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# SYNTHESIS AND CALCIUM CHANNEL ANTAGONIST ACTIVITY OF NEW SYMMETRICAL AND ASYMMETRICAL 4-[2-CHLORO-2-(4-CHLORO-6-METHYL-2-OXO-2H-PYRAN-3-YL)VINYL]-SUBSTITUTED 1,4-DIHYDROPYRIDINES

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*New symmetrical 4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-substituted 1,4-dihydropyridines were synthesized in moderate to good yields via the modified Hantzsch reaction of β-dicarbonyl compounds with (Z)-3-chloro-3-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)acrolein in the presence of an excess amount of $NH_4OAc$. Also, the reaction of β-dicarbonyl compounds with (Z)-3-chloro-3-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)acrolein in the presence of enamino esters and ketones was performed, and asymmetrical 4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-substituted 1,4-dihydropyridines were obtained in moderate to good yields at room temperature. The calcium channel blocking activity of these compounds was assessed. They demonstrated moderate to weak effects, although one compound had a comparable effect ($IC_{50}$ =1.40×10$^{-7}$ M) with respect to the reference drug Nifedipine.*

**Keywords**: calcium channel antagonist, dihydropyridines, 2-pyrone derivatives, Hantzsch reaction.

The 4-aryl-substituted 1,4-dihydropyridines (1,4-DHPs) are among the most studied heterocyclic compounds that present interesting pharmacological and biological properties [1-4]. They have been used as organic calcium channel modulators [5-7], anticonvulsant [8], antidiabetic [9], antiviral [10], radioprotective [11], antitumor [12], antioxidant [13], vasodilator [14], and anti-inflammatory agents [15]. It was proposed that calcium channel modulation depends on the absolute configuration at C-4 and flexibility of both the ester group of 1,4-DHPs and the C-4 aryl group of these compounds [16, 17]. Therefore, the development of new synthetic methods leading to 1,4-DHPs with different substituents [18−20] or heterocycles [21-27] has attracted much attention in organic synthesis. The Hantzsch synthesis is a classical method for the preparation of 1,4-DHPs [28] and has been one of the most important basic reactions in organic chemistry for its use in pharmaceutical synthesis. However, due to the drastic reaction conditions, long reaction times, and low yields, the classical Hantzsch reaction was modified by several methods [29].

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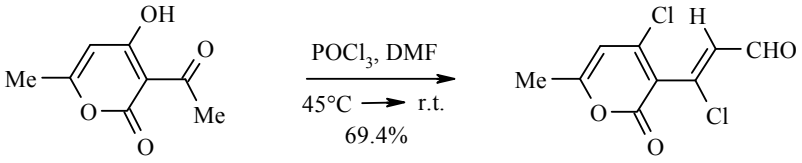
On the other hand, 2H-pyran-2-ones and their analogues have been found to exhibit a wide range of biological activities [30]. Due to the biological importance of 1,4-DHPs and pyrone derivatives, and as a continuation of our work on the synthesis of new pyrone derivatives [31, 32], herein we report the synthesis of 4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-substituted 1,4-DHPs. The calcium channel blocking activities of these compounds were also investigated.

The symmetrical 1,4-DHPs were synthesized by the modified Hantzsch reaction, which involves condensation of an aldehyde, a β-dicarbonyl compound, and ammonium acetate. The asymmetrical 1,4-DHPs were also obtained by the modified Hantzsch reaction, using an aldehyde, β-dicarbonyl compounds, and enaminones.

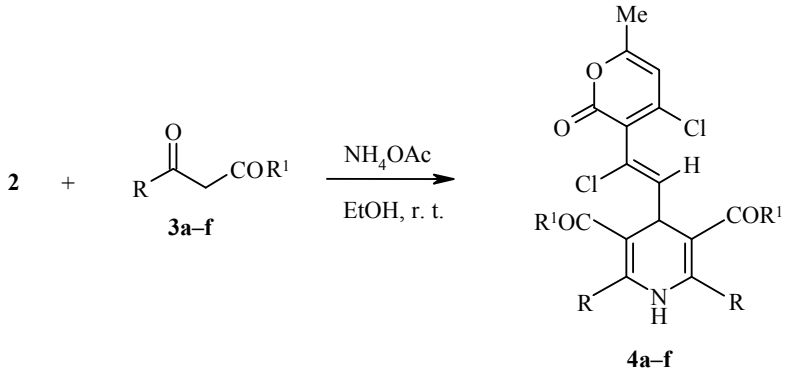
Starting from commercially available 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one (dehydroacetic acid) (**1**), (*Z*)-3-chloro-3-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)acrolein (**2**) was synthesized using the Vilsmeier–Haack reaction [33] (Scheme 1).

Scheme 1




Six examples of the conversion of aldehyde **2** to various 4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-substituted 1,4-DHPs **4a-f** are listed in Table 1. The reactions were performed by adding aldehyde **2** to a mixture of 2 eq. of β-dicarbonyl compounds **3a-f** in ethanol in the presence of an excess amount of $NH_4OAc$ at room temperature (Scheme 2). The reactions were completed within 0.5-1 h, and 1,4-DHPs **4a-f** were obtained in 39-61% yields. The structures of compounds **4a-f** were established from FT-IR, $^1$H NMR, $^{13}$C NMR, mass spectra, and elemental analyses.

Scheme 2




**3,4 a-c** R = Me, **a** $R^1$ = OMe, **b** $R^1$ = OEt, **c** $R^1$ = OBu-*t*;
**d** R = *n*-Pr, $R^1$ = OEt; **e, f** R = Me, **e** $R^1$ = Me, **f** $R^1$ = Ph

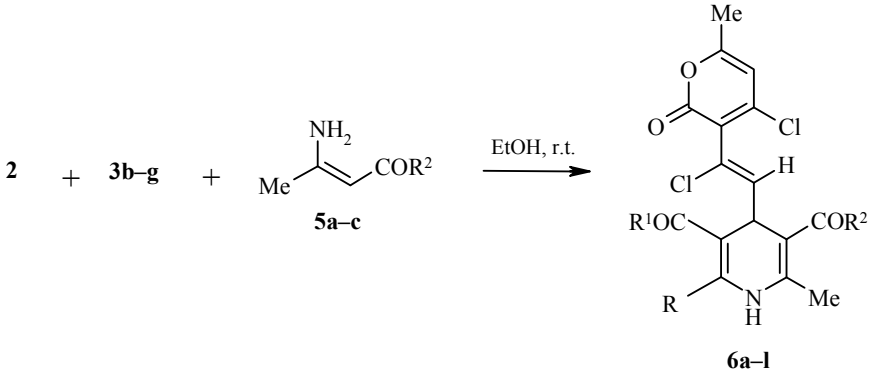
Also, the reaction of aldehyde **2** with β-dicarbonyl compounds **3b-g** in the presence of enamino esters and ketones such as methyl 3-aminobut-2-enoate **5a**, 4-aminopent-3-en-2-one **5b,** and 3-amino-1-phenylbut-2-en-1-one **5c** was investigated and unsymmetrical 4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-substituted 1,4-DHPs **6a-l** were obtained in 21-46% yields (Scheme 3). The results are summarized in Table 2. The structure of compounds **6a-l** were established using FT-IR, $^1$H NMR, and $^{13}$C NMR spectra, mass spectral data, and elemental analyses.

TABLE 1. Reaction Conditions and Yields of 1,4-DHPs **4a-f**

| Entry | β-Dicarbonyl compound | Time, h | Product | Yield, %* |
|---|---|---|---|---|
| 1 | **3a** | 0.5 | **4a** | 55 |
| 2 | **3b** | 0.5 | **4b** | 61 |
| 3 | **3c** | 0.5 | **4c** | 50 |
| 4 | **3d** | 0.5 | **4d** | 47 |
| 5 | **3e** | 1 | **4e** | 39 |
| 6 | **3f** | 1 | **4f** | 41 |

* Yields refer to isolated products.

Scheme 3




**3g** R = $R^1$ = -$CH_2CMe_2CH_2$-; **5 a** $R^2$ = OMe, **b** $R^2$ = Me, **c** $R^2$ = Ph;
**6 a–f** $R^2$ = OMe, **a** R = Me, $R^1$ = OEt, **b** R = Me, $R^1$ = OBu-*t*; **c** R = *n*-Pr, $R^1$ = OEt,
**d** R = $R^1$ = Me, **e** R = Me, $R^1$ = Ph, **f** R = $R^1$ = -$CH_2CMe_2CH_2$-; **g-i** $R^2$ = Me, **g** R = Me,
$R^1$ = OEt, **h** R = Me, $R^1$ = OBu-*t*, **i** R = *n*-Pr, $R^1$ = OEt; **j-l** $R^2$ = Ph, **j** R = Me, $R^1$ = OEt,
**k** R = Me, $R^1$ = OBu-*t*, **l** R = *n*-Pr, $R^1$ = OEt

TABLE 2. Reaction Conditions and Yields of 1,4-DHPs **6a-l**

| Entry | β-Dicarbonyl compound | Enamine | Time, h | Product | Yield, %* |
|---|---|---|---|---|---|
| 1 | **3b** | **5a** | 3 | **6a** | 45 |
| 2 | **3c** | **5a** | 5 | **6b** | 41 |
| 3 | **3d** | **5a** | 5 | **6c** | 46 |
| 4 | **3e** | **5a** | 12 | **6d** | 41 |
| 5 | **3f** | **5a** | 12 | **6e** | 38 |
| 6 | **3g** | **5a** | 2 | **6f** | 36 |
| 7 | **3b** | **5b** | 24 | **6g** | 32 |
| 8 | **3c** | **5b** | 24 | **6h** | 26 |
| 9 | **3d** | **5b** | 24 | **6i** | 32 |
| 10 | **3b** | **5c** | 24 | **6j** | 23 |
| 11 | **3c** | **5c** | 24 | **6k** | 21 |
| 12 | **3d** | **5c** | 24 | **6l** | 21 |

* Yields refer to isolated products.

TABLE 3. Calcium Channel Modulator Activity of Newly Synthesized Compounds in Ileum of Guinea pigs

| Compound | MW | (Mean ± S.E.*) $IC_{50}$ | (Mean ± S.E.) $IC_{30}$ | N |
|---|---|---|---|---|
| **4a** | 428 | $(1.47\pm 0.78)\times10^{-5}$ | $(3.54\pm1.62)\times10^{-6}$ | 3 |
| **4b** | 456 | $(1.35\pm1.27)\times10^{-5}$ | $(9.38\pm7.36)\times10^{-7}$ | 4 |
| **4c** | 512 | $(1.40\pm0.28)\times10^{-7}$ | $(4.74\pm0.84)\times10^{-9}$ | 4 |
| **4d** | 512 | $(9.40\pm2.48)\times10^{-7}$ | $(3.65\pm1.07)\times10^{-7}$ | 4 |
| **4e** | 396 | $(4.00\pm2.00)\times10^{-4}$ | $(7.58\pm0.12)\times10^{-6}$ | 4 |
| **4f** | 520 | $(5.81\pm1.53)\times10^{-6}$ | $(1.55\pm0.47)\times10^{-6}$ | 4 |
| **6a** | 442 | $(8.28\pm1.04)\times10^{-6}$ | $(2.64\pm0.30)\times10^{-6}$ | 4 |
| **6b** | 470 | $(2.28\pm1.37)\times10^{-5}$ | $(5.40\pm1.91)\times10^{-6}$ | 4 |
| **6c** | 470 | $(3.15\pm1.43)\times10^{-5}$ | $(7.22\pm1.52)\times10^{-6}$ | 4 |
| **6d** | 412 | $(3.00\pm0.20)\times10^{-4}$ | $(3.90\pm0.36)\times10^{-5}$ | 4 |
| **6e** | 474 | $(2.51\pm0.20)\times10^{-6}$ | $(1.61\pm0.61)\times10^{-7}$ | 3 |
| **6f** | 452 | $(3.46\pm 2.33)\times10^{-6}$ | $(7.82\pm1.99)\times10^{-7}$ | 4 |
| **6g** | 426 | $(1.78\pm0.78)\times10^{-6}$ | $(4.15\pm2.43)\times10^{-7}$ | 4 |
| **6h** | 454 | $(2.00\pm1.84)\times10^{-4}$ | $(8.73\pm1.87)\times10^{-7}$ | 4 |
| **6i** | 454 | $(2.09\pm1.89)\times10^{-6}$ | $(9.58\pm0.95)\times10^{-7}$ | 4 |
| **6j** | 488 | $(3.30\pm1.29)\times10^{-6}$ | $(1.19\pm0.92)\times10^{-6}$ | 4 |
| **6k** | 516 | $(2.33\pm0.89)\times10^{-6}$ | $(8.93\pm1.47)\times10^{-7}$ | 4 |
| **6l** | 516 | $(2.69\pm0.28)\times10^{-5}$ | $(6.49\pm1.09)\times10^{-6}$ | 4 |
| Nifedipine | 346 | $(6.89\pm0.90)\times10^{-8}$ | $(1.59\pm0.67)\times10^{-8}$ | 3 |

* S.E. - standard error.

The *in vitro* calcium channel antagonist activities ($IC_{30}$ and $IC_{50}$) of 18 compounds were determined as the molar concentration of the test compounds required to produce 30% or 50% inhibition of guinea pig longitudinal ileal smooth muscle (GPLISM). Results are summarized in the Table 3. These compounds demonstrated moderate to weak calcium channel antagonist activity ($10^{-5}$ to $10^{-7}$ M range) relative to the reference drug Nifedipine ($IC_{50} = 6.89\times10^{-8}$ M). As seen in Table 3, the highest activity belongs to compound **4c,** which is nearly 2 times weaker than Nifedipine as the reference drug, although, in the case of $IC_{30}$, **4c** showed a lower value ($IC_{30} = 4.74\times10^{-9}$ M), which means that this compound has higher calcium channel antagonist activity in a lower concentration compared to Nifedipine. On the other hand, **6d** demonstrated the least activity ($IC_{50} = 3.00\times10^{-4}$ M, $IC_{30} = 3.90\times10^{-5}$ M), which is much lower than other compounds, and, in addition, is nearly 1000 times weaker in comparison of Nifedipine. Furthermore, **4e** and **6h** have also weak activity, similar to **6d**. The interesting point about these compounds is the presence of the carbonyl group in one or both sides in positions 3,5 instead of the carboxylate group. This is consistent with previous studies, which showed the decreasing effect of the carbonyl group [34, 35].

In summary, new symmetrical and unsymmetrical 4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-substituted 1,4-DHPs were synthesized in moderate to good yields *via* the modified Hantzsch reaction of β-dicarbonyl compounds with (*Z*)-3-chloro-3-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)acrolein in the presence of an excess amount of $NH_4OAc$ and enamino esters or ketones respectively.

The calcium channel blocking activity of these compounds was evaluated. They demonstrated moderate to weak effects, although one compound, **4c**, had an effect ($IC_{50} = 1.40\times10^{-7}$ M) comparable to the reference drug nifedipine. Some derivatives, however, exhibited very weak activity (**4e**, **6d**, and **6h**), which may be attributed to the conversion of the carboxylate group into the carbonyl moiety in positions 3 and 5.

## EXPERIMENTAL

All chemicals were purchased and used without any further purification. Melting points were determined on a Electrothermal MEL-TEMP apparatus (model 1202D) and are uncorrected. FT-IR spectra were obtained with a Bruker Tensor 27 spectrometer in KBr. NMR spectra were recorded with a Bruker spectrometer operating at 400 or 500 MHz for protons and at 100 or 125 MHz for carbon nuclei. TMS was used as an internal standard. $^1$H and $^{13}$C NMR spectra were recorded for compounds **4a-f**, **6a-c** (at 400 and 100 MHz respectively in $CDCl_3$), **6d**, **6e**, **6g-l** (at 500 and 125 MHz respectively in $CDCl_3$), and **6f** (at 500 and 125 MHz respectively in $CDCl_3$/DMSO-$d_6$). Mass spectra were taken with a Shimadzu (70 eV) mass spectrometer. Elemental analyses were done on an Elementar Vario EL III instrument. The products were purified by PLC on silica gel using hexane–acetone mixture as eluent.

**Synthesis of Symmetrical 1,4-DHPs (General Method)**. To a solution of compound **2** (1 mmol) in ethanol (3 ml), β-dicarbonyl compound (2 mmol) and $NH_4OAc$ (excess amount) were added successively at room temperature (20-25°C), and the mixture was stirred for the appropriate time (0.5-1 h). After completion of the reaction, ethanol was evaporated under reduced pressure. The crude mixture was purified by PLC on silica gel using hexane–acetone, 4:1, to afford the final product.

**Dimethyl 4-[(*Z*)-2-Chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4a).** Pale-yellow solid, 55% yield; mp 182-184°C. FT-IR, ν, cm$^{-1}$: 3303 (NH), 3093, 2989, 2941, 2842, 1732, 1694, 1625, 1550, 1496, 1295, 1108, 850, 776, 737. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 6.06 (1H, d, $^4J$ = 0.8, CH α-pyrone); 5.72 (1H, s, NH); 5.60 (1H, d, $^3J$ = 9.7, CH vinyl); 5.06 (1H, d, $^3J$ = 9.7, CH dihydropyridine); 3.74 (6H, s, $OCH_3$); 2.27 (6H, s, $CH_3$ dihydropyridine); 2.22 (3H, d, $^4J$ = 0.4, $CH_3$ α-pyrone). $^{13}$C NMR spectrum, δ, ppm: 166.8, 160.4, 158.3, 148.3, 144.4, 134.2, 120.9, 118.5, 105.4, 99.1, 50.0, 33.8, 18.7, 18.1. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 427 $[M]^+$ (15), $[M+2]^+$ (9); 392 (85), 368 (87), 300 (65), 224 (100). Found, %: C 52.91; H 4.63; N 3.30. $C_{19}H_{19}Cl_2NO_6$. Calculated, %: C 53.29; H 4.47; N 3.27.

**Diethyl 4-[(*Z*)-2-Chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4b).** Pale-yellow solid, 61% yield; mp 76-78°C. FT-IR, ν, cm$^{-1}$: 3340 (NH), 3095, 2974, 1739, 1694, 1626, 1550, 1487, 1207, 1101, 794, 739. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 6.06 (1H, s, CH α-pyrone); 5.90 (1H, s, NH); 5.59 (1H, d, $^3J$ = 9.7, CH vinyl); 5.05 (1H, d, $^3J$ = 9.7, CH dihydropyridine); 4.14-4.23 (4H, m, $CH_2$ ethyl); 2.27 (6H, s, $CH_3$ dihydropyridine); 2.21 (3H, s, $CH_3$ α-pyrone); 1.32 (6H, t, $^3J$ = 7.1, $CH_3$ ethyl). $^{13}$C NMR spectrum, δ, ppm: 166.4, 160.3, 158.3, 148.3, 144.5, 134.1, 120.9, 117.8, 105.4, 99.1, 58.9, 33.4, 18.6, 18.1, 13.4. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 455 $[M]^+$ (75), $[M+2]^+$ (35); 43 (100). Found, %: C 55.11; H 5.16; N 3.13. $C_{21}H_{23}Cl_2NO_6$. Calculated, %: C 55.27; H 5.08; N 3.07.

**Di-*tert*-butyl 4-[(*Z*)-2-Chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethy-1,4-dihydrolpyridine-3,5-dicarboxylate (4c).** Pale-yellow solid, 50% yield; mp 208-210°C. FT-IR, ν, cm$^{-1}$: 3332 (NH), 3095, 2974, 2928, 1739, 1690, 1647, 1554, 1486, 1232, 1161, 1110, 856, 777, 743. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 6.05 (1H, s, CH α-pyrone); 5.60 (1H, s, NH); 5.59 (1H, d, $^3J$ = 9.6, CH vinyl); 5.07 (1H, d, $^3J$ = 9.6, CH dihydropyridine); 2.23 (6H, s, $CH_3$ dihydropyridine); 2.21 (3H, s, $CH_3$ α-pyrone); 1.52 (18H, s, $CH_3$ *tert*-butyl). $^{13}$C NMR spectrum, δ, ppm: 165.8, 160.3, 158.2, 148.2, 143.1, 134.6, 121.0, 117.5, 105.4, 100.7, 79.0, 33.8, 27.3, 18.7, 18.2. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 511 $[M]^+$ (20), $[M+2]^+$ (17); 454 (25), 196 (100). Found, %: C 58.33; H 6.16; N 2.88. $C_{25}H_{31}Cl_2NO_6$. Calculated, %: C 58.60; H 6.10; N 2.73.

**Diethyl 4-[(*Z*)-2-Chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dipropyl-1,4-dihydropyridine-3,5-dicarboxylate (4d).** Pale-yellow solid, 47% yield; mp 136-138°C. FT-IR, ν, cm$^{-1}$: 3340 (NH), 3098, 2966, 2932, 2870, 1717, 1692, 1635, 1559, 1488, 1366, 1278, 1110, 769, 719. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 6.05 (1H, d, $^4J$ = 0.7, CH α-pyrone); 5.72 (1H, s, NH); 5.57 (1H, d, $^3J$ = 9.7, CH vinyl); 5.09 (1H, d, $^3J$ =9.7, CH dihydropyridine); 4.12-4.24 (4H, m, C$\underline{H}_2$CH$_3$); 2.72-2.80 (2H, m, $CH_2$ propyl); 2.48-2.55 (2H, m, $CH_2$ propyl); 2.21 (3H, s, $CH_3$ α-pyrone); 1.51-1.63 (4H, m, $CH_2$ propyl); 1.33 (6H, t, $^3J$ = 7.1, CH$_2$C$\underline{H}_3$); 0.95

(6H, t, $^3J$ = 7.3, $CH_3$ propyl). $^{13}$C NMR spectrum, δ, ppm: 165.9, 160.3, 158.2, 148.7, 148.2, 133.9, 120.9, 117.8, 105.4, 98.9, 58.9, 33.5, 33.1, 20.8, 18.7, 13.4, 12.8. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 511 $[M]^+$ (55), $[M+2]^+$ (40), $[M+4]^+$ (10); 476 (90), 308 (100). Found: C 58.53; H 6.17; N 2.84. $C_{25}H_{31}Cl_2NO_6$. Calculated, %: C 58.60; H 6.10; N 2.73.

**4-Chloro-3-[(*Z*)-1-chloro-2-(3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridin-4-yl)ethenyl]-6-methyl-2H-pyran-2-one (4e).** Yellow solid, 39% yield; mp 208-210°C. FT-IR, ν, $cm^{-1}$: 3336 (NH), 3092, 2990, 2925, 1718, 1660, 1627, 1588, 1555, 1464, 1357, 1220, 781, 748, 714. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 6.44 (1H, s, NH); 6.10 (1H, s, CH α-pyrone); 5.65 (1H, d, $^3J$ = 9.8, CH vinyl); 4.93 (1H, d, $^3J$ = 9.8, CH dihydropyridine); 2.43 (6H, s, $CH_3$ acetyl); 2.26 (6H, s, $CH_3$); 2.24 (3H, s, $CH_3$). $^{13}$C NMR, δ, ppm: 197.1 (C=O ketone), 160.9, 158.3, 149.1, 144.0, 133.5, 120.1, 117.2, 107.9, 105.5, 35.1, 29.0, 18.9, 18.7. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 396 $[M+H]^+$ (15), $[M+H+2]^+$ (7); 360 (90), 316 (80), 43 (100). Found, %: C 57.25; H 4.66; N 3.77. $C_{19}H_{19}Cl_2NO_4$. Calculated, %: C 57.59; H 4.83; N 3.53.

**4-Chloro-3-[(*Z*)-1-chloro-2-(3,5-dibenzoyl-2,6-dimethyl-1,4-dihydropyridin-4-yl)ethenyl]-6-methyl-2H-pyran-2-one (4f).** Yellow solid, 41% yield; mp 190-192°C. FT-IR, ν, $cm^{-1}$: 3306 (NH), 3058, 2963, 2923, 1735, 1694, 1626, 1549, 1478, 1230, 855, 730, 700. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 7.71-7.73 (4H, m, CH Ph); 7.36-7.43 (6H, m, CH Ph); 6.20 (1H, s, NH); 6.02 (1H, d, $^4J$ = 0.5, CH α-pyrone); 5.74 (1H, d, $^3J$ = 9.2, CH vinyl); 5.06 (1H, d, $^3J$ = 9.2, CH dihydropyridine); 2.19 (3H, s, $CH_3$ α-pyrone ); 2.01 (6H, s, $CH_3$). $^{13}$C NMR spectrum, δ, ppm: 196.5 (C=O ketone), 160.5, 158.2, 148.7, 141.3, 138.8, 134.4, 130.5, 127.4, 127.3, 120.1, 118.9, 108.6, 105.4, 37.8, 18.7, 17.8. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 520 $[M+H]^+$ (20), $[M+H+2]^+$ (12); 77 (100). Found, %: C 66.63; H 4.57; N 2.60. $C_{29}H_{23}Cl_2NO_4$. Calculated, %: C 66.93; H 4.45; N 2.69.

**Synthesis of Asymmetrical 1,4-DHPs (General Method)**. To a solution of compound **2** (1 mmol) in ethanol (3 ml), enamino ester or ketone (1 mmol), and β-dicarbonyl (1 mmol) were added successively at room temperature (20-25°C), and the mixture was stirred for the appropriate time. After completion of the reaction, ethanol was evaporated under reduced pressure. The crude mixture was purified by PLC on silica gel using hexane–acetone, 5:1, to afford the final product.

**(*Z*)-3-Ethyl 5-Methyl 4-[2-Chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (6a).** Pale-yellow solid, 45% yield; mp 60-62°C. FT-IR, ν, $cm^{-1}$: 3335 (NH), 3095, 2983, 2946, 1736, 1695, 1626, 1550, 1491, 1303, 1241, 1105, 858, 777, 738. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 6.06 (1H, s, CH α-pyrone); 6.01 (1H, s, NH); 5.59 (1H, d, $^3J$ = 9.6, CH vinyl); 5.04 (1H, d, $^3J$ = 9.6, CH dihydropyridine); 4.16-4.21 (2H, m, $CH_2$ ethyl); 3.72 (3H, s, $OCH_3$); 2.25 (6H, s, $CH_3$); 2.21 (3H, s, $CH_3$ α-pyrone); 1.32 (3H, t, $^3J$ = 6.8, $CH_3$ ethyl). $^{13}$C NMR spectrum, δ, ppm: 166.8, 166.4, 160.3, 158.3, 148.3, 144.7, 144.5, 134.2, 120.9, 118.1, 105.4, 99.2, 98.7, 58.9, 49.9, 33.6, 18.6, 18.0, 17.9, 13.4. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 441 $[M]^+$ (37), $[M+2]^+$ (26), $[M+4]^+$ (12), 406 (80), 368 (80), 43 (100). Found, %: C 54.01; H 4.73; N 3.34. $C_{20}H_{21}Cl_2NO_6$. Calculated, %: C 54.31; H 4.79; N 3.17.

**(*Z*)-3-*tert*-Butyl 5-Methyl 4-[2-Chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (6b).** Pale-yellow solid, 41% yield; mp 80-82°C. FT-IR, ν, $cm^{-1}$: 3326 (NH), 3095, 2973, 1737, 1689, 1624, 1554, 1492, 1308, 1221, 1107, 855, 781, 740. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 6.08 (1H, s, CH α-pyrone); 5.75 (1H, s, NH); 5.61 (1H, d, $^3J$ = 9.6, CH vinyl); 5.04 (1H, d, $^3J$ = 9.6, CH dihydropyridine); 3.75 (3H, s, $OCH_3$); 2.28 (3H, s, $CH_3$); 2.24 (3H, s, $CH_3$); 2.23 (3H, s, $CH_3$ α-pyrone); 1.54 (9H, s, $CH_3$ *tert*-butyl). $^{13}$C NMR spectrum, δ, ppm: 166.9, 165.8, 160.3, 158.3, 148.3, 144.7, 142.9, 134.4, 120.9, 117.9, 105.4, 101.1, 98.6, 79.3, 49.9, 33.7, 27.4, 18.7, 18.3, 18.2. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 469 $[M]^+$ (15), $[M+2]^+$ (10), 412 (80), 368 (85), 267 (80), 210 (100). Found, %: C 56.01; H 5.53; N 3.22. $C_{22}H_{25}Cl_2NO_6$. Calculated, %: C 56.18; H 5.36; N 2.98.

**(Z)-3-Ethyl 5-Methyl 4-[2-Chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-6-methyl-2-propyl-1,4-dihydropyridine-3,5-dicarboxylate (6c).** Pale-yellow solid, 46% yield; mp 52-54°C; FT-IR, ν, $cm^{-1}$: 3340 (NH), 3095, 2961, 2871, 1737, 1695, 1627, 1550, 1490, 1300, 1201, 1106, 859, 777. $^1$H NMR, δ, ppm (*J*, Hz): 6.08 (1H, s, CH α-pyrone); 5.76 (1H, s, NH); 5.60 (1H, d, $^3J$ = 9.7, CH vinyl); 5.08 (1H, d,

$^3J$ = 9.7, CH dihydropyridine); 4.16-4.25 (2H, m, $CH_2$ ethyl); 3.76 (3H, s, $OCH_3$); 2.60-2.68 (2H, m, $CH_2$ propyl); 2.29 (3H, s, $CH_3$); 2.23 (3H, s, $CH_3$); 1.55-1.63 (2H, m, $CH_2$ propyl); 1.34 (3H, t, $^3J$ = 7.1, $CH_3$ ethyl); 0.97 (3H, t, $^3J$ = 7.3, $CH_3$ propyl). $^{13}$C NMR spectrum, δ, ppm: 166.8, 165.9, 160.3, 158.3, 148.5, 148.3, 144.6, 134.1, 120.9, 118.2, 105.4, 99.1, 98.7, 58.9, 50.0, 33.6, 33.1, 20.8, 18.7, 18.1, 13.4, 12.8. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 468 $[M-H]^+$ (35), $[M-H+2]^+$ (30), $[M-H+4]^+$ (7), 432 (85), 372 (85), 266 (80), 165 (85), 43 (100). Found, %: C 56.13; H 5.74; N 3.04. $C_{22}H_{25}Cl_2NO_6$. Calculated, %: C 56.18; H 5.36; N 2.98.

**(*Z*)-Methyl 5-Acetyl-4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (6d).** Yellow solid, 41% yield; mp 94-96°C; FT-IR, ν, $cm^{-1}$: 3313 (NH), 3084, 2998, 2944, 1725, 1696, 1671, 1629, 1550, 1488, 1304, 1211, 850, 750. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 6.12 (1H, s, CH α-pyrone); 6.02 (1H, s, NH); 5.67 (1H, d, $^3J$ = 9.7, CH vinyl); 5.04 (1H, d, $^3J$ = 9.7, CH dihydropyridine); 3.80 (3H, s, $OCH_3$); 2.43 (3H, s, $CH_3$ acetyl); 2.32 (3H, s, $CH_3$ α-pyrone); 2.27 (6H, s, $CH_3$). $^{13}$C NMR spectrum, δ, ppm: 199.4 (C=O ketone), 167.9, 162.2, 159.8, 150.2, 146.0, 145.3, 135.2, 122.0, 119.4, 108.7, 106.9, 100.8, 51.6, 35.9, 30.2, 20.6, 20.2, 19.5. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 411 $[M]^+$ (35), $[M+2]^+$ (26), 208 (100). Found, %: C 55.30; H 4.88; N 3.55. $C_{19}H_{19}Cl_2NO_5$. Calculated, %: C 55.35; H 4.65; N 3.40.

**(*Z*)-Methyl 5-Benzoyl-4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (6e).** Yellow solid, 38% yield; mp 180-182°C. FT-IR, ν, $cm^{-1}$: 3290 (NH), 3085, 2996, 2949, 1732, 1703, 1632, 1598, 1554, 1434, 1300, 1224, 1052, 857, 777, 746. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 7.79 (2H, d, $^3J$ = 7.4, CH Ph); 7.50-7.53 (1H, m, CH Ph); 7.43-7.46 (2H, m, CH Ph); 6.08 (1H, s, CH α-pyrone); 5.91 (1H, s, NH); 5.72 (1H, d, $^3J$ = 9.4, CH vinyl); 5.18 (1H, d, $^3J$ = 9.4, CH dihydropyridine); 3.73 (3H, s, $OCH_3$); 2.37 (3H, s, $CH_3$); 2.24 (3H, s, $CH_3$); 1.91 (3H, s, $CH_3$). $^{13}$C NMR spectrum, δ, ppm: 198.1 (C=O ketone), 168.2, 161.9, 159.7, 149.9, 146.7, 140.7, 140.1, 135.9, 132.2, 129.2, 128.8, 121.9, 120.2, 110.7, 106.8, 99.8, 51.5, 37.3, 20.1, 19.7, 18.9. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 473 $[M]^+$ (20), $[M+2]^+$ (18), 458 (30), 270 (100). Found, %: C 60.99; H 4.42; N 3.23. $C_{24}H_{21}Cl_2NO_5$. Calculated, %: C 60.77; H 4.46; N 2.95.

**(*Z*)-Methyl 4-[2-Chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6f).** Pale-yellow solid, 36% yield; mp 214-216°C. FT-IR, ν, $cm^{-1}$: 3278 (NH), 3100, 3067, 2953, 1741, 1694, 1618, 1551, 1472, 1381, 1217, 855, 808, 777, 743. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 7.90 (1H, s, CH α-pyrone); 5.99 (1H, s, NH); 5.69 (1H, d, $^3J$ = 9.2, CH vinyl); 4.87 (1H, d, $^3J$ = 9.2, CH dihydropyridine); 3.62 (3H, s, $OCH_3$); 2.24 (2H, s, $CH_2$); 2.21 (2H, s, $CH_2$); 2.13 (3H, s, $CH_3$); 2.11 (3H, s, $CH_3$); 0.96-0.98 (6H, 2s, $CH_3$). $^{13}$C NMR spectrum, δ, ppm: 195.2 (C=O ketone), 168.2, 161.6, 159.6, 150.7, 149.6, 146.5, 137.1, 122.4, 120.9, 108.3, 106.8, 101.6, 51.2, 51.0, 32.6, 31.8, 30.0, 27.2, 20.0, 18.9. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 452 $[M+H]^+$ (35), $[M+H+2]^+$ (18), 248 (100). Found, %: C 58.15; H 5.40; N 3.14. $C_{22}H_{23}Cl_2NO_5$. Calculated, %: C 58.42; H 5.13; N 3.10.

**(*Z*)-Ethyl 5-Acetyl-4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (6g).** Yellow solid, 32% yield; mp 60-62°C. FT-IR, ν, $cm^{-1}$: 3318 (NH), 3093, 2980, 2929, 1737, 1696, 1670, 1628, 1550, 1476, 1303, 1212, 859, 778, 748. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 6.11 (1H, s, CH α-pyrone); 5.88 (1H, s, NH); 5.66 (1H, d, $^3J$ = 9.8, CH vinyl); 5.06 (1H, d, $^3J$ = 9.8, CH dihydropyridine); 4.24-4.31 (2H, m, $CH_2$ ethyl); 2.45 (3H, s, $CH_3$ acetyl); 2.33 (3H, s, $CH_3$ α-pyrone); 2.26-2.28 (6H, 2s, $CH_3$); 1.38 (3H, t, $^3J$ = 7.0, $CH_3$ ethyl). $^{13}$C NMR spectrum, δ, ppm: 199.3 (C=O ketone), 167.4, 162.1, 159.7, 150.1, 145.7, 145.2, 135.2, 122.0, 119.1, 108.8, 106.8, 101.2, 60.6, 35.8, 30.3, 20.6, 20.2, 19.7, 14.9. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 425 $[M]^+$ (15), $[M+2]^+$ (12), 43 (100). Found, %: C 56.26; H 4.85; N 3.33. $C_{20}H_{21}Cl_2NO_5$. Calculated, %: C 56.35; H 4.97; N 3.29.

***tert*-Butyl 5-Acetyl-4-[(1*Z*)-2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (6h).** Yellow solid, 26% yield; mp 74-76°C. FT-IR, ν, $cm^{-1}$: 3337 (NH), 3096, 2971, 2926, 2855, 1738, 1694, 1665, 1628, 1551, 1475, 1381, 1223, 1166, 859, 843, 782. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 6.33 (1H, s, NH); 6.12 (1H, s, CH α-pyrone); 5.63 (1H, d, $^3J$ = 9.8, CH vinyl); 5.05 (1H, d, $^3J$ = 9.8, CH dihydropyridine); 2.43 (3H, s, $CH_3$ acetyl); 2.28 (3H, s, $CH_3$); 2.27 (3H, s, $CH_3$); 2.25 (3H, s, $CH_3$); 1.56 (9H, s, $CH_3$ *tert*-butyl). $^{13}$C NMR spectrum, δ, ppm: 199.2 (C=O ketone), 166.9, 162.1, 159.8, 150.2, 146.0, 144.5,

135.3, 122.0, 118.6, 108.2, 106.9, 102.7, 80.8, 35.9, 30.3, 28.8, 20.5, 20.2, 19.5. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 453 $[M]^+$ (35), $[M+2]^+$ (18), 194 (100). Found, %: C 58.10; H 5.78; N 2.92. $C_{22}H_{25}Cl_2NO_5$. Calculated, %: C 58.16; H 5.55; N 3.08.

**Ethyl 5-Acetyl-4-[(1*Z*)-2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-6-methyl-2-propyl-1,4-dihydropyridine-3-carboxylate (6i).** Yellow solid, 32% yield; mp 54-56°C. FT-IR, ν, $cm^{-1}$: 3322 (NH), 3094, 2964, 2929, 2870, 1737, 1697, 1664, 1628, 1591, 1550, 1477, 1301, 1204, 859, 777. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 6.11 (1H, d, $^4J$ = 0.6, CH α-pyrone); 5.90 (1H, s, NH); 5.65 (1H, d, $^3J$ = 9.8, CH vinyl); 5.06 (1H, d, $^3J$ = 9.8, CH dihydropyridine); 4.21-4.30 (2H, m, $CH_2$ ethyl); 2.66-2.71 (2H, m, $CH_2$ propyl); 2.45 (3H, s, $CH_3$ acetyl); 2.29 (3H, s, $CH_3$); 2.26 (3H, s, $CH_3$); 1.57-1.66 (2H, m, $CH_2$ propyl); 1.37 (3H, t, $^3J$ = 7.1, $CH_3$ ethyl); 0.99 (3H, t, $^3J$ = 7.3, $CH_3$ propyl). $^{13}$C NMR spectrum, δ, ppm: 199.2 (C=O ketone), 167.1, 162.1, 159.7, 150.1, 150.0, 145.5, 135.1, 122.0, 119.1, 108.6, 106.9, 100.9, 60.5, 35.8, 34.6, 30.3, 22.4, 20.5, 20.2, 14.9, 14.2. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 453 $[M]^+$ (18), $[M+2]^+$ (12), 43 (100). Found, % C 57.99; H 5.85; N 3.33. $C_{22}H_{25}Cl_2NO_5$. Calculated, %: C 58.16; H 5.55; N 3.08.

**(*Z*)-Ethyl 5-Benzoyl-4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (6j).** Yellow solid, 23% yield; mp 166-168°C. FT-IR, ν, $cm^{-1}$: 3324 (NH), 3089, 2977, 2925, 1735, 1695, 1627, 1549, 1484, 1300, 1218, 1107, 855, 776, 733, 700. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 7.80 (2H, d, $^3J$ = 7.0, CH Ph); 7.50-7.51 (1H, m, CH Ph); 7.44-7.46 (2H, m, CH Ph); 6.07 (1H, s, CH α-pyrone); 5.91 (1H, s, NH); 5.70 (1H, d, $^3J$ = 9.4, CH vinyl); 5.21 (1H, d, $^3J$ = 9.3, CH dihydropyridine); 4.18-4.21 (2H, m, $CH_2$ ethyl); 2.39 (3H, s, $CH_3$); 2.23 (3H, s, $CH_3$); 1.93 (3H, s, $CH_3$); 1.30 (3H, t, $^3J$ = 6.8, $CH_3$ ethyl). $^{13}$C NMR spectrum, δ, ppm: 198.1 (C=O ketone), 167.7, 161.8, 159.7, 150.0, 146.6, 140.9, 140.2, 135.9, 132.2, 129.3, 128.7, 121.9, 119.9, 110.6, 106.9, 100.1, 60.4, 37.2, 20.1, 19.7, 18.9, 14.8. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 487 $[M]^+$ (35), $[M+2]^+$ (23), 77 (100). Found, %: C 61.25; H 4.42; N 3.01. $C_{25}H_{23}Cl_2NO_5$. Calculated, %: C 61.48; H 4.75; N 2.87.

**(*Z*)-*tert*-Butyl 5-Benzoyl-4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)-vinyl]-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (6k).** Yellow solid, 21% yield; mp 70-72°C. FT-IR, ν, $cm^{-1}$: 3347 (NH), 3091, 2964, 2926, 2857, 1737, 1693, 1628, 1550, 1479, 1261, 1100, 1023, 801, 730. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 7.81 (2H, d, $^3J$ = 7.2, CH Ph); 7.50-7.52 (1H, m, CH Ph); 7.43-7.46 (2H, m, CH Ph); 6.08 (1H, s, CH α-pyrone); 5.88 (1H, s, NH); 5.67 (1H, d, $^3J$ = 9.3, CH vinyl); 5.20 (1H, d, $^3J$ = 9.2, CH dihydropyridine); 2.38 (3H, s, $CH_3$); 2.24 (3H, s, $CH_3$); 1.99 (3H, s, $CH_3$); 1.52 (9H, s, $CH_3$ *tert*-butyl). $^{13}$C NMR spectrum, δ, ppm: 197.9 (C=O ketone), 167.0, 161.8, 159.6, 149.9, 145.5, 141.4, 140.2, 135.9, 132.0, 129.3, 128.6, 121.9, 119.5, 110.2, 106.9, 101.7, 80.5, 37.5, 28.7, 20.1, 19.6, 18.9. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 515 $[M]^+$ (35), $[M+2]^+$ (10), 256 (100). Found, %: C 62.75; H 5.44; N 2.75. $C_{27}H_{27}Cl_2NO_5$. Calculated, %: C 62.80; H 5.27; N 2.71.

**(*Z*)-Ethyl 5-Benzoyl-4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-6-methyl-2-propyl-1,4-dihydropyridine-3-carboxylate (6l).** Yellow solid, 21% yield; mp 56-58°C; FT-IR, ν, $cm^{-1}$: 3322 (NH), 3089, 2962, 2926, 2867, 1737, 1695, 1627, 1549, 1484, 1301, 1215, 1107, 859, 776, 700.; $^1$H NMR spectrum, δ, ppm (*J*, Hz): 7.80 (2H, d, $^3J$ = 7.2, CH Ph); 7.50-7.53 (1H, m, CH Ph); 7.44-7.47 (2H, m, CH Ph); 6.08 (1H, s, CH α-pyrone); 5.95 (1H, s, NH); 5.69 (1H, d, $^3J$ = 9.4, CH vinyl); 5.23 (1H, d, $^3J$ = 9.4, CH dihydropyridine); 4.20 (2H, q, $^3J$ = 7.1, $CH_2$ ethyl); 2.73-2.78 (2H, m, $CH_2$ propyl); 2.24 (3H, s, $CH_3$); 1.95 (3H, s, $CH_3$); 1.62-1.71 (2H, m, $CH_2$ propyl); 1.30 (3H, t, $^3J$ = 7.1, $CH_3$ ethyl); 1.03 (3H, t, $^3J$ = 7.3, $CH_3$ propyl). $^{13}$C NMR spectrum, δ, ppm: 198.0 (C=O ketone), 167.3, 161.8, 159.6, 150.8, 149.9, 141.3, 140.3, 135.9, 132.1, 129.2, 128.7, 121.9, 119.9, 110.4, 106.9, 99.9, 60.3, 37.2, 34.5, 22.4, 20.1, 19.0, 14.7, 14.3. Mass spectrum (EI), *m/z* ($I_{rel}$, %): 515 $[M]^+$ (21), $[M+2]^+$ (15), 105 (100). Found, %: C 62.66; H 5.30; N 3.01. $C_{27}H_{27}Cl_2NO_5$. Calculated, %: C 62.80; H 5.27; N 2.71.

**Pharmacology.** Male albino guinea pigs were purchased from the Shiraz University Animal House Department. They had free access to standard rodent chow and tap water at all times. The animals were housed in a room maintained at 23±2ºC temperature, 55±10% humidity, and on a 12-hour dark/light cycle. The feeding was disrupted one day before starting *in vitro* tests. Guinea pigs (300–450 g) were killed and their intestine

removed above the ileocecal junction. Smooth muscle segments of about 1 cm length were mounted under a resting tension of 500 mg and were maintained at 37ºC in a 20-ml jacketed organ bath containing an oxygenated (95% $O_2$ and 5% $CO_2$) physiological saline solution of the following composition: NaCl 137 mM; $CaCl_2$ 1.8 mM; KCl 2.7 mM; $MgSO_4$ 1.1 mM; $NaH_2PO_4$ 0.4 mM; $NaHCO_3$ 12 mM, and glucose 5 mM. The muscle was equilibrated for 1 h with a solution change every 15 min. The contractions were recorded with a forced displacement transducer (Hugo Sachs, March-Hugstetten, Germany) on a physiograph (Hugo Sachs). All compounds were dissolved in DMSO, and the same volume of solvent was used as the negative control. Nifedipine was used as the positive control. The contraction was elicited with 80 mM KCl. The contractile response was taken as the 100% value for the tonic (slow) component of the response. Test compounds were added in accumulation increment after the dose response for KCl. Test compound-induced relaxation of the contracted muscle was expressed as percent of control. The $IC_{50}$ values were graphically determined from the contraction–response curve [36-38].

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