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One Pot Multicomponent Microwave and Ultrasound Assisted Synthesis and Antimicrobial Activity of 2-(2-Ethoxy-5-substituted-indol-3-ylidene)-1-aryl-ethanones[1]

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Abstract—A novel series of 2-(2-ethoxyindol-3-ylidene)-1-arylethanones and 2-(5-bromo-2-ethoxyindol-3-ylidene)-1-arylethanones were synthesized from 1*H*-indole-2,3-dione or 5-bromo-1*H*-indole-2,3-dione, arylmethylketone and ethyl alcohol in the presence of sulphuric acid (conc.) under microwave and ultrasound irradiation. All newly synthesized compounds were characterized by elemental analysis and spectral methods: IR, ^{1}H and ^{13}C NMR, mass spectra. Evaluation of the *in vitro* antibacterial activity against bacterial (Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli*) and fungal (*Aspergillus niger* and *Candida metapsilosis*) strains revealed high antimicrobial activity of some tested compounds.

Keywords: isatin, chalcone, microwave irradiation, ultrasound irradiation, antimicrobial activity

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INTRODUCTION

The indole ring system is an important structural component of numerous pharmaceutical agents (Fig. 1) [1]. Indole and its analogs possess a wide spectrum of biological activities such as anti-inflammatory [2], antimicrobial [3], antibacterial [4], anticonvulsant [5], and cardiovascular [6]. Isatin(1*H*-Indole-2,3-dione) is applied in synthetic organic chemistry [7] and some of its derivatives demonstrate biological activities including antibacterial [8], antifungal [9], antiviral [10], anti-HIV [11], antiprotozoal [12], anticancer [13], muscle relaxant [14], and anti-allergic [15].

Chalcones demonstrated antioxidant [16], antimalarial [17], antileishmanial [18], antitumor [19], antituberculosis [20], and antibacterial [21] activities. The presence of a reactive α,β-unsaturated keto group in chalcones is responsible for their biological properties, that can be altered depending on the type and position of a substituent on the aromatic rings. Aroylmethyleneindol-2-ones, such as isatin based chalcone, are the essential building blocks in the synthesis of a wide range of spiro derivatives [22] that demonstrate important biological [23] and pharmaceutical [24] activities.

Application of microwave [25] and ultrasonic irradiations [26] as nonconventional energy sources for reactions activation has become a useful widely used method in organic synthesis. According to our studies [27] of the reactions carried out under conventional, microwaves and sonication initiation the best results were achieved under microwave irradiation (Scheme 1).

EXPERIMENTAL

Melting points were determined in open capillary tubes. Purity of the compounds was tested by TLC using silica gel plates 60_{254} (Merck). Microwave irradiation was carried out in the milestone multi SYNTH microwave system. Sonication was performed in Shanghai BUG40-06 ultrasonic cleaner (with a frequency of 25, 40, 59 kHz and a nominal power 250 W). Elemental analysis was determined by using a Thermo Finnigan CHNS analyzer. IR (KBr) spectra were recorded on a Shimadzu FT-IR-8400s spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on Bruker Avance II 400 MHz instrument using TMS as an internal standard. Mass spectra were measured on a GCMS-QP 1000 EX mass spectrometer.

Biological assay. The synthesized compounds were assayed against gram +ve and gram –ve bacterial and fungal cultures.

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[1] The text was submitted by the authors in English.

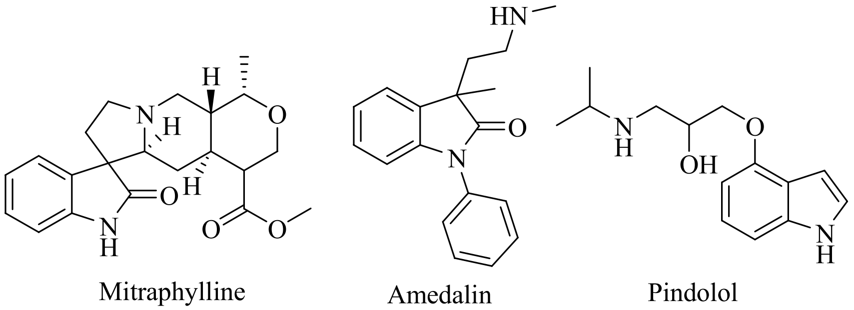
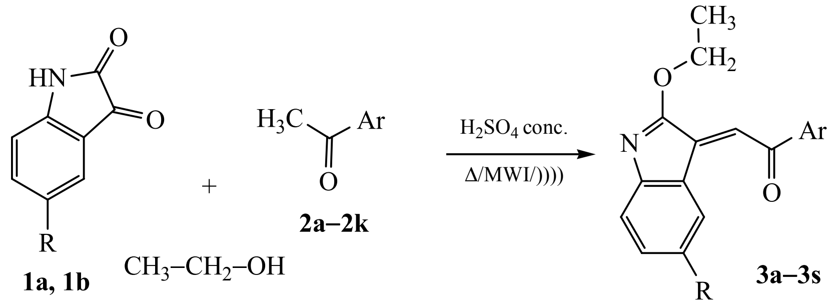


Fig. 1. Indole motif embedded natural compounds.

Antibacterial assay. All synthesized compounds were evaluated for their in vitro antibacterial activity against Gram positive bacteria (*Staphylococcus aureus*) and Gram negative bacteria (*Escherichia coli*). The bacterial cultures were grown in nutrient agar media and sub cultured for the better growth (log phase cultures) in a liquid nutrient broth medium and further sub cultured onto the Petri plates for the experiments. The broth cultures were diluted with sterilized saline to make the final size of inoculum ca 105–106 CFU/mL. The compounds were diluted in acetone, DMSO or diethyl ether for biological assays. Among three solvents diethyl ether has been singled out as the best one. The bacterial culture inoculum was placed on the media and incubated at 37ºC for 24 to 48 h along with the chemical discs dipped and placed over the media. The diameter of zones of bacterial growth inhibition were measured. All experiments were carried out in triplicates and the results were expressed as zone of inhibition in mm. The results were compared with the activity of the standard antibiotic Ampicillin (25, 50, and 100 μg/mL). For the disc diffusion method the test compound was introduced onto the disc and then dried out. Once the disc was completely saturated with the test compound, then it was introduced onto the upper layer of the medium containing the bacterial inoculum. The Petri dishes were incubated overnight at 37ºC for 24 h.

Antifungal assay. The antifungal activity of synthesized compounds was tested against three pathogenic fungi (Aspergillus niger and Candida Metapsilosis) by the poison plate technique. Test compounds were dissolved in diethyl ether (10 mL) before mixing with Potato Dextrose Agar medium (PDA, 90 mL). The concentration of compounds in the medium was adjusted to be 25, 50, and 100 μg/mL. The fungi were incubated in PDA at 25±1ºC for 3–4 days to get good mycelium growth for antifungal assay, then a mycelia disk (ca 0.45 cm) was cut from

Scheme 1.



R = H, Br; Ar = phenyl (**2a**), 4-methylphenyl (**2b**), 4-meothoxyphenyl (**2c**), 4-chlorophenyl (**2d**), 4-bromophenyl (**2e**), 4-nitrophenyl (**2f**), 2-naphthyl (**2g**), 1-naphthyl (**2h**), 2-hydroxyphenyl (**2i**), 2-hydroxy-5-methylphenyl (**2j**), 2-hydroxyl-5-chlorophenyl (**2k**); R = H, Ar = phenyl (**3a**), R = H, Ar = 4-methylphenyl (**3b**), R = H, Ar = 4-meothoxyphenyl (**3c**), R = H, Ar = 4-chlorophenyl (**3d**), R = H, Ar = 4-bromophenyl (**3e**), R = H, Ar = 4-nitrophenyl (**3f**), R = H, Ar = 2-naphthyl (**3g**), R = H, Ar = 1-naphthyl (**3h**), R = H, Ar = 2-hydroxyphenyl (**3i**), R = H, Ar = 2-hydroxy-5-methylphenyl (**3j**), R = H, Ar = 2-hydroxyl-5-chlorophenyl (**3k**), R = Br, Ar = phenyl (**3l**), R = Br, Ar = 4-methylphenyl (**3m**), R = Br, Ar = 4-meothoxyphenyl (**3n**), R = Br, Ar = 4-chlorophenyl (**3o**), R = Br, Ar = 4-bromophenyl (**3p**), R = Br, Ar = 2-naphthyl (**3q**), R = Br, Ar = 1-naphthyl (**3r**), R = Br, Ar = 2-hydroxyphenyl (**3s**).

the culture medium, picked up with a sterilized inoculation needle and inoculated in the center of PDA plate. The inoculated plates were incubated at 25±1°C for 5 days. Diethyl ether in sterilized distilled water was used as control. Grieseofulvin was used as a standard for all treatments. Three replicates were performed. The radial growth of the fungal colonies was measured on the fourth day and the data were statistically analyzed. The in vitro inhibition effects of the test compounds on the fungi were calculated by the formula CV =A – B/A, where A is the diameter of fungi growth on untreated PDA, B is the diameter of fungi on treated PDA, and CV is the rate of inhibition.

Antibacterial and antifungal activities. All products were screened for their antibacterial activity (Table 2) against *Escherichia coli* and *Staphylococcus aureus* using ampicillin as the reference drug. The synthesized compounds **3d, 3f, 3i, 3l, 3o** and **3r** exhibited high antibacterial activity against the tested organisms. Screening of the products for antifungal activity (Table 2, Fig. 2) (against *Aspergillus niger* and *Candida metapsilosis* using grieseofulvin as standard drug) revealed that the compounds **3e, 3f, 3i, 3n,** and **3s** demonstrated antifungal activity against all tested organisms.

Synthesis of 2-(2-ethoxyindol-3-ylidene)-1-aryl-ethanones and 2-(5-bromo-2-ethoxyindol-3-ylidene)-1-arylethanones (3a–3s). *a. Conventional heating method.* A mixture of 1*H*-indole-2,3-dione (**1a**) or 5-bromo-1*H*-indole-2,3-dione (**1b**) (1 mmol), aryl-methylketone **2a–2k** (1 mmol) and ethyl alcohol (10 mL) was refluxed for 5–6 h in the presence of conc. H_2SO_4 (3–4 drops). The progress of the reaction was monitored by TLC upon completion of the reaction. The reaction mixture was cooled down to room temperature and poured over crushed ice. The residue was filtered off, washed with water and purified by column chromatography using silica-gel (petroleum ether : ethyl acetate 10 : 1) to yield title compounds **3a–3s.**

Table 1. Conditions of synthesis of 2-(2-ethoxyindol-3-ylidene)-1-aryl-ethanones and 2-(5-bromo-2-ethoxyindol-3-ylidene)-1-aryl-ethanones (**3a–3s**)

Product no.	Reaction time			Yield, %		
	conventional, h	USI[a], min	MWI[b], min	conventional, h	USI[a], min	MWI[b], min
3a	5.0	50	6.0	66	82	88
3b	5.5	40	4.5	62	84	90
3c	5.0	40	4.0	70	84	92
3d	6.0	50	5.0	66	80	86
3e	6.0	45	5.5	68	79	87
3f	6.0	45	6.0	70	83	86
3g	5.0	45	5.0	72	80	90
3h	5.0	45	5.0	70	78	88
3i	5.0	50	5.5	74	80	90
3j	6.0	45	6.0	72	83	90
3k	5.5	45	6.0	69	81	89
3l	5.0	45	5.5	72	82	90
3m	6.0	40	4.5	66	80	88
3n	5.5	40	4.5	66	80	88
3o	5.0	45	5.0	72	82	90
3p	6.0	45	5.0	74	80	86
3q	5.0	40	5.0	70	83	86
3r	5.0	40	5.0	68	80	87
3s	6.0	45	5.5	70	82	90

[a] Ultrasound irradiation. [b] Microwave irradiation (melting points of the products are >300°C).

b. Ultrasonic irradiation method. A mixture of 1*H*-indole-2,3-dione (**1a**) or 5-bromo-1*H*-indole-2,3-dione (**1b**) (1 mmol), arylmethylketone **2a–2k** (1 mmol), ethyl alcohol 10 mL) and 3–4 drops of conc. H_2SO_4 was subjected to ultrasound irradiation for 40–50 min at 60°C. The progress of the reaction was monitored by TLC upon completion of the reaction. The reaction mixture was cooled down to room temperature and poured over crushed ice. The residue was filtered off, washed with water and purified by column chromatography using silica-gel (petroleum ether: ethyl acetate 10 : 1) to yield title compounds **3a–3s.**

c. Microwave irradiation method. A mixture of 1*H*-indole-2,3-dione (**1a**) or 5-Bromo-1*H*-indole-2,3-dione (**1b**) (1 mmol), arylmethylketone **2a–2k** (1 mmol), ethyl alcohol (10 mL) and 3–4 drops of conc. H_2SO_4 was loaded into a quartz tube and inserted into a Teflon screw capped vial and it was subjected to microwave irradiation at 160W for 4–6 min with 30 s intervals. The progress of the reaction was monitored by TLC upon completion of the reaction. The reaction mixture

Table 2. Inhibition zone of 2-(2-ethoxy-indol-3-ylidene)-1-aryl-ethanones and 2-(5-bromo-2-ethoxy-indol-3-ylidene)-1-aryl-ethanones (**3a–3s**)

Compound no.	Bacterial strains						Fungal strain					
	E. coli (conc. in μg/mL)			*S. aureus* (conc. in μg/mL)			*A. niger* (conc. in μg/mL)			*C. Metapsilosis* (conc. in μg/mL)		
	25	50	100	25	50	100	25	50	100	25	50	100
3a	4	8	11	4	7	9	6	9	15	7	11	16
3b	4	6	9	4	8	10	6	11	14	6	9	18
3c	5	9	12	3	6	8	8	8	18	5	9	16
3d	6	10	13	6	10	12	9	13	19	8	10	17
3e	3	8	9	5	8	10	10	14	20	10	15	21
3f	5	11	13	6	10	12	11	15	21	11	16	20
3g	4	7	11	3	6	8	5	9	14	5	10	19
3h	3	6	8	4	6	11	6	12	15	6	11	17
3i	5	9	12	6	10	13	10	15	19	11	16	21
3j	4	7	10	4	7	9	7	8	16	7	12	16
3k	4	8	9	5	8	11	7	11	14	6	10	18
3l	6	11	14	7	10	14	6	9	19	8	11	18
3m	4	8	12	4	7	9	7	10	15	6	10	18
3n	5	6	10	4	6	10	10	16	20	10	15	22
3o	5	9	12	6	10	12	8	12	19	9	14	20
3p	4	7	10	3	6	8	6	9	16	7	12	20
3q	4	6	9	5	8	9	6	11	18	8	10	19
3r	6	10	13	6	10	13	7	8	19	6	14	20
3s	4	8	11	4	8	10	11	14	21	11	17	22
Ampicillin	6	9	12	6	9	11						
Grieseofulvin							10	14	19	10	15	20

was cooled down to room temperature and poured over crushed ice. The residue was filtered off, washed with water and purified by column chromatography using silica-gel (petroleum ether: ethyl acetate 10 : 1) to yield the title compounds **3a–3s.**

Spectral data. **Compound 3a.** IR spetrum, ν, cm^{-1}: 1246 (C–O), 1589 (C=C), 1635 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.49–1.53 t (3H, –CH$_3$), 4.53–4.58 q (2H, –CH$_2$–), 7.63–7.70 m (4H, ArH), 7.76–7.81 m (1H, ArH), 8.08–8.12 m (2H, ArH), 8.20–8.22 m (1H, ArH), 8.35 s (1H, CH), 8.72–8.75 m (1H, ArH). ^{13}C NMR spectrum, δ$_C$, ppm: 14.4, 62.3, 123.6, 123.8, 125.3, 127.1, 127.5, 129.6, 129.7, 130.1, 136.4, 148.9, 156.6, 166.5. Found, %: C 77.89, H 5.40, N 5.11. $C_{18}H_{15}NO_2$. Calculated, %: C 77.96, H 5.45, N 5.05. *M* 278 [*M* + H]$^+$.

Compound 3b. IR spetrum, ν, cm^{-1}: 1247 (C–O), 1594 (C=C), 1628 (C=O). ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 1.49–1.53 t (3H, –CH$_3$), 2.46 s (3H, CH$_3$), 4.52–4.57 q (2H, –CH$_2$–), 7.35–7.37 d (2H, ArH), 7.59–7.64 m (1H, ArH), 7.74–7.79 m (1H, ArH), 8.10–8.12 d (2H, ArH), 8.20–8.22 m (1H, ArH), 8.37 s (1H, –CH–), 8.71–8.73 m (1H, ArH). ^{13}C NMR spectrum, δ$_C$, ppm: 14.4, 21.4, 62.9, 120.1, 123.9, 125.4, 127.4,

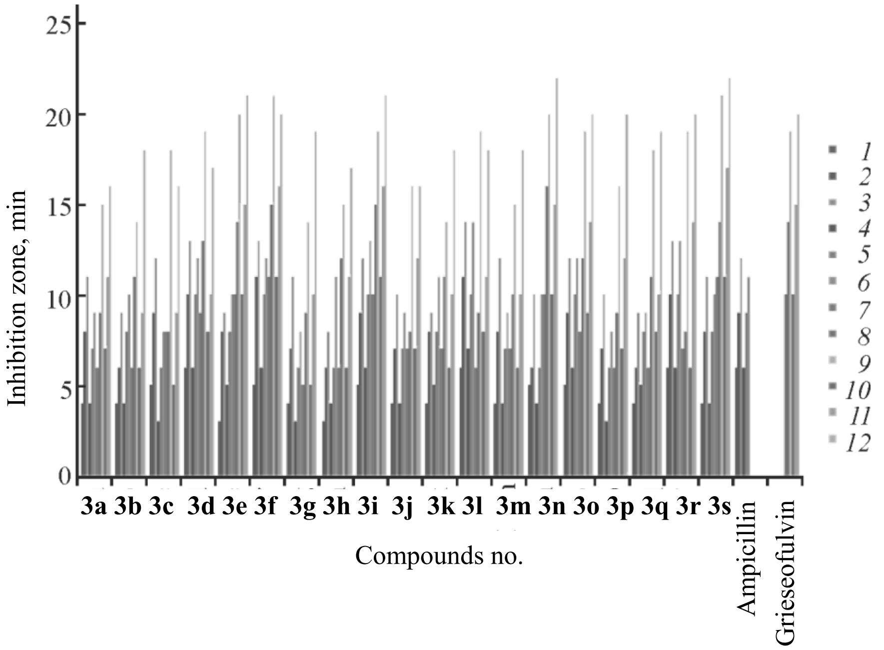


Fig. 2. Graphical representation of antimicrobial (%) inhibition. Concemtration, μg/mL: (*1*) *E. coli* 25, (*2*) *E. coli* 50, (*3*) *E. coli* 100, (*4*) *S. aureus* 25, (*5*) *S. aureus* 50, (*6*) *S. aureus* 100, (*7*) *A. niger* 25, (*8*) *A. niger* 50, (*9*) *A. niger* 100, (*10*) *C. Metapsilosis* 25, (*11*) *C. Metapsilosis* 50, (*12*) *C. Metapsilosis* 100.

127.5, 129.7, 129.8, 130.2, 136.0, 136.1, 139.9, 149.2, 156.7, 166.6. Found, %: C 78.27, H 5.92, N 4.78. $C_{19}H_{17}NO_2$ Calculated, %: C 78.33, H 5.88, N 4.81. *M* 292 $[M + H]^+$.

Compound 3c. IR spetrum, ν, cm^{-1}: 1246 (C–O), 1591 (C=C), 1630 (C=O). ^1H NMR spectrum, δ, ppm: 1.49–1.52 t (3H, $-CH_3$), 3.89 s (3H, OCH_3), 4.52–4.57 q (2H, $-CH_2-$), 7.05–7.07 d (2H, ArH), 7.57–7.61 m (1H, ArH), 7.73–7.77 m (1H, ArH), 8.17–8.19 m (3H, ArH), 8.34 s (1H, –CH–), 8.69–8.71 m (1H, ArH). ^{13}C NMR spectrum, δ_C, ppm: 14.4, 55.4, 61.9, 114.3, 119.8, 123.7, 125.4, 127.3, 128.9, 130.1, 131.4, 135.9, 149.3, 156.3, 161.1, 165.9. Found, %: C 74.28, H 5.62, N 4.51. $C_{19}H_{17}NO_3$ Calculated, %: C 74.25, H 5.58, N 4.56. *M* 308 $[M + H]^+$.

Compound 3d. IR spetrum, ν, cm^{-1}: 1244 (C–O), 1589 (C=C), 1632 (C=O). ^1H NMR spectrum, δ, ppm: 1.49–1.53 t (3H, $-CH_3$), 4.53–4.58 q (2H, $-CH_2-$), 7.51–7.53 d (2H, ArH), 7.62–7.66 m (1H, ArH), 7.77–7.80 m (1H, ArH), 8.16–8.18 d (2H, ArH), 8.20–8.22 d (1H, ArH), 8.35 s (1H, –CH–), 8.73-8.75 d (1H, ArH). ^{13}C NMR spectrum, δ_C, ppm: 14.4, 62.0, 119.7, 124.0, 125.5, 127.9, 128.7, 129.1, 130.1, 130.3, 135.9, 136.3, 137.2, 149.2, 155.4, 166.4. Found, %: C 69.30, H 4.48, N 4.50. $C_{18}H_{14}ClNO_2$. Calculated, %: C 69.35, H 4.53, N 4.49. *M* 312 $[M + H]^+$.

Compound 3e. IR spetrum, ν, cm^{-1}: 1242 (C–O), 1587 (C=C), 1634 (C=O). ^1H NMR spectrum, δ, ppm: 1.49–1.53 t (3H, $-CH_3$), 4.53–4.58 q (2H, $-CH_2-$), 7.63–7.66 m (1H, ArH), 7.67–7.70 d (2H, ArH), 7.76–7.81 m (1H, ArH), 8.08–8.12 d (2H, ArH), 8.20–8.22 d (1H, ArH), 8.35 s (1H, –CH–), 8.72–8.75 d (1H, ArH). ^{13}C NMR spectrum, δ_C, ppm: 14.4, 62.0, 119.7, 124.1, 124.4, 125.5, 128.0, 129.0, 130.0, 130.3, 132.1, 136.3, 137.7, 149.2, 155.4, 166.3. Found, %: C 60.74, H 3.89, N 3.97. $C_{18}H_{14}BrNO_2$. Calculated, %: C 60.69, H 3.96, N 3.93. *M* 356 $[M + H]^+$.

Compound 3f. IR spetrum, ν, cm^{-1}: 1246 (C–O), 1590 (C=C), 1627 (C=O). ^1H NMR spectrum, δ, ppm: 1.49–1.53 t (3H, $-CH_3$), 4.52–4.58 q (2H, $-CH_2-$), 7.17–7.19 m (1H, ArH), 7.49-7.60 m (2H, ArH), 7.71–7.80 m (2H, ArH), 8.13–8.16 m (2H, ArH), 8.29 s (1H, –CH–), 8.66–8.69 d (1H, ArH). ^{13}C NMR spectrum, δ_C, ppm: 14.5, 62.1, 118.9, 119.0, 123.7, 125.8, 127.1, 127.8, 130.7, 132.5, 137.6, 145.9, 157.7, 161.0, 165.9. Found, %: C 67.09, H 4.44, N 8.65. $C_{18}H_{14}N_2O_4$. Calculated, %: C 67.07, H 4.38, N 8.69. *M* 323 $[M + H]^+$.

Compound 3g. IR spetrum, ν, cm^{-1}: 1246 (C–O), 1594 (C=C), 1636 (C=O). ^1H NMR spectrum, δ, ppm: 1.52–1.58 t (3H, $-CH_3$), 4.56–4.61 q (2H, $-CH_2-$), 7.56–7.62 m (3H, ArH), 7.88–7.91 m (3H, ArH), 7.97–8.05 m (2H, ArH), 8.27–8.29 d (1H, ArH), 8.40–8.42 d

(1H, ArH), 8.55 s (1H, –CH–), 8.74–8.76 m (1H, ArH). ^{13}C NMR spectrum, δ_C, ppm: 14.3, 62.2, 122.6, 124.7, 125.1, 125.3, 125.7, 126.1, 126.5, 127.0, 128.0, 128.5, 128.9, 131.8, 133.3, 134.1, 134.9, 147.9, 156.8, 165.7. Found, %: C 80.69, H 5.28, N 4.31. $C_{22}H_{17}NO_2$. Calculated, %: C 80.71, H 5.23, N 4.28. *M* 328 [*M* + H]$^+$.

Compound 3h. IR spetrum, ν, cm^{-1}: 1244 (C–O), 1589 (C=C), 1630 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.44–1.48 t (3H, –CH$_3$), 4.49–4.55 q (2H, –CH$_2$–), 7.48–8.00 m (8H, ArH), 8.09–8.11 m (1H, ArH), 8.22 s (1H, –CH–), 8.73–8.75 d (1H, ArH), 8.83–8.85 d (1H, ArH). ^{13}C NMR spectrum, δ_C, ppm: 14.3, 62.1, 122.6, 125.1, 125.3, 125.4, 126.2, 126.5, 126.9, 128.6, 129.7, 130.8, 131.7, 133.6, 134.4, 134.9, 137.4, 147.7, 156.9, 165.7. Found: C 80.69, H 5.28, N 4.31. $C_{22}H_{17}NO_2$. Calculated, %: C 80.71, H 5.23, N 4.28. *M* 328 [*M* + H]$^+$.

Compound 3i. IR spetrum, ν, cm^{-1}: 1240 (C–O), 1600 (C=C), 1628 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.51–1.55 t (3H, –CH$_3$), 4.55–4.59 q (2H, –CH$_2$–), 7.01–7.05 m (1H, ArH), 7.14–7.16 d (1H, ArH), 7.40–7.45 m (2H, ArH), 7.66–7.70 m (1H, ArH), 7.81–7.83 d (1H, ArH), 7.99–8.02 d (1H, ArH), 8.56 s (1H, –CH–), 8.73–8.76 m (1H, ArH), 14.31 s (1H, –OH). ^{13}C NMR spectrum, δ_C, ppm: 14.5, 62.1, 118.9, 119.0, 123.7, 125.8, 127.1, 127.8, 130.7, 132.5, 137.6, 145.9, 157.7, 161.0, 165.9. Found, %: C 73.66, H 5.21, N 4.82.$C_{18}H_{15}NO_3$. Calculated, %: C 73.71, H 5.15, N 4.78. *M* 294 [*M* + H]$^+$.

Compound 3j. IR spetrum, ν, cm^{-1}: 1241 (C–O), 1586 (C=C), 1622 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.52–1.56 t (3H, –CH$_3$), 2.40 s (3H, –CH$_3$), 4.56–4.62 q (2H, –CH$_2$–), 7.00–7.02 d (1H, ArH), 7.19–7.22 d.d (1H, ArH), 7.61–7.65 m (1H, ArH), 7.76–7.79 m (2H, ArH), 8.07–8.09 d (1H, ArH), 8.52 s (1H, –CH–), 8.68–8.70 m (1H, ArH), 14.47 s (1H, –OH). ^{13}C NMR spectrum, δ_C, ppm: 15.2, 25.1, 63.7, 117.7, 117.9, 122.5, 122.9, 123.4, 124.1, 125.3, 128.4, 129.3, 129.9, 130.9, 134.6, 148.8, 155.9, 158.4, 166.0. Found: C 74.18, H 5.52, N 4.61$C_{19}H_{17}NO_3$. Calculated, %: C 74.25, H 5.58, N 4.56. *M* 308 [*M* + H]$^+$.

Compound 3k. IR spetrum, ν, cm^{-1}: 1240 (C–O), 1586 (C=C), 1629 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.53–1.57 t (3H, –CH$_3$), 4.59–4.64 q (2H, –CH$_2$–), 7.06–7.08 d (1H, ArH), 7.34–7.37 d.d (1H, ArH), 7.67–7.71 m (1H, ArH), 7.81–7.85 m (1H, ArH), 7.96–7.97 d (1H, ArH), 8.10–8.12 d (1H, ArH), 8.48 s (1H, –CH–), 8.74–8.76 d (1H, ArH), 14.47 s (1H, –OH). ^{13}C NMR spectrum, δ_C, ppm: 15.5, 63.5, 117.0, 117.9, 121.9, 122.5, 123.5, 124.4, 125.3, 126.8, 129.7, 131.8, 133.4, 137.4, 142.3, 147.0, 155.29, 158.4, 165.5. Found, %: C 65.88, H 4.35, N 4.34. $C_{18}H_{14}ClNO_3$. Calculated, %: C 65.96, H 4.31, N 4.27. *M* 328 [*M* + H]$^+$.

Compound 3l. IR spetrum, ν, cm^{-1}: 1242 (C–O), 1591 (C=C), 1632 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.49–1.53 t (3H, –CH$_3$), 4.53–4.58 q (2H, –CH$_2$–), 7.51–7.58 m (3H, ArH), 7.83–7.86 m (1H, ArH), 8.07–8.09 d (1H, ArH), 8.18–8.20 d (2H, ArH), 8.43 s (1H, –CH–), 9.01 s (1H, ArH). ^{13}C NMR spectrum, δ_C, ppm: 14.3, 62.1, 121.0, 122.3, 125.1, 127.5, 127.9, 129.0, 130.0, 131.8, 133.4, 134.8, 138.4, 147.8, 156.1, 165.8. Found, %: C 60.75, H 3.90, N 3.88. $C_{18}H_{14}BrNO_2$. Calculated, %: C 60.69, H 3.96, N 3.93. *M* 356 [*M* + H]$^+$.

Compound 3m. IR spetrum, ν, cm^{-1}: 1244 (C–O), 1591 (C=C), 1627 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.49–1.53 t (3H, –CH$_3$), 2.45 s (3H, CH$_3$), 4.52–4.57 q (2H, –CH$_2$–), 7.34–7.36 d (2H, ArH), 7.81–7.83 d (1H, ArH), 8.04–8.07 d (1H, ArH), 8.08–8.10 d (2H, ArH), 8.41 s (1H, –CH–), 8.98 s (1H, ArH). ^{13}C NMR spectrum, δ_C, ppm: 14.3, 21.4, 62.1, 120.8, 121.9, 124.9, 127.9, 129.7, 131.7, 133.3, 134.7, 135.6, 140.2, 147.8, 156.9, 165.9. Found, %: C 61.58, H 4.41, N 3.75. $C_{19}H_{16}BrNO_2$. Calculated, %: C 61.64, H 4.36, N 3.78. *M* 370 [*M* + H]$^+$.

Compound 3n. IR spetrum, ν, cm^{-1}: 1253 (C–O), 1588 (C=C), 1626 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.49–1.53 t (3H, –CH$_3$), 3.90 s (3H, –OCH$_3$), 4.52–4.57 q (2H, –CH$_2$–), 7.05–7.07 d (2H, ArH), 7.80–7.82 m (1H, ArH), 8.02–8.04 d (1H, ArH), 8.18–8.20 d (2H, ArH), 8.38 s (1H, –CH–), 8.96 s (1H, ArH). ^{13}C NMR spectrum, δ_C, ppm: 14.3, 55.4, 62.1, 114.4, 120.6, 121.7, 124.7, 127.9, 128.9, 130.9, 131.6, 133.3, 134.7, 147.9, 156.6, 161.3, 165.9. Found, %: C 59.12, H 4.15, N 3.59. $C_{19}H_{16}BrNO_3$. Calculated, %: C 59.08, H 4.18, N 3.63. *M* 386 [*M* + H]$^+$.

Compound 3o. IR spetrum, ν, cm^{-1}: 1249 (C–O), 1590 (C=C), 1629 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.49–1.53 t (3H, –CH$_3$), 4.53–4.58 q (2H, –CH$_2$–), 7.50–7.52 d (2H, ArH), 7.82–7.85 m (1H, ArH), 8.04–8.06 d (1H, ArH), 8.13–8.15 d (2H, ArH), 8.38 s (1H, –CH–), 8.99 s (1H, ArH). ^{13}C NMR spectrum, δ_C, ppm: 14.3, 62.2, 120.6, 122.5, 125.1, 127.9, 128.6, 128.7, 129.1, 129.2, 131.8, 133.6, 135.0, 136.3, 136.8, 147.8, 155.7, 165.7. Found, %: C 55.39, H 3.30, N 3.64. $C_{18}H_{13}BrClNO_2$. Calculated, %: C 55.34, H 3.35, N 3.59. *M* 389 [*M* + H]$^+$.

Compound 3p. IR spetrum, ν, cm^{-1}: 1249 (C–O), 1589 (C=C), 1628 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.49-1.53 t (3H, –CH$_3$), 4.53–4.58 q (2H, –CH$_2$–), 7.66–7.68 d (2H, ArH), 7.83–7.85 m (1H, ArH), 8.04-8.07 m (3H, ArH), 8.38 s (1H, –CH–), 8.99 s (1H, ArH). ^{13}C NMR spectrum, δ$_C$, ppm: 14.3, 62.2, 120.5, 122.5, 124.7, 127.9, 128.9, 131.8, 132.2, 133.6, 135.0, 137.2, 147.8, 155.7, 165.7. Found, %: C 49.74, H 3.05, N 3.16. $C_{18}H_{13}Br_2NO_2$. Calculated, %: C 49.69, H 3.01, N 3.22. *M* 434 [*M* + H]$^+$.

Compound 3q. IR spetrum, ν, cm^{-1}: 1242 (C–O), 1591 (C=C), 1633 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.51–1.54 t (3H, –CH$_3$), 4.54–4.59 q (2H, –CH$_2$–), 6.96–7.00 m (1H, ArH), 7.07–7.09 m (1H, ArH), 7.37–7.41 m (1H, ArH), 7.80–7.94 m (3H, ArH), 8.53 s (1H, –CH–), 8.94 s (1H, ArH), 14.31 s (1H, –OH). ^{13}C NMR spectrum, δ$_C$, ppm: 15.6, 63.2, 116.9, 118.0, 121.9, 122.3, 123.5, 124.4, 125.3, 126.8, 129.7, 131.8, 133.3, 135.6, 137.4, 142.3, 147.0, 155.3, 158.4, 165.8. Found, %: C 58.12, H 3.83, N 3.81. $C_{18}H_{14}BrNO_3$. Calculated, %: C 58.08, H 3.79, N 3.76. *M* 372 [*M* + H]$^+$.

Compound 3r. IR spetrum, ν, cm^{-1}: 1245 (C–O), 1595 (C=C), 1630 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.44–1.48 t (3H, –CH$_3$), 4.50–4.55 q (2H, –CH$_2$–), 7.51–7.75 m (3H, ArH), 7.89–7.91 d (1H, ArH), 7.94–8.09 m (5H, ArH), 8.27 s (1H, –CH–), 9.10 s (1H, ArH). ^{13}C NMR spectrum, δ$_C$, ppm: 14.3, 62.2, 122.7, 125.0, 125.2, 125.4, 126.2, 126.9, 128.0, 128.6, 129.8, 130.9, 131.7, 133.6, 134.0, 134.5, 137.4, 147.7, 159.3, 165.7. Found, %: C 65.12, H 3.91, N 3.40. $C_{22}H_{16}BrNO_2$. Calculated, %: C 65.04, H 3.97, N 3.45. *M* 406 [*M* + H]$^+$.

Compound 3s. IR spetrum, ν, cm^{-1}: 1246 (C–O), 1602 (C=C), 1629 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.52–1.56 t (3H, –CH$_3$), 4.56–4.61 q (2H, –CH$_2$–), 7.55–7.57 m (2H, ArH), 7.84–7.87 m (2H, ArH), 7.89–8.02 m (2H, ArH), 8.11–8.13 d (1H, ArH), 8.37–8.39 m (1H, ArH), 8.58 s (1H, –CH–), 8.64 s (1H, ArH), 9.10 s (1H, ArH). ^{13}C NMR spectrum, δ$_C$, ppm: 14.4, 62.2, 121.2, 122.3, 124.6, 125.1, 126.6, 127.1, 127.3, 127.8, 128.8, 128.9, 131.8, 133.4, 133.5, 134.1, 134.9, 135.7, 147.8, 156.8, 165.9. Found, %: C 65.09, H 3.92, N 3.48. $C_{22}H_{16}BrNO_2$. Calculated, %: C 65.04, H 3.97, N 3.45. *M* 406 [*M* + H]$^+$.

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