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Design and stereoselective synthesis of novel isosteviol-fused pyrazolines and pyrazoles as potential anticancer agents

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ABSTRACT

Two series of novel isosteviol-fused pyrazoline and pyrazole derivatives were facilely synthesized *via* intramolecular 1,3-dipolar cycloaddition and condensation reaction, respectively. All compounds were characterized by NMR, IR and HRMS spectra. The stereochemistry of compounds **9b**, **10**, **11a** and **11v** were further confirmed by X-ray crystallographic analysis. The antiproliferative activities of the structurally related pyrazoline and pyrazole derivatives were tested *in vitro* on four human malignant cell lines (SGC 7901, A549, Raji and HeLa): Our results revealed that isosteviol-fused pyrazole derivatives exhibited noteworthy cytotoxic activities. Among them, 2,4-di-Cl-phenylpyrazole derivative **11t** displayed better cytotoxities with IC_{50} values: 2.71, 3.18, 1.09 and 13.52 μM against SGC 7901, A549, Raji and HeLa, respectively, compared to cisplatin (IC_{50} values: 7.56, 17.78, 17.32 and 14.31 μM, respectively).

1. Introduction

Cancer is a leading cause of death worldwide, accounting for 8.7 million deaths (around 14% of all deaths) in 2012. Although many chemotherapeutic agents, such as cisplatin, 5-fluorouracil and taxol, have been developed to treat different kinds of cancer effectively, some side effects could happen simultaneously. Therefore, it is important and urgent to develop novel compounds as anticancer agents with higher bioactivities and lower side effects [1,2]. Functionalization of natural products with known pharmacophore moieties [3–5] and synthesis of their hybrid compounds [6,7] are the most widely used approaches for obtaining novel therapeutic agents in medicinal chemistry.

Isosteviol (ent-16-ketobeyeran-19-oic acid **1**) is a tetracyclic diterpenoid with a beyerane skeleton, obtained by acid hydrolysis of stevioside [8,9]. In recent years, isosteviol derivatives have attracted scientific attention because of their remarkably broad spectrum of biological activities including anti-inflammatory [10], glucocorticoid agonist [11], antihypertension [12], antitumor [13], antiproliferation [14] and other biologic activities [15–20]. Especially, Wu and co-workers reported that isosteviol derivatives with exo-methylene cyclopentanone fragment had favorable cytotoxicity [21,22]. Meanwhile, the 15- and/or 16-functionalized isosteviol derivatives, obtained by means of group-conversion or structural modification in our laboratory, had good cytotoxic activities [23,24], which prompted us to further investigate new isosteviol derivatives fused with heterocycles to develop novel stronger anticancer agents for therapeutic use.

It is well known that a number of multicyclic compounds containing heterocycle fragments exhibit a wide variety of biological activities [25–31]. Pyrazoline and pyrazole are important structural fragments of many bioactive compounds [32–34]. Kim and co-workers revealed recently that compound **A** (Fig. 1) showed potential ALK5 inhibitory activity as transforming growth factor-β type 1 receptor kinase inhibitors [35]. Synchronously, Janos wolfling et al. reported that the cytotoxicity could be greatly improved when *p*-methoxyphenylpyrazoline fragment was introduced to the ring-D of steroid (Fig. 1, Compound **B**) [36]. In addition, the carbothioamide-substituted pyrazole isosteviol derivative (Fig. 1, Compound **C**), obtained in our laboratory, had good cytotoxic

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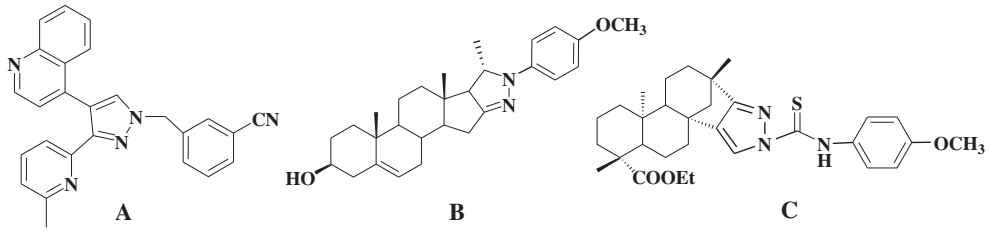


Fig. 1. Chemical structures of compounds **A**–**C**.

activities (IC_{50} values: 9.65, 17.73, 6.51 and 13.91 μM against SGC 7901, A549, Raji and HeLa cell lines, respectively). Based on these facts and in continuation of our previous work, a series of novel compounds containing pyrazole and pyrazoline ring fused with isosteviol structure were designed and synthesized for the purpose of new antitumor agent discovery.

2. Results and discussion

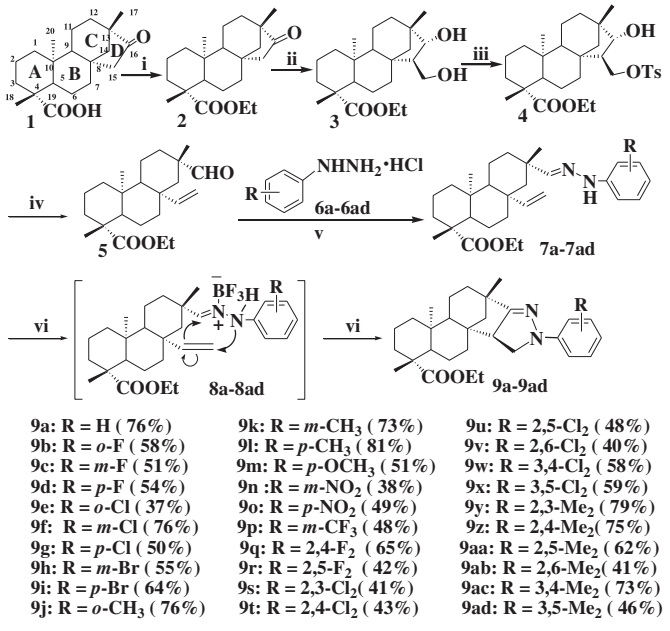
2.1. Chemistry

Isosteviol derivative **5** was synthesized as shown in Scheme 1 according to the procedure previously described [23]. Treatment of isosteviol **1** with CH_3CH_2Br and KOH in DMSO afforded the corresponding ethyl ester of isosteviol **2** in 96% yield. Compound **3** was stereoselectively synthesized *via* one pot Tollens' reaction in 90% yield. Treatment of compound **3** with 4-methylphenylsulfonyl chloride in pyridine furnished compound **4** (75%), which was further converted to the ring opening product **5** in 96% yield *via* Grob fragmentation of compound **4** in the presence of NaOH in CH_3CN.

The presence of the formyl group and the vinyl moiety in compound **5** makes the molecule suitable for condensation with hydrazine compounds and subsequent intramolecular 1,3-dipolar cycloaddition to give fused heteroatom-containing frameworks *via* intramolecular sequences [37]. Thus, the phenylhydrazones of compound **5** as olefinic azomethine imine precursors were expected to undergo Lewis acid mediated 1,3-dipolar cycloadditions. In this regard, a series of novel compounds containing a pyrazoline ring fused with isosteviol structure were stereoselectively synthesized *via* 1,3-dipolar cycloaddition (Scheme 1). Aldehyde **5** was therefore initially reacted with phenylhydrazines **6a**–**6ad** to furnish the corresponding phenylhydrazones **7a**–**7ad**. The obtained compounds were readily underwent intramolecular cycloaddition in the presence of a catalytic amount of $BF_3 \cdot OEt_2$ to afford pyrazoline derivatives **9a**–**9ad** in 38%–81% yields. Compounds **7j**–**7l** containing an electron-donating group on the aromatic ring readily underwent heterocycle formation within 20 min to give **9j**–**9l** in excellent yields. In contrast, the halogen-substituted phenylhydrazone **7b**–**7i** and those containing an electron-withdrawing group on the aromatic moiety (**7n**–**7p**) proved to be more stable, and a longer reaction time was needed at the same temperature for appreciable conversion.

Compounds **9a**–**9ad** were characterized by IR, ^1H NMR, ^{13}C NMR and HRMS, respectively. The presence of signals at δ_H 4.24, 3.51, 2.97 and δ_C 173.0 in the NMR of compound **9b** confirmed the formation of pyrazoline ring. In addition, the relativity signals in the NOESY spectrum indicated the α orientation of the protons at C-15 on D-ring of isosteviol. The stereostructure of **9b** was further confirmed by X-ray crystallographic analysis (Fig. 2).

Since pyrazole usually behaves as bioactive subunit in various natural products, we intended to introduce the pyrazole fragment to the skeleton of isosteviol in order to construct a novel family of bioactive molecules for the discovery of antitumor agent. Meanwhile, the different effects of pyrazole and pyrazoline fragment in the isosteviol molecules on antitumor activities could also be investigated. Therefore, a series of pyrazole derivatives **11a**–**11ad** were designed and synthesized *via* the following procedure (Scheme 2).



9a: R = H (76%) **9b:** R = *o*-F (58%) **9c:** R = *m*-F (51%) **9d:** R = *p*-F (54%) **9e:** R = *o*-Cl (37%) **9f:** R = *m*-Cl (76%) **9g:** R = *p*-Cl (50%) **9h:** R = *m*-Br (55%) **9i:** R = *p*-Br (64%) **9j:** R = *o*-CH_3 (76%)

9k: R = *m*-CH_3 (73%) **9l:** R = *p*-CH_3 (81%) **9m:** R = *p*-OCH_3 (51%) **9n :**R = *m*-NO_2 (38%) **9o:** R = *p*-NO_2 (49%) **9p:** R = *m*-CF_3 (48%) **9q:** R = 2,4-F_2 (65%) **9r:** R = 2,5-F_2 (42%) **9s:** R = 2,3-Cl_2(41%) **9t:** R = 2,4-Cl_2 (43%)

9u: R = 2,5-Cl_2 (48%) **9v:** R = 2,6-Cl_2 (40%) **9w:** R = 3,4-Cl_2 (58%) **9x:** R = 3,5-Cl_2 (59%) **9y:** R = 2,3-Me_2 (79%) **9z:** R = 2,4-Me_2(75%) **9aa:** R = 2,5-Me_2 (62%) **9ab:** R = 2,6-Me_2(41%) **9ac:** R = 3,4-Me_2 (73%) **9ad:** R = 3,5-Me_2 (46%)

Scheme 1. *Reagents and conditions*: (i) EtBr, DMSO, KOH, rt, 3 h, 96%; (ii) HCHO, C_2H_5ONa, C_2H_5OH, 60 °C, 3 h, 90%; (iii) TsCl, Pyr, rt, 18 h, 75%; (iv) NaOH, CH_3CN, rt, 3 h, 96%; (v) **6a**–**6ad**, sodium acetate, C_2H_5OH, reflux; (vi) toluene, $BF_3 \cdot OEt_2$, reflux, (38%–81%).

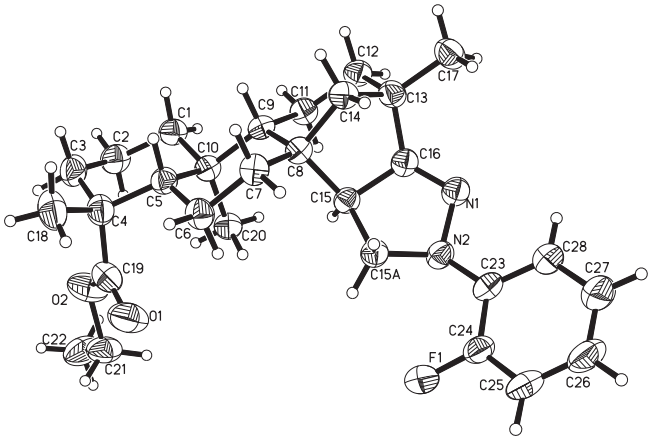
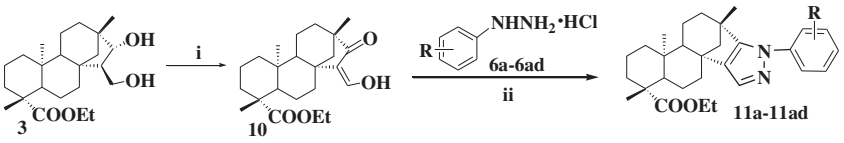


Fig. 2. X-ray structure of compound **9b**.



11a: R = H (76%)	**11k:R = *o*-CH_3 (56%)**	**11u: R = 2,5-Cl_2 (76%)**
11b: R = *o*-F (87%)	**11l: R = *m*-CH_3 (87%)**	**11v: R = 2,6-Cl_2 (56%)**
11c: R = *m*-F (93%)	**11m:R = *p*-CH_3 (89%)**	**11w: R = 3,4-Cl_2 (75%)**
11d: R = *p*-F (91%)	**11n: R = *o*-NO_2 (61%)**	**11x: R = 3,5-Cl_2(60%)**
11e: R = *o*-Cl (87%)	**11o :R = *m*-NO_2 (89%)**	**11y: R = 2,3-Me_2(56%)**
11f: R = *m*-Cl (76%)	**11p: R = *p*-NO_2 (57%)**	**11z: R = 2,4-Me_2 (63%)**
11g: R = *p*-Cl (50%)	**11q: R = 2,4-F_2(87%)**	**11aa: R = 2,5-Me_2 (79%)**
11h: R = *o*-Br (55%)	**11r: R = 2,5-F_2 (88%)**	**11ab: R = 2,6-Me_2 (69%)**
11i: R = *m*-Br (64%)	**11s: R = 2,3-Cl_2 (92%)**	**11ac: R = 3,4-Me_2 (59%)**
11j: R = *p*-Br (76%)	**11t: R = 2,4-Cl_2 (90%)**	**11ad: R = 3,5-Me_2 (81%)**

Scheme 2. *Reagents and conditions*: (i)TCC, CH_2Cl_2, rt, 1.5 h, 62%; (ii) **6a**–**ad**, isopropanol, reflux, (50%–91%).

Treatment of compound **3** with TCC in CH_2Cl_2 afforded the corresponding product **10** in 62% yield. The structure of product **10** was confirmed unambiguously by the disappearance of the signals at δ_H 3.98, 3.63 and 3.56 in the ^{1}H NMR spectra, and the appearance of signals at δ_H 12.09 and 7.15 in the ^{1}H NMR and δ_C 215.1, 156.1, 121.3 in the ^{13}C NMR spectra. The stereostructure of **10** was confirmed by X-ray crystallographic analysis (Fig. 3), indicating that the 15-formyl group profitably exists as its enol form.

Condensation of **10** with phenylhydrazines **6a**–**6ad** in isopropanol provided the pyrazole derivatives **11a**–**11ad** in 50%–91% yields. The structures of compounds **11a**–**11ad** were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS, respectively. In the ^{1}H and ^{13}C NMR spectra of **11v**, additional resonances were observed at δ_H 7.48, 7.43, 7.34 and δ_C 153.3, 136.0, 135.8, 135.6, 135.2, 130.6, 129.6, 128.4, 128.3, suggesting the introduction of 2,6-di-Cl-phenylpyrazole fragment. In addition, the stereostructure and regiochemistry of **11v** and **11a** were further confirmed by X-ray crystallographic analysis (Fig. 4 and Fig. 5).

2.2. Evaluation of cytotoxic activity

The *in vitro* cytotoxic activities of these compounds were then evaluated against four cancer cell lines, including gastric cancer (SGC 7901), lung cancer (A549), lympha cancer (Raji) and cervical cancer (Hela) in comparison with cisplatin as the positive control.

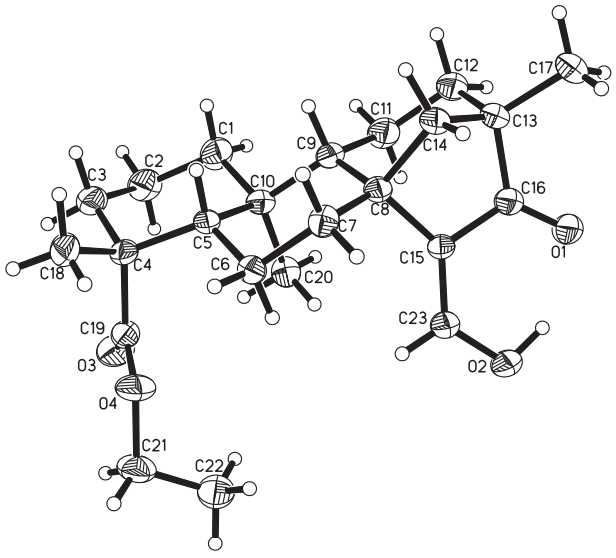


Fig. 3. X-ray structure of compound **10**.

The cell growth inhibitory potencies of the investigated compounds, expressed as IC_{50} values (Table 1 and Table 2), demonstrated that several of the derivatives exerted pronounced antiproliferative effects on the four cell lines, which were similar to or higher than those of cisplatin. Specifically, the pyrazole derivatives **11a**–**11ad** displayed much higher cytotoxicities than those of the pyrazoline derivatives **9a**–**9ad**, indicating that pyrazole heterocyclic fragment may play an important role in their cytotoxic activities.

As shown in Table 1, most of the pyrazoline derivatives **9a**–**9ad** showed better inhibitory activities against Raji cell than those in SGC 7901, A549 and Hela cell lines. Interestingly, several of pyrazole derivatives showed better inhibitory activities against Raji cell than those of cisplatin. Meanwhile, compounds containing an electron-donating group on the aromatic ring were more potent against SGC 7901 cell than the halogen-substituted compounds (**9l**, **9m** and **9y**–**9ac** vs **9b**–**9k** and **9n**–**9x**). Among the mono-substituted pyrazoline derivatives (**9b**–**9p)**, compound **9l** with *p*-CH_3 substitution exhibited better cytotoxic activities with IC_{50} value of 29.39, 13.67, 3.91 and 29.14 μM against SGC 7901, A549, Raji and Hela cell lines, respectively.

As shown in Table 2, all of the pyrazole derivatives **11a**–**11ad** had better cytotoxic activities than their precursor isosteviol. In addition, most of pyrazole derivatives **11a**–**11ad**, especially, *meta*-substituted compounds, showed much higher inhibitory activities against Raji cell than those in SGC 7901, A549 and Hela cell lines. Meanwhile, among the mono-substituted pyrazole derivatives (**11b**–**11p)**, NO_2-substituted compounds (**11n**–**11p**) displayed weaker cytotoxic activity than the other mono-substituted derivatives whereas *m*-CH_3-substituted pyrazole **11l** displayed the best cytotoxic activity. Among the di-substituted pyrazole derivatives (**11q**–**11ad**), compounds **11y**–**11ad** with two methyl

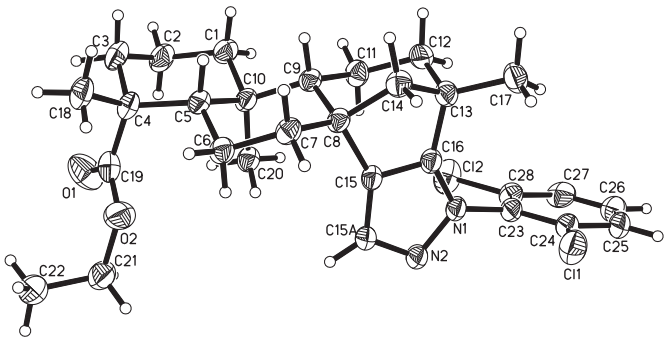


Fig. 4. X-ray structure of compound **11v**.

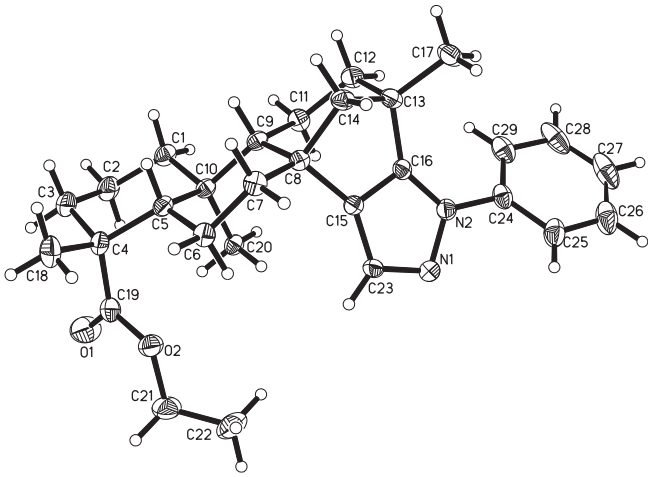


Fig. 5. X-ray structure of compound **11a**.

substituents showed much higher cytotoxic activities than the other di-substituted pyrazole derivatives. Especially, compound **11ab**, with 2,6-dimethyl phenyl as the aromatic substituent, was proved to be an outstandingly potent cytotoxic compound on the four cell lines. More importantly, all of pyrazole derivatives (**11a**–**11ad**) showed superior cytotoxic activities to Cisplatin resistant Raji cell. Specifically, pyrazole derivative **11t** exhibited noteworthy cytotoxic activities with IC_{50} value: 2.71, 3.18, 1.09 and 13.52 μM against SGC 7901, A549, Raji and Hela cell lines, respectively, and all superior than that of Cisplatin. The currently known structure–activity relationships offer a promising possibility for further rational design of more derivatives.

Table 1
Cytotoxic activities of isosteviol-fused pyrazoline derivatives *in vitro*.

Compound	R	Cytotoxic activities (IC_{50}, μM)			
		SGC 7901	A549	Raji	Hela
1		>50	>50	>50	>50
9a	H	>50	28.33	13.95	>50
9b	*o*-F	34.67	32.62	17.23	>50
9c	*m*-F	>50	>50	29.10	>50
9d	*p*-F	>50	>50	4.51	>50
9e	*o*-Cl	>50	>50	>50	>50
9f	*m*-Cl	>50	>50	4.57	>50
9g	*p*-Cl	>50	>50	>50	>50
9h	*m*-Br	>50	>50	25.05	>50
9i	*p*-Br	>50	>50	>50	>50
9j	*o*-CH_3	>50	>50	19.89	>50
9k	*m*-CH_3	>50	>50	>50	>50
9l	*p*-CH_3	29.39	13.67	3.91	29.14
9m	*p*-OCH_3	34.02	17.84	12.25	31.21
9n	*m*-NO_2	>50	>50	>50	>50
9o	*p*-NO_2	>50	>50	>50	>50
9p	*m*-CF_3	>50	>50	7.21	>50
9q	2,4-F_2	>50	>50	13.53	>50
9r	2,5-F_2	>50	20.21	27.36	>50
9s	2,3-Cl_2	>50	>50	22.14	>50
9t	2,4-Cl_2	>50	>50	22.87	>50
9u	2,5-Cl_2	>50	>50	25.63	>50
9v	2,6-Cl_2	>50	11.57	>50	>50
9w	3,4-Cl_2	>50	>50	>50	>50
9x	3,5-Cl_2	>50	>50	>50	24.55
9y	2,3-Me_2	31.85	>50	8.82	>50
9z	2,4-Me_2	28.49	>50	11.18	>50
9aa	2,5-Me_2	22.54	>50	12.63	30.32
9ab	2,6-Me_2	16.61	17.55	5.63	28.77
9ac	3,4-Me_2	32.49	>50	8.36	>50
9ad	3,5-Me_2	>50	>50	>50	>50
Cisplatin		7.56	17.78	17.32	14.31

Table 2
Cytotoxic activities of isosteviol-fused pyrazole derivatives *in vitro*.

Compound	R	Cytotoxic activities (IC_{50}, μM)			
		SGC 7901	A549	Raji	Hela
1		>50	>50	>50	>50
11a	H	17.60	25.38	11.43	42.45
11b	*o*-F	35.64	26.99	4.15	>50
11c	*m*-F	35.81	19.17	3.40	>50
11d	*p*-F	25.57	22.34	7.01	>50
11e	*o*-Cl	25.42	21.50	10.11	34.65
11f	*m*-Cl	26.32	28.24	9.54	>50
11g	*p*-Cl	8.44	35.30	13.82	>50
11h	*o*-Br	30.32	17.42	11.35	41.10
11i	*m*-Br	34.92	26.52	3.27	>50
11j	*p*-Br	29.64	23.14	4.78	>50
11k	*o*-CH_3	35.34	19.01	7.71	15.15
11l	*m*-CH_3	13.55	12.36	4.84	>50
11m	*p*-CH_3	34.91	18.80	8.61	>50
11n	*o*-NO_2	15.63	42.33	14.35	>50
11o	*m*-NO_2	>50	>50	7.40	>50
11p	*p*-NO_2	>50	>50	10.15	>50
11q	2,4-F_2	28.40	20.11	9.96	>50
11r	2,5-F_2	>50	>50	7.11	>50
11s	2,3-Cl_2	>50	>50	5.13	>50
11t	2,4-Cl_2	2.71	3.18	1.09	13.52
11u	2,5-Cl_2	>50	>50	11.72	>50
11v	2,6-Cl_2	27.11	33.16	5.70	34.93
11w	3,4-Cl_2	>50	>50	17.13	>50
11x	3,5-Cl_2	>50	>50	15.85	>50
11y	2,3-Me_2	19.33	18.17	3.26	37.45
11z	2,4-Me_2	18.70	16.52	6.55	43.29
11aa	2,5-Me_2	32.96	17.06	7.94	34.33
11ab	2,6-Me_2	9.17	11.81	2.09	20.34
11ac	3,4-Me_2	38.06	15.76	6.50	38.17
11ad	3,5-Me_2	>50	>50	12.49	>50
Cisplatin		7.56	17.78	17.32	14.31

3. Conclusion

In summary, two series of novel isosteviol derivatives containing pyrazoline and pyrazole heterocyclic fragments were stereoselectively synthesized in high yields by functional interconversions in ring D of the tetracyclic diterpene isosteviol. The *in vitro* cytotoxic activities against four human tumor cell lines were evaluated. The results revealed that introduction of pyrazoline and pyrazole heterocyclic fragments to isosteviol were beneficial to the cytotoxic activities. Furthermore, pyrazole derivatives **11a**–**11ad** showed superior cytotoxic activities to cisplatin against Raji cell. Specifically, compound **11t** (IC_{50} values: 2.71, 3.18, 1.09 and 13.52 μM against SGC 7901, A549, Raji and HeLa, respectively) had the most potent cytotoxicity, which may be exploitable as a lead compound for the development of potent antitumor agents. Further efforts aiming at developing potent anticancer agents based on appropriately modified D-ring fused heterocyclic analogs are continuing in our laboratory, which will be reported in due course.

4. Experimental

4.1. General methods

All reagents and solvents were obtained from commercial suppliers. All the reactions were monitored by TLC. Melting points were determined on a Beijing Keyi XT5 apparatus and the temperature was not corrected. IR spectra were recorded as KBr pellets on a Thermo Nicolet (IR200) spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400 and 100 MHz, respectively, with TMS as internal standard. Mass spectra were taken by Waters Q-Tof micro mass spectrometer. X-ray analysis was taken on a Rigaku RAXIS-IV.

4.2. General procedure for cytotoxicity assay

In vitro cytotoxicity study: Cell lines of human gastric cancer SGC-7901, human lung adenocarcinoma A549 and human cervical carcinoma Hela were purchased from the Type Culture Collection of the Chinese Academy of Sciences, Shanghai, China. Human B lymphoma Raji ecll line was obtained from China Center for Type Culture Collection, Wuhan, China. Cells were cultured in RPMI-1640 medium with 10% FBS, 100 U/mL of penicillin and 100 μg/mL of streptomycin in a 5% CO_2 humidified atmosphere at 37 °C. Cell cytotoxicity was assayed by MTT method. Briefly, cells were seeded in 96-well tissue culture plates and incubated with compounds (0–50 μmol/L) for 48 h at 37 °C, 5% CO_2. Following treatment, MTT (0.5 mg/mL) was added. After an additional 4 h of incubation, the reaction was terminated by removal of the supernatant. Then 200 μl of DMSO was added to each well to dissolve the formazan product. Optical density (OD) of each well was measured at 570 nm with PowerWaveX Microplate Scanning Spectrophotometer (Biotek Instruments, Inc). Then the inhibitory percentage of each compound at various concentrations to the cell proliferation was calculated.

4.3. The preparation of isosteviol derivatives

4.3.1. Ent-16-oxobeyeran-19-oic acid (**1**) [9]

Isosteviol **1** was synthesized by hydrolysis of stevioside with dilute sulfuric acid. Mp 228–230 °C; IR (KBr): 3455, 2954, 2927, 2852, 2679, 1738, 1697, 1474, 1453, 1406, 1372, 1320, 1271, 1238, 1179, 950, 797 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 2.64 (dd, J = 18.6, 3.8 Hz, 1H), 2.17 (d, J = 13.4 Hz, 1H), 1.90–1.82 (m, 2H), 1.81 (d, J = 18.6 Hz 1H), 1.77–1.38 (m, 10H), 1.26 (s, 3H), 1.22–1.14 (m, 3H), 1.07–0.99 (m, 1H), 0.98 (s, 3H), 0.95–0.88 (m, 1H), 0.79 (s, 3H); HRMS (ESI, m/z) calcd for $C_{20}H_{30}O_3Na$ $[M + Na]^+$ 341.2093. Found: 341.2085.

4.3.2. Ethyl ent-16-oxobeyeran-19-oate (**2**)

The isosteviol ethyl ester **2** was obtained by treating isosteviol with CH_3CH_2Br and KOH in DMSO at room temperature in 92% yield according to the literature method [38]. Mp 125–127 °C; IR (KBr): 2957, 2926, 2847, 1726, 1451, 1377, 1227, 1146, 1096, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 4.10 (q, J = 7.2 Hz, 2H), 2.96 (dd, J = 18.4, 2.8 Hz, 1H), 2.17 (d, J = 11.2 Hz, 1H), 1.99 (d, J = 18.8 Hz, 1H), 1.88–1.58 (m, 8H), 1.47–1.28 (m, 6H), 1.26 (t, J = 7.2 Hz, 3H), 1.24–1.19 (m, 2H), 1.18 (s, 3H), 1.07 (s, 3H), 1.05–0.84 (m, 1H), 0.77 (s, 3H); HRMS (ESI, m/z) calcd for $C_{22}H_{34}O_3Na$ $[M + Na]^+$ 369.2406. Found: 369.2400.

4.3.3. Ethyl ent-15α-hydroxymethyl-16β-hydroxybeyeran-19-oate (**3**) [38]

To a stirred solution of compound **2** (0.346 g, 1 mmol) and C_2H_5ONa (0.136 g, 2 mmol) in ethanol (20 mL) was added 37% formaldehyde aqueous solution (2 mL). After stirring for 3 h at 60 °C, the mixture was concentrated under vacuum, and extracted with $CHCl_3$ and H_2O, at last the organic layer was washed with saturated NaCl aqueous solution, dried with $MgSO_4$ and concentrated under vacuum to give white powder **8** (0.34 g, 90%). Mp 181–182 °C; IR (KBr): 3435, 2940, 2838, 1720, 1458, 1378, 1234, 1179, 1153, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 4.09 (q, J = 7.2 Hz, 2H), 3.98 (dd, J = 9.7, 5.0 Hz, 1H), 3.63 (d, J = 4.7 Hz, 1H), 3.56 (t, J = 10.2 Hz, 1H), 2.16 (d, J = 13.0 Hz, 1H), 2.05 (m, 1H), 1.83–1.56 (m, 9H), 1.43–1.37 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 1.22–1.19 (m, 1H), 1.16 (s, 3H), 1.08–0.95 (m, 4H), 0.94 (s, 3H), 0.88–0.86 (m, 1H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 86.7, 64.9, 60.0, 57.5, 57.0, 54.2, 50.2, 43.6, 42.4, 40.8, 39.6, 38.1, 37.9, 34.8, 33.0, 28.9, 25.0, 22.1, 19.5, 18.8, 14.1, 13.2; HRMS (ESI, m/z) calcd for $C_{23}H_{38}O_4Na$ $[M + Na]^+$ 401.2668. Found: 401.2664.

4.3.4. Ethyl ent-15α-(4-toluenesulfonyl)-oxymethyl-16β-hydroxy beyeran-19-oate (**4**)

A mixture of compound **3**(0.378 g, 1 mmol) and 4-methyl phenylsulfonyl chloride (0.238 g, 1.1 mmol) in pyridine (5 mL) was stirred at room temperature for 18 h. Then the reaction mixture was filtered, and the filtrate was extracted with CH_2Cl_2 and HCl aqueous solution (5 M). At last, the organic layer was washed with saturated NaCl aqueous solution, dried with $MgSO_4$ and the filtrate was concentrated. The residue was purified by column chromatography on silica (petroleum ether/ethyl acetate = 4:1, v/v) to give product **4** (0.399 g, 75%). IR (KBr): 3541, 2950, 2928, 2851, 1718, 1598, 1458, 1361, 1177, 1151, 1097, 1020, 948, 924, 816, 779, 665, 555 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.82 (d, J = 8.2 Hz, 2H), 7.37 (t, J = 8.2 Hz, 1H), 4.32 (dd, J = 9.8, 3.6 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.96 (t, J = 9.8 Hz, 1H), 3.47 (d, J = 7.5 Hz, 1H), 3.46 (s, 3H), 2.33 (m, 1H), 2.18 (m, 2H), 1.80–1.28 (m, 8H), 1.23 (t, J = 7.1 Hz, 3H), 1.19–1.11 (m, 1H), 1.16 (s, 3H), 1.10–0.93 (m, 5H), 0.88 (s, 3H), 0.86–0.79 (m, 3H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 144.8, 132.9, 129.8, 129.8, 127.7, 127.7, 84.9, 72.8, 59.9, 57.4, 56.8, 53.8, 47.6, 43.5, 42.8, 40.9, 39.5, 38.0, 37.8, 34.6, 33.0, 28.8, 24.8, 21.9, 21.6, 19.3, 18.7, 14.0, 12.9; HRMS (ESI, m/z) calcd for $C_{30}H_{44}O_6SNa$ $[M + Na]^+$ 555.2757. Found: 555.2742.

4.3.5. Ring opening product (**5**)

A mixture of compound **4** (0.532 g, 1 mmol) and NaOH (0.048 g, 1.1 mmol) in dry CH_3CN (5 mL) was stirred at room temperature for 3 h. Then the reaction mixture was filtered, the filtrate was concentrated, and the residue was extracted with CH_2Cl_2 and H_2O. At last, the organic layer was washed with saturated NaCl aqueous solution, dried with $MgSO_4$ and the filtrate was concentrated. The residue was crystallized from $CHCl_3$ to give product **5** (0.345 g, 96%). Mp 116.5–117.8 °C; IR (KBr): 3072, 2937, 2796, 2704, 1716, 1458, 1384, 1238, 1183, 1029, 912, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.27 (d, J = 1.6 Hz, 1H), 5.95 (dd, J = 17.6, 10.8 Hz, 1H), 5.12 (d, J = 10.0 Hz, 1H), 5.08 (d, J = 3.2 Hz, 1H), 4.01 (m, 2H), 2.28 (m, 1H), 2.13 (m, 2H), 1.88–1.39 (m, 9H), 1.26 (d, J = 13.2 Hz, 1H), 1.20 (t, J = 7.2 Hz, 3H), 1.14 (s, 3H), 1.10–0.89 (m, 5H), 0.88 (s, 3H), 0.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 205.2, 177.3, 142.5, 113.6, 59.9, 57.7, 57.5, 55.2, 46.1, 43.7, 40.8, 40.1, 39.6, 38.1, 38.0, 32.3, 28.7, 24.6, 20.0, 19.1, 17.4, 14.0, 13.2; HRMS (ESI, m/z) calcd for $C_{23}H_{36}O_3Na$ $[M + Na]^+$ 383.2562. Found: 383.2560.

4.3.6. General procedure for synthesis of compounds **9a–9ad**

A mixture of compound **5** (0.360 g, 1 mmol) and various phenylhydrazines **6a–6ad** (0.145–0.225 g, 1 mmol) in dry EtOH (10 mL) were stirred at 78 °C in the presence of CH_3COONa (0.099 g, 1.2 mmol). After completion of the reaction monitored by TLC, the solution was then poured into water (10 mL), the white precipitate was filtered and washed with water and dried. The crude product was recrystallized from ethyl acetate/light petroleum ether to give compounds **7a–7ad**. Then to a solution of compounds **7a–7ad** (0.450–0.529 g, 1 mmol) in toluene (5 mL), 48% $BF_3 \cdot OEt_2$ (48% solution in Et_2O, 0.05 mL, 0.17 mmol) was added dropwise and the mixture was heated under a nitrogen atmosphere at 118 °C. After completion of the reaction monitored by TLC, water (10 mL) was added to the mixture, which was next neutralized with $NaHCO_3$, and the organic phase was separated and dried over Na_2SO_4. After evaporation in vacuo, the crude product was purified by column chromatography to give product **9a–9ad**.

*4.3.6.1. Pyrazoline derivative **9a**.* Yield 76%; Mp 98.3–100.2 °C; IR (KBr): 3054, 2926, 2849, 1720, 1599, 1497, 1454, 1378, 1323, 1292,

1259, 1229, 1175, 1151, 1092, 1027, 991, 852, 751, 693, 517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.28 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 7.6 Hz, 2H), 6.86 (t, J = 7.2 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.98 (t, J = 8.6 Hz, 1H), 3.51–3.46 (m, 1H), 2.99 (dd, J = 14.0, 8.6 Hz, 1H), 2.21–2.18 (m, 1H), 1.90–1.70 (m, 5H), 1.67–1.54 (m, 4H), 1.45–1.33 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.25–1.21 (m, 2H), 1.19 (s, 6H), 1.16–0.86 (m, 4H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 172.2, 149.1, 128.9, 128.9, 119.7, 114.3, 114.3, 60.0, 58.6, 57.2, 56.7, 55.2, 49.7, 43.6, 42.0, 39.7, 39.7, 38.2, 37.8, 35.4, 35.2, 29.0, 21.8, 21.3, 19.7, 18.8, 14.1, 13.1; HRMS (ESI, m/z) calcd for $C_{29}H_{41}N_2O_2$ $[M + H]^+$ 449.3168. Found: 449.3170.

4.3.6.2. Pyrazoline derivative ***9b***. Yield 58%; Mp 124.2–125.8 °C; IR (KBr): 3067, 2953, 2848, 1720, 1635, 1610, 1495, 1455, 1379, 1320, 1293, 1253, 1229, 1176, 1149, 1101, 1027, 976, 849, 818, 749, 562 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.58–7.53 (m, 1H), 7.07–7.01 (m, 2H), 6.92–6.87 (m, 1H), 4.26–4.20 (m, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.53–3.48 (m, 1H), 2.97 (dd, J = 14.4, 8.6 Hz, 1H), 2.20–2.17 (m, 1H), 1.87–1.73 (m, 5H), 1.65–1.53 (m, 4H), 1.45–1.35 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.25–1.23 (m, 2H), 1.22 (s, 3H), 1.18 (s, 3H), 1.16–0.89 (m, 4H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 173.0, 152.5 (d, J = 242.3 Hz), 137.9 (d, J = 8.8 Hz), 124.3 (d, J = 3.4 Hz), 121.9 (d, J = 7.4 Hz), 119.6 (d, J = 3.2 Hz), 116.0 (d, J = 20.5 Hz), 60.0, 58.9 (d, J = 6.6 Hz), 57.1, 56.7, 53.4, 50.3, 43.6, 42.1, 39.8, 39.8, 38.2, 37.8, 35.3, 35.2, 29.0, 21.8, 21.4, 19.7, 18.8, 14.1, 13.2; HRMS (ESI, m/z) calcd for $C_{29}H_{40}FN_2O_2$ $[M + H]^+$ 467.3074. Found: 467.3076.

4.3.6.3. Pyrazoline derivative ***9c***. Yield 51%; Mp 80.8–82.5 °C; IR (KBr): 3077, 2953, 2849, 1720, 1611, 1581, 1492, 1454, 1378, 1344, 1322, 1296, 1267, 1229, 1180, 1149, 1094, 1029, 927, 852, 763, 681, 522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.21–7.16 (m, 1H), 6.87–6.83 (m, 1H), 6.80–6.78 (m, 1H), 6.55–6.50 (m, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.94 (t, J = 8.6 Hz, 1H), 3.50–3.44 (m, 1H), 3.00 (dd, J = 14.4, 8.6 Hz, 1H), 2.21–2.18 (m, 1H), 1.90–1.73 (m, 5H), 1.66–1.52 (m, 4H), 1.45–1.34 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.25–1.20 (m, 2H), 1.20 (s, 3H), 1.19 (s, 3H), 1.17–0.89 (m, 4H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 172.3, 163.6 (d, J = 241.3 Hz), 150.6 (d, J = 10.6 Hz), 130.0 (d, J = 9.7 Hz), 109.4 (d, J = 2.2 Hz), 105.9 (d, J = 21.6 Hz), 101.5 (d, J = 28.8 Hz), 60.0, 58.5, 57.1, 56.7, 54.7, 49.7, 43.6, 42.0, 39.7, 39.7, 38.2, 37.8, 35.4, 35.2, 29.0, 21.8, 21.3, 19.7, 18.8, 14.2, 13.1; HRMS (ESI, m/z) calcd for $C_{29}H_{40}FN_2O_2$ $[M + H]^+$ 467.3074. Found: 467.3077.

4.3.6.4. Pyrazoline derivative ***9d***. Yield 54%; Mp 114.8–116.5 °C; IR (KBr): 3053, 2951, 2848, 1720, 1630, 1606, 1506, 1452, 1379, 1323, 1294, 1221, 1177, 1151, 1098, 1028, 976, 850, 825, 517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.07–7.03 (m, 2H), 6.98–6.94 (m, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.93 (t, J = 8.6 Hz, 1H), 3.50–3.44 (m, 1H), 2.92 (dd, J = 14.4, 8.6 Hz, 1H), 2.21–2.18 (m, 1H), 1.90–1.70 (m, 5H), 1.67–1.52 (m, 4H), 1.45–1.34 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.25–1.21 (m, 2H), 1.19 (s, 3H), 1.18 (s, 3H), 1.161–0.89 (m, 4H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 172.3, 157.2 (d, J = 236.2 Hz), 145.8 (d, J = 2.0 Hz), 115.4 (d, J = 7.7 Hz), 115.4 (d, J = 7.7 Hz), 115.3 (d, J = 22.4 Hz), 115.3 (d, J = 22.4 Hz), 60.0, 58.6, 57.1, 56.7, 55.9, 50.0, 43.6, 42.0, 39.7, 39.7, 38.2, 37.8, 35.4, 35.2, 29.0, 21.8, 21.3, 19.7, 18.8, 14.1, 13.1; HRMS (ESI, m/z) calcd for $C_{29}H_{40}FN_2O_2$ $[M + H]^+$ 467.3074. Found: 467.3078.

4.3.6.5. Pyrazoline derivative ***9e***. Yield 37%; Mp 190.5–192.3 °C; IR (KBr): 3057, 2956, 2842, 1717, 1637, 1588, 1514, 1469, 1378, 1319, 1282, 1249, 1227, 1148, 1092, 1039, 1016, 978, 848, 752, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.52 (dd, J = 8.0, 1.4 Hz, 1H), 7.35 (dd, J = 8.0, 1.4 Hz, 1H), 7.22 (dt, J = 7.2, 1.4 Hz, 1H), 7.01 (dt, J = 7.2, 1.4 Hz, 1H), 4.33 (t, J = 8.6 Hz, 1H), 4.16–4.07 (m, 2H), 3.57–3.51 (m, 1H), 2.74 (dd, J = 14.4, 8.6 Hz, 1H), 2.21–2.17 (m, 1H), 1.84–1.68 (m, 5H), 1.65–1.53 (m, 4H), 1.46–1.31 (m, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.25 (s, 3H), 1.21–1.20 (m, 1H), 1.17 (s, 3H), 1.13–0.87 (m, 4H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 173.9, 147.7, 130.2, 127.5, 126.2, 124.5, 122.1, 60.5, 60.0, 58.7, 57.2, 56.8, 50.5, 43.6, 42.2, 39.9, 39.8, 38.2, 37.8, 35.2, 35.2, 29.0, 21.7, 21.6, 19.7, 18.8, 14.0, 13.3; HRMS (ESI, m/z) calcd for $C_{29}H_{40}ClN_2O_2$ $[M + H]^+$ 483.2778. Found: 483.2773; $[M+2 + H]^+$ 485.2778. Found: 485.2771.

4.3.6.6. Pyrazoline derivative ***9f***. Yield 76%; Mp 143.4–144.6 °C; IR (KBr): 3055, 2946, 2850, 1712, 1622, 1595, 1567, 1485, 1451, 1375, 1342, 1260, 1242, 1181, 1153, 1096, 1033, 992, 852, 827, 758, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.16 (t, J = 8.0 Hz, 1H), 7.10 (t, J = 2.0 Hz, 1H), 6.95–6.92 (m, 1H), 6.81–6.79 (m, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.94 (t, J = 8.6 Hz, 1H), 3.50–3.44 (m, 1H), 2.99 (dd, J = 14.4, 8.6 Hz, 1H), 2.21–2.18 (m, 1H), 1.90–1.73 (m, 5H), 1.65–1.53 (m, 4H), 1.46–1.34 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.25–1.21 (m, 2H), 1.19 (s, 3H), 1.19 (s, 3H), 1.16–0.89 (m, 4H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 172.4, 150.0, 134.6, 129.9, 119.2, 114.1, 112.2, 60.0, 58.5, 57.1, 56.7, 54.7, 49.7, 43.6, 42.1, 39.7, 39.7, 38.2, 37.8, 35.3, 35.2, 29.0, 21.8, 21.3, 19.7, 18.8, 14.2, 13.1; HRMS (ESI, m/z) calcd for $C_{29}H_{40}ClN_2O_2$ $[M + H]^+$ 483.2778. Found: 483.2777; $[M+2 + H]^+$ 485.2778. Found: 485.2785.

4.3.6.7. Pyrazoline derivative ***9g***. Yield 50%; Mp 87.9–89.6 °C; IR (KBr): 3052, 2953, 2848, 1720, 1628, 1596, 1492, 1456, 1378, 1322, 1261, 1228, 1150, 1093, 1029, 976, 851, 821, 496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.22–7.19 (m, 2H), 7.03–7.00 (m, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.94 (t, J = 8.6 Hz, 1H), 3.50–3.44 (m, 1H), 2.95 (dd, J = 14.4, 8.6 Hz, 1H), 2.21–2.18 (m, 1H), 1.90–1.73 (m, 5H), 1.70–1.52 (m, 4H), 1.45–1.35 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.25–1.21 (m, 2H), 1.19 (s, 3H), 1.18 (s, 3H), 1.16–0.89 (m, 4H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 172.4, 147.7, 128.7, 128.7, 124.3, 115.3, 115.3, 60.0, 58.5, 57.1, 56.7, 55.0, 49.8, 43.6, 42.0, 39.7, 39.7, 38.2, 37.8, 35.4, 35.2, 29.0, 21.8, 21.3, 19.7, 18.8, 14.1, 13.1; HRMS (ESI, m/z) calcd for $C_{29}H_{40}ClN_2O_2$ $[M + H]^+$ 483.2778. Found: 483.2775; $[M+2 + H]^+$ 485.2778. Found: 485.2791.

4.3.6.8. Pyrazoline derivative ***9h***. Yield 55%; Mp 141.5–143.2 °C; IR (KBr): 3062, 2953, 2848, 1720, 1590, 1560, 1479, 1377, 1339, 1323, 1229, 1178, 1150, 1095, 1029, 985, 851, 766, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.26–7.24 (m, 1H), 7.10 (t, J = 8.0 Hz, 1H), 6.99–6.94 (m, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.93 (t, J = 8.6 Hz, 1H), 3.49–3.44 (m, 1H), 2.98 (dd, J = 14.4, 8.6 Hz, 1H), 2.21–2.18 (m, 1H), 1.90–1.73 (m, 5H), 1.65–1.52 (m, 4H), 1.45–1.34 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.25–1.22 (m, 2H), 1.19 (s, 3H), 1.18 (s, 3H), 1.16–0.86 (m, 4H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 172.5, 150.1, 130.2, 122.9, 122.1, 116.9, 112.7, 60.0, 58.5, 57.1, 56.7, 54.6, 49.7, 43.6, 42.1, 39.7, 39.7, 38.2, 37.8, 35.3, 35.2, 29.0, 21.8, 21.3, 19.7, 18.8, 14.2, 13.1; HRMS (ESI, m/z) calcd for $C_{29}H_{40}BrN_2O_2$ $[M + H]^+$ 527.2273. Found: 527.2277; $[M+2 + H]^+$ 529.2273. Found: 529.2250.

4.3.6.9. Pyrazoline derivative ***9i***. Yield 64%; Mp 90.5–92.2 °C; IR (KBr): 3059, 2952, 2848, 1720, 1628, 1590, 1489, 1454, 1378, 1322, 1293, 1261, 1229, 1176, 1151, 1096, 1029, 976, 852, 819, 511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.36–7.32 (m, 2H), 6.98–6.95 (m, 2H), 4.11 (q, J = 7.2 Hz, 2H), 3.93 (t, J = 8.6 Hz, 1H), 3.50–3.44 (m, 1H), 2.95 (dd, J = 14.4, 8.6 Hz, 1H), 2.21–2.17 (m, 1H), 1.90–1.72 (m, 5H), 1.65–1.52 (m, 4H), 1.46–1.35 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.25–1.21 (m, 2H), 1.19 (s, 3H), 1.18 (s, 3H), 1.15–0.89 (m, 4H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 172.4, 148.1, 131.6, 131.6, 115.8, 115.8, 111.5, 60.0, 58.5, 57.1, 56.7, 54.9, 49.8, 43.6, 42.0, 39.7, 39.7, 38.2, 37.8, 35.3, 35.2, 29.0, 21.8, 21.3, 19.7, 18.8, 14.2, 13.1;

HRMS (ESI, *m*/*z*) calcd for $C_{29}H_{40}BrN_2O_2$ $[M + H]^+$ 527.2273. Found: 527.2271; $[M+2 + H]^+$ 529.2273. Found: 529.2241.

4.3.6.10. Pyrazoline derivative ***9j***. Yield 76%; Mp 131.1–131.8 °C; IR (KBr): 3062, 2952, 2848, 1720, 1630, 1598, 1491, 1454, 1378, 1321, 1254, 1231, 1178, 1151, 1095, 1027, 977, 850, 756, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.21–7.13 (m, 3H), 6.98 (dt, *J* = 14.4, 8.6 Hz, 1H), 4.13–4.07 (m, 2H), 3.78 (t, *J* = 8.6 Hz, 1H), 3.48–3.43 (m, 1H), 2.83 (dd, *J* = 14.4, 8.6 Hz, 1H), 2.41 (s, 3H), 2.20–2.17 (m, 1H), 1.85–1.73 (m, 5H), 1.67–1.55 (m, 4H), 1.45–1.29 (m, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.24–1.21 (m, 1H), 1.21 (s, 3H), 1.17 (s, 3H), 1.14–0.89 (m, 4H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 172.8, 148.9, 131.0, 130.9, 126.4, 123.5, 118.8, 60.0, 59.7, 58.8, 57.2, 56.8, 50.2, 43.6, 42.0, 39.8, 39.8, 38.2, 37.8, 35.3, 35.3, 29.0, 21.8, 21.5, 19.8, 19.2, 18.8, 14.1, 13.3; HRMS (ESI, *m*/*z*) calcd for $C_{30}H_{43}N_2O_2$ $[M + H]^+$ 463.3325. Found: 463.3326.

4.3.6.11. Pyrazoline derivative ***9k***. Yield 73%; Mp 110.1–111.8 °C; IR (KBr): 3060, 2952, 2849, 1721, 1601, 1491, 1457, 1378, 1324, 1295, 1264, 1229, 1176, 1151, 1096, 1029, 992, 851, 773, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.15 (t, *J* = 8.0 Hz, 1H), 6.96 (s, 1H), 6.89 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.96 (t, *J* = 8.6 Hz, 1H), 3.49–3.43 (m, 1H), 2.97 (dd, *J* = 14.4, 8.6 Hz, 1H), 2.34 (s, 3H), 2.21–2.18 (m, 1H), 1.90–1.70 (m, 5H), 1.67–1.53 (m, 4H), 1.46–1.33 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.26–1.21 (m, 2H), 1.19 (s, 6H), 1.15–0.89 (m, 4H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 171.8, 149.2, 138.7, 128.7, 120.5, 115.0, 111.4, 60.0, 58.6, 57.2, 56.7, 55.2, 49.6, 43.6, 42.0, 39.7, 39.7, 38.2, 37.8, 35.4, 35.2, 29.0, 21.9, 21.2, 21.4, 19.8, 18.8, 14.2, 13.1; HRMS (ESI, *m*/*z*) calcd for $C_{30}H_{43}N_2O_2$ $[M + H]^+$ 463.3325. Found: 463.3327.

4.3.6.12. Pyrazoline derivative ***9l***. Yield 81%; Mp 74.5–76.3 °C; IR (KBr): 3095, 2950, 2848, 1720, 1616, 1513, 1456, 1377, 1322, 1234, 1179, 1150, 1095, 1030, 976, 852, 806, 516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.08 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.95 (t, *J* = 8.8 Hz, 1H), 3.49–3.43 (m, 1H), 2.92 (dd, *J* = 14.4, 8.6 Hz, 1H), 2.28 (s, 3H), 2.21–2.17 (m, 1H), 1.89–1.66 (m, 5H), 1.64–1.52 (m, 4H), 1.45–1.31 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.25–1.20 (m, 2H), 1.19 (s, 3H), 1.18 (s, 3H), 1.15–0.86 (m, 4H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 171.8, 147.3, 129.4, 129.4, 129.0, 114.5, 114.5, 60.0, 58.6, 57.2, 56.7, 55.7, 49.7, 43.6, 42.0, 39.8, 39.7, 38.2, 37.8, 35.4, 35.3, 29.0, 21.9, 21.4, 20.5, 19.8, 18.8, 14.2, 13.1; HRMS (ESI, *m*/*z*) calcd for $C_{30}H_{43}N_2O_2$ $[M + H]^+$ 463.3325. Found: 463.3320.

4.3.6.13. Pyrazoline derivative ***9m***. Yield 51%; Mp 59.5–61.3 °C; IR (KBr): 3043, 2950, 2847, 1719, 1626, 1508, 1459, 1379, 1323, 1287, 1239, 1177, 1150, 1096, 1033, 975, 851, 823, 526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.08–7.06 (m, 2H), 6.86–6.84 (m, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.92 (t, *J* = 8.6 Hz, 1H), 3.77 (s, 3H), 3.49–3.43 (m, 1H), 2.89 (dd, *J* = 14.4, 8.6 Hz, 1H), 2.21–2.17 (m, 1H), 1.89–1.73 (m, 5H), 1.71–1.53 (m, 4H), 1.45–1.35 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.25–1.20 (m, 2H), 1.19 (s, 3H), 1.18 (s, 3H), 1.15–0.89 (m, 4H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 172.0, 153.7, 143.9, 115.9, 115.9, 114.4, 114.4, 60.0, 58.6, 57.2, 56.7, 56.6, 55.6, 50.0, 43.6, 41.9, 39.8, 39.7, 38.2, 37.8, 35.4, 35.3, 29.0, 21.9, 21.4, 19.8, 18.8, 14.1, 13.1; HRMS (ESI, *m*/*z*) calcd for $C_{30}H_{43}N_2O_3$ $[M + H]^+$ 479.3274. Found: 479.3269.

4.3.6.14. Pyrazoline derivative ***9n***. Yield 38%; Mp 185.5–187.3 °C; IR (KBr): 3095, 2955, 2845, 1716, 1616, 1568, 1525, 1486, 1461, 1381, 1340, 1255, 1226, 1149, 1097, 1025, 850, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.81 (t, *J* = 2.0 Hz, 1H), 7.67–7.65 (m, 1H), 7.43–7.40 (m, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 4.16–4.10 (m, 2H), 4.02 (t, *J* = 8.6 Hz, 1H), 3.55–3.49 (m, 1H), 3.73 (dd, *J* = 14.4, 8.6 Hz, 1H), 2.22–2.18 (m, 1H), 1.92–1.73 (m, 5H), 1.67–1.53 (m, 4H), 1.46–1.37 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.27–1.22 (m, 2H), 1.20 (s, 6H), 1.16–0.94 (m, 4H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 173.2, 149.4, 149.0, 129.5, 120.0, 113.7, 108.0, 60.1, 58.4, 57.1, 56.6, 54.4, 49.8, 43.6, 42.1, 39.7, 39.7, 38.2, 37.8, 35.3, 35.2, 29.0, 21.8, 21.3, 19.7, 18.8, 14.2, 13.1; HRMS (ESI, *m*/*z*) calcd for $C_{29}H_{40}N_3O_4$ $[M + H]^+$ 494.3019. Found: 494.3021.

4.3.6.15. Pyrazoline derivative ***9o***. Yield 49%; Mp 186.8–188.7 °C; IR (KBr): 2953, 2927, 2851, 1720, 1595, 1502, 1456, 1383, 1317, 1179, 1109, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 8.14 (d, *J* = 9.2 Hz, 2H), 6.98 (d, *J* = 9.2 Hz, 2H), 4.13 (m, 2H), 4.06 (m, 1H), 3.54 (t, *J* = 17.2 Hz, 1H), 3.25 (dd, *J* = 13.6, 9.2 Hz, 1H), 2.26 (m, 3H), 1.92–1.73 (m, 4H), 1.68–1.30 (m, 7H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 1.16–0.83 (m, 4H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.1, 174.7, 151.7, 138.8, 125.8, 125.8, 111.9, 111.9, 60.0, 58.2, 57.0, 56.5, 52.6, 49.5, 43.5, 42.3, 39.6, 38.1, 37.6, 35.1, 35.0, 29.6, 29.0, 21.7, 21.2, 19.6, 18.7, 14.1, 13.0; HRMS (ESI, *m*/*z*) calcd for $C_{29}H_{39}N_3O_4Na$ $[M + Na]^+$ 516.2838. Found: 516.2845.

4.3.6.16. Pyrazoline derivative ***9p***. Yield 48%; Mp 112.8–114.2 °C; IR (KBr): 2955, 2850, 1721, 1610, 1588, 1493, 1454, 1379, 1347, 1318, 1281, 1255, 1230, 1163, 1123, 1067, 1029, 996, 853, 785, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.34 (t, *J* = 8.0 Hz, 1H), 7.28–7.23 (m, 2H), 7.07 (d, *J* = 7.6 Hz, 1H), 4.15–4.10 (m, 2H), 4.00 (t, *J* = 9.0 Hz, 1H), 3.53–3.47 (m, 1H), 3.02 (dd, *J* = 14.2, 8.6 Hz, 1H), 2.21–2.18 (m, 1H), 1.92–1.70 (m, 5H), 1.67–1.53 (m, 4H), 1.46–1.36 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.25–1.21 (m, 2H), 1.19 (s, 6H), 1.16–0.90 (m, 4H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 172.6, 149.1, 131.1 (q, *J* = 31.0 Hz), 129.3, 124.3 (q, *J* = 270.8 Hz), 117.1, 115.7 (q, *J* = 4.4 Hz), 110.4 (q, *J* = 3.9 Hz), 60.0, 58.5, 57.1, 56.7, 54.6, 49.7, 43.6, 42.1, 39.7, 39.7, 38.2, 37.8, 35.4, 35.2, 29.0, 21.8, 21.3, 19.7, 18.8, 14.2, 13.1; HRMS (ESI, *m*/*z*) calcd for $C_{30}H_{40}F_3N_2O_2$ $[M + H]^+$ 517.3042. Found: 517.3040.

4.3.6.17. Pyrazoline derivative ***9q***. Yield 65%; Mp 104.7–106.2 °C; IR (KBr): 3074, 2955, 2849, 1721, 1637, 1595, 1503, 1453, 1380, 1322, 1256, 1223, 1177, 1142, 1026, 977, 948, 846, 809, 598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.54–7.48 (m, 1H), 6.85–6.77 (m, 2H), 4.17–4.09 (m, 3H), 3.53–3.48 (m, 1H), 2.88 (dd, *J* = 14.4, 8.6 Hz, 1H), 2.21–2.17 (m, 1H), 1.88–1.71 (m, 5H), 1.68–1.53 (m, 4H), 1.45–1.30 (m, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.25–1.24 (m, 1H), 1.22 (s, 3H), 1.17 (s, 3H), 1.14–0.88 (m, 4H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 173.6 (m), 157.8 (dd, *J* = 242.5, 11.7 Hz), 152.7 (dd, *J* = 246.4, 12.4 Hz), 134.5 (dd, *J* = 9.1, 3.2 Hz), 120.5 (dd, *J* = 7.5, 3.5 Hz), 110.8 (dd, *J* = 21.2, 3.4 Hz), 104.3 (t, *J* = 25.6 Hz), 60.0, 59.5 (d, *J* = 5.5 Hz), 58.6, 57.1, 56.7, 50.6, 43.6, 42.1, 39.7, 39.7, 38.2, 37.8, 35.2, 35.2, 29.0, 21.8, 21.4, 19.7, 18.8, 14.1, 13.2; HRMS (ESI, *m*/*z*) calcd for $C_{29}H_{39}F_2N_2O_2$ $[M + H]^+$ 485.2980. Found: 485.2982.

4.3.6.18. Pyrazoline derivative ***9r***. Yield 42%; Mp 115.7–116.3 °C; IR (KBr): 2955, 2850, 1721, 1624, 1587, 1502, 1459, 1380, 1323, 1294, 1235, 1180, 1150, 1097, 1027, 982, 853, 971, 761, 607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.33–7.26 (m, 1H), 6.99–6.92 (m, 1H), 6.56–6.50 (m, 1H), 4.31–4.25 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.53–3.47 (m, 1H), 2.99 (dd, *J* = 14.4, 8.6 Hz, 1H), 2.21–2.17 (m, 1H), 1.87–1.70 (m, 5H), 1.68–1.52 (m, 4H), 1.45–1.34 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.25–1.22 (m, 2H), 1.22 (s, 3H), 1.18 (s, 3H), 1.14–0.85 (m, 4H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 173.3, 159.0 (d, *J* = 237.2 Hz), 148.0 (d, *J* = 237.0 Hz), 138.7 (t, *J* = 10.5 Hz), 116.5 (dd, *J* = 23.4, 10.0 Hz), 107.0 (dd, *J* = 24.3, 7.8 Hz), 106.3 (dd, *J* = 28.3, 3.7 Hz), 60.1, 58.5, 58.3 (d, *J* = 7.9 Hz), 57.1, 56.7, 50.4, 43.6, 42.1, 39.8, 39.7, 38.2, 37.8, 35.2, 35.1, 29.0, 21.8, 21.4, 19.7, 18.8, 14.1, 13.2; HRMS (ESI, *m*/*z*) calcd for $C_{29}H_{39}F_2N_2O_2$ $[M + H]^+$ 485.2980. Found: 485.2978.

4.3.6.19. Pyrazoline derivative ***9s***. Yield 41%; Mp 182.4–183.6 °C; IR (KBr): 3063, 2953, 2848, 1720, 1633, 1577, 1450, 1419, 1379, 1323, 1290, 1255, 1230, 1177, 1150, 1095, 1027, 989, 849, 779, 737, 710, 642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.44 (dd, J = 8.0, 2.0 Hz, 1H), 7.19 (dd, J = 8.0, 2.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 4.34 (t, J = 8.6 Hz, 1H), 4.18–4.05 (m, 2H), 3.57–3.51 (m, 1H), 2.73 (dd, J = 14.4, 8.6 Hz, 1H), 2.21–2.17 (m, 1H), 1.86–1.74 (m, 5H), 1.64–1.52 (m, 4H), 1.45–1.32 (m, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.24 (s, 3H), 1.23–1.19 (m, 1H), 1.17 (s, 3H), 1.13–0.89 (m, 4H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 174.3, 149.5, 133.6, 127.4, 125.2, 124.8, 120.1, 60.1, 58.7, 57.1, 56.7, 53.4, 50.5, 43.6, 42.2, 39.8, 39.8, 38.2, 37.8, 35.2, 35.1, 28.9, 21.7, 21.5, 19.7, 18.8, 14.1, 13.3; HRMS (ESI, m/z) calcd for $C_{29}H_{39}Cl_2N_2O_2$ $[M + H]^+$ 517.2389. Found: 517.2385; $[M+2 + H]^+$ 519.2389. Found: 519.2378.

4.3.6.20. Pyrazoline derivative ***9t***. Yield 43%; Mp 102.7–104.1 °C; IR (KBr): 3096, 2952, 2848, 1723, 1635, 1584, 1555, 1473, 1328, 1322, 1261, 1228, 1173, 1148, 1098, 1054, 1027, 978, 853, 817, 774, 561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.46 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.18 (dd, J = 8.4, 2.4 Hz, 1H), 4.31 (t, J = 8.6 Hz, 1H), 4.16–4.07 (m, 2H), 3.56–3.50 (m, 1H), 2.70 (dd, J = 14.4, 8.6 Hz, 1H), 2.21–2.17 (m, 1H), 1.87–1.67 (m, 5H), 1.64–1.52 (m, 4H), 1.44–1.32 (m, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.24 (s, 3H), 1.21–1.20 (m, 1H), 1.17 (s, 3H), 1.13–0.86 (m, 4H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 174.3, 146.4, 129.9, 128.8, 127.5, 126.5, 122.8, 60.3, 60.0, 58.7, 57.1, 56.7, 50.6, 43.6, 42.2, 39.8, 39.7, 38.2, 37.8, 35.2, 35.1, 29.0, 21.7, 21.5, 19.7, 18.8, 14.0, 13.3; HRMS (ESI, m/z) calcd for $C_{29}H_{39}Cl_2N_2O_2$ $[M + H]^+$ 517.2389. Found: 517.2390; $[M+2 + H]^+$ 519.2389. Found: 519.2380.

4.3.6.21. Pyrazoline derivative ***9u***. Yield 48%; Mp 154.9–156.3 °C; IR (KBr): 3094, 2945, 2844, 1722, 1637, 1580, 1509, 1460, 1393, 1320, 1248, 1227, 1171, 1150, 1093, 1049, 1012, 976, 879, 799, 605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.52 (d, J = 2.5 Hz, 1H), 7.26 (d, J = 2.5 Hz, 1H), 6.96 (dd, J = 8.5, 2.5 Hz, 1H), 4.37 (t, J = 8.8 Hz, 1H), 4.16–4.05 (m, 2H), 3.56–3.50 (m, 1H), 2.74 (dd, J = 14.4, 8.6 Hz, 1H), 2.21–2.17 (m, 1H), 1.86–1.73 (m, 5H), 1.69–1.53 (m, 4H), 1.46–1.29 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.25 (s, 3H), 1.24–1.19 (m, 2H), 1.17 (s, 3H), 1.14–0.87 (m, 4H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 174.5, 148.4, 133.0, 131.1, 124.0, 123.9, 121.9, 60.0, 59.9, 58.6, 57.1, 56.7, 50.5, 43.6, 42.2, 39.8, 39.7, 38.2, 37.8, 35.2, 35.1, 29.0, 21.7, 21.5, 19.7, 18.8, 14.0, 13.2; HRMS (ESI, m/z) calcd for $C_{29}H_{39}Cl_2N_2O_2$ $[M + H]^+$ 517.2389. Found: 517.2391; $[M+2 + H]^+$ 519.2389. Found: 519.2382.

4.3.6.22. Pyrazoline derivative ***9v***. Yield 40%; Mp 154.9–156.3 °C; IR (KBr): 3060, 2924, 2848, 1720, 1628, 1558, 1446, 1377, 1322, 1229, 1178, 1150, 1095, 1026, 975, 848, 779, 699, 561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.31 (d, J = 8.0 Hz, 2H), 7.08 (t, J = 8.0 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.81 (dd, J = 9.2, 8.0 Hz, 1H), 3.56–3.51 (m, 1H), 3.39 (dd, J = 14.4, 8.6 Hz, 1H), 2.20–2.17 (m, 1H), 1.87–1.71 (m, 5H), 1.67–1.51 (m, 4H), 1.45–1.28 (m, 2H), 1.25 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.22–1.18 (m, 2H), 1.17 (s, 3H), 1.15–0.85 (m, 4H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 169.9, 142.1, 135.3, 135.3, 129.3, 129.3, 127.8, 60.0, 58.3, 57.4, 57.2, 56.8, 50.4, 43.6, 41.8, 40.2, 39.8, 38.2, 37.8, 35.4, 35.3, 29.0, 21.7, 21.1, 19.7, 18.8, 14.1, 13.2; HRMS (ESI, m/z) calcd for $C_{29}H_{39}Cl_2N_2O_2$ $[M + H]^+$ 517.2389. Found: 517.2386; $[M+2 + H]^+$ 519.2389. Found: 519.2379.

4.3.6.23. Pyrazoline derivative ***9w***. Yield 58%; Mp 89.8–91.3 °C; IR (KBr): 2925, 2849, 1720, 1591, 1554, 1479, 1379, 1322, 1294, 1230, 1150, 1095, 1025, 990, 853, 802, 528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.27 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 6.90 (dd, J = 8.8, 2.4 Hz, 1H), 4.15–4.09 (m, 2H), 3.92 (t, J = 8.6 Hz, 1H), 3.50–3.45 (m, 1H), 2.97 (dd, J = 14.4, 8.6 Hz, 1H), 2.21–2.18 (m, 1H), 1.90–1.73 (m, 5H), 1.64–1.54 (m, 4H), 1.45–1.35 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.26–1.21 (m, 2H), 1.19 (s, 3H), 1.18 (s, 3H), 1.15–0.93 (m, 4H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 172.9, 148.3, 132.5, 130.3, 121.9, 115.5, 113.6, 60.0, 58.5, 57.1, 56.6, 53.4, 49.8, 43.6, 42.1, 39.7, 39.7, 38.2, 37.8, 35.3, 35.2, 29.0, 21.8, 21.3, 19.7, 18.8, 14.2, 13.1; HRMS (ESI, m/z) calcd for $C_{29}H_{39}Cl_2N_2O_2$ $[M + H]^+$ 517.2389. Found: 517.2387; $[M+2 + H]^+$ 519.2389. Found: 519.2375.

4.3.6.24. Pyrazoline derivative ***9x***. Yield 59%; Mp 211.4–213.6 °C; IR (KBr): 3085, 2927, 2849, 1721, 1586, 1557, 1457, 1380, 1321, 1231, 1177, 1150, 1096, 1024, 983, 852, 822, 794, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 6.94 (d, J = 1.8 Hz, 2H), 6.79 (t, J = 1.8 Hz, 1H), 4.15–4.08 (m, 2H), 3.91 (t, J = 8.6 Hz, 1H), 3.50–3.44 (m, 1H), 3.01 (dd, J = 14.4, 8.6 Hz, 1H), 2.21–2.18 (m, 1H), 1.90–1.73 (m, 5H), 1.64–1.51 (m, 4H), 1.46–1.34 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 1.25–1.21 (m, 2H), 1.19 (s, 3H), 1.18 (s, 3H), 1.15–0.89 (m, 4H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.1, 173.0, 150.1, 135.1, 135.1, 118.7, 112.2, 112.2, 60.0, 58.4, 57.1, 56.6, 54.3, 49.7, 43.6, 42.1, 39.7, 39.7, 38.2, 37.8, 35.3, 35.2, 29.0, 21.8, 21.3, 19.7, 18.7, 14.2, 13.1; HRMS (ESI, m/z) calcd for $C_{29}H_{39}Cl_2N_2O_2$ $[M + H]^+$ 517.2389. Found: 517.2386; $[M+2 + H]^+$ 519.2389. Found: 519.2414.

4.3.6.25. Pyrazoline derivative ***9y***. Yield 79%; Mp 138.2–139.8 °C; IR (KBr): 3054, 2952, 2848, 1718, 1629, 1582, 1496, 1378, 1320, 1255, 1230, 1178, 1150, 1096, 1025, 978, 851, 778, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.12 (d, J = 7.2 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 7.2 Hz, 1H), 4.14–4.06 (m, 2H), 3.74 (t, J = 8.6 Hz, 1H), 3.49–3.44 (m, 1H), 2.75 (dd, J = 14.4, 8.6 Hz, 1H), 2.32 (s, 3H), 2.28 (s, 3H), 2.20–2.17 (m, 1H), 1.87–1.73 (m, 5H), 1.67–1.53 (m, 4H), 1.46–1.29 (m, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.22 (s, 3H), 1.20–1.18 (m, 1H), 1.17 (s, 3H), 1.16–0.86 (m, 4H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.3, 173.0, 149.2, 137.6, 130.1, 125.8, 125.7, 117.5, 60.9, 60.0, 58.9, 57.2, 56.8, 50.4, 43.6, 42.0, 39.8, 39.8, 38.2, 37.8, 35.3, 35.3, 29.0, 21.8, 21.6, 20.5, 19.8, 18.8, 14.6, 14.1, 13.3; HRMS (ESI, m/z) calcd for $C_{31}H_{45}N_2O_2$ $[M + H]^+$ 477.3481. Found: 477.3480.

4.3.6.26. Pyrazoline derivative ***9z***. Yield 75%; Mp 152.2–153.8 °C; IR (KBr): 2952, 2848, 1721, 1630, 1502, 1452, 1378, 1320, 1255, 1229, 1177, 1150, 1095, 1027, 977, 850, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.10 (d, J = 8.0 Hz, 1H), 6.98 (s, 1H), 6.96 (d, J = 8.0 Hz, 1H), 4.13–4.06 (m, 2H), 3.75 (t, J = 8.6 Hz, 1H), 3.47–3.41 (m, 1H), 2.77 (dd, J = 14.4, 8.6 Hz, 1H), 2.37 (s, 3H), 2.27 (s, 3H), 2.20–2.16 (m, 1H), 1.85–1.72 (m, 5H), 1.67–1.54 (m, 4H), 1.44–1.28 (m, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.24–1.22 (m, 1H), 1.20 (s, 3H), 1.17 (s, 3H), 1.16–0.89 (m, 4H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 172.6, 146.7, 133.0, 131.6, 131.0, 126.9, 119.2, 60.3, 60.0, 58.9, 57.2, 56.8, 50.3, 43.6, 42.0, 39.8, 39.8, 38.2, 37.8, 35.3, 35.3, 29.0, 21.8, 21.5, 20.7, 19.8, 18.9, 18.8, 14.1, 13.3; HRMS (ESI, m/z) calcd for $C_{31}H_{45}N_2O_2$ $[M + H]^+$ 477.3481. Found: 477.3482.

4.3.6.27. Pyrazoline derivative ***9aa***. Yield 62%; Mp 62.2–64.3 °C; IR (KBr): 2952, 2848, 1721, 1069, 1557, 1504, 1454, 1411, 1378, 1321, 1257, 1230, 1178, 1151, 1095, 1028, 980, 849, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.04 (d, J = 8.0 Hz, 1H), 7.00 (s, 1H), 6.80 (d, J = 8.0 Hz, 1H), 4.14–4.04 (m, 2H), 3.77 (t, J = 8.6 Hz, 1H), 3.48–3.42 (m, 1H), 2.81 (dd, J = 14.4, 8.6 Hz, 1H), 2.36 (s, 3H), 2.30 (s, 3H), 2.20–2.17 (m, 1H), 1.85–1.70 (m, 5H), 1.65–1.55 (m, 4H), 1.46–1.29 (m, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.22 (s, 3H), 1.22–1.20 (m, 1H), 1.17 (s, 3H), 1.14–0.86 (m, 4H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 172.7, 148.7, 135.9, 130.8, 127.7, 124.2, 119.5, 60.0, 59.9, 58.8, 57.2, 56.8, 50.2, 43.6, 42.0, 39.8, 39.8, 38.2, 37.8, 35.3, 35.3, 29.0, 21.8, 21.5, 21.2, 19.8, 18.8, 18.8, 14.1, 13.3; HRMS (ESI, m/z) calcd for $C_{31}H_{45}N_2O_2$ $[M + H]^+$ 477.3481. Found: 477.3479.

*4.3.6.28. Pyrazoline derivative **9ab**.* Yield 41%; Mp 57.6–58.3 °C; IR (KBr): 2953, 2848, 1721, 1621, 1467, 1378, 1322, 1231, 1178, 1151, 1097, 1027, 979, 851, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.00 (s, 3H), 4.12–4.04 (m, 2H), 3.66 (t, J = 8.6 Hz, 1H), 3.47–3.41 (m, 1H), 3.18 (dd, J = 14.4, 8.6 Hz, 1H), 2.34 (s, 6H), 2.18–2.17 (m, 1H), 1.87–1.66 (m, 5H), 1.63–1.56 (m, 4H), 1.54–1.28 (m, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.23 (s, 3H), 1.22–1.18 (m, 1H), 1.17 (s, 3H), 1.15–0.87 (m, 4H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.3, 167.6, 144.8, 136.4, 136.4, 129.0, 129.0, 126.2, 60.0, 59.2, 58.3, 57.2, 56.8, 50.0, 43.6, 41.6, 40.1, 39.8, 38.2, 37.9, 35.6, 35.4, 29.0, 21.7, 21.4, 19.8, 19.6, 19.6, 18.8, 14.0, 13.2; HRMS (ESI, m/z) calcd for $C_{31}H_{45}N_2O_2$ $[M + H]^+$ 477.3481. Found: 477.3484.

*4.3.6.29. Pyrazoline derivative **9ac**.* Yield 73%; Mp 75.6–76.8 °C; IR (KBr): 2927, 2849, 1721, 1611, 1571, 1504, 1452, 1379, 1326, 1258, 1228, 1177, 1150, 1095, 1026, 850, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.02 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 8.0, 2.4 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.94 (t, J = 8.6 Hz, 1H), 3.48–3.42 (m, 1H), 2.91 (dd, J = 14.4, 8.6 Hz, 1H), 2.25 (s, 3H), 2.21–2.19 (m, 1H), 2.19 (s, 3H), 1.89–1.70 (m, 5H), 1.67–1.52 (m, 4H), 1.45–1.32 (m, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.25–1.20 (m, 1H), 1.19 (s, 3H), 1.18 (s, 3H), 1.17–0.89 (m, 4H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 171.7, 147.7, 137.0, 129.9, 127.8, 116.0, 111.9, 60.0, 58.6, 57.2, 56.7, 55.8, 49.7, 43.6, 42.0, 39.8, 39.7, 38.2, 37.8, 35.4, 35.3, 29.0, 21.9, 21.4, 20.1, 19.8, 18.8, 18.8, 14.2, 13.2; HRMS (ESI, m/z) calcd for $C_{31}H_{45}N_2O_2$ $[M + H]^+$ 477.3481. Found: 477.3479.

*4.3.6.30. Pyrazoline derivative **9ad**.* Yield 46%; Mp 156.6–158.2 °C; IR (KBr): 2950, 2848, 1721, 1597, 1464, 1379, 1345, 1299, 1228, 1095, 1032, 993, 851, 824, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 6.75 (s, 2H), 6.52 (s, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.95 (t, J = 8.6 Hz, 1H), 3.48–3.42 (m, 1H), 2.96 (dd, J = 14.4, 8.6 Hz, 1H), 2.29 (s, 6H), 2.21–2.17 (m, 1H), 1.90–1.70 (m, 5H), 1.67–1.55 (m, 4H), 1.45–1.32 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.23–1.20 (m, 2H), 1.19 (s, 6H), 1.15–0.89 (m, 4H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.2, 171.6, 149.2, 138.5, 138.5, 121.6, 112.1, 112.1, 60.0, 58.6, 57.2, 56.7, 55.2, 49.6, 43.6, 42.0, 39.7, 39.7, 38.2, 37.8, 35.4, 35.2, 29.0, 21.9, 21.5, 21.5, 21.4, 19.8, 18.8, 14.2, 13.1; HRMS (ESI, m/z) calcd for $C_{31}H_{45}N_2O_2$ $[M + H]^+$ 477.3481. Found: 477.3484.

*4.3.7. Synthesis of compound **10***

Compound **3** (0.378 g, 1 mmol) was dissolved in CH_2Cl_2 (20 mL) and then TCC/Silica gel (0.334 g) was added. After stirring at room temperature for 1.5 h, the reaction mixture was filtered and washed with CH_2Cl_2. At last the combined organic phases were washed with saturated NaCl aqueous solution, dried with Na_2SO_4 and the filtrate was concentrated. The residue was purified by column chromatography on silica (petroleum ether/ethyl acetate = 3:1, v/v) to give product **10** (0.233 g, 62%). Mp 110.7–112.6 °C; IR (KBr): 3439, 2955, 2924, 2850, 1719, 1668, 1602, 1457, 1392, 1342, 1233, 1207, 1183, 1156, 1093, 1038, 958, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 12.0 (d, J = 1.1 Hz, 1H), 7.15 (s, 1H), 4.14–4.09 (q, J = 6.1 Hz, 2H), 2.18–1.37 (m, 14H), 1.30–1.26 (t, J = 7.0 Hz, 3H), 1.21 (s, 3H), 1.18 (s, 2H), 1.02 (s, 3H), 0.98–0.74 (m, 2H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 215.1, 177.2, 156.1, 121.3, 60.0, 56.5, 56.3, 55.0, 47.3, 43.7, 41.3, 40.4, 38.3, 38.1, 38.0, 36.1, 28.9, 22.3, 20.9, 19.6, 18.9, 14.2, 12.3; HRMS (ESI, m/z) calcd for $C_{23}H_{34}O_4Na$ $[M + Na]^+$ 397.2355. Found: 397.2354.

*4.3.8. General procedure for synthesis of compounds **11a–11ad***

A mixture of compound **10** (0.376 g, 1 mmol) and various phenylhydrazines **6a–6ad** (0.145–0.225 g, 1 mmol) in isopropanol (10 mL) were stirred under reflux. After completion of the reaction monitored by TLC, the reaction mixture was concentrated under vacuum, and extracted with $CH_3CO_2C_2H_5$ and H_2O. At last the organic layer was washed with saturated NaCl aqueous solution, dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica to give product **11a–11ad**.

*4.3.8.1. Pyrazole derivative **11a**.* Yield 76%; Mp 135.7–136.9 °C; IR (KBr): 3093, 3047, 2927, 2848, 1718, 1600, 1530, 1508, 1450, 1418, 1382, 1362, 1320, 1235, 1181, 1150, 1096, 1060, 1022, 985, 857, 767, 700, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.44–7.29 (m, 6H), 4.23–4.05 (m, 2H), 2.21–2.17 (m, 2H), 2.08–1.94 (m, 3H), 1.87–1.34 (m, 7H), 1.32–1.29 (t, J = 7.2 Hz, 3H), 1.27–1.25 (m, 1H), 1.22 (s, 3H), 1.20–1.14 (m, 2H), 1.05 (s, 3H), 1.04–0.82 (m, 3H), 0.60 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$, ppm): δ 177.4, 151.2, 139.9, 134.8, 131.5, 128.8, 128.8, 127.1, 123.5, 123.5, 68.0, 60.0, 57.1, 52.5, 43.8, 42.5, 41.5, 40.3, 38.2, 38.1, 37.8, 35.8, 29.7, 29.0, 22.6, 21.4, 19.0, 14.2, 12.7; HRMS (ESI, m/z) calcd for $C_{29}H_{39}N_2O_2$ $[M + H]^+$ 447.3012. Found: 447.3011.

*4.3.8.2. Pyrazole derivative **11b**.* Yield 87%; Mp 146.7–147.9 °C; IR (KBr): 3093, 2924, 2851, 1719, 1617, 1595, 1513, 1462, 1413, 1377, 1310, 1223, 1179, 1149, 1094, 1025, 989, 860, 818, 770, 689, 647, 510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.47–7.45 (m, 1H), 7.43 (s, 1H), 7.39–7.33 (m, 1H), 7.23–7.16 (m, 2H), 4.20–4.06 (m, 2H), 2.21–2.15 (m, 2H), 2.08–1.94 (m, 3H), 1.84–1.35 (m, 7H), 1.32–1.29 (t, J = 7.2 Hz, 3H), 1.27–1.25 (m, 1H), 1.22 (s, 3H), 1.21–1.16 (m, 2H), 1.06–0.95 (m, 2H), 0.93 (s, 3H), 0.92–0.87 (m, 1H), 0.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 156.4 (d, J = 249.4 Hz), 153.5, 135.4, 130.5, 129.6 (d, J = 7.6 Hz), 128.4, 128.1 (d, J = 11.6 Hz), 124.4 (d, J = 3.8 Hz), 116.2 (d, J = 19.7 Hz), 67.8, 60.0, 57.1, 52.7, 43.8, 42.8, 41.6, 40.2, 38.1, 38.1, 37.8, 34.8 (d, J = 3.5 Hz), 29.0, 22.6, 21.3, 21.1, 19.0, 14.2, 12.7; HRMS (ESI, m/z) calcd for $C_{29}H_{38}FN_2O_2$ $[M + H]^+$ 465.2917. Found: 465.2916.

*4.3.8.3. Pyrazole derivative **11c**.* Yield 93%; Mp 147.0–147.9 °C; IR (KBr): 3095, 2942, 2863, 1710, 1611, 1532, 1502, 1456, 1403, 1378, 1360, 1239, 1180, 1148, 1089, 1032, 970, 871, 783, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.41 (s, 1H), 7.39–7.35 (m, 1H), 7.20–7.17 (m, 2H), 7.04–7.00 (m, 1H), 4.20–4.05 (m, 2H), 2.21–2.17 (m, 2H), 2.07–1.93 (m, 3H), 1.87–1.38 (m, 7H), 1.32–1.29 (t, J = 7.2 Hz, 3H), 1.27–1.24 (m, 1H), 1.22 (s, 3H), 1.21–1.17 (m, 2H), 1.10 (s, 3H), 1.06–0.88 (m, 3H), 0.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 162.6 (d, J = 245.4 Hz), 151.3, 141.3 (d, J = 9.9 Hz), 135.3, 132.1, 130.0 (d, J = 8.9 Hz), 118.9 (d, J = 3.0 Hz), 113.9 (d, J = 21.0 Hz), 110.9 (d, J = 24.5 Hz), 68.1, 60.0, 57.0, 52.5, 43.8, 42.5, 41.6, 40.2, 38.2, 38.1, 37.7, 35.7, 29.0, 22.6, 21.9, 21.3, 19.0, 14.2, 12.6; HRMS (ESI, m/z) calcd for $C_{29}H_{38}FN_2O_2$ $[M + H]^+$ 465.2917. Found: 465.2920.

*4.3.8.4. Pyrazole derivative **11d**.* Yield 91%; Mp 118.3–120.1 °C; IR (KBr): 3086, 2944, 2847, 1717, 1626, 1518, 1450, 1385, 1217, 1151, 1096, 1025, 988, 850, 526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.40–7.35 (m, 3H), 7.14–7.08 (m, 2H), 4.20–4.07 (m, 2H), 2.22–2.16 (m, 2H), 2.07–1.93 (m, 3H), 1.84–1.34 (m, 7H), 1.32–1.29 (t, J = 7.2 Hz, 3H), 1.27–1.25 (m, 1H), 1.22 (s, 3H), 1.20–1.17 (m, 2H), 1.03 (s, 3H), 1.03–0.83 (m, 3H), 0.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 161.5 (d, J = 245.3 Hz), 151.4, 136.1 (d, J = 2.8 Hz), 134.8, 131.4, 125.4 (d, J = 8.3 Hz), 125.4 (d, J = 8.3 Hz), 115.7 (d, J = 22.7 Hz), 115.7 (d, J = 22.7 Hz), 67.9, 60.0, 57.1, 52.5, 43.8, 42.5, 41.5, 40.3, 38.2, 38.1, 37.7, 35.9, 29.0, 22.6, 21.8, 21.4, 19.0, 14.2, 12.6; HRMS (ESI, m/z) calcd for $C_{29}H_{38}FN_2O_2$ $[M + H]^+$ 465.2917. Found: 465.2915.

*4.3.8.5. Pyrazole derivative **11e**.* Yield 87%; Mp 121.6–123.0 °C; IR (KBr): 3091, 2951, 2846, 1719, 1592, 1510, 1469, 1447, 1414, 1380, 1235, 1180, 1150, 1090, 1043, 985, 853, 764, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.51–7.49 (d, J = 7.8 Hz, 1H), 7.42 (s, 1H),

7.40–7.31 (m, 3H), 4.22–4.06 (m, 2H), 2.20–2.17 (m, 2H), 2.08–1.97 (m, 3H), 1.85–1.36 (m, 8H), 1.33–1.29 (t, J = 7.2 Hz, 3H), 1.23 (s, 3H), 1.21–1.15 (m, 2H), 1.06–0.86 (m, 3H), 0.84 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.5, 153.5, 137.8, 135.0, 132.5, 130.2, 130.0, 129.5, 127.0, 127.0, 67.2, 60.0, 57.1, 52.6, 43.8, 43.0, 41.1, 40.3, 38.2, 38.1, 37.8, 35.1, 29.0, 22.6, 21.4, 21.1, 19.0, 14.2, 12.7; HRMS (ESI, m/z) calcd for $C_{29}H_{38}ClN_2O_2$ $[M + H]^+$ 481.2622 Found: 481.2621; $[M+2 + H]^+$ 483.2622. Found: 483.2608.

4.3.8.6. Pyrazole derivative ***11f***. Yield 76%; Mp 117.0–118.3 °C; IR (KBr): 3081, 2937, 2847, 1715, 1625, 1594, 1531, 1497, 1465, 1378, 1341, 1231, 1178, 1148, 1097, 1073, 1025, 996, 867, 779, 686, 643 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.45–7.45 (t, J = 2.0 Hz, 1H),7.41 (s, 1H), 7.37–7.33 (t, J = 8.0 Hz, 1H), 7.31–7.26 (m, 2H), 4.20–4.07 (m, 2H), 2.21–2.17 (m, 2H), 2.07–1.92 (m, 3H), 1.86–1.38 (m, 8H), 1.32–1.29 (t, J = 7.2 Hz, 3H), 1.22 (s, 3H), 1.21–1.17 (m, 2H), 1.09 (s, 3H), 1.06–0.88 (m, 3H), 0.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 151.3, 140.9, 135.4, 134.5, 132.1, 129.8, 127.0, 123.6, 121.4, 68.1, 60.0, 57.0, 52.5, 43.8, 42.5, 41.6, 40.2, 38.2, 38.1, 37.7, 35.7, 29.0, 22.6, 22.0, 21.4, 19.0, 14.2, 12.6; HRMS (ESI, m/z) calcd for $C_{29}H_{38}ClN_2O_2$ $[M + H]^+$ 481.2622. Found: 481.2620; $[M+2 + H]^+$ 483.2622. Found: 483.2661.

4.3.8.7. Pyrazole derivative ***11g***. Yield 50%; Mp 171.4–172.3 °C; IR (KBr): 3098, 3065, 2955, 2845, 1719, 1597, 1502, 1464, 1446, 1418, 1384, 1361, 1336, 1233, 1181, 1149, 1092, 1030, 984, 835, 523 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.41–7.34 (m, 5H), 4.20–4.06 (m, 2H), 2.21–2.16 (m, 2H), 2.07–1.35 (m, 11H), 1.31 (t, J = 7.2 Hz, 3H), 1.22 (s, 3H), 1.20–1.16 (m, 2H), 1.06 (s, 3H), 1.05–0.95 (m, 3H), 0.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 151.3, 138.4, 135.1, 132.6, 131.9, 128.9, 128.9, 124.6, 124.6, 68.0, 60.0, 57.0, 52.4, 43.8, 42.4, 41.5, 40.2, 38.1, 38.0, 37.7, 35.7, 28.9, 22.5, 21.9, 21.3, 18.9, 14.1, 12.6; HRMS (ESI, m/z) calcd for $C_{29}H_{38}N_2O_2$ $[M + H]^+$ 481.2622 Found: 481.2622; $[M+2 + H]^+$ 483.2622. Found: 483.2636.

4.3.8.8. Pyrazole derivative ***11h***. Yield 55%; Mp 142.8–143.9 °C; IR (KBr): 3088, 3058, 2952, 2847, 1715, 1632, 1588, 1533, 1509, 1447, 1380, 1341, 1322, 1303, 1235, 1180, 1149, 1093, 1028, 986, 852, 766, 655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.69–7.67 (d, J = 7.6 Hz, 1H), 7.41 (s, 1H), 7.38–7.31 (m, 3H), 4.17–4.11 (m, 2H), 2.21–1.36 (m, 13H), 1.31 (t, J = 7.2 Hz, 3H), 1.25 (s, 3H), 1.20–0.86 (m, 5H), 0.84 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.5, 153.2, 139.4, 134.9, 133.2, 130.5, 129.6, 129.4, 127.7, 122.6, 67.1, 60.0, 57.1, 52.5, 43.8, 43.0, 41.0, 40.2, 38.1, 38.1, 37.8, 35.1, 29.0, 22.6, 21.4, 21.1, 19.0, 14.2, 12.7; HRMS (ESI, m/z) calcd for $C_{29}H_{38}BrN_2O_2$ $[M + H]^+$ 525.2117. Found: 525.2117; $[M+2 + H]^+$ 527.2117. Found: 527.2106.

4.3.8.9. Pyrazole derivative ***11i***. Yield 64%; Mp 118.8–119.5 °C; IR (KBr): 3083, 2939, 2847, 1714, 1626, 1592, 1496, 1469, 1375, 1227, 1180, 1148, 1092, 1027, 994, 871, 789, 757, 690, 642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.61 (t, J = 1.9 Hz, 1H), 7.44 (ddd, J = 8.0, 1.8, 1.2 Hz, 1H), 7.41 (s, 1H), 7.35 (ddd, J = 8.0, 1.9, 1.2 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 4.20–4.07 (m, 2H), 2.21–2.17 (m, 2H), 2.07–1.92 (m, 3H), 1.86–1.36 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.27–1.23 (m, 1H), 1.22 (s, 3H), 1.21–1.17 (m, 2H), 1.09 (s, 3H), 1.06–0.88 (m, 3H), 0.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 151.3, 141.0, 135.4, 132.1, 130.0, 130.0, 126.5, 122.3, 121.8, 68.1, 60.0, 57.0, 52.5, 43.8, 42.5, 41.6, 40.2, 38.2, 38.1, 37.7, 35.7, 29.0, 22.6, 22.0, 21.4, 19.0, 14.2, 12.6; HRMS (ESI, m/z) calcd for $C_{29}H_{38}BrN_2O_2$ $[M + H]^+$ 525.2117. Found: 525.2112; $[M+2 + H]^+$ 527.2117. Found: 527.2081.

4.3.8.10. Pyrazole derivative ***11j***. Yield 76%; Mp 174.8–175.5 °C; IR (KBr): 3095, 2950, 2929, 2845, 1719, 1626, 1592, 1528, 1499, 1463, 1446, 1416, 1396, 1232, 1180, 1150, 1091, 1029, 984, 833, 520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.55 (d, J = 8.8 Hz, 2H), 7.40 (s, 1H), 7.29 (d, J = 8.8 Hz, 2H), 4.20–4.07 (m, 2H), 2.21–2.16 (m, 2H), 2.07–1.92 (m, 3H), 1.83–1.33 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.27–1.23 (m, 1H), 1.22 (s, 3H), 1.20–1.16 (m, 2H), 1.06 (s, 3H), 1.05–0.87 (m, 3H), 0.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 151.3, 139.0, 135.2, 132.0, 131.9, 131.9, 124.9, 124.9, 120.5, 68.0, 60.0, 57.0, 52.5, 43.8, 42.5, 41.6, 40.2, 38.2, 38.1, 37.7, 35.8, 29.0, 22.6, 21.9, 21.3, 19.0, 14.2, 12.6; HRMS (ESI, m/z) calcd for $C_{29}H_{38}BrN_2O_2$ $[M + H]^+$ 525.2117. Found: 525.2119; $[M+2 + H]^+$ 527.2117. Found: 527.2114.

4.3.8.11. Pyrazole derivative ***11k***. Yield 56%; Mp 115.2–116.7 °C; IR (KBr): 3088, 2940, 2870, 2847, 1714, 1636, 1584, 1512, 1465, 1446, 1416, 1377, 1320, 1225, 1170, 1150, 1094, 1016, 989, 854, 771, 722, 454 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.37 (s, 1H), 7.33–7.31 (m, 1H), 7.30–7.26 (m, 1H), 7.24–7.20 (m, 1H), 7.18–7.16 (m, 1H), 4.20–4.08 (m, 2H), 2.21–2.15 (m, 2H), 2.11 (s, 3H), 2.09–1.97 (m, 3H), 1.82–1.36 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.30–1.25 (m, 1H), 1.23 (s, 3H), 1.20–1.17 (m, 2H), 1.06–0.84 (m, 3H), 0.81 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.5, 152.6, 139.0, 136.0, 134.2, 130.7, 129.1, 128.8, 127.4, 125.9, 67.2, 60.0, 57.1, 52.7, 43.8, 42.9, 41.0,40.3, 38.2, 38.1, 37.9, 35.5, 29.0, 22.6, 21.6, 21.3, 19.0, 17.2, 14.2, 12.7; HRMS (ESI, m/z) calcd for $C_{30}H_{41}N_2O_2$ $[M + H]^+$ 461.3168. Found: 461.3167.

4.3.8.12. Pyrazole derivative ***11l***. Yield 87%; Mp 119.2–120.5 °C; IR (KBr): 3088, 2954, 2848, 1712, 1611, 1593, 1529, 1501, 1447, 1409, 1380, 1235, 1181, 1150, 1093, 1026, 855, 786, 694, 644 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.39 (s, 1H), 7.31–7.27 (m, 2H), 7.17–7.12 (m, 2H), 4.23–4.05 (m, 2H), 2.39 (s, 3H), 2.21–2.16 (m, 2H), 2.08–1.93 (m, 3H), 1.86–1.37 (m, 8H), 1.31 (t, J = 7.2 Hz, 3H), 1.22 (s, 3H), 1.20–1.17 (m, 2H), 1.05 (s, 3H), 1.03–0.88 (m, 3H), 0.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 151.2, 139.8, 138.9, 134.6, 131.4, 128.5, 127.9, 124.3, 120.6, 68.0, 60.0, 57.1, 52.6, 43.8, 42.5, 41.5, 40.3, 38.2, 38.1, 37.8, 35.9, 29.0, 22.6, 21.9, 21.4, 21.3, 19.0, 14.2, 12.7; HRMS (ESI, m/z) calcd for $C_{30}H_{41}N_2O_2$ $[M + H]^+$ 461.3168. Found: 461.3169.

4.3.8.13. Pyrazole derivative ***11m***. Yield 89%; Mp 193.8–194.5 °C; IR (KBr): 3096, 3048, 2946, 2844, 1719, 1612, 1521, 1446, 1418, 1384, 1360, 1337, 1233, 1182, 1150, 1091, 1030, 984, 825, 521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.38 (s, 1H), 7.27 (t, J = 6.6 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 4.21–4.06 (m, 2H), 2.38 (s, 3H), 2.21–2.19 (m, 1H), 2.16 (dd, J = 9.9, 2.8 Hz, 1H), 2.04–1.37 (m, 11H), 1.31 (t, J = 7.2 Hz, 3H), 1.22 (s, 3H), 1.20–1.16 (m, 2H), 1.04 (s, 3H), 1.02–0.88 (m, 3H), 0.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 151.2, 137.5, 136.9, 134.5, 131.1, 129.3, 129.3, 123.5, 123.5, 67.9, 59.9, 57.0, 52.5, 43.8, 42.5, 41.4, 40.2, 38.1, 38.1, 37.8, 35.8, 28.9, 22.6, 21.8, 21.3, 21.0, 19.0, 14.1, 12.6; HRMS (ESI, m/z) calcd for $C_{30}H_{41}N_2O_2$ $[M + H]^+$ 461.3168. Found: 461.3167.

4.3.8.14. Pyrazole derivative ***11n***. Yield 61%; Mp 185.9–187.5 °C; IR (KBr): 3095, 2958, 2931, 2869, 2849, 1726, 1609, 1536, 1519, 1448, 1364, 1225, 1149, 1094, 1029, 989, 853, 784, 758, 524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.94 (dd, J = 8.0, 1.4 Hz, 1H), 7.66 (dt, J = 7.6, 1.4 Hz, 1H), 7.55 (dt, J = 7.6, 1.4 Hz, 1H), 7.45 (dd, J = 7.6, 1.4 Hz, 1H), 7.39 (s, 1H), 4.17–4.07 (m, 2H), 2.25–2.18 (m, 2H), 2.06–1.95 (m, 3H), 1.82–1.36 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.27–1.24 (m, 1H), 1.22 (s, 3H), 1.20–1.16 (m, 2H), 1.06–1.00 (m, 2H), 0.98 (s, 3H), 0.95–0.87 (m, 1H), 0.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 152.9, 146.0, 136.3, 133.5, 132.7, 131.1, 129.1, 128.8, 125.0, 67.4, 60.0, 57.0, 52.4, 43.8, 42.9, 41.4, 40.2, 38.1, 38.1, 37.7, 35.4, 29.0, 22.5, 21.9, 21.1, 19.0, 14.2, 12.6; HRMS (ESI, m/z) calcd for $C_{29}H_{38}N_3O_4$ $[M + H]^+$ 492.2862. Found: 492.2865.

4.3.8.15. Pyrazole derivative ***11o***. Yield 89%; Mp 138.9–140.7 °C; IR (KBr): 3108, 3085, 2951, 2899, 2841, 1723, 1618, 1590, 1537, 1494,

1444, 1401, 1353, 1232, 1177, 1145, 1085, 1027, 998, 895, 858, 753, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 8.25 (t, J = 2.0 Hz, 1H), 8.17 (dd, J = 8.0, 2.0 Hz, 1H), 7.86 (dd, J = 8.0, 1.0 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.46 (s, 1H), 4.22–4.06 (m, 2H), 2.24–2.17 (m, 2H), 2.07–1.90 (m, 4H), 1.83–1.38 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.27–1.25 (m, 1H), 1.23 (s, 3H), 1.21–1.18 (m, 1H), 1.13 (s, 3H), 1.07–0.87 (m, 3H), 0.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 151.5, 148.3, 140.8, 136.1, 133.0, 129.9, 128.5, 121.3, 117.8, 68.1, 60.0, 57.0, 52.4, 43.8, 42.5, 41.8, 40.2, 38.1, 38.1, 37.6, 35.6, 29.0, 22.5, 22.1, 21.3, 19.0, 14.2, 12.6; HRMS (ESI, m/z) calcd for $C_{29}H_{38}N_3O_4$ $[M + H]^+$ 492.2862. Found: 492.2861.

4.3.8.16. Pyrazole derivative ***11p***. Yield 57%; Mp 196.3–198.1 °C; IR (KBr): 3101, 3093, 2965, 2937, 2841, 1711, 1595, 1520, 1472, 1454, 1407, 1382, 1337, 1238, 1182, 1158, 1106, 1038, 982, 855, 752, 692, 640, 596, 515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 8.32 (d, J = 8.9 Hz, 2H), 7.60 (d, J = 8.9 Hz, 2H), 7.49 (s, 1H), 4.19–4.09 (m, 2H), 2.24–2.18 (m, 2H), 2.07–1.40 (m, 11H), 1.31 (t, J = 7.1 Hz, 3H), 1.23 (s, 3H), 1.22–1.17 (m, 2H), 1.15 (s, 3H), 1.06–0.93 (m, 3H), 0.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.3, 151.6, 145.7, 144.6, 136.6, 133.7, 124.6, 124.6, 122.7, 122.7, 68.3, 60.0, 56.9, 52.3, 43.7, 42.4, 41.9, 40.1, 38.1, 38.0, 37.4, 35.4, 28.9, 22.5, 22.1, 21.3, 18.9, 14.1, 12.6; HRMS (ESI, m/z) calcd for $C_{29}H_{38}N_3O_4$ $[M + H]^+$ 492.2862. Found: 492.2862.

4.3.8.17. Pyrazole derivative ***11q***. Yield 87%; Mp 144.8–145.7 °C; IR (KBr): 3077, 2943, 2853, 1720, 1608, 1526, 1441, 1379, 1315, 1266, 1225, 1147, 1107, 1048, 1023, 959, 882, 830, 622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.46–7.41 (m, 2H), 6.98–6.92 (m, 2H), 4.20–4.06 (m, 2H), 2.21–2.15 (m, 2H), 2.07–1.93 (m, 3H), 1.81–1.37 (m, 8H), 1.31 (t, J = 7.2 Hz, 3H), 1.22 (s, 3H), 1.21–1.16 (m, 2H), 1.06–0.96 (m, 1H), 0.93 (s, 3H), 0.91–0.87 (m, 2H), 0.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 162.1 (dd, J = 249.4, 10.9 Hz), 156.7 (dd, J = 252.0, 12.5 Hz), 153.6, 135.6, 130.6, 129.4 (d, J = 10.2 Hz), 124.7 (dd, J = 11.6, 4.0 Hz), 111.6 (dd, J = 22.3, 3.9 Hz), 104.6 (dd, J = 26.2, 23.5 Hz), 67.7, 60.0, 57.1, 52.6, 43.8, 42.8, 41.5, 40.2, 38.1, 38.1, 37.8, 34.8 (d, J = 3.2 Hz), 29.0, 22.6, 21.2, 21.1, 19.0, 14.1, 12.7; HRMS (ESI, m/z) calcd for $C_{29}H_{37}F_2N_2O_2$ $[M + H]^+$ 483.2823. Found: 483.2826.

4.3.8.18. Pyrazole derivative ***11r***. Yield 88%; Mp 177.8–178.3 °C; IR (KBr): 3086, 2927, 2854, 1717, 1626, 1515, 1443, 1384, 1333, 1242, 1180, 1151, 1107, 1039, 837, 813, 770, 644, 575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.44 (s, 1H), 7.26–7.04 (m, 3H), 4.20–4.07 (m, 2H), 2.21–2.15 (m, 2H), 2.07–1.92 (m, 3H), 1.84–1.35 (m, 8H), 1.31 (t, J = 7.2 Hz, 3H), 1.22 (s, 3H), 1.20–1.16 (m, 2H), 1.06–0.99 (m, 1H), 0.97 (s, 3H), 0.95–0.87 (m, 2H), 0.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 158.1 (dd, J = 243.4, 2.6 Hz), 153.6, 152.3 (dd, J = 245.1, 2.9 Hz), 135.9, 131.2, 128.9 (dd, J = 14.4, 10.8 Hz), 117.0 (dd, J = 22.5, 8.9 Hz), 115.9 (dd, J = 22.4, 7.7 Hz), 115.2 (d, J = 25.7 Hz), 68.0, 60.0, 57.0, 52.6, 43.8, 42.7, 41.8, 40.2, 38.1, 38.1, 37.7, 34.6 (d, J = 4.2 Hz), 29.0, 22.6, 21.3, 21.1, 19.0, 14.2, 12.7; HRMS (ESI, m/z) calcd for $C_{29}H_{37}F_2N_2O_2$ $[M + H]^+$ 483.2823. Found: 483.2821.

4.3.8.19. Pyrazole derivative ***11s***. Yield 92%; Mp 151.4–152.2 °C; IR (KBr): 3084, 2954, 2921, 2851, 1715, 1582, 1535, 1499, 1459, 1424, 1380, 1337, 1304, 1240, 1184, 1151, 1093, 1072, 1045, 998, 853, 794, 777, 717, 524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.57–7.55 (m, 1H), 7.42 (s, 1H), 7.29–7.25 (m, 2H), 4.20–4.06 (m, 2H), 2.21–2.17 (m, 2H), 2.08–1.97 (m, 3H), 1.82–1.36 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.27–1.25 (m, 1H), 1.23 (s, 3H), 1.21–1.15 (m, 2H), 1.06–0.90 (m, 3H), 0.85 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 153.4, 139.4, 135.3, 133.8, 131.8, 131.0, 129.8, 127.8, 127.0, 67.2, 60.0, 57.1, 52.6, 43.8, 43.0, 41.2, 40.2, 38.1, 38.1, 37.8, 35.1, 29.7, 29.0, 22.6, 21.1, 19.0, 14.2, 12.7; HRMS (ESI, m/z) calcd for $C_{29}H_{37}Cl_2N_2O_2$ $[M + H]^+$ 515.2232. Found: 515.2228; $[M+2 + H]^+$ 517.2232. Found: 517.2222.

4.3.8.20. Pyrazole derivative ***11t***. Yield 90%; Mp 147.7–148.9 °C; IR (KBr): 3090, 3063, 2954, 2848, 1712, 1559, 1533, 1503, 1467, 1448, 1380, 1339, 1305, 1235, 1181, 1151, 1100, 1042, 985, 858, 834, 807, 628, 511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.52 (d, J = 2.0 Hz, 1H), 7.41 (s, 1H), 7.33 (dd, J = 8.4, 2.0 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 4.21–4.06 (m, 2H), 2.21–2.17 (m, 2H), 2.07–1.95 (m, 3H), 1.81–1.36 (m, 8H), 1.31 (t, J = 7.2 Hz, 3H), 1.22 (s, 3H), 1.21–1.16 (m, 2H), 1.06–0.90 (m, 3H), 0.86 (s, 3H), 0.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 153.6, 136.5, 135.5, 135.4, 133.4, 130.2, 129.9, 129.9, 127.4, 67.2, 60.0, 57.1, 52.6, 43.8, 43.0, 41.2, 40.2, 38.1, 38.1, 37.8, 35.0, 29.0, 22.6, 21.5, 21.1, 19.0, 14.2, 12.7; HRMS (ESI, m/z) calcd for $C_{29}H_{37}Cl_2N_2O_2$ $[M + H]^+$ 515.2232. Found: 515.2233; $[M+2 + H]^+$ 517.2232. Found: 517.2221.

4.3.8.21. Pyrazole derivative ***11u***. Yield 76%; Mp 192.9–194.3 °C; IR (KBr): 3086, 2955, 2848, 1719, 1585, 1511, 1467, 1448, 1383, 1338, 1232, 1181, 1149, 1092, 1043, 996, 852, 832, 799, 582 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.43 (d, J = 8.4 Hz, 1H), 7.42 (s, 1H), 7.36 (dd, J = 8.4, 2.4 Hz, 2H), 4.20–4.08 (m, 2H), 2.21–2.17 (m, 2H), 2.07–1.95 (m, 3H), 1.82–1.36 (m, 8H), 1.31 (t, J = 7.2 Hz, 3H), 1.22 (s, 3H), 1.20–1.16 (m, 2H), 1.06–0.90 (m, 3H), 0.89 (s, 3H), 0.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 153.6, 138.1, 135.5, 132.6, 130.9, 130.8, 130.2, 130.0, 129.7, 67.3, 60.0, 57.1, 52.6, 43.8, 43.0, 41.2, 40.2, 38.1, 38.1, 37.8, 35.0, 29.0, 22.6, 21.5, 21.1, 19.0, 14.2, 12.7; HRMS (ESI, m/z) calcd for $C_{29}H_{37}Cl_2N_2O_2$ $[M + H]^+$ 515.2232. Found: 515.2234; $[M+2 + H]^+$ 517.2232. Found: 517.2224.

4.3.8.22. Pyrazole derivative ***11v***. Yield 56%; Mp 181.5–182.6 °C; IR (KBr): 3086, 2983, 2949, 2847, 1721, 1631, 1565, 1512, 1463, 1436, 1378, 1340, 1234, 1181, 1152, 1093, 1042, 984, 855, 791, 751, 531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.48 (s, 1H), 7.44–7.41 (m, 2H), 7.33 (t, J = 8.0 Hz, 1H), 4.20–4.08 (m, 2H), 2.22–2.18 (m, 2H), 2.09–1.98 (m, 3H), 1.86–1.34 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.27–1.25 (m, 1H), 1.23 (s, 3H), 1.21–1.17 (m, 2H), 1.06–0.89 (m, 3H), 0.88 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.5, 153.3, 136.0, 135.8, 135.6, 135.2, 130.6, 129.6, 128.4, 128.3, 67.0, 60.0, 57.1, 52.5, 43.8, 43.2, 41.0, 40.2, 38.1, 38.1, 37.8, 34.7, 29.0, 22.6, 20.9, 20.5, 19.0, 14.2, 12.7; HRMS (ESI, m/z) calcd for $C_{29}H_{37}Cl_2N_2O_2$ $[M + H]^+$ 515.2232. Found: 515.2229; $[M+2 + H]^+$ 517.2232. Found: 517.2243.

4.3.8.23. Pyrazole derivative ***11w***. Yield 75%; Mp 157.4–158.6 °C; IR (KBr): 3096, 2942, 2852, 1626, 1593, 1534, 1495, 1465, 1417, 1377, 1319, 1228, 1160, 1129, 1025, 997, 855, 832, 808, 638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.55 (d, J = 2.4 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.41 (s, 1H), 7.27 (dd, J = 8.6, 2.4 Hz, 1H), 4.20–4.07 (m, 2H), 2.21–2.17 (m, 2H), 2.06–1.91 (m, 3H), 1.83–1.40 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.25–1.24 (m, 1H), 1.22 (s, 3H), 1.21–1.16 (m, 2H), 1.10 (s, 3H), 1.06–0.88 (m, 3H), 0.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 151.4, 139.2, 135.6, 132.8, 132.4, 130.8, 130.4, 125.1, 122.3, 68.0, 60.0, 57.0, 52.4, 43.8, 42.5, 41.7, 40.2, 38.1, 38.1, 37.6, 35.7, 29.0, 22.5, 22.0, 21.3, 19.0, 14.2, 12.6; HRMS (ESI, m/z) calcd for $C_{29}H_{37}Cl_2N_2O_2$ $[M + H]^+$ 515.2232. Found: 515.2234; $[M+2 + H]^+$ 517.2232. Found: 517.2227.

4.3.8.24. Pyrazole derivative ***11x***. Yield 60%; Mp 204.9–206.6 °C; IR (KBr): 3076, 2957, 2927, 2851, 1711, 1593, 1530, 1490, 1450, 1381, 1362, 1237, 1182, 1152, 1111, 1096, 1026, 1000, 862, 806, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.41 (s, 1H), 7.34 (d, J = 1.8 Hz, 2H), 7.30 (t, J = 1.8 Hz, 1H), 4.22–4.05 (m, 2H), 2.21–2.17 (m, 2H), 2.05–1.91 (m, 3H), 1.85–1.36 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.27–

1.24 (m, 1H), 1.22 (s, 3H), 1.21–1.14 (m, 2H), 1.13 (s, 3H), 1.06–0.83 (m, 3H), 0.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 151.4, 141.4, 135.9, 135.1, 135.1, 132.7, 126.8, 121.6, 121.6, 68.1, 60.0, 57.0, 52.4, 43.8, 42.4, 41.7, 40.2, 38.1, 38.1, 37.6, 35.6, 29.0, 22.5, 22.1, 21.3, 19.0, 14.2, 12.6; HRMS (ESI, *m*/*z*) calcd for $C_{29}H_{37}Cl_2N_2O_2$ $[M + H]^+$ 515.2232. Found: 515.2230; $[M+2 + H]^+$ 517.2232. Found: 517.2224.

4.3.8.25. Pyrazole derivative ***11y***. Yield 56%; Mp 139.1–140.6 °C; IR (KBr): 3087, 2955, 2870, 2850, 1717, 1583, 1529, 1506, 1469, 1448, 1386, 1234, 1179, 1149, 1092, 1042, 985, 852, 785, 718, 603 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.36 (s, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 6.5 Hz, 1H), 4.20–4.08 (m, 2H), 2.31 (s, 3H), 2.21–2.15 (m, 2H), 2.09–1.96 (m, 3H), 1.94 (s, 3H), 1.82–1.36 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.29–1.25 (m, 1H), 1.23 (s, 3H), 1.20–1.16 (m, 2H), 1.06–0.84 (m, 3H), 0.80 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.5, 152.8, 139.0, 138.0, 134.7, 134.1, 130.2, 128.9, 125.3, 125.3, 67.2, 60.0, 57.2, 52.7, 43.8, 42.9, 40.9, 40.3, 38.2, 38.1, 38.0, 35.5, 29.0, 22.6, 21.7, 21.3, 20.2, 19.0, 14.2, 14.2, 12.7; HRMS (ESI, *m*/*z*) calcd for $C_{31}H_{43}N_2O_2$ $[M + H]^+$ 475.3325. Found: 475.3327.

4.3.8.26. Pyrazole derivative ***11z***. Yield 63%; Mp 114.0–115.6 °C; IR (KBr): 3090, 2950, 2867, 2847, 1719, 1615, 1519, 1449, 1377, 1321, 1302, 1235, 1180, 1151, 1094, 1041, 1029, 989, 847, 818, 653, 600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.35 (s, 1H), 7.07 (s, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 4.20–4.07 (m, 2H), 2.35 (s, 3H), 2.21–2.14 (m, 2H), 2.06 (s, 3H), 2.04–1.96 (m, 3H), 1.82–1.36 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.29–1.25 (m, 1H), 1.22 (s, 3H), 1.20–1.15 (m, 2H), 1.05–0.84 (m, 3H), 0.82 (s, 3H), 0.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.5, 152.7, 138.6, 136.5, 135.6, 134.1, 131.3, 128.9, 127.2, 126.5, 67.2, 60.0, 57.2, 52.7, 43.8, 42.9, 40.9, 40.3, 38.2, 37.9, 35.5, 29.7, 29.0, 22.6, 21.6, 21.3, 21.1, 19.0, 17.1, 14.2, 12.7; HRMS (ESI, *m*/*z*) calcd for $C_{31}H_{43}N_2O_2$ $[M + H]^+$ 475.3325. Found: 475.3322.

4.3.8.27. Pyrazole derivative ***11aa***. Yield 79%; Mp 136.5–137.6 °C; IR (KBr): 3089, 2950, 2843, 1719, 1620, 1581, 1516, 1447, 1376, 1323, 1233, 1178, 1148, 1093, 1063, 1028, 974, 852, 827, 653, 606 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.35 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.98 (s, 1H), 4.20–4.07 (m, 2H), 2.32 (s, 3H), 2.21–2.15 (m, 2H), 2.08–2.207 (m, 1H), 2.05 (s, 3H), 2.03–1.97 (m, 2H), 1.82–1.36 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.29–1.25 (m, 1H), 1.23 (s, 3H), 1.20–1.16 (m, 2H), 1.06–0.86 (m, 3H), 0.82 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.5, 152.5, 138.8, 135.7, 134.1, 132.6, 130.4, 129.5, 129.0, 128.0, 67.2, 60.0, 57.1, 52.7, 43.8, 42.9, 40.9, 40.3, 38.2, 38.1, 38.0, 35.5, 29.0, 22.6, 21.6, 21.3, 20.7, 19.0, 16.7, 14.2, 12.7; HRMS (ESI, *m*/*z*) calcd for $C_{31}H_{43}N_2O_2$ $[M + H]^+$ 475.3325. Found: 475.3323.

4.3.8.28. Pyrazole derivative ***11ab***. Yield 69%; Mp 173.1–174.0 °C; IR (KBr): 3088, 2950, 2847, 1602, 1529, 1505, 1467, 1449, 1377, 1299, 1235, 1180, 1150, 1095, 1026, 988, 852, 782, 578 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.40 (s, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.10–7.07 (m, 2H), 4.22–4.07 (m, 2H), 2.21–2.13 (m, 2H), 2.10–2.04 (m, 2H), 2.02 (s, 3H), 2.01–1.98 (m, 1H), 1.97 (s, 3H), 1.85–1.35 (m, 8H), 1.31 (t, J = 7.2 Hz, 3H), 1.23 (s, 3H), 1.21–1.17 (m, 2H), 1.06–0.85 (m, 3H), 0.78 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.5, 152.3, 138.3, 136.9, 136.3, 134.4, 129.0, 128.7, 127.8, 127.7, 67.3, 60.0, 57.2, 52.5, 43.8, 42.9, 40.9,,40.3, 38.1, 38.1, 38.0, 35.2, 29.0, 22.6, 21.1, 20.7, 19.0, 17.1, 17.1, 14.2, 12.7; HRMS (ESI, *m*/*z*) calcd for $C_{31}H_{43}N_2O_2$ $[M + H]^+$ 475.3325. Found: 475.3322.

4.3.8.29. Pyrazole derivative ***11ac***. Yield 59%; Mp 124.1–125.3 °C; IR (KBr): 3091, 2930, 2869, 2847, 1719, 1613, 1586, 1512, 1449, 1377, 1338, 1321, 1239, 1181, 1151, 1092, 1029, 978, 879, 852, 817, 646 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.37 (s, 1H), 7.22 (d, J = 1.6 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.08 (dd, J = 8.0, 2.0 Hz, 1H), 4.21–4.06 (m, 2H), 2.29 (s, 3H), 2.28 (s, 3H), 2.21–2.15 (m, 2H), 2.07–1.93 (m, 3H), 1.84–1.35 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.27–1.25 (m, 1H), 1.22 (s, 3H), 1.20–1.16 (m, 2H), 1.10 (s, 3H), 1.02–0.87 (m, 3H), 0.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 151.1, 137.7, 137.2, 135.6, 134.4, 131.0, 129.7, 124.8, 120.8, 67.9, 60.0, 57.1, 52.6, 43.8, 42.5, 41.4, 40.3, 38.2, 38.1, 37.8, 35.9, 29.0, 22.6, 21.9, 21.4, 19.8, 19.4, 19.0, 14.2, 12.7; HRMS (ESI, *m*/*z*) calcd for $C_{31}H_{43}N_2O_2$ $[M + H]^+$ 475.3325. Found: 475.3321.

4.3.8.30. Pyrazole derivative ***11ad***. Yield 81%; Mp 215.5–216.3 °C; IR (KBr): 3088, 2955, 2850, 1712, 1605, 1526, 1496, 1463, 1404, 1379, 1323, 1234, 1182, 1152, 1091, 1030, 971, 852, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.37 (s, 1H), 7.02 (s, 2H), 6.95 (s, 1H), 4.21–4.07 (m, 2H), 2.35 (s, 6H), 2.21–2.15 (m, 2H), 2.07–1.93 (m, 3H), 1.86–1.38 (m, 7H), 1.31 (t, J = 7.2 Hz, 3H), 1.27–1.24 (m, 1H), 1.22 (s, 3H), 1.20–1.17 (m, 2H), 1.06 (s, 3H), 1.03–0.88 (m, 3H), 0.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 151.1, 139.7, 138.5, 138.5, 134.4, 131.2, 128.7, 121.3, 121.3, 68.0, 60.0, 57.1, 52.6, 43.8, 42.5, 41.5, 40.3, 38.2, 38.1, 37.8, 35.9, 29.0, 22.6, 21.9, 21.4, 21.2, 21.2, 19.0, 14.1, 12.7; HRMS (ESI, *m*/*z*) calcd for $C_{31}H_{43}N_2O_2$ $[M + H]^+$ 475.3325. Found: 475.3322.

4.4. X-ray crystallographic analysis

X-ray crystal data of compounds **9b**, **10**, **11v** and **11a** were collected by a Rigaku AFC5R diffractometer with graphite-monochromated Cu-Kα radiation (λ = 0.71073 Å). The structure was solved by the direct method and refined with a full-matrix least squares method.

4.4.1. Crystal data for compound **9b**

$C_{29}H_{39}FN_2O_2$, M = 466.62, orthorhombic, space group $P2_1$, a = 8.2822(9), b = 7.9215(9), c = 19.349(2), V = 1268.4(2) Å^3, Z = 2, μ (Cu Kα) = 0.644 cm^{-1}, F(000) = 504, D_c = 1.222 mg/mm^3, crystal dimensions: 0.30 × 0.28 × 0.25 mm, A total of 9627 reflections were collected using the $\omega - 2\theta$ scan technique to a maximum 2θ value, and 4364 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final R and R_w values were 0.0466 and 0.1146, respectively. The maximum and minimum peaks in the difference map were 0.122 and −0.115 e Å^{-3}, respectively. The data has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 917721.

4.4.2. Crystal data for compound **10**

$C_{23}H_{34}O_4$, M = 374.50, orthorhombic, space group $P2_1$, a = 6.8882(14), b = 11.523(2), c = 13.459(3), V = 1053.8(4) Å^3, Z = 2, μ (Cu Kα) = 0.079 cm^{-1}, F(000) = 408, D_c = 1.180 mg/mm^3, crystal dimensions: 0.20 × 0.20 × 0.20 mm, A total of 3307 reflections were collected using the $\omega - 2\theta$ scan technique to a maximum 2θ value, and 1845 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final R and R_w values were 0.0663 and 0.1797, respectively. The maximum and minimum peaks in the difference map were 0.283 and −0.250 e Å^{-3}, respectively. The data has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 917818.

4.4.3. Crystal data for compound **11v**

$C_{29}H_{36}Cl_2N_2O_2$, M = 515.50, orthorhombic, space group $P2_1$, a = 12.6459(5), b = 8.3831(3), c = 13.3872(5), V = 1340.69(9) Å^3, Z = 2, μ (Cu Kα) = 2.396 cm^{-1}, F(000) = 548, D_c = 1.277 mg/mm^3, crystal dimensions: 0.24 × 0.20 × 0.20 mm, A total of 10,911 reflections were collected using the $\omega - 2\theta$ scan technique to a maximum 2θ value, and 4707 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final R and R_w values were 0.0644

and 0.1809, respectively. The maximum and minimum peaks in the difference map were 0.156 and −0.236 e Å^{-3}, respectively. The data has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 917722.

4.4.4. Crystal data for compound ***11a***

$C_{29}H_{38}N_2O_2$, $M = 446.61$, orthorhombic, space group $P2_12_12_1$, $a = 7.0203(14)$, $b = 16.816(3)$, $c = 21.249(4)$, $V = 2508.5(9)$ Å^3, $Z = 4$, μ (Cu Kα) = 0.074 cm^{-1}, $F(000) = 968$, $D_c = 1.183$ mg/mm^3, crystal dimensions: 0.20 × 0.18 × 0.18 mm, A total of 7545 reflections were collected using the $\omega - 2\theta$ scan technique to a maximum 2θ value, and 4146 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final R and R_w values were 0.0647 and 0.1320, respectively. The maximum and minimum peaks in the difference map were 0.163 and −0.154 e Å^{-3}, respectively. The data has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 924756.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.04.044.

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