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Discovery of diphenylmethane analogs as anti-bovine diarrhea viral agents

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ABSTRACT

Based on antiviral screening of our diphenylmethane derivatives prepared as steroid substitutes, we identified a 1,1-diphenylcyclobutane analog (**9**) and two diethyldiphenylsilane analogs (**12** and **13**) as superior lead compounds with potent anti-bovine viral diarrhea virus (BVDV) activity, having 50% effective concentration (EC_{50}: based on reduction of BVDV replication-induced cell destruction) and 50% cytotoxic concentration (CC_{50}: based on reduction of viable cell number) values of 6.2–8.4 μM and >100 μM, respectively, in Madin–Darby bovine kidney (MDBK) cells infected with BVDV.

HCV infection is thought to be a major cause of human hepatitis globally.[1,2] Currently, the standard treatment for chronic hepatitis C consists of pegylated interferon (IFN)-α in combination with the nucleoside analog ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide). However, the virus cannot be eliminated from approximately half of infected patients treated with this combination.[3] Therefore, alternative agents for the treatment and prevention of HCV infection are urgently needed. HCV belongs to the *Flaviviridae* family, as does bovine viral diarrhea virus (BVDV),[1] and because HCV does not replicate efficiently in cell cultures or animals, BVDV is thought to be a good model for human HCV.[4–6]

We have been engaged in structural development studies of anti-BVDV agents based on a γ-carboline skeleton, which was derived from thalidomide.[7,8] These previous studies were inspired by our successful development of α-glucosidase inhibitors derived from thalidomide, because α-glucosidase inhibitors may elicit antiviral activity through inhibition of normal trimming of viral envelope glycoprotein which is necessary for viral maturation/proliferation.[9–11]

On the other hand, we recently reported that some of our α-glucosidase inhibitors derived from thalidomide also act as ligands for liver X receptor (LXR), a member of the nuclear receptor superfamily, whose physiological ligands are oxysterols, including 24(*S*),25-epoxycholesterol (EC) and 22-(*R*)-hydroxycholesterol (HC).[12–15] We also found that several typical synthetic/natural LXR ligands copossess α-glucosidase-inhibitory activity.[13,15] This led us hypothesize a relationship between structures exhibiting α-glucosidase-inhibitory activity and the steroid skeleton; we have also proposed a multi-template hypothesis for molecular design of biologically active compounds.[15,16] The multi-template hypothesis is based on the fact that there exist only a limited number of protein domain folding structures in spite of the existence of a huge number of protein amino acid sequences.[16–18] This hypothesis has led us to design and synthesize various nuclear receptor ligands and steroid-related enzyme inhibitors with a 3,3-diphenylpentane skeleton.[16,19–22] These considerations suggested that 3,3-diphenylpentane and/or related skeleton(s) might be superior multi-templates that can substitute for a steroid skeleton.

In this context, we decided to examine the anti-BVDV activity of our 3,3-diphenylpentane derivatives prepared as nuclear receptor ligands. Anti-BVDV activity of the compounds was evaluated in Madin–Darby bovine kidney (MDBK) cells infected with BVDV (Nose strain), as described previously.[6,23] Here, we report the discovery of anti-BVDV activity of 3,3-diphenylpentane derivatives, as well as structural development studies to increase the activity. The anti-BVDV activity and cytotoxicity of the test compounds are presented as EC_{50} and CC_{50} values, where EC_{50} is the 50% effective concentration based on the reduction of BVDV replication-induced cell destruction, and CC_{50} is the 50% cytotoxic concentration based on the reduction of viable cell number. The selectivity index (SI) is determined as CC_{50}/EC_{50}.

First we screened anti-BVDV activity of our 3,3-diphenylpentane derivatives prepared as nuclear receptor ligands.[19–21] Among these compounds, we found that our potent androgen receptor (AR)/vitamin D receptor (VDR) dual ligand, DPP-0111 (**1**),[20]

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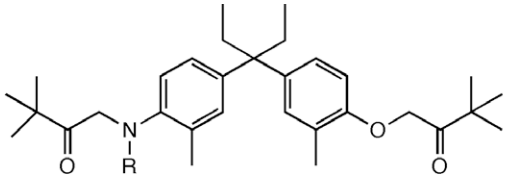
possesses moderate but promising anti-BVDV activity with EC_{50}/CC_{50} values of 8.9/82 μM (Fig. 1). Its VDR-selective analog, DPP-1023 (**2**),[20] was also active (EC_{50}/CC_{50} = 25/43 μM), but its anti-BVDV and cytotoxic activities were weaker and stronger than those of **1**, respectively, resulting in a decrease of SI value from 9.21 to 1.72. This result suggests that a hydroxyl group(s) and/or a hydrogen donor(s) on the side chain(s) enhances the cytotoxic activity. Therefore, we prepared the *N*-benzyl analog of **1**, which does not possess a hydrogen donor (**3**: Fig. 1).[24] As expected, the cytotoxic activity of **1** disappeared upon N-benzylation (EC_{50}/CC_{50} = 28/>100 μM), while the anti-BVDV activity of **3** remained (though it was weaker than that of **1**).

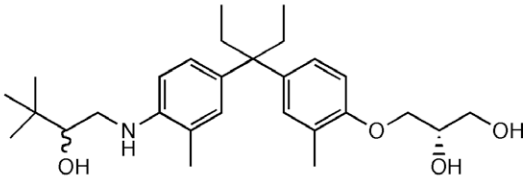
To confirm this hydrogen donor effect, several derivatives containing a hydrogen donor(s) (compounds **4**–**7**) were prepared (Fig. 2), using methods described previously.[19–22,25–28] Briefly, a bisphenol-type core skeleton was prepared by condensation of phenol or *o*-cresol with pentan-3-one or cyclohexanone. Treatment of the obtained bisphenol derivatives with aniline or *o*-toluidine gave core skeletons of **5** and **7**. The phenolic hydroxyl and/or amino group were acylated/alkylated by using usual organic synthetic methods.

All of these compounds (**4**–**7**) bearing an aryl-XH (X = O or N) group(s) showed moderate (unfavorable) cytotoxic activity with CC_{50} values of 39–50 μM, as expected. Therefore, we chose the bis-pivaloylmethyloxyphenylmethane skeleton for further structural development, and synthesized compounds **8**–**10** (Fig. 3) using the methods described previously.[19–22,29–31] As expected, compounds **8**–**10** all showed no apparent cytotoxicity (CC_{50} values of the compounds were all >100 μM) without any decrease of anti-BVDV activity (EC_{50} values of the compounds were 6.3–13.2 μM).

The anti-BVDV activity of compounds **8**–**10** decreased in the following order: **9** (cyclobutyl) > **8** (dimethyl) ≥ /≈**10** (cyclopentyl). This higher activity of **9** compared with **8** and **10** seems to be attributable to the strained geometry around the quaternary methine carbon atom. Preliminary calculation based on the MMFF 94 force field indicated that the dihedral angle between the two phenyl rings of **9** (106.9°) is smaller than those of compounds **8** and **10** (109–111°) (Fig. 4). Nevertheless, the distance between the two phenyl carbons bound to the methine carbon of **9** (2.61 Å) was calculated to be longer than those of compounds **8** and **10** (2.52–2.55 Å), because of the lengthened C–C bond between the methine carbon and the adjacent phenyl carbon of compound **9**, at least as determined with the MMFF 94 force field calculation method (Fig. 4). Of course, the calculated angles/distances may not be correct, and in fact, other calculation methods, including those based on B3LYP/3-21G, B3LYP/6-31G and MP2/6-31+G*, gave different values individually. However, regardless of the correctness of the calculated values, these considerations led us to design silyl analogs **11**–**14** (Fig. 5), in which the corresponding dihedral angles and distances were calculated to be 103–104° and 2.98–2.99 Å, respectively, by means of the same MMFF 94 force field-based calculation method (Fig. 4).

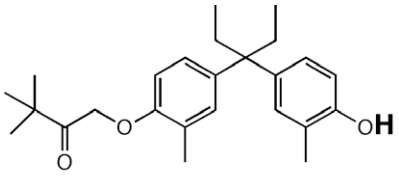


	EC_{50} (μM)	CC_{50} (μM)	SI
1: DPP-0111, R=H	8.9	82	9.21
3: R=Bn	28	>100	-

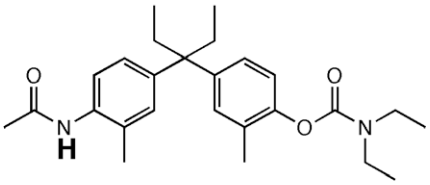


	EC_{50} (μM)	CC_{50} (μM)	SI
2: DPP-1023	25	43	1.72

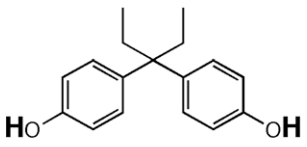
Figure 1. Anti-BVDV activity of DPP-0111 (**1**), DPP-1023 (**2**) and *N*-benzyl analog of DPP-0111 (**3**).



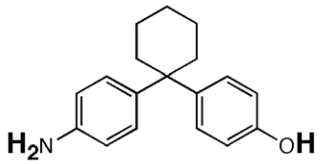
4	EC_{50} (μM)	CC_{50} (μM)	SI
	8.6	45	5.23



5	EC_{50} (μM)	CC_{50} (μM)	SI
	10	50	5.00



6	EC_{50} (μM)	CC_{50} (μM)	SI
	10	39	3.90



7	EC_{50} (μM)	CC_{50} (μM)	SI
	>42	42	-

Figure 2. Anti-BVDV activity of diphenylpentane derivatives bearing a hydrogen donor group(s).

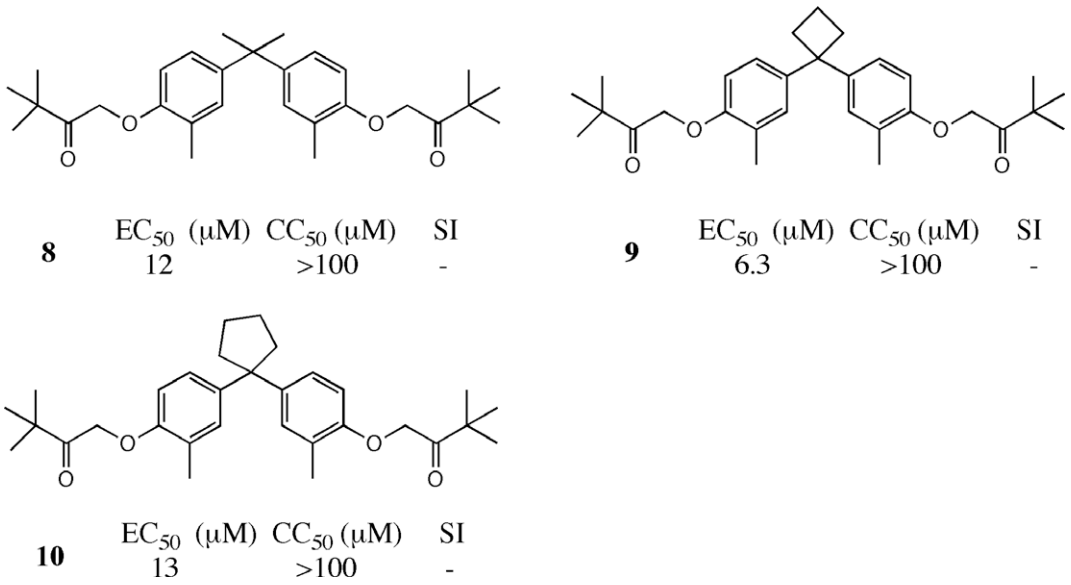


Figure 3. Anti-BVDV activity of bis-pivaloyloxyphenylmethane derivatives.

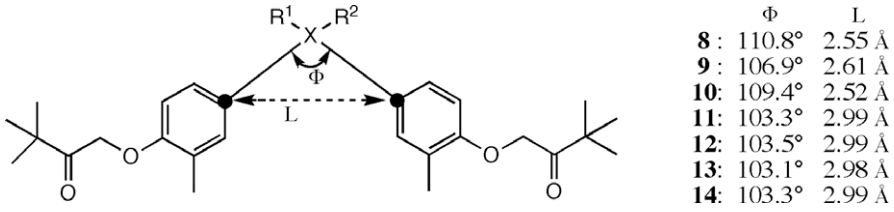


Figure 4. Dihedral angle between the two phenyl rings and distance between the two phenyl carbons bound to the nethine carbon of compounds **8**–**4** calculated based on MMFF 94 force field.

Compounds **11**–**14** were synthesized as shown in Scheme 1 by applying the method described by Tagle et al.[32] Briefly, 4-bromo-2-methylphenol (prepared from *o*-cresol by treatment with NBS in CH_3CN) or *p*-bromophenol was reacted with dichlorodiethylsilane or dichlorodimethylsilane in the presence of *n*-BuLi in THF. The resulting bisphenylsilane derivative was further treated with 1-chloropinacolone in the presence of NaH in DMF, giving compounds **11–14**.[33–36] Compound **11** showed similar activity to that

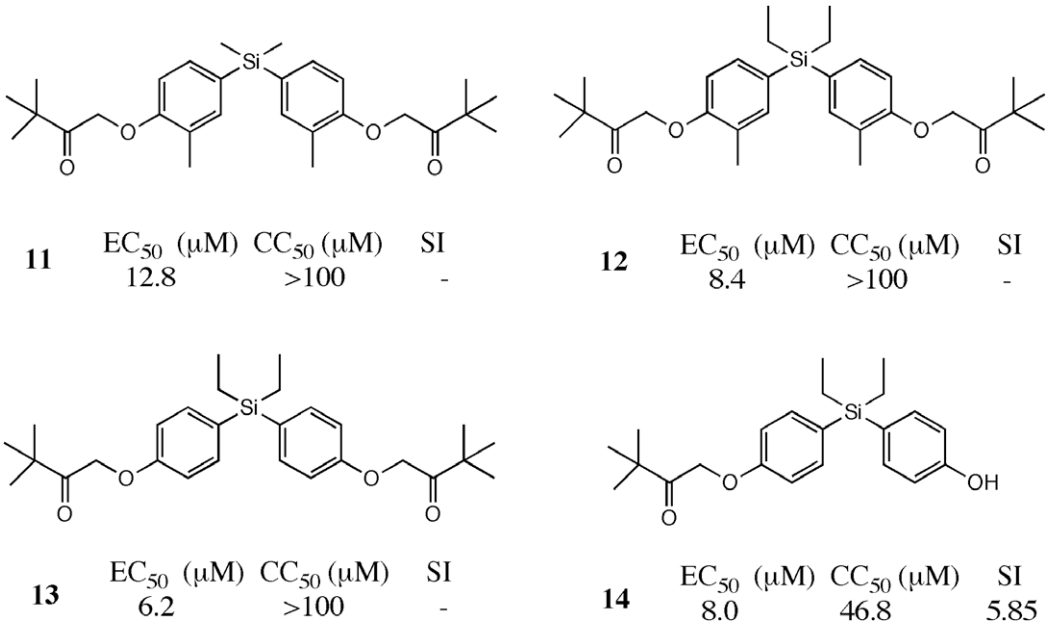
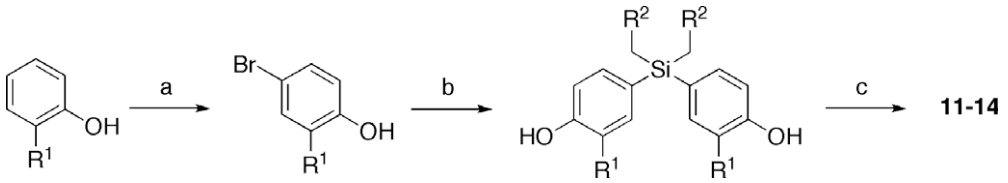


Figure 5. Anti-BVDV activity of bis-pivaloyloxyphenylsilane derivatives.



Scheme 1. R^1/R^2 = H or CH_3. Reagents and conditions: (a) NBS, CH_3CN, 75%; (b) *n*-BuLi, $SiEt_2Cl_2$ (or $SiMe_2Cl_2$), THF, 52%; (c) NAH, 1-chloropinacolone, DMF, 19%.

of the corresponding carbon analog **8**, and compounds **12** and **13** showed potent anti-BVDV activity, comparable to that of **9**, with no apparent cytotoxicity, as expected (Fig. 5). In the case of silyl analogs, the existence of a hydroxyl group, that is, compound **14**, resulted in appearance of cytotoxicity, as was the case for the carbon analogs (Fig. 2). The anti-BVDV activity and the cytotoxicity elicited by **14** are similar to those elicited by the corresponding carbon analog **4**. Although we could prepare potent anti-BVDV agents (**12** and **13**) designed based on MMFF 94 force field-based calculation, it was found to be difficult to discuss the observed structure–activity relationships by the use of other calculation methods, including B3LYP/3-21G, B3LYP/6-31G and MP2/6-31+G*. For example, calculation using B3LYP/3-21G gave a quite small differences between the dihedral angles of Ph-C-Ph and Ph-Si-Ph, that is, 110–111° and 109–110°, respectively. The distances between the two phenyl carbons bound to the methine carbon of dimethyl, diethyl, cyclobutyl and cyclopentyl derivatives were calculated to be 2.52–2.54 Å (almost no difference), and those of silyl analogs were calculated to be ca. 3.12 Å by the same B3LYP/3-21G calculation method.

In conclusion, among the compounds presented in this Letter, the cyclobutane analog (**9**) and silyl analogs (**12** and **13**) showed superior activity with EC_{50}/CC_{50} values of 6.3/>100, 8.4/>100 μM and 6.2/>100 μM, respectively. The SI values of these compounds exceeded at least 11.9, suggesting that they represent superior lead compounds for the development of novel antiviral agents. Mechanistic studies, especially identification of the target molecule(s) of compounds **9**, **12** and **13**, are under way.

Acknowledgments

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24. *1-(N-Benzyl-N-(4-(3-(4-(3,3-dimethyl-2-oxobutylhydroxy)-3-methylphenyl)pentan-3-yl)-2-methylphenyl)amino)-3,3-dimethylbutan-2-one* (**3**): Pale yellow amorphous. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 7.30–7.20 (m, 5H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.91–6.87 (m, 4H), 6.49 (d, *J* = 9.4 Hz, 1H), 4.83 (s, 2H), 4.30 (s, 2H), 3.88 (s, 2H), 2.31 (s, 3H), 2.23 (s, 3H), 2.00 (q, *J* = 7.3 Hz, 4H), 1.25 (s, 9H), 0.99 (s, 9H), 0.57 (t, *J* = 7.3 Hz, 6H). HRMS (FAB, *m/z*, $[M+H]^+$) calcd for $C_{38}H_{52}NO_3$, 570.3947; found 570.3939.
25. *1-(4-(3-(4-Hydroxy-3-methylphenyl)pentan-3-yl)-2-methylphenoxy)-3,3-dimethylbutan-2-one* (**4**): White crystals. Mp 95–97 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 691–685 (m, 4H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 8.1 Hz, 1H), 4.83 (s, 2H), 4.50 (s, 1H), 2.23 (s, 3H), 2.19 (s, 3H), 2.00 (q, *J* = 7.3 Hz, 4H), 1.25 (s, 9H), 0.59 (t, *J* = 7.3 Hz, 6H). HRMS (FAB, *m/z*, $[M+H]^+$) calcd for $C_{25}H_{34}O_3$, 382.2508; found 382.2508.
26. *4-(3-(4-Acetamido-3-methylphenyl)pentan-3-yl)-2-methylphenyl diethylcarbamate* (**5**): White foam. Mp 58–62 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$) 7.66 (d, *J* = 9.0 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 1H), 6.98–6.93 (m, 4H), 6.86 (s, 1H), 3.45 (q, *J* = 6.8 Hz, 2H), 3.38 (q, *J* = 6.8 Hz, 2H), 2.19 (s, 3H), 2.19 (s, 3H), 2.15 (s, 3H), 2.04 (q, *J* = 7.3 Hz, 4H), 1.26 (t, *J* = 6.8 Hz, 3H), 1.19 (t, *J* = 6.8 Hz, 3H), 0.59 (t, *J* = 7.3 Hz, 6H). HRMS (FAB, *m/z*, $[M+H]^+$) calcd for $C_{26}H_{37}N_2O_3$, 425.2804; found 425.2787.
27. *3,3-Bis(4-hydroxyphenyl)pentane* (**6**): White crystals. Mp 201–203 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 7.02 (d, *J* = 8.6 Hz, 4H), 6.71 (d, *J* = 8.6 Hz, 4H), 4.63 (s, 1H), 2.02 (q, *J* = 7.3 Hz, 4H), 0.60 (t, *J* = 7.3 Hz, 6H). HRMS (FAB, *m/z*, $[M+H]^+$) calcd for $C_{17}H_{20}O_2$, 256.1463; found 256.1467.
28. *4-(1-(4-Aminophenyl)cyclohexyl)phenol* (**7**): White crystals. Mp 142–143 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 7.10 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 8.6 Hz, 2H), 4.77 (br s, 1H), 3.55 (br s, 2H), 2.18–2.05 (m, 4H), 1.53–1.47 (m, 6H). HRMS (FAB, *m/z*, $[M+H]^+$) calcd for $C_{18}H_{21}NO_3$, 267.1623; found 267.1630.
29. *2,2-Bis[4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl]propane* (**8**): White crystals. Mp 119–121 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 6.99 (s, 2H), 6.93 (dd, *J* = 8.6, 2.6 Hz, 2H), 6.49 (d, *J* = 8.6 Hz, 2H), 4.84 (s, 4H), 2.25 (s, 6H), 1.59 (s, 6H), 1.25 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3/\delta$): 210.0, 154.1, 143.5, 129.6, 126.4, 124.7, 110.4, 69.5, 43.2, 41.5, 31.0, 26.3, 16.6. HRMS (FAB, $[M+H^+]$) calcd for $C_{29}H_{41}O_4$, 453.3005, found 453.3011.
30. *1,1-Bis[4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl]cyclobutane* (**9**): White solid. Mp 73–75 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 7.05 (s, 2H), 7.00 (dd, *J* = 8.6, 2.7 Hz, 2H), 6.52 (d, *J* = 8.6 Hz, 2H), 4.81 (s, 4H), 2.64 (t, *J* = 7.7 Hz, 4H), 2.26 (s, 6H), 1.91 (quint, *J* = 7.7 Hz, 2H), 1.25 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3/\delta$): 210.0, 154.1, 142.8, 128.9, 126.8, 124.1, 110.8, 69.6, 49.9, 43.2, 35.1, 26.3, 16.6, 16.5. HRMS (FAB, $[M^+]$) calcd for $C_{30}H_{40}O_4$, 464.2927, found 464.2931.
31. *1,1-Bis[4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl]cyclopentane* (**10**): White crystals. Mp 68–70 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 7.01 (s, 2H), 6.98 (dd, *J* = 8.6, 2.6 Hz, 2H), 6.48 (d, *J* = 8.6 Hz, 2H), 4.81 (s, 4H), 2.24 (s, 6H), 2.22–2.18 (m, 4H), 1.67–1.65 (m, 4H), 1.24 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3/\delta$): 210.0, 154.1, 141.8, 129.8, 126.4, 124.8, 110.5, 69.6, 54.3, 43.2, 38.8, 26.4, 23.0, 16.6. HRMS (FAB, $[M^+]$) calcd for $C_{31}H_{42}O_4$, 478.3083, found 478.3104.
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33. *Bis(3-methyl-4-(3,3-dimethyl-2-oxobutoxy)phenyl)dimethylsilane* (**11**): White crystals. Mp 120–122 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 7.27 (s, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 6.58 (d, *J* = 7.9 Hz, 2H), 4.87 (s, 4H), 2.28 (s, 6H), 1.25 (s, 18H), 0.46 (s, 6H); HRMS (FAB, *m/z*, $[M]^+$) calcd for $C_{28}H_{40}O_4Si$, 468.2696; found 468.2700.

34. *Bis(3-methyl-4-(3,3-dimethyl-2-oxobutoxy)phenyl)diethylsilane* (**12**): White crystals. Mp 88–91 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 7.25 (s, 2H), 7.22 (d, J = 8.5 Hz, 2H), 6.59 (d, J = 8.5 Hz, 2H), 4.87 (s, 4H), 2.28 (s, 6H), 1.26 (s, 18H), 0.99–0.97 (m, 10H); HRMS (FAB, m/z, $[M]^+$) calcd for $C_{30}H_{44}O_4Si$, 496.3009; found 496.2995.
35. *Bis(4-(3,3-dimethyl-2-oxobutoxy)phenyl)diethylsilane* (**13**): White crystals. Mp 40–42 °C. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 7.39 (d, J = 8.5 Hz, 4H), 6.85 (d, J = 8.5 Hz, 4H), 4.87 (s, 4H), 1.25 (s, 18H), 1.01–0.97 (m, 10H); HRMS (FAB, $[M^+]$) calcd for $C_{28}H_{40}O_4Si$, 468.2696, found 468.2700.
36. *(4-(3,3-Dimethyl-2-oxobutoxy)phenyl)(4-hydroxyphenyl)diethylsilane* (**14**): Coloress oil. ^{1}H NMR (500 MHz, $CDCl_3/\delta$): 7.49 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 4.89 (s, 2H), 4.79 (s, 1H), 1.26 (s, 9H), 1.02–0.95 (m, 10H); HRMS (FAB, $[M^+]$) calcd for $C_{22}H_{30}O_3Si$, 370.1964, found 370.1967.