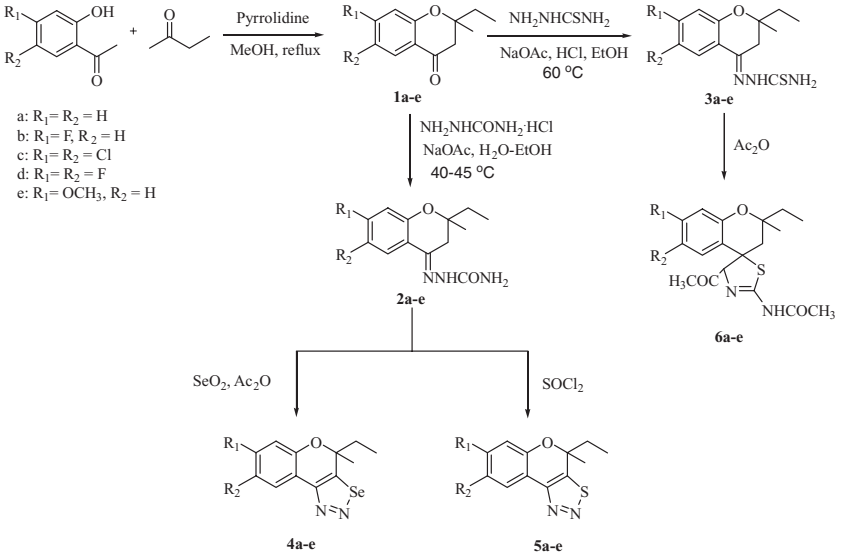
All the synthesized compounds were screened for antibacterial activities against *Staphylococcus aureus* and *Escherichia coli* and for antifungal activity against *Candida albicansa* and *A. fumigatus* at two conc. (500 and 1000 μg/mL). The compounds tested are compared against the standards (vancomycin and fluconazole) by measuring the diameter of zone of inhibition. All the compounds tested exhibited moderate activity at 1000 μg/mL,

Table II Characterization data of the synthesized compounds

				Conventional		Ultrasound		Microwave		
Entry	Compound No.	R_1	R_2	Time(h)	Yield(%)[a]	Time(min)	Yield(%)[a]	Time(min)	Yield(%)[a]	Mp/bp (°C)
1	**4a**	H	H	3	70	30	82	10	91	150[b]
2	**4b**	F	H	3	73	30	84	10	95	175[b]
3	**4c**	Cl	Cl	3	71	30	80	10	89	157[b]
4	**4d**	F	F	3	68	30	78	10	86	189[b]
5	**4e**	OCH_3	H	3	69	30	79	10	88	173[b]
6	**5a**	H	H	2	74	20	88	05	97	127[b]
7	**5b**	F	H	2	73	20	85	05	95	135[b]
8	**5c**	Cl	Cl	2	70	20	82	05	91	142[b]
9	**5d**	F	F	2	72	20	83	05	93	131[b]
10	**5e**	OCH_3	H	2	69	20	80	05	89	167[b]
11	**6a**	H	H	4	65	45	81	15	90	76
12	**6b**	F	H	4	68	45	84	15	92	79
13	**6c**	Cl	Cl	4	62	45	70	15	88	98
14	**6d**	F	F	4	67	45	86	15	93	78
15	**6e**	OCH_3	H	4	71	45	89	15	96	88

[a]Isolated yields.
[b]Boiling point.

and very few compounds at 500 μg/mL conc. Were found to be active against the bacteria and fungi. The results are described in Table S1 (Supplemental Materials, available online).



Scheme 1 Synthesis of novel thiadiazoles, selenadiazoles, and spirocyclic benzopyran by ultrasonic and microwave irradiation.

CONCLUSION

The experimental results show that the conventional methods are time-consuming and gives less yield as compared to modern methods such as microwave and sonication. We have synthesized a series of selenium and sulfur containing compounds, and among them, some of compounds are promising and show significant in vitro antifungal activity. The results suggest that selenium and sulfur are potent broad-spectrum antifungal agents with low toxicity.

EXPERIMENTAL

All the melting points were taken in open capillaries and are uncorrected. Cem Discover (Maximum current 6.3 A and 50/33 KHz frequency model No. 908010, USA) microwave oven was used for microwave irradiation. Bandelin Sonorex (35 KHz frequency) ultrasonic bath was used for ultrasonic irradiation. IR spectra were recorded in nujal on a Perkin-Elmer 1420 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian (300 MHz) spectrometer in DMSO as a solvent with TMS as internal standards. Mass spectra were recorded on a Kcatos MS-80 mass spectrometer.

Antibacterial Activity

All the compounds were screened for antibacterial activities against *Staphylococcus aureus* (MRSAE 710) and *Escherichia coli* (ESS 2231) using vancomycin as a standard, and

for antifungal activity against *Candida albicansa* (TCC 14503) and *A. fumigatus* (ATCC 16424) using fluconazole as a standard.

General Procedure: Compounds 1a–e

To a well stirred solution of 2-hydroxy acetophenone (0.01 mol) and butan-2-one (0.011 mol) in methanol (10 mL), pyrrolidine (0.012 mol) was added at room temperature. The reaction mixture was refluxed for 2–3 h. The completion of the reaction was monitored by TLC. The reaction mixture was quenched by crushed ice and extracted with ethyl acetate. The organic layer was washed by brine (2 × 15 mL) and dried over anhydrous sodium sulfate, and the solvent was removed under pressure to obtain the crude products. The obtained residues were purified by column chromatography on silica gel 60 (by packing wet column with silica gel 60, Merck, Darmstadt, Germany) by adsorbing residue on silica gel, and methylenedichloride and methanol (9:1) elutes were used. After evaporation of solvent, the pure desired compounds (**1a–e**) with high purity and 78–91% yield were obtained.

Compounds 2a–e

Semicarbazide hydrochloride (0.012 mol) and sodium acetate (0.015 mol) were taken in a conical flask and dissolved in distilled water (30 mL). To liberate a free base, the content was warmed on a water bath until a clear solution was obtained. To this reaction mixture, compound **1** (0.01 mol) was dissolved in ethanol (10 mL) and was added dropwise into the above reaction mass. Then the contents were warmed on a water bath for 3 h at 40–45°C, and the progress of the reaction was monitored by TLC. After the complete conversion, the contents were cooled. The white colored solid was separated out, which was filtered and recrystallized from ethanol to get pure product **2**.

Compounds 3a–e

To a well stirred solution of compound **1** (0.01 mol) in ethanol, a few drops of conc. HCl and an ethanolic solution of thiosemicarbazide (0.01 mol) were added dropwise with constant stirring. The reaction mixture was maintained at 60°C for 2 h on a water bath. After cooling, the solid product was filtered off and purified by column chromatography as described for compounds **1a–e** to yield 89–93% **3a–e**.

Compounds 4a–e

Method (A) conventional method. Compound **2** (0.01 mol) was dissolved in acetic acid (15 mL) and warmed to 60°C with stirring. To this, selenium dioxide (0.05 mol) was added portionwise. The stirring was continued at 60°C for 2–3 h until the evolution of gas ceased. After completion of the reaction as monitored by TLC, the contents were filtered to remove the deposited selenium. The filtrate was then poured over crushed ice, and the solid obtained was filtered, washed thoroughly with cold water, then with sodium carbonate solution, and again with water. The obtained compound was purified by column chromatography on silica gel 60 (by packing wet column with silica gel 60 [Merck,

Darmstadt, Germany]) by elution with methylene chloride and methanol (9:1). Evaporation of the solvent yielded **4a–e** with high purity.

Method (B) ultrasound method. The solution of compound **2** (0.01 mol) and acetic acid (15 mL) was irradiated under ultrasonic irradiation for 3 min. To this, selenium dioxide (0.05 mol) was added portionwise, and the irradiation was continued until the evolution of gas ceased. The progress of the reaction was monitored by TLC, and after completion of the reaction, the contents were filtered to remove the deposited selenium. The filtrate was then poured over crushed ice, and the obtained solid was filtered, washed thoroughly with cold water, then with sodium carbonate solution, and again with water. The same chromatographic workup was used to purify the products.

Method (C) microwave method. Compound **2** (0.01 mol) and selenium dioxide (0.05 mol) were dissolved in acetic acid (15 mL) in a 50 mL borosilicate glass tube. The reaction mixture was then irradiated inside a microwave oven for 10 min at an output of 500 Watts power, with short interruptions for 1 min. The progress of the reaction was monitored by TLC. After completion, the contents were filtered to remove the deposited selenium. The filtrate was then poured over crushed ice, and the obtained solid was filtered, washed thoroughly with cold water, then with sodium carbonate solution, and again with water. The obtained product **4** was purified by the column chromatographic technique described above.

Compounds 5a–e

Method (A) conventional method. In a 50 mL round bottom flask, compound **2** was dissolved (0.01 mol) in freshly distilled thionyl chloride (15 mL) at 0–5°C with constant stirring. The reaction was stirred for 4 h at 35–38°C. After completion of the reaction as monitored by TLC, it was poured in to ice cold water. The product was extracted with dichloromethane (50 mL), and the organic layer was washed with a 10% sodium bicarbonate solution. The organic layer was separated and dried over sodium sulfate, and the solvent was distilled out on a rotary evaporator until the compounds were purified by column chromatographic technique as described in compound **1a–e** to get compounds **5a–e**.

Method (B) ultrasound method. In a 50 mL round bottom flask, compound **2** (0.01 mol) was dissolved in freshly distilled thionyl chloride (15 mL) at 0–5°C with constant stirring. The mixture was subjected for ultrasound irradiation for 20 min. Progress of reaction was monitored with the help of TLC. After completion of the reaction, the contents were poured onto crushed ice. The product was extracted with dichloromethane, and the organic layer was washed with a 10% sodium bicarbonate solution. The organic layer was separated and dried over sodium sulfate, and the solvent was distilled out on a rotary evaporator to yield the desired product.

Method (C) microwave method. In a 50 mL borosilicate glass tube, compound **2** (0.01 mol) was dissolved in freshly distilled thionyl chloride (15 mL) at 0–5°C with constant stirring. The reaction mixture was irradiated inside a microwave oven for 10 min at an output of 500 Watts power, with short interruptions of 1 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents were cooled and poured into crushed ice. The product was extracted with dichloromethane, and the organic layer was washed with 10% sodium bicarbonate solution. It was separated and dried over sodium sulfate, and the solvent was removed by a rotary evaporator to get the desired product.

Compounds 6a–e

Method (A) conventional method. The solution of compound **3** (0.01 mol) in freshly distilled acetic anhydride (20 mL) was heated on an oil bath at 60–70°C for 4 h. After completion of reaction as monitored by TLC, the resulting contents were poured over crushed ice with vigorous stirring to give a pale yellow product, which was purified by the column chromatographic technique as described in compound **1a–e** to get compounds 6**a–e**.

Method (B) ultrasound method. In a 100 mL round bottom flask, a solution of compound **3** (0.01 mol) and freshly distilled acetic anhydride (15 mL) was subjected for ultrasound irradiation for 45 min. The progress of the reaction was monitored with the help of TLC. After completion of the reaction, the contents were poured into crushed ice with vigorous stirring. The solid obtained was then filtered and recrystallized from ethanol.

Method (C) microwave method. A mixture of compound **3** (0.01 mol) and freshly distilled acetic anhydride (15 mL) was taken in a 50 mL borosilicate glass beaker. The reaction mixture was irradiated inside a microwave oven for 15 min at an output of 500 Watts power, with short interruptions of 1 min. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled and poured into crushed ice with vigorous stirring. The solid obtained was then filtered and recrystallized from ethanol.

Spectral Data of Principle Compounds

1a: IR (KBr, cm^{-1}): 2974, 1692, 1608, 1239. ^{1}H NMR (DMSO-d_6, δ ppm): 0.91 (3H, t, CH_3); 1.32 (3H, s, CH_3); 1.62–1.78 (2H, m, CH_2); 2.79 (2H, q, CH_2); 6.98 (2H, m, Ar-H); 7.52 (1H, t, $J = 7.5$ Hz, Ar-H); 7.69 (1H, d, $J = 7.8$ Hz, Ar-H). MS: 191.33 (m + 1). ^{13}C NMR ($CDCl_3$, δ ppm): 7.84, 23.24, 31.93, 46.88, 81.26, 118.20, 120.27, 120.46, 126.29, 136.03, 159.78, 182.68.

1b: IR (KBr, cm^{-1}): 2987, 1677, 1611, 1245. ^{1}H NMR ($CDCl_3$, δ ppm): 0.92 (3H, t, CH_3); 1.35 (3H, s, CH_3); 1.62–1.81 (2H, m, CH_2); 2.90 (2H, q, CH_2); 7.05 (2H, m, Ar-H); 7.75 (1H, m, Ar-H); MS: 209.83 (m + 1). ^{13}C NMR (DMSO-d_6, δ ppm): 7.77, 24.27, 33.90, 49.48, 91.55, 129.28 130.34, 135.42, 146.32, 155.14, 169.77, 188.67.

1c: IR (KBr, cm^{-1}): 3077, 1677, 1610, 1167. ^{1}H NMR (DMSO-d_6, δ ppm): 1.0 (3H, t, CH_3); 1.43 (3H, s, CH_3); 1.72–1.86 (2H, m, CH_2); 2.73 (2H, q, CH_2); 7.54 (1H, s, Ar-H); 7.75 (1H, s, Ar-H); MS: 259.85 (m + 1). ^{13}C NMR (DMSO-d_6, δ ppm): 7.81, 23.18, 31.73, 46.84, 83.09, 121.87 124.28, 124.52, 125.32, 135.58, 159.70, 190.90.

1d: IR (KBr, cm^{-1}): 3145, 1665, 1600, 1152. ^{1}H NMR (DMSO-d_6, δ ppm): 1.0 (3H, t, CH_3); 1.43 (3H, s, CH_3); 1.72–1.86 (2H, m, CH_2); 2.73 (2H, q, CH_2); 7.54 (1H, m, Ar-H); 7.75 (1H, m, Ar-H); MS: 226.45 (m + 1). ^{13}C NMR (DMSO-d_6, δ ppm): 9.18, 24.10, 33.77, 47.82, 85.10, 122.77 125.38, 126.22, 128.65, 139.88, 165.70, 192.45.

1e: IR (KBr, cm^{-1}): 3014, 1669, 1605, 1167. ^{1}H NMR (DMSO-d_6, δ ppm): 1.0 (3H, t, CH_3); 1.72–1.86 (2H, m, CH_2); 2.73 (2H, q, CH_2); 3.47 (3H, OCH_3), 7.54 (1H, d, $J =$ 8.6 Hz, Ar-H); 7.75 (1H, d, $J = 7.2$ Hz, Ar-H), 7.78 (1H, d, $J = 3.5$ Hz, Ar-H), MS: 220.56 (m + 1). ^{13}C NMR (DMSO-d_6, δ ppm): 8.14, 24.26, 32.56, 47.45, 87.14, 122.57 126.54, 127.47, 126.25, 135.65, 160.70, 197.90

2a: IR (KBr, cm^{-1}): 3471, 1715, 1581, 1123. ^{1}H NMR (DMSO-d_6, δ ppm): 0.90 (3H, t, CH_3); 1.21 (3H, s, CH_3); 1.61 (2H, m, CH_2); 2.71 (2H, q, CH_2); 6.55 (2H, s, NH_2); 6.78 (1H, d, $J = 7.0$ Hz, Ar-H); 6.86 (1H, m, Ar-H); 7.19 (1H, t, $J = 7.4$ & 3 Hz, Ar-H); 8.07 (1H, d, $J = 7.6$ Hz, Ar-H); 9.40 (1H, s, NH). MS: 247.29 (m + 1). ^{13}C NMR ($CDCl_3$,

δ ppm): 8.20, 24.29, 32.70, 33.79, 39.40, 79.00, 123.45, 123.89, 124.77, 125.61, 129.13, 136.23, 148.20, 158.45.

2b: IR (KBr, cm^{-1}): 3521, 17141, 1551, 1123. ^1H NMR (DMSO-d_6, δ ppm): 0.93 (3H, t, CH_3); 1.32 (3H, s, CH_3); 1.77 (2H, m, CH_2); 2.54 (2H, q, CH_2); 6.52 (2H, s, NH_2); 6.70 (1H, d, $J = 7.5$ Hz, Ar-H); 7.23 (1H, m, Ar-H); 7.25 (1H, m, Ar-H); 9.40 (1H, s, NH). MS: 265.29 (m + 1). ^{13}C NMR ($CDCl_3$, δ ppm): 9.14, 25.30, 35.21, 36.56, 49.45, 85.12, 125.44, 126.91, 127.87, 128.59, 132.11, 138.27, 155.20, 1654.45.

2c: IR (KBr, cm^{-1}): 3517, 1725, 1589, 1133. ^1H NMR (DMSO-d_6, δ ppm): 0.91 (3H, t, CH_3); 1.25 (3H, s, CH_3); 1.56 (2H, m, CH_2); 3.19 (2H, q, CH_2); 7.60 (1H, s, Ar-H); 7.85 (1H, s, Ar-H), 8.42 (2H, s, NH_2); 10.42 (1H, s,). MS: 316.29 (m + 1). ^{13}C NMR ($CDCl_3$, δ ppm): 8.22, 23.39, 31.79, 33.89, 39.37, 79.62, 123.00, 123.30, 123.71, 125.81, 129.83, 136.63, 148.90, 157.57.

3a: IR (KBr, cm^{-1}): 3668, 1686, 1574, 1230. ^1H NMR (DMSO-d_6, δ ppm): 0.90 (3H, t, CH_3); 1.21 (3H, s, CH_3); 1.63 (2H, m, CH_2); 2.91 (2H, q, CH_2); 6.78 (1H, d, $J = 7.2$ Hz, Ar-H); 6.86 (1H, t, $J = 7.8$ Hz, Ar-H); 8.02 (2H, s, NH_2); 8.20 (2H, m, Ar-H); 10.34 (1H, s, NH). MS: 263.35 (m + 1). ^{13}C NMR ($CDCl_3$, δ ppm): 9.45, 22.35, 30.77, 34.79, 40.47, 80.67, 124.52, 125.30, 126.52, 127.85, 130.74, 137.25, 150.90, 155.57

3d: IR (KBr, cm^{-1}): 3674, 1696, 1564, 1245. ^1H NMR (DMSO-d_6, δ ppm): 0.95 (3H, t, CH_3); 1.26 (3H, s, CH_3); 1.58 (2H, m, CH_2); 2.80- 2.91 (2H, q, CH_2); 6.85–6.90 (1H, m, Ar-H); 7.30 (1H, m, Ar-H); 8.22 (2H, s, NH_2); 10.35 (1H, s, NH). MS: 2323.65 (m + 1). ^{13}C NMR ($CDCl_3$, δ ppm): 9.12, 21.56, 31.32, 35.23, 41.52, 85.75, 127.55, 127.53, 129.45, 131.44, 133.77, 141.84, 158.74, 165.25.

3e: IR (KBr, cm^{-1}): 3601, 1645, 1565, 1247. ^1H NMR (DMSO-d_6, δ ppm): 0.85 (3H, t, CH_3); 1.11 (3H, s, CH_3); 1.40–1.62 (2H, m, CH_2); 2.62–2.80 (2H, q, CH_2); 3.78 (3H, s, OCH_3) 6.80 (1H, d, $J = 8.5$ Hz, Ar-H); 6.85 (2H, t, $J = 7.0$ & 3 Hz, Ar-H); 7.58 (2H, s, NH_2); 9.42 (1H, s, NH). MS: 293.75 (m+1).

4a: IR (KBr, cm^{-1}): 2973, 1679, 1614, 1228. ^1H NMR (DMSO-d_6, δ ppm): 0.92 (3H, t, CH_3); 1.79 (3H, s, CH_3); 1.97–2.0 (2H, m, CH_2); 7.08 (1H, d, $J = 8$ Hz, Ar-H); 7.31 (2H, t, $J = 7.3$ & 2.8 Hz, Ar-H); 7.55 (1H, d, $J = 7.8$ Hz, Ar-H). MS: 279.26 (m + 1).

4c: IR (KBr, cm^{-1}): 3073, 1666, 1610, 1211. ^1H NMR (DMSO-d_6, δ ppm): 0.94 (3H, t, CH_3); 1.77 (3H, s, CH_3); 1.67–2.0 (2H, m, CH_2); 7.63 (1H, s, Ar-H); 7.99 (1H, s, Ar-H); MS: 348.26 (m + 1). ^{13}C NMR (DMSO-d_6, δ ppm): 8.61, 28.32, 35.33, 86.05, 120.50, 122.92, 123.06,126.56, 130.21, 147.11, 151.98, 160.47.

4e: IR (KBr, cm^{-1}): 2985, 1691, 1625, 1218. ^1H NMR (DMSO-d_6, δ ppm): 0.92 (3H, t, CH_3); 1.65 (3H, s, CH_3); 1.93–1.98 (2H, m, CH_2); 3.80 (3H, s, OCH_3) 6.88 (1H, d, $J =$ 8.85 Ar-H); 6.95 (1H, d, $J = 7.21$ Hz, Ar-H); 7.59 (1H, d, $J = 3$ Hz, Ar-H). MS: 309.22 (m + 1).

5a: IR (KBr, cm^{-1}): 2940, 1670, 1627, 1233. ^1H NMR (DMSO-d_6, δ ppm): 0.91 (3H, t, CH_3); 1.70 (3H, s, CH_3); 2.00 (2H, m, CH_2); 7.11 (2H, m, Ar-H,); 7.35 (1H, d, Ar-H, $J =$ 7.3 Hz); 8.03 (1H, d, $J = 7.5$ Hz, Ar-H). MS: 233.19 (m + 1). 232.30. ^{13}C NMR (DMSO-d_6, δ ppm): 9.31, 27.32, 36.32, 87.05, 122.70, 122.92, 125.45,127.47, 132.23, 150.11, 155.44, 165.54.

5b: IR (KBr, cm^{-1}): 3025, 1741, 1710, 1125. ^1H NMR (DMSO-d_6, δ ppm): 0.91 (3H, t, CH_3); 1.67 (3H, s, CH_3); 2.19 (2H, m, CH_2); 6.90 -7.15 (2H, dd, $J = 7.2$ & 2 Hz, Ar-H); 7.55 (1H, d, $J = 7.1$ Hz, Ar-H). MS: 250.49. ^{13}C NMR (DMSO-d_6, δ ppm): 10.22, 29.12, 37.78, 89.25, 127.77, 130.92, 135.45,139.47, 144.23, 151.56, 157.47, 169.59.

5e: IR (KBr, cm^{-1}): 2956, 1650, 1632, 1243. ^1H NMR (DMSO-d_6, δ ppm): 0.93 (3H, t, CH_3); 1.65 (3H, s, CH_3); 2.10 (2H, m, CH_2); 3.83 (3H, s, OCH_3); 6.90 -7.15 (2H, d,

$J = 8.5$ Hz, Ar-H); 7.55 (1H, d, $J = 7.9$ Hz, Ar-H). MS: 263.39 (m + 1).262.32. ^{13}C NMR (DMSO-d_6, δ ppm): 9.54, 21.57, 35.77, 85.55, 125.52, 133.25, 137.40,139.45, 148.25, 155.76, 159.49, 174.55.

6a: IR (KBr, cm^{-1}): 2939, 1710, 1621, 1237. ^{1}H NMR (DMSO-d_6, δ ppm): 0.892 (3H, m, CH_3), 1.19 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.91 (3H, s, CH_3), 2.05 (2H, s, CH_2), 6.75 (1H, d, $J = 7.2$ Hz, Ar-H), 7.11 (1H, t, $J = 7.3$ & 3 Hz, Ar-H), 7.25 (2H, m, Ar-H) 11.71 (1H, s, NH). MS: 347.43 (m + 1).

6b: IR (KBr, cm^{-1}): 2949, 1700, 1611, 1245. ^{1}H NMR (DMSO-d_6, δ ppm): 0.89 (3H, m, CH_3), 1.19 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.95 (2H, t, CH_2), 3.25 (2H, s, CH_2), 6.95 (1H, m, Ar-H), 7.11 (2H, m, Ar-H), 11.91 (1H, s, NH). MS: 366.35 (m + 1).

6c: IR (KBr, cm^{-1}): 2976, 1714, 1627, 1235. ^{1}H NMR (DMSO-d_6, δ ppm): 0.96 (3H, m, CH_3), 1.59 (2H, m, CH_2), 1.62 (2H; m, CH_2) 1.89 (3H, s, CH_3); 1.91 (3H, s, CH_3), 2.84 (2H, q, CH_2), 3.74 (3H, s, CH_3), 6.75 (1H, s, Ar-H), 7.50 (1H, bs), 7.64 (1H; s, Ar-H); 9.89 (1H, s, NH). MS: 416.32 (m + 1).

6d: IR (KBr, cm^{-1}): 2970, 1710, 1615, 1225. ^{1}H NMR (DMSO-d_6, δ ppm): 0.91 (3H, m, CH_3), 1.25 (3H, s, CH_3), 1.35 (3H; s, CH_3) 1.89 (2H, t, CH_2); 2.01 (3H, s, CH_3), 2.24 (3H, s, CH_3), 3.4 (2H, s, CH_2), 7.15 (1H, dd, $J = 7.8$ & 2.9 Hz, Ar-H), 7.33 (1H, m), 11.79 (1H, s, NH). MS: 383.41 (m + 1).

6e: IR (KBr, cm^{-1}): 3016,1740, 1633, 1245. ^{1}H NMR (DMSO-d_6, δ ppm): 0.95 (3H, m, CH_3), 1.20 (3H, s, CH_3), 1.80–1.97 (6H, 2×CH_3) 2.8 (2H; m, CH_2) 3.78 (3H, s, OCH_3); 7.45 (1H, d, $J = 8.35$ Hz, Ar-H), 8.10 (1H, d, $J = 7.5$ Hz, Ar-H), 8.25 (1H; d, $J = 3$ Hz, Ar-H); 9.87 (1H, s, NH). MS: 457.55 (m + 1).

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