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Synthesis and characterization of H-cardanol incorporated C(3)-aminoisoindolinones

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A facile and high-yielding synthesis of the hydrophobic and the hexane soluble H-cardanol incorporated C(3)-aminoisoindolinones has been successfully achieved. Additionally, the synthesis of the H-cardanol embedded tetracyclic C(3)-aminoisoindolinones has also been successfully achieved. The H-cardanol incorporated isoindolinones are low melting, lipophilic solids and readily soluble in hydrocarbon solvents - a property useful for topical administration of medicinal drugs. The UV-Vis spectra of the C(3)-aminoisoindolinones with two H-cardanol units do not indicate an intramolecular association between the two aromatic rings.

Keywords: H-Cardanol, *m*-Cresol, C(3)-Aminoisoindolinones

Hydrogenated cardanol (H-cardanol, 3-pentadecylphenol) **1** is a renewable and sustainable fine chemical derived from cashew nut shell liquid (CNSL)[1]. The CNSL is a caustic waste generated in industrial quantities during cashew nut processing[2]. Vacuum distillation of the CNSL at 2 mm and 220°C, followed by catalytic hydrogenation provides hydrogenated cardanol **1** (H-cardanol; Fig. 1)[3]. The H-cardanol **1** is a phenol with a *normal* 15-C hydrocarbon chain attached at its *meta*-position. The phenolic hydroxyl group in **1** provides a convenient handle for further chemical modification. The hydrocarbon chain incorporates unique fat-soluble and hydrophobic characteristics, and this property is extremely useful for many applications of the molecule, including topical administration of medicinal drugs[4]. Till recently researchers used H-cardanol for technological applications; particularly as a key starting material for the preparation of biocomposites[5], resins[6], surfactants[7], plasticizers[8], lubricants[9] and emulsifiers[10], *etc*. It has, however, a great potential as a fine chemical for the synthesis of medicinal drugs and agricultural chemicals[11]. For the past decade, we have been working on exploiting the synthetic potential of H-cardanol[12]. We have showcased its use in the synthesis of hydrophobic heterocyclic compounds like 4*H*-chromenes, modified fat-soluble natural products, and fat-soluble coloured molecules like porphyrins. In continuation of our work on the synthesis and characterization of isoindolinones[13], we were attracted towards the synthesis and characterization of the H-cardanol incorporated C(3)-aminoisoindolinones like **2** and **3** (Fig. 1). The C(3)-aminoisoindolinones (highlighted portion in **2**) are nitrogen incorporated heterocyclic compounds with a wide range of applications in medicinal and pharmaceutical fields[14]. For example, tetracyclic C(3)-aminoisoindolinone **4** is a potent anti-tumour agent[15]. The tricyclic isoindolinone **5** is an experimental anti-viral drug used for treatment against the infections caused by the respiratory syncytial virus (RSV)[16]. Some of the C(3)-substituted isoindolinones show anticancer activity by inhibiting interactions between MDM2-p53 proteins; the interactions are essential prerequisite for cell division[17]. Moreover, the molecules built on isoindolinone core exhibit anti-inflammatory[18], antihypertensive[19], antipsychotic[20], antiulcer[21], antirheumatics[22], antitussives[23], and anorectic activity[24]. We think that the fat-soluble molecules like **2** and **3**, having an isoindolinone head group, will form micelles and become useful in topical drug delivery[25]. Herein we report a facile synthesis and characterization of the isoindolinones like **2-3**.

Results and Discussion

The H-cardanol based amine **6a** is the starting compound for our work. We prepared it from H-cardanol **1a** by following the three-step protocol (Scheme 1). In the first step, H-cardanol **1a** was

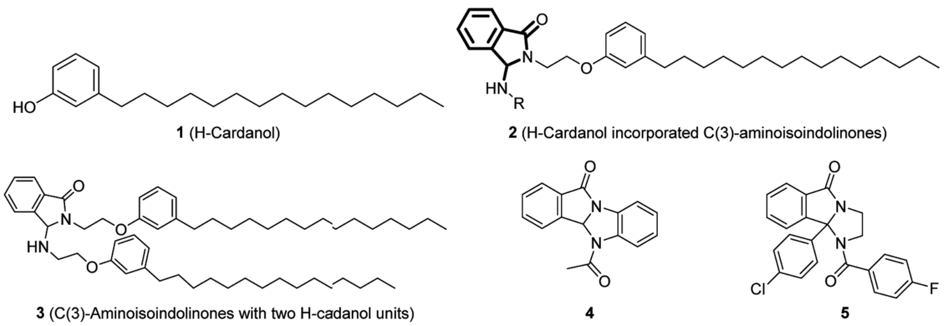
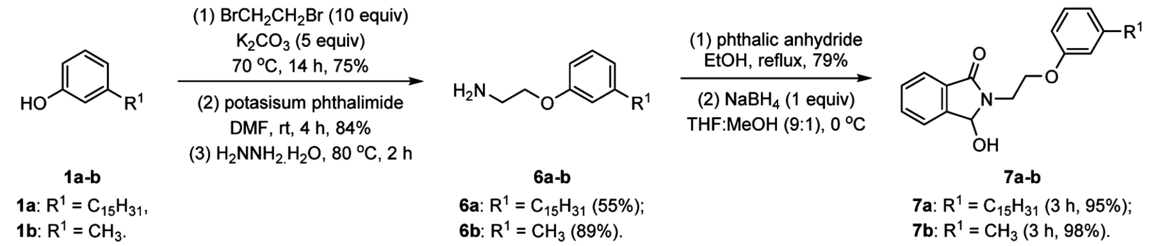
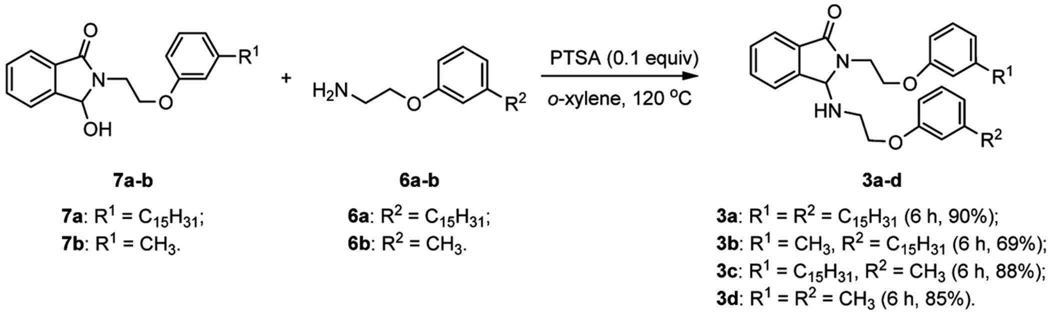


Fig. 1 — Structures of H-cardanol **1**, H-cardanol incorporated C(3)-aminoisoindolinone **2**, C(3)-aminoisoindolinone with two H-cardanol units **3** and lead candidates **4** and **5**



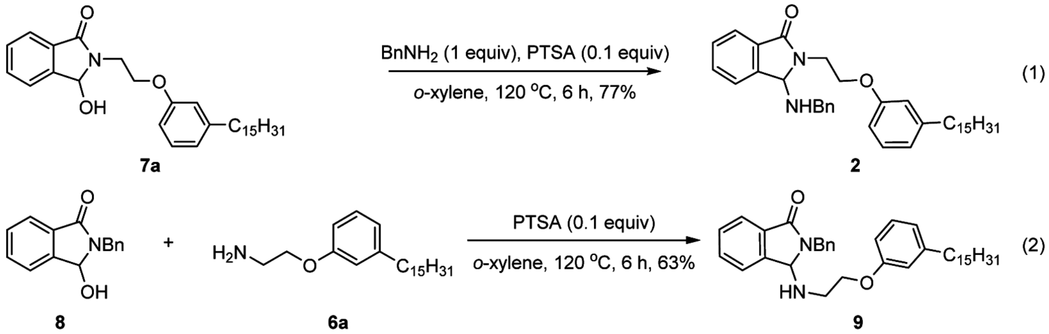
Scheme 1 — Synthesis of H-cardanol and *m*-cresol incorporated C(3)-hydroxyl isoindolinones



Scheme 2 — Synthesis of H-cardanol and *meta*-cresol incorporated C(3)-aminoisoindolinones

converted into the two-carbon homologated bromide by treating with 1,2-dibromoethane[26]. In the second step, the reaction of the bromide with potassium phthalimide delivered phthalimide bound H-cardanol. This derivative upon treatment with hydrazine provided H-cardanol derived amine **6a** in good yield (overall 55%). Our procedure is higher-yielding and less cumbersome compared to the reported method[27]. The reaction of the amine **6a** with phthalic anhydride provided the phthalimide which upon reduction with sodium borohydride furnished the C(3)-hydroxyl isoindolinone **7a** in 95% yield. For the purposes of comparison of properties of the isoindolinones with the 15C chain of H-cardanol *e.g.*, **3a** (Scheme 2) with those of the isoindolinones without the chain *e.g*. **3d** (Scheme 2) we prepared the *meta*-cresol incorporated C(3)-hydroxy isoindolinone **7b** from the amine **6b**.

The reaction of C(3)-hydroxyl isoindolinone **7a** with benzylamine under *p*-tolunesulfonic acid (PTSA) catalysis in *o*-xylene at 120°C according to the procedure we have previously developed[28], delivered H-cardanol incorporated isoindolinone **2** as a white solid in 77% yield (**Equation 1**, Scheme 3). The structure of **2** was confirmed on the basis of its spectra (IR, ^{1}H, ^{13}C, DEPT-135 NMR and HRMS). Its IR spectrum displayed a strong band at 1695 cm^{-1} for the lactam carbonyl group. The characteristic singlet for C(3)H at δ 5.81 ppm, and the signals displaying ddd, and dd pattern for benzylic CH$_2$ at 3.67 ppm and 3.47 ppm and a broad singlet accounting for 24H



Scheme 3 — Synthesis of H-cardanol and benzyl group incorporated isoindolinones

at 1.29 ppm in its ^{1}H NMR spectrum supported the assigned structure. The ^{13}C NMR spectrum of **2** displayed signals for the lactam C(1) at 167.9 ppm and C(3) at 74.2 ppm. As anticipated, there were sixteen signals in the aromatic region. The reaction of the isoindolinone **8**, which has a benzyl substitution at N(2) with the **6a** provided **9** (an isomer of **2**) in 63% yield (**Equation 2**, Scheme 3). The isoindolinones **2** and **9** were readily and highly soluble in hexane and move with hexane in SiO_2 TLC / column chromatography.

After demonstrating facile synthesis of the mono-H-cardanol incorporated isoindolinones, we targeted the preparation of the isoindolinones **3a**, which has two H-cardanol units (Scheme 2). Simultaneously, we have also targeted three more isoindolinones **3b-d**, having one / two units of *meta*-cresol (Scheme 2). The PTSA catalysed displacement of C(3)OH in **7a** with the H-cardanol derived primary amine **6a** furnished the *bis*-H-cardanol incorporated isoindolinone **3a** in 90% yield as a waxy solid. The ^{1}H NMR spectrum of **3a** displayed C(3)H of isoindolinone at 5.7 ppm as a singlet, and $(CH_2)_{24}$ at 1.27 as a broad singlet. The diastereotopic OCH_2 and NCH_2 signals appeared in two sets, six out of eight of them appeared between 3.6-4.4 ppm as multiplet and two of them appeared at 2.7 ppm. This differentiation could be due to the shielding effect of the neighbouring phenyl rings on the hydrogens of methylene of the adjacent H-cardanol unit. The ^{13}C NMR spectrum of **3a** displayed a signal at 167 ppm due to lactam carbonyl, two signals at 158 ppm due to two (Ar)$\underline{C}$-O and two signals at 67 and 73 due to O$\underline{C}H_2$ carbons. Three more reactions of **7a**/**7b** with the H-cardanol derived primary amine **6a** or *m*-cresol derived primary amine **6b** furnished isoindolinones **3b-d** in good yield (Scheme 2). The spectra of **3b-d** matched well with the parent **2**. The isoindolinone **3a** with two H-cardanol units were a waxy solid (Mp = 30-32°C). It was highly soluble in hexane and was sparingly soluble in methanol. On the other hand, the isoindolinones **3b** and **3c** which have one unit of 15C chain were semisolids. Both of them were freely soluble in hexane. The isoindalone **3d**, which has two *meta*-cresol units was a white crystalline solid with a sharp melting point (Mp = 98°C). It was nearly insoluble in hexane.

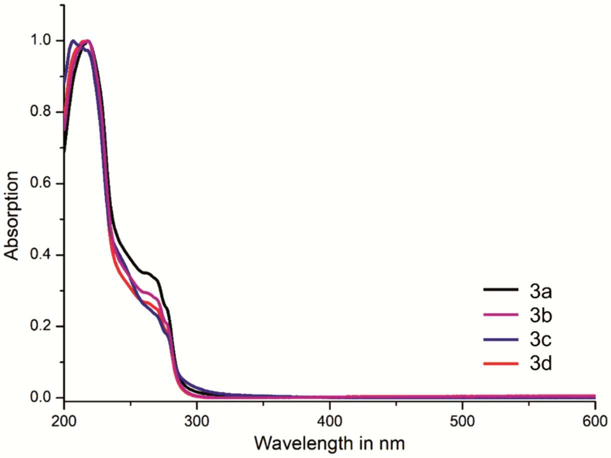


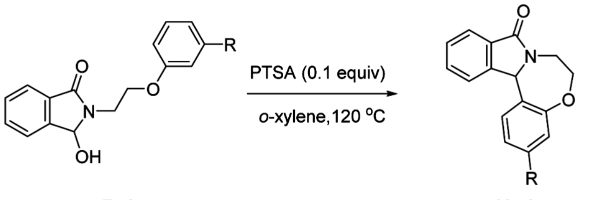
Fig. 2 — UV-Vis spectra of H-cardanol incorporated isoindolinones **3a-d** in MeOH

Molecules like **3** have two phenyl rings in the neighbourhood, suitably positioned for exhibiting stabilizing stacking interactions. To further consolidate the stacking interactions between two phenyl rings, the 15C chains present in **3a** may exhibit stabilizing hydrophobic interactions. We recorded UV-Vis spectra of 1μ molar solutions of **3a-d** in MeOH (Fig. 2), a solvent in which the aggregation of the isoindolinones were expected to be maximum. The spectra showed two maxima, one at about 220 nm due to Ar-C=O substructure and the other a series of maxima at about 272 nm due to the aromatic rings. There was no bathochromic shift in the absorption maxima of **3a** which has two H-cardanol units. However, there was a noticeable hyperchromic effect. The data indicated that there were no significant intramolecular hydrophobic interactions of consequence.

Reflecting our interest in the utilization of hydrogenated cardanol in synthesis, we carried out PTSA catalysed intramolecular cyclization reaction of **7a** to realize tetracyclic product **10a** in excellent yield (Scheme 4). For purposes of comparison of spectral data we repeated the reaction on **7b** which had *m*-cresol moiety, to realize **10b** in excellent yield. As anticipated, the isoindolinone **10a** was readily soluble in hexane and was stable at RT.

Experimental Section

The melting points were recorded with an open-ended capillary tube with a VEEGO VMP-DS instrument and is uncorrected. The progress of all reactions were monitored by TLC using hexanes and ethyl acetate mixture as eluent. Silica gel G and GF 254 and glass plates were used for making analytical TLC plates. The spots were visualized through short exposure to iodine vapor or UV light. Column chromatography was performed on silica gel (100-200 mesh) using increasing percentages of ethyl acetate in hexanes. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and DEPT-135 spectra were recorded for $CDCl_3$ or DMSO-d_6 with a Bruker Avance 400 spectrometer with TMS as the internal standard. UV-Vis spectra were recorded in MeOH as a solvent using a Shimadzu UV-2450 double-beam spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6350 B Q-TOF mass spectrometer using electrospray ionization mode. IR spectra were recorded as KBr pellets with a Nicolet-6700 FT-IR spectrometer. Cardanol oil was purchased from Sabari Industries Sedurapet, Puducherry, India. Cardanol was hydrogenated using the Parr hydrogenation apparatus at the Indian Institute of Technology Madras, Chennai to obtain H-cardanol.



7a-b

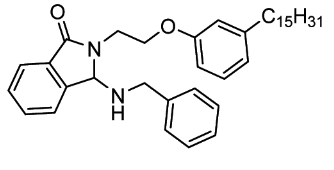
7a: R = $C_{15}H_{31}$;
7b: R = CH_3.

10a-b

10a: R = $C_{15}H_{31}$ (2 h, 96%);
10b: R = CH_3 (1 h, 92%).

Scheme 4 — Intramolecular cyclization of H-cardanol incorporated isoindolinones

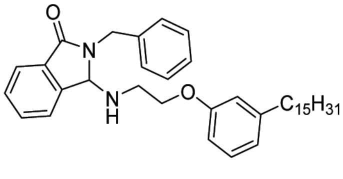
General procedure for the synthesis of 3-(benzylamino)-2-(2-(3-pentadecyl phenoxy)ethyl) isoindolin-1-one, 2



2

An oven-dried round bottom flask connected to a reflux condenser was charged with 3-hydroxy-2-(2-(3-pentadecylphenoxy)ethyl)isoindolin-1-one **7a** (100 mg, 0.20 mmol), benzylamine (22 mg, 0.20 mmol) and *p*-toluenesulfonic acid (3.5 mg, 0.02 mmol). To this 5 mL of *o*-xylene was added. The round bottom flask was lowered into a preheated (120°C) oil bath. The resulting reaction mixture was agitated by using magnetic stirrer. Upon completion of the reaction (TLC, 6 h), the reaction mixture was cooled to RT, and PTSA was quenched with solid $NaHCO_3$ (10 mg). The solvent was evaporated by using a rotary evaporator. The crude products were directly subjected to column chromatography to afford 3-(benzylamino)-2-(2-(3-pentadecylphenoxy) ethyl)isoindolin-1-one **2** as a white solid (91 mg, 77% yield). m.p.60°C. IR (KBr): 3391, 2924, 2854, 1695, 1596, 1511, 1465, 1391, 1246, 1157, 1045, 748, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.4 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.51 (td, *J* = 7.3, 1.0 Hz, 1H), 7.32 – 7.29 (m, 2H), 7.27 – 7.23 (m, 3H), 7.21 – 7.16 (m, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.69 (dd, *J* = 3.8, 1.7 Hz, 2H), 5.81 (s, 1H), 4.33 – 4.28 (m, 1H), 4.27 – 4.19 (m, 2H), 3.67 (ddd, *J* = 13.0, 8.6, 3.8 Hz, 1H), 3.47 (d, *J* = 13.1 Hz, 1H), 3.28 (d, *J* = 13.1 Hz, 1H), 2.57 – 2.52 (m, 2H), 1.78 (s, 1H), 1.60 – 1.51 (m, 2H), 1.29 (s, 24H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9 (C), 158.1 (C), 144.8 (C), 143.3 (C), 139.7 (C), 132.7 (C), 131.9 (CH), 129.3 (CH), 129.1 (CH), 128.4 (CH), 128.0 (CH), 127.1 (CH), 123.3 (CH), 123.2 (C), 121.4 (CH), 114.5 (CH), 111.2 (CH), 74.2 (CH), 67.4 (CH_2), 45.2 (CH_2), 38.7 (CH_2), 36.0 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.68 (CH_2), 29.61 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI): *m/z* Calcd for $C_{38}H_{53}N_2O_2$ (M + H) 569.4107. Found: 569.4087.

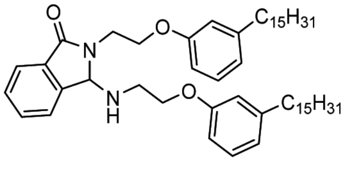
2-Benzyl-3-((2-(3-pentadecylphenoxy) ethyl)amino) isoindolin-1-one, 9



9

White solid (152 mg, 63% yield). m.p.58°C. IR (KBr): 3388, 2920, 2849, 1689, 1598, 1510, 1467, 1392, 1247, 1158, 1046, 749, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.88 (m, 1H), 7.87 (d, *J* = 7.1 Hz, 1H), 7.54 – 7.52 (m, 1H), 7.44 (d, *J* = 6.8 Hz, 1H), 7.21 – 7.17 (m, 4H), 7.13 (d, *J* = 2.5 Hz, 1H), 6.99 (s, 1H), 6.76 (dd, *J* = 16.1, 7.5 Hz, 1H), 6.51 (d, *J* = 9.0 Hz, 1H), 6.43 – 6.32 (m, 1H), 5.46 (s, 1H), 5.37 (d, *J* = 15.4 Hz, 2H), 4.35 (dd, *J* = 22.0, 15.7 Hz, 2H), 3.71 (t, *J* = 5.0 Hz, 1H), 3.52 (t, *J* = 5.2 Hz, 1H), 3.01 (s, 1H), 2.52 (dd, *J* = 14.3, 7.6 Hz, 2H), 1.75 (s, 1H), 1.56 (s, 2H), 1.25 (s, 23H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7 (C), 158.1 (C), 144.7 (C), 136.6 (C), 132.6 (C), 131.9 (C), 129.7 (CH), 128.9 (CH), 128.7 (CH), 127.6 (CH), 127.4 (CH), 126.9 (CH), 124.2 (CH), 123.8 (CH), 121.2 (CH), 114.4 (CH), 111.0 (CH), 76.2 (CH), 66.6 (CH_2), 43.4 (CH_2), 36.0 (CH_2), 31.9 (CH_2), 31.5 (CH_2), 31.4 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI): *m/z* Calcd for $C_{38}H_{53}N_2O_2$ (M + H) 569.4107. Found: 569.4087.

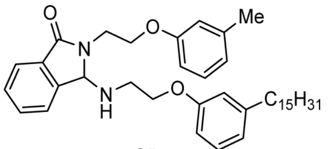
2-(2-(3-Pentadecylphenoxy)ethyl)-3-((2-(3-pentadecylphenoxy)ethyl)amino)isoindolin-1-one, 3a



3a

Waxy solid (152 mg, 90% yield). m.p.32°C. IR (KBr): 3356, 2926, 2855, 1694, 1595, 1456, 1403, 1258, 1157, 1049, 778, 742, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.4 Hz, 1H), 7.59 (m, 1H), 7.59 – 7.53 (m, 1H), 7.52 – 7.46 (m, 1H), 7.17 (td, *J* = 8.0, 3.6 Hz, 2H), 6.77 (dd, *J* = 10.9, 10.3 Hz, 3H), 6.73 – 6.62 (m, 3H), 5.78 (s, 1H), 4.35 – 4.18 (m, 3H), 3.94 (dt, *J* = 7.1, 5.2 Hz, 2H), 3.71 – 3.61 (m, 1H), 2.73 (dt, *J* = 12.3, 5.9 Hz, 1H), 2.57 – 2.52 (m, 4H), 2.36 (dt, *J* = 12.6, 4.1 Hz, 1H), 1.58 (dd, *J* = 13.7, 7.0 Hz, 4H), 1.31 – 1.23 (m, 48H), 0.89 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8 (C), 158.5 (C), 158.2 (C), 144.9 (C), 144.7 (C), 143.36 (C), 132.8 (C), 131.8 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 123.35 (CH), 123.30 (CH), 121.4 (CH), 121.2 (CH), 114.8 (CH), 114.5 (CH), 111.3 (CH), 111.2 (CH), 73.9 (CH), 67.3 (CH_2), 40.0 (CH_2), 38.5 (CH_2), 36.0 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 29.74 (CH_2), 29.71 (CH_2), 29.6 (CH_2), 29.58 (CH_2), 29.57 (CH_2), 29.43 (CH_2), 29.41 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI): *m/z* Calcd for $C_{54}H_{85}N_2O_3$ (M + H) 809.6560. Found: 809.6547.

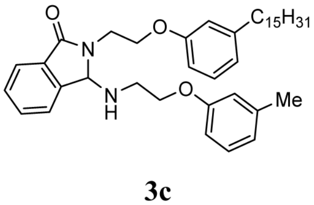
3-((2-(3-Pentadecylphenoxy)ethyl)amino)-2-(2-(*m*-tolyloxy)ethyl)isoindolin-1-one, 3b



3b

Waxy solid (150 mg, 69% yield). IR (KBr): 3351, 3046, 2923, 1696, 1596, 1458, 1405, 1259, 1158, 1049, 875, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 20.6, 7.5 Hz, 1H), 7.60 (dd, *J* = 15.9, 7.9 Hz, 2H), 7.54 – 7.46 (m, 1H), 7.21 – 7.10 (m, 2H), 6.81 – 6.65 (m, 6H), 5.78 (s, 1H), 4.34 – 4.17 (m, 3H), 3.95 (d, *J* = 4.2 Hz, 2H), 3.73 – 3.59 (m, 1H), 2.77 – 2.68 (m, 1H), 2.56 (d, *J* = 7.1 Hz, 2H), 2.42 – 2.34 (m, 1H), 2.33 – 2.27 (m, 3H), 1.58 (s, 2H), 1.28 (s, 25H), 0.92 – 0.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9 (C), 158.5 (C), 158.2 (C), 144.7 (C), 143.3 (C), 139.7 (C), 132.8 (C), 131.8 (CH), 129.3 (CH), 129.2 (CH), 129.16 (CH), 129.13 (CH), 123.3 (CH), 122.0 (CH), 121.2 (CH), 115.2 (CH), 114.8 (CH), 111.3 (CH), 111.1 (CH), 73.9 (CH), 67.39 (CH_2), 67.34 (CH_2), 40.0 (CH_2), 38.5 (CH_2), 38.4 (CH_2), 36.0 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 29.7 (CH_2), 29.69 (CH_2), 29.64 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 22.7 (CH_2), 21.5 (CH_3), 14.1 (CH_3); HRMS (ESI): *m/z* Calcd for $C_{40}H_{57}N_2O_3$ (M + H) 613.4369. Found: 613.4350.

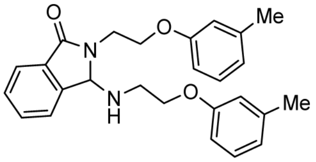
2-(2-(3-Pentadecylphenoxy)ethyl)-3-((2-(*m*-tolyloxy) ethyl)amino)isoindolin-1-one, 3c



3c

Waxy solid (112 mg, 88% yield). IR (KBr): 3343, 2924, 2855, 1694, 1595, 1458, 1403, 1259, 1159, 1049, 776, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 16.1, 7.5 Hz, 1H), 7.59 (dd, *J* = 15.6, 7.7 Hz, 2H), 7.51 (dd, *J* = 14.9, 7.3 Hz, 1H), 7.25 (s, 1H), 7.23 – 7.10 (m, 2H), 6.78 (dd, *J* = 10.1, 6.3 Hz, 3H), 6.69 (d, *J* = 11.8 Hz, 2H), 5.78 (d, *J* = 16.0 Hz, 1H), 4.26 (dd, *J* = 17.3, 9.3 Hz, 3H), 3.94 (dd, *J* = 10.7, 5.1 Hz, 2H), 3.75 – 3.54 (m, 1H), 2.81 – 2.65 (m, 1H), 2.60 – 2.49 (m, 2H), 2.38 (dd, *J* = 13.5, 9.6 Hz, 1H), 2.32 (d, *J* = 16.1 Hz, 3H), 1.86 (s, 1H), 1.57 (s, 2H), 1.26 (d, 16 Hz, 24H), 0.89 (dd, *J* = 9.4, 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8 (C), 158.5 (C), 158.2 (C), 144.9 (C), 143.3 (C), 139.5 (C), 132.8 (C), 131.8 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 123.3 (CH), 123.2 (CH), 121.8 (CH), 121.4 (CH), 115.3 (CH), 114.6 (CH), 111.3 (CH), 111.2 (CH), 73.9 (CH), 67.37 (CH_2), 67.36 (CH_2), 40.0 (CH_2), 38.5 (CH_2), 38.4 (CH_2), 36.0 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 29.71 (CH_2), 29.70 (CH_2), 29.68 (CH_2), 29.62 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 22.7 (CH_2), 21.5 (CH_3), 14.1 (CH_3); HRMS (ESI): *m/z* Calcd for $C_{40}H_{57}N_2O_3$ (M + H) 613.4369. Found: 613.4346.

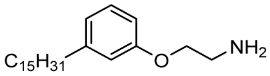
2-(2-(*m*-Tolyloxy)ethyl)-3-((2-(*m*-tolyloxy)ethyl) amino)isoindolin-1-one, 3d



3d

White solid (125 mg, 85% yield). m.p.98°C. IR (KBr): 3342, 3039, 2926, 1690, 1596, 1479, 1404, 1259, 1161, 1050, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.4 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.50 (qd, *J* = 6.8, 2.3 Hz, 1H), 7.15 (td, *J* = 7.8, 3.8 Hz, 2H), 6.77 (d, *J* = 7.5 Hz, 2H), 6.74 – 6.63 (m, 4H), 5.76 (s, 1H), 4.32 – 4.17 (m, 3H), 3.96 – 3.87 (m, 2H), 3.65 (ddd, *J* = 13.3, 8.9, 3.8 Hz, 1H), 2.76 – 2.67 (m, 1H), 2.36 (dt, *J* = 12.6, 4.3 Hz, 2H), 2.30 (d, *J* = 3.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8 (C), 158.5 (C), 158.2 (C), 143.3 (C), 139.7 (C), 139.5 (C), 132.8 (C), 131.8 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 123.34 (CH), 123.30 (CH), 122.0 (CH), 121.8 (CH), 115.4 (CH), 115.2 (CH), 111.3 (CH), 111.1 (CH), 73.9 (CH), 67.4 (CH_2), 67.3 (CH_2), 40.0 (CH_2), 38.5 (CH_2), 21.5 (CH_3), 21.4 (CH_3); HRMS (ESI): *m/z* Calcd for $C_{26}H_{29}N_2O_3$ (M + H) 417.2178. Found: 417.2161.

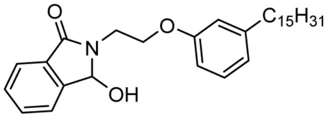
General procedure for the synthesis of 2-(3-pentadecylphenoxy)ethan-1-amine, 6a



6a

To a suspension of 2-(2-(3-pentadecylphenoxy)ethyl)isoindoline-1,3-dione (500 mg, 1.0 mmol) in CH_3CN (20 mL) was added $NH_2NH_2.H_2O$ (262 mg, 5.2 mmol), and the mixture was stirred at 70 °C for 2 h. The reaction medium was cooled to 0°C, filtered, and the filtrate was concentrated under reduced pressure to give 2-(3 pentadecylphenoxy) ethan-1-amine **6a** as a yellow oil (200 mg, 55% yield). IR (KBr): 3443, 2924, 2855, 1633, 1454, 1260, 1034, 607 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (t, *J* = 7.8 Hz, 1H), 6.81 – 6.67 (m, 3H), 3.97 (t, *J* = 5.2 Hz, 2H), 3.07 (t, *J* = 5.2 Hz, 2H), 2.60 – 2.54 (m, 2H), 1.67 (s, 2H), 1.63 – 1.57 (m, 2H), 1.26 (s, 24H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9 (C), 144.7 (C), 129.2 (CH), 121.1 (CH), 114.8 (CH), 111.5(CH), 70.0 (CH_2), 41.7 (CH_2), 36.1 (CH_2), 32.0 (CH_2), 31.5 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.77 (CH_2), 29.70 (CH_2), 29.6 (CH_2), 29.47 (CH_2), 29.46 (CH_2), 22.7 (CH_2), 14.2 (CH_3); HRMS (ESI): *m/z* Calcd for $C_{23}H_{42}NO$ (M + H) 348.3266. Found: 348.3280.

General procedure for the synthesis of 3-hydroxy-2-(2-(3-pentadecylphenoxy)ethyl) isoindolin-1-one, 7a

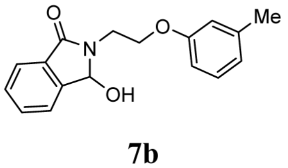


7a

To a stirred solution of 2-(2-(3-pentadecylphenoxy)ethyl)isoindoline-1,3-dione (100 mg, 0.20 mmol) in a mixture of tetrahydrofuran and methanol (9:1 mL) was added sodium borohydride (8 mg, 0.20 mmol) over 10 min at -10°C. The resulting mixture was stirred at -10°C for 3 h. Subsequently, excess sodium borohydride was quenched with aqueous 3 N HCl (2 mL). The solvent was evaporated under reduced pressure resulting in a white solid which was washed with water to provide 3-hydroxy-2-(2-(3-pentadecylphenoxy)ethyl) isoindolin-1-one **7a** (95 mg, 95% yield). m.p.78°C. IR (KBr): 3403, 2921, 2851, 1692, 1596, 1455, 1385, 1330, 1258, 1167, 1048, 784, 736, 690 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.73 (d, *J* = 7.5 Hz, 1H), 7.65 – 7.53 (m, 2H), 7.48 (td, *J* = 7.3, 1.3 Hz, 1H), 7.21 – 7.12 (m, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.74 – 6.66 (m, 2H), 6.00 (s, 1H), 4.26 – 4.14 (m, 2H), 3.99 – 3.91 (m, 1H), 3.88 – 3.81 (m, 1H), 2.62 – 2.47 (m, 2H), 1.56 (dd, *J* = 14.8, 7.2 Hz, 2H), 1.26 (d, *J* = 12.3 Hz, 24H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7 (C), 158.0 (C), 144.9 (C), 144.0 (C), 132.3 (CH), 131.2 (C), 129.7 (CH), 129.3 (CH), 123.37 (CH), 123.32 (CH), 121.6 (CH), 114.6 (CH), 111.3 (CH), 82.9 (CH), 66.7 (CH_2), 39.4 (CH_2), 36.0 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI): *m/z* Calcd for $C_{31}H_{46}NO_3$ (M + H) 480.3478. Found: 480.3482.

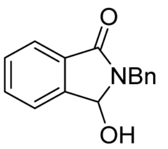
3-Hydroxy-2-(2-(*m*-tolyloxy)ethyl)isoindolin-1-one, 7b



7b

White solid (98 mg, 98% yield). m.p.125°C. IR (KBr): 3339, 3034, 2935, 2872, 1649, 1608, 1437, 1296, 1257, 1158, 1054, 951, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.61 – 7.50 (m, 2H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.67 (dd, *J* = 11.2, 3.0 Hz, 2H), 5.97 (s, 1H), 4.41 (s, 1H), 4.12 (t, *J* = 5.1 Hz, 2H), 3.88 – 3.67 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8 (C), 158.0 (C), 144.1 (C), 139.6 (C), 132.3 (CH), 131.1 (C), 129.6 (CH), 129.3 (CH), 123.3 (CH), 123.2 (CH), 122.2 (CH), 115.3 (CH), 111.2 (CH), 82.9 (CH), 66.5 (CH_2), 39.2 (CH_2), 21.4 (CH_3); HRMS (ESI): *m/z* Calcd for $C_{17}H_{18}NO_3$ (M + H) 284.1287. Found: 284.1285.

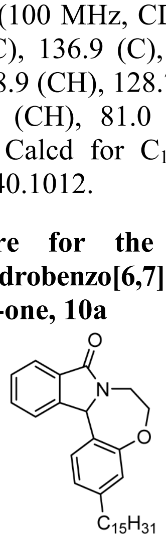
2-Benzyl-3-hydroxyisoindolin-1-one, 8



8

White solid (99 mg, 98% yield). m.p.138°C. IR (KBr): 3204, 2929, 2703, 1661, 1440, 1309, 1212, 1114, 1056, 918, 792, 745, 698, 519 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1): δ 7.56 – 7.53 (m, 3H), 7.53 – 7.50 (m, 1H), 7.43 – 7.40 (m, 1H), 7.27 (d, *J* = 4.3 Hz, 2H), 7.25 – 7.20 (m, 2H), 5.52 (d, *J* = 8 Hz, 1H), 4.67 (d, *J* = 14.7 Hz, 2H), 4.12 (d, *J* = 14.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1): δ 167.5 (C), 144.4 (C), 136.9 (C), 132.3 (CH), 131.3 (C), 129.6 (CH), 128.9 (CH), 128.7 (CH), 127.8 (CH), 123.6 (CH), 123.5 (CH), 81.0 (CH), 42.5 (CH_2); HRMS (ESI): *m/z* Calcd for $C_{15}H_{14}NO_2$ (M + H) 240.1025. Found: 240.1012.

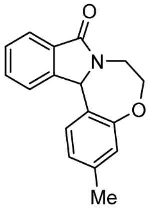
General procedure for the synthesis of 3-pentadecyl-6,7-dihydrobenzo[6,7][1,4] oxazepino[5,4-a]isoindol-9(13b*H*)-one, 10a



10a

The reaction tube was charged with 3-hydroxy-2-(2-(3-pentadecyl phenoxy)ethyl) isoindolin-1-one (100 mg, 0.20 mmol), and *p*-toluenesulfonic acid (4 mg, 0.02 mmol). To this 5 mL of *o*-xylene was added. The reaction tube was kept stirring at 120°C for 2 h. Upon completion of the reaction (observed on TLC), the reaction mixture was cooled to RT and PTSA was quenched with solid $NaHCO_3$ (10 mg). The solvent was evaporated by using a rotary evaporator. The crude product was directly subjected to column chromatography to give 3-pentadecyl-6,7-dihydrobenzo[6,7][1,4]oxazepino [5,4-*a*]isoindol-9(13*bH*)-one as a waxy solid (93 mg, 96% yield). IR (KBr): 3456, 2912, 2852, 1698, 1615, 1464, 1399, 1296, 1255, 1146, 1043, 746, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.5 Hz, 1H), 7.69 – 7.52 (m, 3H), 6.98 (dd, *J* = 9.8, 4.8 Hz, 2H), 6.82 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.79 (s, 1H), 4.59 – 4.43 (m, 2H), 3.96 – 3.83 (m, 1H), 3.69 (ddd, *J* = 14.3, 11.2, 3.5 Hz, 1H), 2.59 – 2.51 (m, 2H), 1.63 – 1.53 (m, 2H), 1.34 – 1.22 (m, 24H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1 (C), 159.8 (C), 145.3 (C), 142.3 (C), 132.7 (C), 131.1 (CH), 128.7 (CH), 126.9 (C), 126.8 (CH), 124.9 (CH), 124.5 (CH), 124.1 (CH), 122.0 (CH), 71.8 (CH_2), 61.5 (CH), 44.4 (CH_2), 35.3 (CH_2), 31.94 (CH_2), 31.19 (CH_2), 29.7 (CH_2), 29.69 (CH_2), 29.67 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI): *m/z* Calcd for $C_{31}H_{44}NO_2$ (M + H) 462.3372. Found: 462.3367.

3-Methyl-6,7-dihydrobenzo[6,7][1,4]oxazepino[5,4-a]isoindol-9(13b*H*)-one, 10b



10b

White solid (86 mg, 92% yield). m.p.105°C. IR (KBr): 3476, 3041, 2924, 1698, 1613, 1409, 1294, 1151, 1115, 1048, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.64 (dd, *J* = 10.6, 4.3 Hz, 1H), 7.59 – 7.45 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.77 (s, 1H), 4.55 – 4.40 (m, 2H), 3.86 (dd, *J* = 16.7, 7.4 Hz, 1H), 3.68 (dd, *J* = 13.1, 9.1 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1 (C), 159.7 (C), 142.3 (C), 140.2 (C), 132.7 (C), 131.1 (CH), 128.7 (CH), 126.8 (CH), 126.7 (C), 124.87 (CH), 124.80 (CH), 124.4 (CH), 122.8 (CH), 71.8 (CH_2), 61.4 (CH), 44.4 (CH_2), 20.9 (CH_3); HRMS (ESI): *m/z* Calcd for $C_{17}H_{16}NO_2$ (M + H) 266.1181. Found: 266.1178.

Conclusions

We demonstrated a facile and high-yielding synthesis of H-cardanol and *m*-cresol incorporated C(3)-aminoisoindolinones. Furthermore, we have developed H-cardanol embedded tetracyclic C(3)-aminoisoindolinone by intramolecular cyclization. The absorption properties of H-cardanol or *m*-cresol incorporated C(3)-aminoisoindolinones were evaluated using UV-Vis spectra. Hopefully, the H-cardanol bound isoindolinones will find application as drug delivery vehicles and also as soft materials.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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