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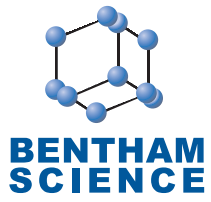
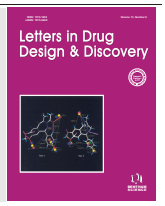


Synthesis and Microbial Evaluation of Versatile Base Catalyzed Chiral Tetrahydrobenzofuran Derivatives *via* Multicomponent Reaction



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Abstract: A base catalyzed sequential one-pot protocol for an effective preparation of *3-(substitutedphenyl) -6,6-dimethyl-2-(substitutedphenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one derivatives* have been described. One-pot reaction of aromatic aldehydes, various phenacyl bromide and dimedone gives corresponding substituted benzofurans in economically affordable yields with stereo specificity at **2nd** and **3rd** position via formation of substituted pyridinium ylides. Newly synthesized compounds were characterized by different spectral techniques such as IR, ^{1}H NMR, ^{13}C NMR and Mass spectrometry. Furthermore, the structure of compound **4f** was unambiguously assigned by X-ray crystallography. All the synthesized compounds were subjected to *in-vitro* antimicrobial screening against a panel of pathogenic strains of bacteria to evaluate their potency as a MIC. Some of the compounds were found to be equipotent or extra potent than commercial antibiotics against some active strains.

Keywords: Tetrahydrobenzofurans, dimedone, multicomponent reactions (MCRs), antimicrobial activity, MIC, XRD study.

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INTRODUCTION

One pot synthesis in organic chemistry was performed through tandem, domino or cascade reactions [1, 2] and has become a substantial area of research [3-10] due to improved atom economy. Generally one-pot transformations are carried out by multistep chain reactions under same reaction conditions. Two or more steps are applied, if above reaction conditions is not fruitful, by addition of correct sequence of reactants. There are so many cases were found in literature to form desire products using two or more than two starting materials which possess minimum requirement for the formation of single desired products used in one reaction vessel is known as a Multicomponent reactions [11, 12], that coupled all reactants in such a way to maintain same reaction conditions.

Among various heterocycles in nature as well as in commercially collected biologically active compounds, benzofuran derivatives constitutes major cluster. The diverse medicinally activity in different benzofurans specifies that this compound is of an undisputed attentiveness preferably due to their potential applications and pronounced biological activities as pharmacological agents. Moreover, because of its wide range of biological activities, their structure activity relationships have generated attention among therapeutic chemists, and this has terminated in the discovery of many lead molecules in several disease conditions as a simplest strategic way. The outstanding progress of benzofuran derivatives in diverse diseases in a very short period of time proves its magnitude and efficacy for medicinal chemistry research [13].

In recent eras benzofuran scaffolds drawn considerable attention due to their reflective biological, physiological and chemotherapeutic properties as well as their extensive occurrence in nature [14, 15]. Derivatives of benzofuran shows potent biological properties such as antihyperglycemic agents [16], severe analgesic properties [17], anti-parasitic [18], antimicrobial [19], anticancer, cytochrome P450 19 (CYP19) [20] and kinase inhibitor [21] activities.

By applying diversity of MCRs to generate potent heterocycles, particularly substituted benzofuran, may direct to give a medicinally persuasive motif. The most common way to attain this concept is aromatization to particular heterocycles by the easiest way and commercially affordable route. Aromatization of substituted cyclohexenones to the corresponding phenol or phenyl ether or benzofurans derivatives has been attracted a great deal of attention for a long time [22]. Preferably MCRs of cyclohexenones to aromatization is a great way to synthesized pharmacologically diverse benzofuran nucleus. Inspired by these findings, we herein report the synthesis of variety of tetrahydrobenzofurans **4a-4x, 4a'-4h'** and their anti-microbial activity at a minimum inhibitory concentration (MIC). Activity data reveal that not all but most of the compounds exhibited potency against a specific strain and give comparable MIC than control compounds.

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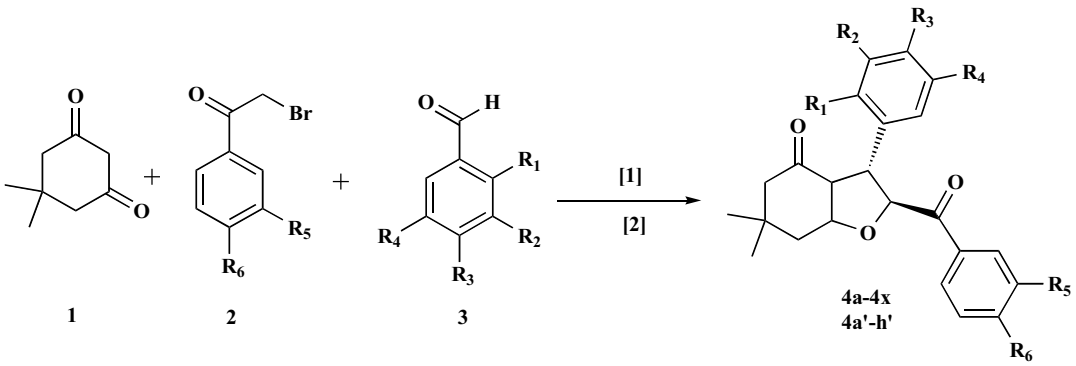


Scheme (1). Synthetic pathway for compounds **4a-4x, 4a'-4h'**.
Reaction and condition*: 1) Acetonitrile, Pyridine, Reflux, 80 ^{o} C; 2) Triethylamine, Reflux, 80 ^{o} C
*Both steps were performed insitu reaction mixture.

RESULTS AND DISCUSSION

General

Due to vast application and importance of benzofuran, many efforts have been carried out to design a more potent benzofuran scaffold. To fulfill the target, 3,5,6,7-tetrahedro-*2H*-benzofuran-4-ones were prepared by the condensation of phenacylbromides, dimedone, and various substituted aromatic aldehydes by Wang *et al.* [22].

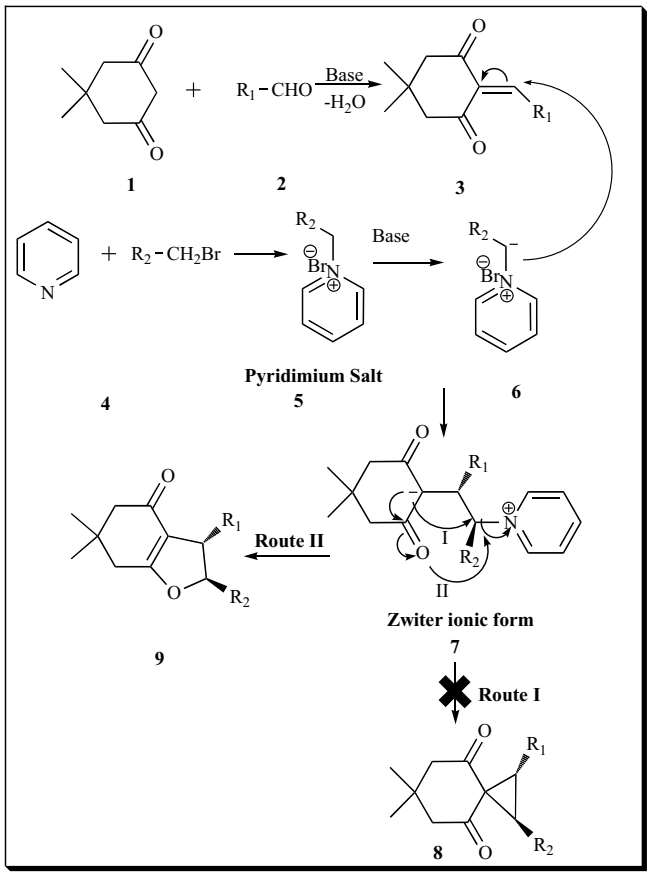
Chemistry

Synthesis of all compounds was successfully accomplished using universal organic synthetic pathways and their chemical structure was illuminated by general spectroscopic analysis (^{1}H and ^{13}C NMR, IR, MS and XRD).

Condensation of dimedone **1**, various phenacyl bromide **2** and substituted aromatic aldehyde **3** using acetonitrile as a solvent and pyridine as a basic catalyst under reflux for 3h, later on addition of Et_3N and continuation of the reaction for appropriate time (Table **1**) gave fused system of *3-(substitutedphenyl)-6,6-dimethyl-2-(substitutedphenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4 (2H)-derivatives* (**4a-4x**, **4a'-4h'**) (Scheme **1**).

The results validated that aromatic aldehyde and phenacyl bromide carrying either electron-donating or electron-withdrawing groups are well tolerated under the optimized reaction condition to yield the desired products in better purity. A proposed mechanism [23] for the formation of product **4a-4x**, **4a'-4h'** is shown in Scheme (**2**).

The reaction proceeds through pyridinium ylide intermediate in one-pot reaction. The reaction is proceeding by the reaction of dimedone **1** with aromatic aldehyde **2** to furnish arylidene intermediate **3**. Pyridinium salt **5** was generated by the condensation of phenacyl bromide **4** with pyridine which later on reacts with arylidene intermediate **3** to give the zwitter ionic salt **7**. If reaction is proceeding via route I, the formation cyclopropane **8** derivatives are possible which involves intramolecular substitution of the carbanion displacing the pyridine, which is not observed here. In case of route II, the final product 2,3-dihydrofuran **9** was furnished due to replacement of more stable enolate by pyridine, which can be confirmed by analytical and spectral data. Further confirmation of trans product and substituents position was carried out by XRD study of compound **4f** (Fig. **1**).



Scheme (2). Proposed Reaction mechanism for the final structure.

The geometry of **4a-4x**, **4a'-4h'** are clearly assigned as the trans-diastereomer with the help of the vicinal coupling constants of methine protons, which showed ^{3}JHH values ~ **2 Hz** and also from the literature [24-26].

Table 1. Effect of various substituents on completion of reaction time and related yield.

Code	R_1	R_2	R_3	R_4	R_5	R_6	Time* (hrs)		Yield (%)	
							Performed at RT	Performed at 70 °C	Performed at RT	Performed at 70 °C
4a	H	H	Cl	H	H	OCH_3	8	8	89	94
4b	H	$OCH_2CP^{\dagger}$	$OCHF_2$	H	H	OCH_3	13	15	82	84
4c	H	OCH_3	OCH_3	OCH_3	H	OCH_3	14	12	77	86
4d	H	OCH_3	H	H	H	OCH_3	14	12	76	85
4e	H	H	OC_2H_5	H	H	OCH_3	12	10	75	88
4f	H	H	Br	H	H	OCH_3	11	10	81	90
4g	H	H	CH_3	H	H	OCH_3	15	11.5	84	90
4h	NO_2	H	H	H	H	OCH_3	16	12	70	79
4i	H	H	Cl	H	H	Br	8	8	79	90
4j	H	$OCH_2CP^{\dagger}$	$OCHF_2$	H	H	Br	18	16	81	89
4k	H	OCH_3	OCH_3	OCH_3	H	Br	15	13	76	88
4l	H	OCH_3	H	H	H	Br	15	10	74	87
4m	H	H	OC_2H_5	H	H	Br	11	9	75	85
4n	H	H	Br	H	H	Br	11	10	81	88
4o	H	H	CH_3	H	H	Br	16	14	84	90
4p	NO_2	H	H	H	H	Br	16	13	69	73
4q	H	H	Cl	H	H	NO_2	8	8	82	91
4r	H	$OCH_2CP^{\dagger}$	$OCHF_2$	H	H	NO_2	19	14	81	86
4s	H	OCH_3	OCH_3	OCH_3	H	NO_2	13	16	76	84
4t	H	OCH_3	H	H	H	NO_2	13	13	77	86
4u	H	H	OC_2H_5	H	H	NO_2	12	11	74	89
4v	H	H	Br	H	H	NO_2	11	10	81	90
4w	H	H	CH_3	H	H	NO_2	14	15	83	88
4x	NO_2	H	H	H	H	NO_2	16	18	64	73
4a’	H	H	Cl	H	H	CH_3	8	8	78	89
4b’	H	$OCH_2CP^{\dagger}$	$OCHF_2$	H	H	CH_3	16	15	81	85
4c’	H	OCH_3	OCH_3	OCH_3	H	CH_3	13.5	11.5	75	89
4d’	H	OCH_3	H	H	H	CH_3	13	11	79	89
4e’	H	H	OC_2H_5	H	H	CH_3	12.5	9	74	88
4f’	H	H	Br	H	H	CH_3	11	10	82	89
4g’	H	H	CH_3	H	H	CH_3	15	14	88	89
4h’	NO_2	H	H	H	H	CH_3	16	14.5	66	71

*Given time noted after completion of reaction (Included addition of pyridine and TEA)
†CP = Cyclopropyl group

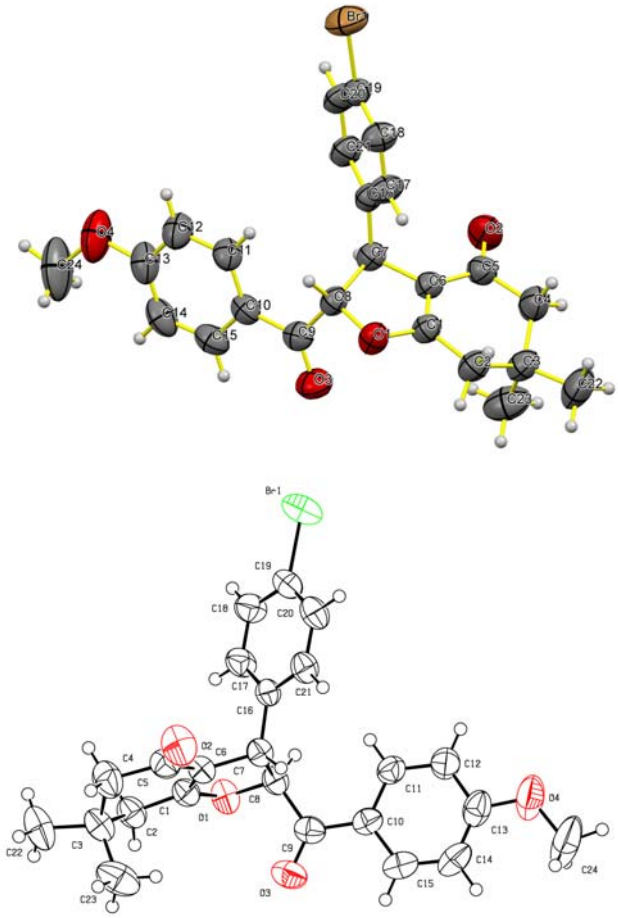


Fig. (1). ORTEP view of crystal structure **4f**.

In the IR spectrum of compounds, carbonyl ketone group present in the final product (**4a-4x**, **4a'-4h'**) shows a confirmatory band at ~**1680** - **1705** cm^{-1}. By NMR spectra, doublet for the proton of chiral carbon C2 and C3 was observed at ~ **4.5 δ ppm** and ~ **6.5 δ ppm** respectively. Moreover, the presence of two methyl group in dimedone ring was observed at ~ **1.0 δ** ppm. Further confirmation of the final product was carried out by the absence of an ethylene proton (~ **3.6 δ ppm**) (exist between two carbonyl group in dimedone ring). The ^{13}C NMR spectrum of the product **4a-4x**, **4a'-4h'** exhibited, two methyl group carbon of benzofuran ring signal was appeared at ~ **28.00 δ** ppm, two methylene carbons give signal at ~ **38.80** and ~ **50.57 δ ppm** respectively. One methylene group signals appeared in down filed due to the de-shielding effect of carbonyl group.

XRD Crystal Study

Single crystal X-ray analysis of a suitable quality crystal of compound **4f** was performed with a **Rigaku SCX mini diffractometer** using graphite monochromated Mo-Kα radiation. (λ= 0.71069 A^o) and operating at 50 kV and 30 mA. A single crystal was mounted loop with protective oil and placed under a flow of nitrogen gas at 20 + 1^{o}C to a maximum 2θ value of 55.0^o. Direct method was used for the solution of structure and expanded using Fourier techniques. Non-hydrogen atoms and hydrogen atoms were refined by anisotropically and riding model respectively. The 4944 observed reflection and 262 variable parameters were used for the least –squares refinement and full-matrix final cycle and converged (largest parameter shift was 0.00 times its esd) with un-weighted and weighted agreement factors. The standard deviation of an observation of unit weight was 1. 01. Unit weights were used. Final difference of Fourier map corresponded to 0. 35 and -0. 40 e- /Å^3 were maximum and minimum peaks respectively. SHELXL-97 software was used for calculations to derive crystal structure.

Crystal Preparation

Pure compound **9a** was taken in 5.5 ml methanol, 4.0 ml acetonitrile and 0.5 ml dimethylformamide, heated it up to 50 ºC for 10-15 minutes till it dissolved. Charcoal (0.5 gm) was added and further it was heated up to 50 ºC for 5 minutes. The hot solution was filtered, allowed to cool gradually and kept in a stoppered conical flask. The crystals were grown up due to thin layer evaporation. Table **2** summarizes the crystallographic data for compound **4f**. An ORTEP view of the title compounds **5f** with atomic labeling is shown in Fig. (**1**) **(CCDC No. 1402955)**.

Antimicrobial Screening

Method

Different pathogenic bacteria like *E.coli*, Methicillin resistant *Staphylococcus aureus* (MRSA), *Streptococcus aureus* and *Klebsiella pnemoniea* for MIC tests were procured from clinical laboratories and the cultures were maintained by repeated transfers in N-Agar slants. Minimum inhibitory concentration of assayed compound was determined by broth dilution method, under defined test conditions, and inhibits the visible growth of the bacterium being investigated. The susceptibilities of assayed compounds towards bacteria were determined by measurement of MIC and also to evaluate the activity of new antimicrobial agents. For broth dilution, Bacteria (3x108 cells/ml) were inoculated into Nutrient broth medium containing of different concentrations of the compound (2,4,6,8,10,20,40 µg/ml). Growth was assessed after incubation for 24 h and the MIC value was assessed by observation for the absence of visual turbidity.

The results are shown in the Table **3** including MIC of the antibiotics (Ampicillin and Cephazoline) available in the market against the pathogens.

Activity Assay

MIC results of synthesized compounds (Table **3***) shows that some of the compounds exhibited its potency against pathogens. Out of synthesized 32 compounds only 16 compounds described lower to medium activity. (*Compounds which have lower activity are not shown in Table **3**).

It is clear from activity that compounds with methoxy (-OCH_3) group in phenacyl moiety (**4a-4h**) gives activity

Table 2. Crystal and experimental data of compounds 4f.

Compound ID	4f
CCDC Deposition Number	1402955
Empirical Formula	$C_{24}H_{23}BrO_4$
Formula Weight	455.35
Crystal Color, Habit	colorless, block
Crystal Dimensions (mm)	0.890 x 0.560 x 0.350 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 12.0788(8) Å
	b = 10.0022(7) Å
	c = 18.279(2) Å
	b = 101.719(2) ^{o}
	γ = 103.623(5) ^{o}
	V = 2162.3(3) Å^3
Space Group	$P2_1/c$ (#14)
Z value	4
D_{calc}	1.399 g/cm^3
F(000)	936.00
μ(MoKα)	19.331 cm^{-1}
ω oscillation Range	-120.0 - 60.0^o
Exposure Rate	10.0 sec./^{o}
Detector Position	52.00 mm
2θmax	55.0^o
No. of Reflections Measured	Total: 21405: Unique: 4944
R_{int}	0.0398
R_1 (I>2.00 σ(I))	0.0439
R (All reflections)	0.0736
WR_2 (All reflections)	0.1184
Largest diff. peak and hole(e. Å$^{-)3}$	0.35, -0.40
Goodness of Fit	1.013

against *E.coli* strain. Furthermore these compounds are inactive in other pathogens *i.e*. Methicillin resistant *Staphylococcus aureus (MRSA), Streptococcus* aureus and *Klebsiella pnemoniea.* More notable facts from results, group possesses electron withdrawing group in phenacyl moiety only exhibited potency. It is also clear by observe the compounds (4a'-4h') which shows better activity as compared to other. Out of that, compounds **4b'** and **4c'** exhibited good activity against *E.coli*, *Streptococcus* aureus and *Klebsiella pnemoniea* strain. While other compounds in this series (28a-35a) except **4a'** shows potency against *Klebsiella pnemoniea* strain. By more concentrating on compound 4a' which shows activity against *Staphylococcus aureus (MRSA)* and *Streptococcus* aureus that is not showed by other compounds in same series.

Table 3. Antimicrobial MIC screening of synthesized compounds (4a-4x, 4a'-4h').

Compounds	MIC value (μg/ml)			
	E.coli (-)	MRSA (+)	*Streptococcus aureus (+)*	*Klebsiella pnemoniea (-)*
4a	8	-	-	-
4b	8	-	-	-
4c	8	-	-	-
4d	8	-	-	-
4e	10	-	-	-
4f	8	-	-	-
4g	8	-	-	-
4h	8	-	-	-
4a'	-	12	12	-
4b'	10	-	10	8
4c'	10	-	12	8
4d'	-	-	-	8
4e'	-	-	-	8
4f'	-	-	-	10
4g'	-	-	-	8
4h'	-	-	-	10
Ampicillin	-	50	30	-
Cephazoline	3	-	-	6

Material and Method

General

Chemicals and solvents were purchased from the Sigma-Aldrich Chemical Co., Merck chemical, Finar and Spectrochem Ltd. The entire chemicals were used without further purification. Precoated plates of silica gel G60 F254 (0.2 mm, Mfg. by Merck) were used for thin-layer chromatography. Visualization was made under UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on an IR Affinity-1S spectrophotometer (Shimadzu). For ^{1}H (400 MHz) and ^{13}C (101.1 MHz) NMR spectral analysis Bruker AVANCE II spectrometer was used. The position of signals were depicted in δ ppms with reference to TMS as an internal standard using $CDCl_3$ as a solvent. GCMS-QP 2010

mass spectrometer was used for determining a molecular weight with the help of direct inlet probe method. BUCHI rotary evaporator was used for the isolation of products and recovery of solvents. Melting points were measured in open capillaries and are uncorrected.

Chemistry

Synthetic procedure for the 3-(4-chlorophenyl)-6,6-dimethyl-2-(substituted phenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one. (4a-4x, 4a'-4h')

To a 100 ml RBF containing acetonitrile (10 ml), add dimedone **1** (3.57 mmole), phenacyl bromide **2** (3.92 mmole), aromatic aldehyde **3** (3.57 mmole) and pyridine (5.6 ml, 7.14 mmole) were heated at reflux temperature for 3.0 hrs. Add triethyl amine and the reaction mixture was heated up to reflux temperature for appropriate time (Table **1**). After completion of the reaction, the resulting mixture was cooled to room temperature, poured in to ice cold water; stir the reaction mixture at RT for 10 hrs. The solid separated was filtered and washed with water to give final products. Recrystallization was carried out using ethanol to afford analytically pure products **4a-4x, 4a'-4h'**.

3-(4-Chlorophenyl)-6,6-dimethyl-2-(4-methoxyphenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4 (2H)-one (4a)

Yield: 94 %; mp 219 ^{o}C ; IR (cm^{-1}): 3030.22 (Aromatic C-H stretching), 1699.32 (Ketonic group), 1645.64, 1587.06, 1464.69 (Aromatic ring skeleton), 1396.89 (C-H bending), 1226.13 (C-O Stretching), 848.10 (*p*-substituted aromatic ring), 786 (C-Cl stretching); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.95 (m, 2H), 7.58 (m, 2H), 7.42 (m, 2H), 7.03 (m, 2H), 5.94 (d, *J* = 1.9 Hz, 1H), 4.84 (d, *J* = 2.0 Hz, 1H), 3.79 (s, 3H), 2.60 (q, *J* = 16.4 Hz, 2H), 2.19 (q, *J* = 15.2 Hz, 2H), 1.15 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 195.77, 185.23, 171.91, 162.88, 136.96, 131.44, 130.35, 128.07, 127.54, 116.57, 114.09, 84.50, 55.15, 51.22, 41.75, 31.45, 25.96; MS: *m/z* 410.9 (M^{+}); Molecular formula: $C_{24}H_{23}ClO_4$.

3-(3-Cyclopropylmethoxy,4-diflouromethoxyphenyl)-6,6-dimethyl-2-(4-methoxyphenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one (4b)

Yield: 84 %; mp 189 ^{o}C ; IR (cm^{-1}): 3028.02 (Aromatic C-H stretching), 1695.32 (Ketonic group), 1646.63, 1589.22, 1465.71 (Aromatic ring skeleton), 1395 (C-F stretching), 1385.89 (C-H bending), 1229.16 (C-O Stretching), 839.16 (*p*-substituted aromatic ring); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.89 (m, 2H), 7.30 (m, 1H), 7.15 (m, 2H), 7.03 (m, 2H), 6.65 (s, 1H), 5.92 (d, *J* = 2.8 Hz, 1H), 4.57 (d, *J* = 2.8 Hz, 1H), 3.84 (d, *J*= 2.9 Hz, 2H), 3.80 (s, 3H), 2.62 (q, *J* = 16.3 Hz, 2H), 2.20 (q, *J* = 15.9 Hz, 2H), 1.22 (m, 1H), 1.13 (s, 6H), 0.66 (m, 2H), 0.41 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 195.80, 186.24, 172.90, 162.66, 150.91, 146.25, 138.92, 132.45, 128.26, 122.22, 119.44, 118.96, 118.55, 117.98, 116.51, 114.98, 114.10, 85.45, 73.09, 54.17, 50.97, 51.25, 41.77, 31.49, 24.97, 10.70, 7.85; MS: *m/z* 512.5 (M^{+}); Molecular formula: $C_{29}H_{30}F_2O_6$.

3-(3,4,5-Trimethoxyphenyl)-6,6-dimethyl-2-(4-methoxyphenylcarbonyl)-3,5,6,7-tetrahydro-1-benzo furan-4(2H)-one (4c)

Yield: 86 %; mp 244 ^{o}C ; IR (cm^{-1}): 3031.00 (Aromatic C-H stretching), 1693.32 (Ketonic group), 1649.22, 1586.02, 1466.69 (Aromatic ring skeleton), 1384.80 (C-H bending), 1249.10 (C-O Stretching), 842.09 (*p*-substituted aromatic ring); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.87 (m, 2H), 7.03 (m, 4H), 5.91 (d, *J* = 3.4 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 9H), 2.64 (q, *J* = 15.9 Hz, 2H), 2.19 (q, *J* = 15.0 Hz, 2H), 1.14 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 196.55, 185.28, 170.96, 162.49, 152.10, 138.07, 133.30, 131.44, 128.19, 115.97, 114.09, 112.40, 85.59, 61.15, 55.18, 55.19, 53.22, 51.82, 41.56, 30.94, 25.87; MS: *m/z* 466.5 (M^{+}); Molecular formula: $C_{27}H_{30}O_7$.

3-(3-Methoxyphenyl)-6,6-dimethyl-2-(4-methoxyphenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran -4(2H)-one (4d)

Yield: 85 %; mp 209 ^{o}C; IR (cm^{-1}): 3030.70 (Aromatic C-H stretching), 1694.42 (Ketonic group), 1642.21, 1589.52, 1467.70 (Aromatic ring skeleton), 1388.72 (C-H bending), 1252.12 (C-O Stretching), 845.29 (*p*-substituted aromatic ring); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.95 (m, 2H), 7.31 (m, 2H), 7.11 (d, J = 2.6 Hz, 1H), 7.03 (m, 2H), 6.86 (m, 1H), 5.95 (d, *J* = 1.9 Hz, 1H), 4.81 (d, *J* = 1.8 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 2.59 (q, *J* = 16.3 Hz, 2H), 2.20 (q, *J* = 15.9 Hz, 2H), 1.12 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 194.99, 184.22, 170.97, 164.84, 158.15, 140.95, 132.40, 128.96, 127.18, 124.18, 117.49, 115.07, 85.05, 54.56, 55.45, 51.97, 50.29, 42.95, 30.95, 24.93; MS: *m/z* 406.5 (M^{+}); Molecular formula: $C_{25}H_{20}O_5$.

3-(4-Ethoxyphenyl)-6,6-dimethyl-2-(4-methoxyphenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one (4e)

Yield: 88 %; mp 198 ^{o}C ; IR (cm^{-1}): 3032.79 (Aromatic C-H stretching), 1696.32 (Ketonic group), 1642.21, 1586.22, 1469.67 (Aromatic ring skeleton), 1386.62 (C-H bending), 1256.02 (C-O Stretching), 846.39 (*p*-substituted aromatic ring); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.90 (m, 2H), 7.43 (m, 2H), 7.03 (m, 2H), 6.91 (m, 2H), 5.93 (d, *J* = 2.9 Hz, 1H), 4.56 (d, *J* = 2.5 Hz, 1H), 4.05 (q, *J* = 5.9 Hz, 2H), 3.79 (s, 3H), 2.65 (q, *J* = 16.6 Hz, 2H), 2.17 (q, *J* = 15.7 Hz, 2H), 1.34 (t, *J* = 5.9 Hz, 3H), 1.18 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 197.79, 184.25, 170.98, 163.80, 158.88, 133.60, 132.41, 128.58, 127.95, 117.58, 115.81, 114.08, 84.46, 63.82, 54.19, 52.59, 42.72, 32.42, 25.92, 15.59; MS: *m/z* 420.5 (M^{+}); Molecular formula: $C_{25}H_{28}O_5$.

2-[(4-Bromophenyl)carbonyl]-3-(4-chlorophenyl)-6,6-dimethyl-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one (4i)

Yield: 90 %; mp 230 ^{o}C ; IR (cm^{-1}): 3031.09 (Aromatic C-H stretching), 1690.89(Ketonic group), 1651.01, 1581.29, 1460.60 (Aromatic ring skeleton), 1389.63 (C-H bending), 1250.50 (C-O Stretching), 846.39 (*p*-substituted aromatic ring), 551.33(C-Br stretching); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.91 (m, 2H), 7.74 (m, 2H), 7.57 (m, 2H), 7.42 (m, 2H), 5.92 (d, *J* = 2.9 Hz, 1H), 4.55 (d, *J* = 3.0 Hz, 1H), 2.66 (q,

J = 16.2 Hz, 2H), 2.15 (q, *J* = 15.5 Hz, 2H), 1.21 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.29, 184.02, 172.28, 137.91, 135.81, 131.95, 131.06, 130.34, 126.91, 127.64, 123.80, 117.50, 85.58, 52.64, 41.82, 33.40, 27.59; MS: *m/z* 459.8 (M^+); Molecular formula: $C_{23}H_{20}BrClO_3$.

2-[(4-Bromophenyl)carbonyl]-3-(3-cyclopropylmethoxy,4-diflouromethoxyphenyl)-6,6-dimethyl-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one (4j)

Yield: 89 %; mp 259 °C ; IR (cm^{-1}): 3030.22 (Aromatic C-H stretching), 1692.55(Ketonic group), 1648.51, 1525.20, 1430.61 (Aromatic ring skeleton), 1380.60 (C-H bending), 1253.45(C-O Stretching), 1165 (C-F Stretching), 845.22 (*p*-substituted aromatic ring), 549.30 (C-Br stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (m, 2H), 7.74 (m, 2H), 7.41 (m, 1H), 7.24 (m, 2H), 6.65 (s, 1H), 5.93 (d, *J* = 2.0 Hz, 1H), 4.79 (d, *J* = 2.0, Hz, 1H), 3.81 (d, *J* = 7.5 Hz, 2H), 2.61 (q, *J* = 16.6 Hz, 2H), 2.19 (q, *J* = 15.3 Hz, 2H), 1.22 (m, 1H), 1.19 (s, 6H), 0.66 (m, 2H), 0.41 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.06, 184.92, 172.90, 152.93, 147.18, 137.90, 135.88, 133.02, 133.08, 123.84, 128.25, 119.04, 117.95, 117.56, 117.90, 116.56, 115.87, 85.52, 73.80, 51.48, 52.28, 42.07, 32.46, 26.09, 11.72, 7.98; MS: *m/z* 561.4 (M^+); Molecular formula: $C_{28}H_{27}BrF_2O_5$.

2-[(4-Bromophenyl)carbonyl]-3-(3,4,5-trimethoxyphenyl)-6,6-dimethyl-3,5,6,7-tetrahydro-1-benzo furan-4(2H)-one (4k)

Yield: 88 %; mp 255 °C ; IR (cm^{-1}): 3030.56 (Aromatic C-H stretching), 1669.04(Ketonic group), 1645.50, 1556.56, 1420.66 (Aromatic ring skeleton), 1356.59 (C-H bending), 1251.05 (C-O Stretching), 846.82 (*p*-substituted aromatic ring), 546.90 (C-Br stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (m, 2H), 7.74 (m, 2H), 6.97 (d, *J* = 1.1 Hz, 2H), 5.90 (d, *J* = 3.4 Hz, 1H), 4.56 (d, *J* = 3.4 Hz, 1H), 3.70 (s, 9H), 2.69 (q, *J* = 16.9 Hz, 2H), 2.22 (q, *J* = 15.0 Hz, 2H), 1.22 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.70, 184.22, 172.93, 154.10, 137.97, 135.80, 132.83, 133.29, 131.87, 122.95, 115.89, 111.49, 84.52, 60.58, 56.12, 51.28, 52.23, 42.70, 32.46, 25.97; MS: *m/z* 515.4 (M^+); Molecular formula: $C_{26}H_{27}BrO_6$.

2-[(4-Bromophenyl)carbonyl]-3-(3-methoxyphenyl)-6,6-dimethyl-3,5,6,7-tetrahydro-1-benzo furan-4(2H)-one (4l)

Yield: 87 %; mp 241 °C ; IR (cm^{-1}): 3034.16 (Aromatic C-H stretching), 1670.54 (Ketonic group), 1645.59, 1558.46, 1430.86 (Aromatic ring skeleton), 1376.39 (C-H bending), 1255.26 (C-O Stretching), 849.85 (*p*-substituted aromatic ring), 500.97 (C-Br stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (m, 2H), 7.74 (m, 2H), 7.30 (m, 2H), 7.08 (d, *J* = 2.8 Hz, 1H), 6.86 (d, *J* = 7.1 Hz, 1H), 5.93 (d, *J* = 3.2 Hz, 1H), 4.64 (d, *J* = 3.2 Hz, 1H), 3.72 (s, 3H), 2.62 (q, *J* = 16.2 Hz, 2H), 2.20 (q, *J* = 15.3 Hz, 2H), 1.26 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.54, 186.03, 171.92, 158.13, 144.05, 135.80, 133.24, 130.64, 129.60, 122.85, 122.01, 115.40, 114.03, 84.52, 55.51, 51.25, 51.01, 42.70, 32.40, 26.90; MS: *m/z* 455.3 (M^+); Molecular formula: $C_{24}H_{23}BrO_4$.

2-[(4-Bromophenyl)carbonyl]-3-(4-methoxyphenyl)-6,6-dimethyl-3,5,6,7-tetrahydro-1-benzofuran -4(2H)-one (4m)

Yield: 85 %; mp 228 °C ; IR (cm^{-1}): 3032.15 (Aromatic C-H stretching), 1679.26 (Ketonic group), 1632.66, 1555.62, 1402.99 (Aromatic ring skeleton), 1350.55 (C-H bending), 1247.75 (C-O Stretching), 849.98 (*p*-substituted aromatic ring), 551.39 (C-Br stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (m, 2H), 7.74 (m, 2H), 7.42 (m, 2H), 6.89 (m, 2H), 5.93 (d, *J* = 2.2 Hz, 1H), 4.84 (d, *J* = 2.1 Hz, 1H), 4.05 (q, *J* = 5.9 Hz, 2H), 2.63 (q, *J* = 16.6 Hz, 2H), 2.22 (q, *J* = 15.5 Hz, 2H), 1.34 (t, *J* = 5.9 Hz, 3H), 1.16 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.07, 184.22, 170.92, 158.81, 135.81, 133.65, 131.26, 130.67, 128.55, 121.84, 115.51, 114.88, 84.51, 64.30, 52.52, 42.74, 32.49, 24.97, 15.06; MS: *m/z* 469.4 (M^+); Molecular formula: $C_{24}H_{23}BrO_4$.

3-(4-Chlorophenyl)-6,6-dimethyl-2-(4-nitrophenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4 (2H)-one (4q)

Yield: 91 %; mp 185 °C ; IR (cm^{-1}): 3030.19 (Aromatic C-H stretching), 1705.07 (Ketonic group), 1627.92, 1519.91, 1466.59 (Aromatic ring skeleton), 1519.31 (C–NO_2 stretching), 1396.46 (C-H bending), 1219.01 (C-O Stretching), 840.96 (*p*-substituted aromatic ring), 686.86 (C-Cl stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (m, 2H), 8.27 (m, 2H), 7.57 (m, 2H), 7.42 (m, 2H), 5.94 (d, *J* = 2.1 Hz, 1H), 5.00 (d, *J* = 2.3 Hz, 1H), 2.60 (q, *J* = 16.3 Hz, 2H), 2.21 (q, *J* = 15.7 Hz, 2H), 1.22 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.27, 186.21, 172.09, 145.91, 138.61, 135.59, 132.31, 126.91, 125.96, 125.01, 116.59, 85.52, 55.20, 41.70, 32.44, 26.06; MS: *m/z* 425.9 (M^+); Molecular formula: $C_{23}H_{20}ClNO_5$.

3-(3-Cyclopropylmethoxy,4-diflouromethoxyphenyl)-6,6-dimethyl-2-(4-nitrophenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one (4r)

Yield: 86 %; mp 212 °C ; IR (cm^{-1}): 3003.99(Aromatic C-H stretching), 1708.77 (Ketonic group), 1637.62, 1520.81, 1468.59 (Aromatic ring skeleton), 1539.91 (C–NO_2 stretching), 1396.96 (C-H bending), 1239.61 (C-O Stretching), 1160.59 (C-F stretching), 849.76 (*p*-substituted aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (m, 2H), 8.28 (m, 2H), 7.32 (t, *J* = 1.3 Hz, 1H), 7.04 (m, 2H), 6.65 (s, 1H), 5.96 (d, *J* = 1.7 Hz, 1H), 4.98 (d, *J* = 1.8 Hz, 1H), 3.81 (d, *J* = 7.7 Hz, 2H), 2.67 (q, *J* = 16.7 Hz, 2H), 2.20 (q, *J* = 15.6 Hz, 2H), 1.22 (m, 1H), 1.30 (s, 6H), 0.66 (m, 2H), 0.41 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.70, 184.20, 172.90, 152.29, 149.54, 146.15, 138.61, 139.91, 131.59, 126.01, 122.23, 119.64, 118.95, 118.16, 117.22, 116.55, 116.87, 85.51, 74.80, 52.40, 52.22, 42.74, 31.25, 26.91, 11.75, 7.99; MS: *m/z* 527.5 (M^+); Molecular formula: $C_{28}H_{27}F_2NO_7$.

3-(3,4,5-Trimethoxyphenyl)-6,6-dimethyl-2-(4-nitrophenylcarbonyl)-3,5,6,7-tetrahydro-1-benzo furan-4(2H)-one (4s)

Yield: 84 %; mp 199 °C ; IR (cm^{-1}): 3013.69 (Aromatic C-H stretching), 1710.17 (Ketonic group), 1639.92, 1530.71,

1472.49 (Aromatic ring skeleton), 1569.71 (C–NO_2 stretching), 1376.96 (C-H bending), 1249.01 (C-O Stretching), 850.16 (*p*-substituted aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (m, 2H), 8.28 (m, 2H), 6.97 (d, *J* = 1.1 Hz, 2H), 5.94 (d, *J* = 1.9 Hz, 1H), 5.00 (d, *J* = 2.0 Hz, 1H), 3.70 (s, 9H), 2.55 (q, *J* = 16.1 Hz, 2H), 2.10 (q, *J* = 15.0 Hz, 2H), 1.31 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 198.07, 186.22, 170.95, 153.12, 145.96, 138.72, 137.17, 132.30, 129.83, 125.08, 117.55, 112.02, 85.51, 62.50, 55.12, 53.20, 50.26, 42.70, 32.46, 26.06; MS: *m/z* 481.5 (M^+); Molecular formula: $C_{26}H_{27}NO_8$.

3-(3-Methoxyphenyl)-6,6-dimethyl-2-(4-nitrophenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4 (2H)-one (4t)

Yield: 86 %; mp 189 °C ; IR (cm^{-1}): 3012.19 (Aromatic C-H stretching), 1711.67 (Ketonic group), 1649.02, 1560.61, 1462.49 (Aromatic ring skeleton), 1579.81 (C–NO_2 stretching), 1377.56 (C-H bending), 1259.61 (C-O Stretching), 849.66 (*p*-substituted aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (m, 2H), 8.28 (m, 2H), 7.26 (m, 2H), 7.04 (m, 1H), 6.86 (d, J = 7.5 Hz, 1H), 5.92 (d, *J* = 2.2 Hz, 1H), 4.99 (d, *J* = 2.3 Hz, 1H), 3.72 (s, *3H*), 2.59 (q, *J* = 16.9 Hz, 2H), 2.23 (q, *J* = 14.7 Hz, 2H), 1.24 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.07, 186.13, 172.90, 158.15, 147.95, 144.16, 138.61, 132.41, 130.18, 126.05, 122.01, 115.49, 114.03, 85.52, 54.58, 52.42, 51.71, 42.70, 35.46, 24.09; MS: *m/z* 421.4 (M^+); Molecular formula: $C_{24}H_{23}NO_6$.

3-(4-Methoxyphenyl)-6,6-dimethyl-2-(4-nitrophenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4 (2H)-one (4u)

Yield: 89 %; mp 201 °C ; IR (cm^{-1}): 3010.29 (Aromatic C-H stretching), 1719.68 (Ketonic group), 1629.42, 1565.60, 1460.46 (Aromatic ring skeleton), 1559.91 (C–NO_2 stretching), 1357.96 (C-H bending), 1269.79 (C-O Stretching), 850.22 (*p*-substituted aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (m, 2H), 8.28 (m, 2H), 7.44 (m, 2H), 6.88 (m, 2H), 5.94 (d, *J* = 2.0 Hz, 1H), 4.98 (d, *J* = 1.8 Hz, 1H), 4.05 (q, *J* = 5.9 Hz, 2H), 2.66 (q, *J* = 15.8 Hz, 2H), 2.22 (q, *J* = 15.4 Hz, 2H), 1.34 (t, *J* = 5.9 Hz, 3H), 1.19 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.70, 186.22, 172.09, 160.81, 149.91, 138.61, 133.06, 131.40, 129.57, 126.02, 117.58, 115.83, 85.52, 64.31, 52.20, 42.71, 32.44, 26.19, 16.04; MS: *m/z* 435.5 (M^+); Molecular formula: $C_{24}H_{23}NO_6$.

3-(4-Chlorophenyl)-2-[(3,4-dichlorophenyl)carbonyl]-6,6-dimethyl-3,5,6,7-tetrahydro-1-benzo furan-4(2H)-one (4a')

Yield: 89 %; mp 201 °C ; IR (cm^{-1}): 3003.99 (Aromatic C-H stretching), 1705.07 (Ketonic group), 1627.92, 1581.63, 1465.90 (Aromatic ring skeleton), 1388.75 (C-H bending), 1211.30 (C-O Stretching), 833.25 (*p*-substituted aromatic ring), 671.23 (C-Cl stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, *J* = 1.9 Hz, 1H), 7.91 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.57 (m, 2H), 7.42 (m, 2H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.00 (d, *J* = 2.0 Hz, 1H), 2.64 (q, *J* = 16.7 Hz, 2H), 2.20 (q, *J* = 15.8 Hz, 2H), 1.23 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.37, 186.03, 171.91, 136.96, 135.10, 133.08, 131.09, 130.37, 130.08, 127.84, 127.97, 127.14, 117.50, 85.00, 53.02, 41.70, 32.15, 26.06; MS: *m/z* 449.8 (M^+); Molecular formula: $C_{23}H_{19}Cl_3O_3$.

3-(3-Cyclopropylmethoxy,4-diflouromethoxyphenyl)-2-[(3,4-dichlorophenyl)carbonyl]-6,6-di methyl-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one (4b')

Yield: 85 %; mp 256 °C ; IR (cm^{-1}): 3013.08 (Aromatic C-H stretching), 1709.17 (Ketonic group), 1639.22, 1556.23, 1456.80 (Aromatic ring skeleton), 1386.47 (C-H bending), 1212.81 (C-O Stretching), 1186.05 (C-F stretching), 834.26 (*p*-substituted aromatic ring), 673.03 (C-Cl stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, *J* = 1.8 Hz, 1H), 7.82 (m, 2H), 7.43 (m, 1H), 7.22 (dd, *J* = 2.0, 1.0 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.65 (s, 1H), 5.94 (d, *J* = 2.0 Hz, 1H), 5.02 (d, *J* = 2.2 Hz, 1H), 3.81 (d, *J* = 7.6 Hz, 2H), 2.61 (q, *J* = 16.6 Hz, 2H), 2.21 (q, *J* = 15.5 Hz, 2H), 1.22 (m, 1H), 1.18 (s, 6H), 0.66 (m, 2H), 0.41 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.37, 186.03, 172.93, 154.02, 147.16, 139.91, 136.18, 134.07, 132.01, 132.34, 128.80, 127.80, 122.05, 120.61, 119.91, 117.50, 117.00, 116.51, 115.18, 85.14, 74.09, 52.87, 51.20, 42.70, 31.41, 26.09, 12.07, 7.90; MS: *m/z* 551.4 (M^+); Molecular formula: $C_{28}H_{26}Cl_2F_2O_5$.

3-(3,4,5-Trimethoxyphenyl)-2-[(3,4-dichlorophenyl)carbonyl]-6,6-dimethyl-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one (4c')

Yield: 89 %; mp 240 °C ; IR (cm^{-1}): 3012.87 (Aromatic C-H stretching), 1710.16 (Ketonic group), 1629.02, 1559.93, 1458.90 (Aromatic ring skeleton), 1389.56 (C-H bending), 1215.89 (C-O Stretching), 839.58 (*p*-substituted aromatic ring), 679.63 (C-Cl stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, *J* = 1.9 Hz, 1H), 7.92 (m, 1H), 7.83 (d, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 1.1 Hz, 2H), 5.95 (d, *J* = 1.9 Hz, 1H), 5.01 (d, *J* = 2.0 Hz, 1H), 3.70 (s, 9H), 2.60 (q, *J* = 16.2 Hz, 2H), 2.20 (q, *J* = 15.4 Hz, 2H), 1.30 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.30, 186.21, 172.90, 154.12, 139.01, 137.12, 134.35, 133.18, 132.09, 131.05, 128.28, 127.80, 117.28, 112.40, 85.50, 60.21, 58.03, 52.22, 51.02, 41.74, 31.46, 26.04; MS: *m/z* 505.4 (M^+); Molecular formula: $C_{26}H_{26}Cl_2O_6$.

3-(3-Methoxyphenyl)-2-[(3,4-dichlorophenyl)carbonyl]-6,6-dimethyl-3,5,6,7-tetrahydro-1-benzo furan-4(2H)-one (4d')

Yield: 89 %; mp 206 °C ; IR (cm^{-1}): 3014.56 (Aromatic C-H stretching), 1719.17 (Ketonic group), 1625.89, 1551.74, 1461.89 (Aromatic ring skeleton), 1398.06 (C-H bending), 1216.65 (C-O Stretching), 840.58 (*p*-substituted aromatic ring), 680.63 (C-Cl stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, *J* = 2.0 Hz, 1H), 7.79 (m, 2H), 7.30 (m, 2H), 7.11 (m, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 5.94 (d, *J* = 3.2 Hz, 1H), 4.54 (d, *J* = 3.2 Hz, 1H), 3.72 (s, 3H), 2.65 (q, *J* = 16.6 Hz, 2H), 2.23 (q, *J* = 15.3 Hz, 2H), 1.09 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.86, 186.20, 172.91, 160.44, 144.16, 136.11, 135.01, 133.08, 131.30, 128.81, 128.00, 127.08, 123.21, 117.41, 116.01, 85.51, 55.52, 52.40, 52.01, 43.74, 32.41, 26.01; MS: *m/z* 445.3 (M^+); Molecular formula: $C_{24}H_{22}Cl_2O_4$.

3-(4-Methoxyphenyl)-2-[(3,4-dichlorophenyl)carbonyl]-6,6-dimethyl-3,5,6,7-tetrahydro-1-benzo furan-4(2H)-one (4e')

Yield: 88 %; mp 211 °C ; IR (cm^{-1}): 3016.07 (Aromatic C-H stretching), 1718.19 (Ketonic group), 1629.76, 1552.75,

1462.86 (Aromatic ring skeleton), 1378.90 (C-H bending), 1219.60 (C-O Stretching), 846.50 (*p*-substituted aromatic ring), 678.93 (C-Cl stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, *J* = 1.9 Hz, 1H), 7.80 (m, 2H), 7.45 (m, 2H), 6.91 (m, 2H), 5.94 (d, *J* = 3.2 Hz, 1H), 4.54 (d, *J* = 3.3 Hz, 1H), 4.04 (q, *J*= 14.29 Hz, 2H), 2.69 (q, *J* = 15.9 Hz, 2H), 2.21 (q, *J* = 15.4 Hz, 2H), 1.34 (t, *J* = 5.9 Hz, 3H), 1.15 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.07, 189.20, 172.90, 160.02, 136.17, 135.01, 133.61, 132.01, 132.04, 130.77, 129.84, 127.50, 118.07, 115.81, 85.52, 64.30, 51.20, 43.55, 32.44, 27.98, 17.56; MS: *m/z* 459.4 (M^+); Molecular formula: $C_{24}H_{22}Cl_2O_4$.

CONCLUSION

In this short article, we have synthesized various biologically active tetrahydrobenzofurans and check their potency as an antimicrobial agent. The structure was confirmed by most acceptable techniques *i.e*. XRD study which gives idea regarding confirmation and isomerism in desired adducts. Many compounds give better MIC compared to standard drugs (Ampicillin and Cephazoline). By inspecting MIC data it gives idea to increase the level of microbial activity of compounds by the change in specific position as well as specific group more especially electron withdrawing group positioned at *p*- position.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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(For more experimental and crystal data, refer supplementary file).

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