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ORIGINAL PAPER

Synthesis, antibacterial and antioxidant activity of novel 2,3-dihydroquinazolin-4(1*H*)-one derivatives of dehydroabietylamine diterpene

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Abstract A series of novel 2,3-dihydroquinazolin-4(1*H*)-ones was synthesized by a three-component reaction between dehydroabietylamine (DHA) diterpene, isatoic anhydride and different aromatic aldehydes in the presence of a catalytic amount of *p*-toluenesulfonic acid (13 mol%). Diastereomeric products were separated by preparative thin-layer chromatography and their structures were characterized by ^{1}H and ^{13}C NMR, HMQC, IR and HR-ESI-MS. Antioxidant activities of the synthesized compounds were assessed by two different methods including DPPH and β-carotene-linoleic acid bleaching assays. Antibacterial activities of the compounds were also evaluated against two Gram-positive and one Gram-negative bacterial strains and in the case of *Bacillus cereus* a considerable inhibitory effect (MIC 4–16 μg/ml) was observed.

Keywords 2,3-Dihydroquinazolin-4(1*H*)-ones · Dehydroabietylamine · Diastereomers · Multi-component reaction

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Introduction

2,3-Dihydroquinazolin-4(1*H*)-ones are a class of heterocyclic compounds which have attracted much attention because of their wide range of medicinal and pharmaceutical activities such as antibacterial [1], anticancer [2, 3], antifungal [4], antimalarial [5] and diuretic [6, 7]. Synthesis of this class of compounds has been carried out with different methods including a three-component coupling of isatoic anhydride, primary amines, and aldehydes with different catalysts [8–11].

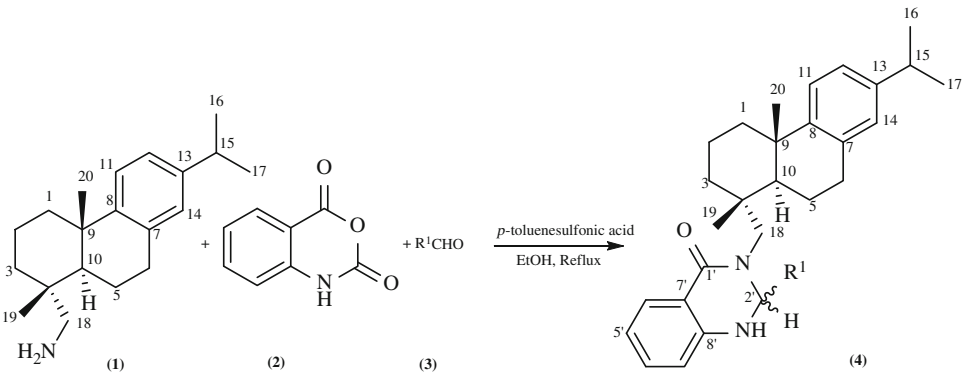
Dehydroabietylamine (DHA) is an abietane diterpenic amine derived from abietic acid. DHA can be isolated from an industrial product of natural rosin amine D [12]. Abietic acid is also the main component of rosin and produced worldwide about 1.2 million tons annually. Derivatives of DHA exhibited a wide range of biological properties including antiinflammatory [13, 14], antibacterial [15, 16], antifungal [17] and antitumor activity [12, 18].

Many researches have been developed recently on combining two or more biological active cores in one molecule. The results have shown that this unification sometime cause a synergism which increases the biological activity or sometime an antagonist activity to tune the pharmacological properties [19, 20]. In continuation of our research on one-pot multi-component reactions [21, 22], herein we report the reaction of dehydroabietylamine as a natural diterpenic primary amine with isatoic anhydride and different aromatic aldehydes to obtain a series of novel 2,3-dihydroquinazolin-4(1*H*)-one derivatives. The synthesized compounds have been also evaluated for their potential antimicrobial and antioxidant activities.

Results and discussion

In this work, our strategy was based on the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives using DHA as a

Scheme 1 Three-component synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives of dehydroabietylamine with 13 mol% of *p*-TSA



source of primary amine. Also, *p*-TSA was used for the first time in the three-component reaction of primary amine, isatoic anhydride and aromatic aldehyde for the construction of the target molecules. Scheme 1 outlines the general synthetic pathway.

DHA **1**, isatoic anhydride **2** and aromatic aldehydes **3** were treated with catalytic amounts of *p*-TSA in ethanol under reflux condition. Thus, the desired products were obtained as a mixture of two diastereomers in good yields. The results are summarized in Table 1. Seven aromatic aldehydes were used as model compounds in the reaction with electron releasing and electron withdrawing groups in different positions.

The percentage of each diastereomer was determined by analytical HPLC (Table 1). As can be seen in Table 1, the stereoisomers were produced in nearly equal amounts and were separated by preparative TLC using dichloromethane as eluent. Appearance of a H-2′ signal at $\delta = 5.7$ ppm in ^{1}H NMR and C2′ signal at $\delta = 72$ ppm in ^{13}C NMR spectra are the most important evidence and distinguished peaks in the production of the corresponding 2,3-dihydroquinazolin-4(1*H*)-ones skeleton. A multiplet at 2.85 ppm shows the isopropyl hydrogen of DHA moiety. The signals at $\delta = 2.3$ and 4.4 ppm in ^{1}H NMR spectra resemble the two diastereotopic hydrogens with large geminal coupling constant ($J = 14.0$ Hz) between H_{18a} and H_{18b} at the connection of two cores. HMQC experiment corroborated the presence of two geminal protons ($H_{18a,b}$) attached to the same carbon. These two diastereotopic protons showed a 0.22 ppm difference in DHA, while the chemical shifts were separated about 2.00 ppm in the products.

The chiral DHA has induced a diastereomeric discrimination on the products which make them separable on TLC. It should be emphasized that in contrast to our anticipation, addition of a new chiral center to DHA was not accompanied with a high diastereoselectivity in the products.

Antioxidant activities of the synthesized compounds and DHA were investigated by two different methods, i.e., in vitro DPPH assay and lipid oxidation inhibition by

Table 1 Physical data of 2,3-dihydroquinazolin-4(1*H*)-one derivatives of DHA and the percentages of the diastereomers

Entry	R^1	Color	Time (h)	Mp (°C)	λ_{max}	Overall yield %	Percentage (%)[a]
4a1	Ph	White	48	272–274	261, 335	72	63.3
4a2	Ph	White	48	150–152	261, 335		36.7
4b1	*p*-ClC_6H_4	White	48	224–226	238, 330	80	43.8
4b2	*p*-ClC_6H_4	White	48	111–113	238, 330		56.2
4c1	*p*-$O_2NC_6H_4$	Yellow	48	256–258	237, 264, 327	80	44.5
4c2	*p*-$O_2NC_6H_4$	Yellow	48	234–237	237, 264, 327		55.5
4d1	*p*-$CH_3C_6H_4$	Pale yellow	48	248–250	241, 330	74	61.7
4d2	*p*-$CH_3C_6H_4$	Pale yellow	48	128–130	241, 330		38.3
4e1	*p*-HOC_6H_4	Pale yellow	48	130–132	239, 333	70	36.5
4e2	*p*-HOC_6H_4	Pale yellow	48	134–136	239, 333		63.5
4f1	*m*-HOC_6H_4	White	48	135–137	237, 332	60	37.2
4f2	*m*-HOC_6H_4	White	48	148–150	237, 332		62.8
4g1	*p*-BrC6H4	White	48	129–131	246, 334	80	46.4
4g2	*p*-BrC6H4	White	48	148–150	246, 334		53.6

[a] Calculated by HPLC analysis

Table 2 Antioxidant activity of products, DHA and BHT by DPPH and β-carotene-linoleic acid methods

Sample	DPPH assay IC_{50} (μg/ml)	β-Carotene assay $A_{Sample}/A_{BHT}*100$
4a1	>2000	57.0
4a2	>2000	50.1
4b1	>2000	39.6
4b2	>2000	32.6
4c1	>2000	103.9
4c2	>2000	97.3
4d1	>2000	155.8
4d2	>2000	149.9
4e1	>2000	17.5
4e2	>2000	15.7
4f1	>2000	76.5
4f2	>2000	84.8
4g1	>2000	96.8
4g2	>2000	99.3
DHA	>2000	-
BHT	34.4	100

Table 3 Antibacterial activity of the synthesized compounds and DHA against tested bacteria

Sample	*E. coli* MIC (μg/ml)	*S. aureus* MIC (μg/ml)	*B. cereus* MIC (μg/ml)
4a1	128	128	32
4a2	128	128	16
4b1	128	128	32
4b2	128	128	>128
4c1	128	128	32
4c2	128	128	32
4d1	128	128	64
4d2	128	128	16
4e1	128	128	16
4e2	128	128	16
4f1	128	128	4
4f2	128	128	4
4g1	128	128	32
4g2	128	128	16
DHA	32	32	128
Chloramphenicol	2	0.5	0.25

β-carotene-linoleic acid method. The applied methods are complementary for hydrophilic and lipophilic bioactive components, respectively. The results are represented in Table 2. It seems that, due to the high lipophilicity of the synthesized compounds, they did not show any antioxidant activity in DPPH assay. However, in the β-carotene-linoleic acid assay, most of them showed higher activities than DHA. It should be correlated to the nonpolar nature of the products. Some derivatives like **4d1** and **4d2** showed considerable activity even better than BHT as a commercial antioxidant compound. Most of the diastereomers showed approximately equal activity.

For antibacterial activity, all the diastereomers had the minimum inhibitory concentration (MIC) of 128 μg/ml against *E. coli* and *S. aureus*, while DHA had the MIC of 32 μg/ml for both strains. However, most of the products showed a better inhibitory effect against *B. cereus* than DHA. The best result was found for **4f1** and **4f2**, the *m*-hydroxy benzaldehyde derivatives which both had MIC of 4 μg/ml. The data were compared to the chloramphenicol as an antibiotic standard (Table 3). In fact, the aforementioned products with two potent antibacterial cores were anticipated to have a greater activity compared to the starting material, but it seems that they did not have a synergistic effect to show a better antibacterial activity than DHA.

Experimental

Instrument and chemicals

Thin-layer chromatography was carried out on silica gel $60F_{254}$ aluminium plate and preparative thin-layer plates were made manually with silica gel $60F_{254}$ with gypsum (Merck, Darmstadt, Germany). Melting points were determined on a Barnstead Electrothermal 9,200 apparatus and were not corrected. Bruker tensor 27 spectrometer was used to record the fourier transform infrared spectra (FT-IR) using KBr pellets. Nuclear magnetic resonance (^{1}H NMR, 300 MHz; ^{13}C NMR, 75 MHz) spectra were recorded on a Bruker AC 300 spectrometer. *J* values are given in Hertz. HR-ESIMS spectra were acquired on a Bruker micrOTOF ESI–MS system in positive mode. Ions were detected from *m/z* 200–1400 at a scan rate of 1 Hz. Mass calibration was performed using sodium formate clusters (10 mM solution of NaOH in 50/50 % v/v isopropanol/water containing 0.2 % formic acid). The UV–Vis absorbance was read in a Powerwave XS2 Microplate spectrophotometer (Bio-Tek Instruments, Inc.). Dehydroabietylamine, isatoic anhydride and all aldehydes were obtained from Merck-Schuchardt (Hohenbrunn, Germany). 2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical and β-carotene were purchased from Fluka (Neu-Ulm, Germany). 2,6-di-*tert*-butyl-4-methylphenol (BHT) and other solvents and reagents were obtained from Merck (Darmstadt, Germany).

General procedure for the one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones with DHA and different aldehydes (4a–g)

To a solution of isatoic anhydride (1 mmol), dehydroabietylamine (1.2 mmol) and the aldehyde (1 mmol) in EtOH (5 ml), *p*-TSA (0.1 g: 0.5 mmol, 13 mol %) was added. The solution was heated under reflux for about 48 h. The reaction progress was monitored by TLC (dichloromethane). Then, water (30 ml) was added and the precipitated product was filtered and dried until isolation by preparative thin-layer chromatography.

Benzaldehyde derivatives (4a1, 4a2)

Total yield: 72 %, diastereomeric ratio (**4a1**:**4a2** 63:37).

4a1: IR (KBr, cm^{-1}): 3,315, 2,926, 2,857, 1,631, 1,508, 1,459. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.95 (d, $J = 7.9$ Hz, 1H, H_{Ar}), 7.29–6.77 (m, 10H, H_{Ar}), 6.54 (d, $J = 8.0$ Hz, 1H, H_{Ar}), 5.73 (s, 1H, $H_{2'}$), 4.98 (br s, 1H, NH), 4.41 (d, $J = 14.0$ Hz, 1H, H_{18b}), 2.99–2.90 (m, 2H, $H_{aliphatic}$), 2.85 (sep, 1H, $H_{15(iPr)}$), 2.37 (d, $J = 14.0$ Hz, 1H, H_{18a}), 2.31–0.78 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 164.9, 147.3, 145.4, 144.7, 140.1, 135.3, 133.3, 128.9, 128.6, 128.5, 127.0, 126.1, 123.9, 123.6, 119.2, 117.0, 115.0, 73.6 (C2′), 56.3 (C18), 45.1, 40.2, 38.2, 37.7, 37.0, 33.4, 30.5, 26.2, 24.0, 19.7, 19.2, 18.7. HRMS (ESI) calculated for $C_{34}H_{41}N_2O$: 493.3213 $[M + H]^+$, found: 493.3208.

4a2: IR (KBr, cm^{-1}): 3,315, 2,926, 2,859, 1,632, 1,509, 1,457. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.97 (d, $J = 7.9$ Hz, 1H, H_{Ar}), 7.29–6.77 (m, 10H, H_{Ar}), 6.56 (d, $J = 8.0$ Hz, 1H, H_{Ar}), 5.69 (s, 1H, $H_{2'}$), 4.88 (br s, 1H, NH), 4.35 (d, $J = 14.0$ Hz, 1H, H_{18b}), 3.03–2.90 (m, 2H, $H_{aliphatic}$), 2.85 (sep, 1H, $H_{15(iPr)}$), 2.44 (d, $J = 14.0$ Hz, 1H, H_{18a}), 2.32–0.80 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 165.0, 147.4, 145.6, 144.5, 140.2, 134.2, 133.4, 129.0, 128.8, 128.5, 126.9, 125.9, 124.2, 124.0, 119.2, 116.6, 114.9, 72.8 (C2′), 54.8 (C18), 45.7, 40.9, 38.2, 37.8, 37.5, 33.4, 30.3, 25.9, 24.0, 19.5, 18.6, 18.5. HRMS (ESI) calculated for $C_{34}H_{41}N_2O$: 493.3213 $[M + H]^+$, found: 493.3216.

4-Chloro benzaldehyde derivatives (4b1, 4b2)

Total yield: 80 %, diastereomeric ratio (**4b1**:**4b2** 44:56).

4b1: IR (KBr, cm^{-1}): 3,317, 2,926, 2,863, 1,625, 1,499, 1,459, 1,162. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.94 (d, $J = 7.4$ Hz, 1H, H_{Ar}), 7.31–6.65 (m, 9H, H_{Ar}), 6.60 (d, $J = 8.3$ Hz, 1H, H_{Ar}), 5.70 (s, 1H, $H_{2'}$), 5.36 (br s, 1H, NH), 4.39 (d, $J = 14.0$ Hz, 1H, H_{18b}), 3.00–2.90 (m, 2H, $H_{aliphatic}$), 2.83 (sep, 1H, $H_{15(iPr)}$), 2.37 (d, $J = 14.0$ Hz, 1H, H_{18a}), 2.28–0.79 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 164.9, 147.3, 145.5, 144.6, 138.7, 134.5, 134.0, 133.5, 129.0, 128.5, 127.5, 127.0, 123.9, 123.7, 119.3, 116.9, 115.2, 72.9 (C2′), 56.4 (C18), 45.2, 40.2, 38.2, 37.7, 37.0, 33.5, 30.5, 26.1, 24.0, 19.7, 19.2, 18.7. HRMS (ESI) calculated for $C_{34}H_{40}ClN_2O$: 527.2824 $[M + H]^+$, found: 527.2811.

4b2: IR (KBr, cm^{-1}): 3,311, 2,927, 2,868, 1,635, 1,490, 1,457, 1,161. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.96 (d, $J = 7.5$ Hz, 1H, H_{Ar}), 7.27–6.80 (m, 9H, H_{Ar}), 6.57 (d, $J = 8.0$ Hz, 1H, H_{Ar}), 5.70 (s, 1H, $H_{2'}$), 5.23 (br s, 1H, NH), 4.41 (d, $J = 14.0$ Hz, 1H, H_{18b}), 3.06–2.95 (m, 2H, $H_{aliphatic}$), 2.85 (sep, 1H, $H_{15(iPr)}$), 2.40 (d, $J = 14.0$ Hz, 1H, H_{18a}), 2.33–0.78 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 165.0, 147.3, 145.7, 144.5, 138.8, 134.6, 134.2, 133.6, 129.1, 128.5, 127.3, 126.9, 124.2, 124.0, 119.3, 116.5, 115.2, 72.1 (C2′), 55.2 (C18), 46.0, 40.4, 38.3, 37.8, 37.6, 33.5, 30.3, 25.8, 24.0, 19.5, 18.6, 18.4. HRMS (ESI) calculated for $C_{34}H_{40}ClN_2O$: 527.2824 $[M + H]^+$, found: 527.2822.

4-Nitro benzaldehyde derivatives (4c1, 4c2)

Total yield: 80 %, diastereomeric ratio (**4c1**:**4c2** 45:55).

4c1: IR (KBr, cm^{-1}): 3,311, 2,943, 1,633, 1,517, 1,344. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.14 (d, $J = 7.7$ Hz, 2H, H_{Ar}), 7.94 (d, $J = 7.6$ Hz, 1H, H_{Ar}), 7.45 (d, $J = 7.7$ Hz, 2H, H_{Ar}), 7.27–6.82 (m, 5H, H_{Ar}), 6.64 (d, $J = 8.3$ Hz, 1H, H_{Ar}), 5.80 (s, 1H, $H_{2'}$), 5.33 (s, 1H, NH), 4.46 (d, $J = 13.9$ Hz, 1H, H_{18b}), 2.96–2.86 (m, 2H, $H_{aliphatic}$), 2.80 (sep, 1H, $H_{15(iPr)}$), 2.36 (d, $J = 14.0$ Hz, 1H, H_{18a}), 2.27–0.81 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 164.7, 147.9, 147.4, 147.1, 145.6, 144.0, 135.1, 133.7, 128.6, 127.2, 127.0, 124.0, 123.9, 123.7, 120.0, 117.2, 115.6, 72.6 (C2′), 56.7 (C18), 45.1, 40.3, 38.1, 37.6, 36.7, 33.4, 30.4, 26.1, 24.0, 19.7, 19.2, 18.7. HRMS (ESI) calculated for $C_{34}H_{40}N_3O_3$: 538.3064 $[M + H]^+$, found: 538.3046.

4c2: IR (KBr, cm^{-1}): 3,307, 2,930, 1,633, 1,516, 1,345. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.16 (d, $J = 8.3$ Hz, 2H, H_{Ar}), 7.97 (d, $J = 7.3$ Hz, 1H, H_{Ar}), 7.44 (d, $J = 8.3$ Hz, 2H, H_{Ar}), 7.28–6.84 (m, 5H, H_{Ar}), 6.59 (d, $J = 7.8$ Hz, 1H, H_{Ar}), 5.78 (s, 1H, $H_{2'}$), 5.03 (s, 1H, NH), 4.47 (d, $J = 13.9$ Hz, 1H, H_{18b}), 3.07–2.97 (m, 2H, $H_{aliphatic}$), 2.87 (sep, 1H, $H_{15(iPr)}$), 2.41 (d, $J = 13.8$ Hz, 1H, H_{18a}), 2.27–0.90 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 164.8, 148.1, 147.2, 147.1, 145.7, 143.7, 134.0, 133.8, 128.7, 127.0, 126.9, 124.2, 124.1, 123.9, 120.2, 117.1, 115.6, 71.8 (C2′), 55.5 (C18), 45.9, 40.4, 38.2, 37.7, 37.5, 33.4, 30.2, 25.8, 24.0, 19.6, 18.6, 18.4. HRMS (ESI) calculated for $C_{34}H_{40}N_3O_3$: 538.3064 $[M + H]^+$, found: 538.3052.

4-Methyl benzaldehyde derivatives (4d1, 4d2)

Total yield 74 %, diastereomeric ratio (**4d1**:**4d2** 62:38).

4d1: IR (KBr, cm^{-1}): 3,319, 2,925, 2,857, 1,631, 1,508, 1,459. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.93 (d, $J = 7.7$ Hz, 1H, H_{Ar}), 7.25–6.63 (m, 9H, H_{Ar}), 6.53 (d, $J = 7.8$ Hz, 1H, H_{Ar}), 5.68 (s, 1H, $H_{2'}$), 4.98 (br s, 1H, NH), 4.36 (d, $J = 14.0$ Hz, 1H, H_{18b}), 2.99–2.89 (m, 2H, $H_{aliphatic}$), 2.81 (sep, 1H, $H_{15(iPr)}$), 2.46 (d, $J = 14.0$ Hz, 1H, H_{18a}), 2.29 (s, 3H, CH_3-Ph), 2.25–0.81 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 164.9, 147.3, 145.4, 144.7, 138.5, 137.1, 134.0, 133.3, 129.5, 128.5, 127.0, 126.0, 123.9, 123.6, 119.1, 116.2, 114.9, 73.2 (C2′), 56.2 (C18), 45.1, 40.1, 38.1, 37.6, 36.9, 33.4, 30.9, 26.1, 24.0, 21.1, 19.6, 19.2, 18.7. HRMS (ESI) calculated for $C_{35}H_{43}N_2O$: 507.3370 $[M + H]^+$, found: 507.3375.

4d2: IR (KBr, cm^{-1}): 3,314, 2,925, 2,857, 1,636, 1,506, 1,457. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.93 (d, $J = 7.7$ Hz, 1H, H_{Ar}), 7.25–6.63 (m, 9H, H_{Ar}), 6.52 (d, $J = 8.4$ Hz 1H, H_{Ar}), 5.70 (s, 1H, $H_{2'}$),5.01 (br s, 1H, NH), 4.36 (d, $J = 14.0$ Hz, 1H, H_{18b}), 3.08–2.98 (m, 2H, $H_{aliphatic}$), 2.88 (sep, 1H, $H_{15(iPr)}$), 2.46 (d, $J = 14.0$ Hz, 1H, H_{18a}), 2.31 (s, 3H, CH_3-Ph), 2.28–0.75 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 165.1, 147.4, 145.6, 144.7, 138.6, 137.3, 134.3, 133.4, 129.6, 128.5, 126.9, 125.8, 124.2, 124.0, 119.0, 116.5, 114.9, 72.7 (C2′), 54.9 (C18), 45.8, 40.4, 38.3, 37.8, 37.5, 33.5, 30.3, 25.9, 24.0, 21.1, 19.5, 18.7, 18.6. HRMS (ESI) calculated for $C_{35}H_{43}N_2O$: 507.3370 $[M + H]^+$, found: 507.3374.

4-Hydroxy benzaldehyde derivatives (4e1, 4e2)

Total yield 70 %, diastereomeric ratio (**4e1**:**4e2** 37:63).

4e1: IR (KBr, cm^{-1}): 3,378, 2,927, 1,625, 1,605. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.89 (d, $J = 7.8$ Hz, 1H, H_{Ar}), 7.23–6.70 (m, 10H, H_{Ar} and OH), 6.56 (d, $J = 8.1$ Hz, 1H, H_{Ar}), 5.64 (s, 1H, $H_{2'}$),4.85 (br s, 1H, NH), 4.36 (d, $J = 14.1$ Hz, 1H, H_{18b}), 2.99–2.89 (m, 2H, $H_{aliphatic}$), 2.81 (sep, 1H, $H_{15(iPr)}$), 2.33 (d, $J = 14.1$ Hz, 1H, H_{18a}), 2.23–0.81 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 165.6, 157.5, 147.2, 145.4, 144.9, 135.3, 133.9, 133.7, 130.9, 128.6, 127.3, 127.0, 123.9, 123.6, 119.2, 115.9, 114.9, 73.6 (C2′), 56.0 (C18), 44.7, 40.3, 38.0, 37.6, 36.8, 33.4, 30.4, 26.2, 24.0, 19.7, 19.4, 18.7. HRMS (ESI) calculated for $C_{34}H_{41}N_2O_2$: 509.3163 $[M + H]^+$, found: 509.3181.

4e2: IR (KBr, cm^{-1}): 3,384, 2,906, 1,630, 1,505. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.93 (d, $J = 7.8$ Hz, 1H, H_{Ar}), 7.39–6.73 (m, 10H, H_{Ar} and OH), 6.52 (d, $J = 8.1$ Hz, 1H, H_{Ar}), 5.62 (s, 1H, $H_{2'}$), 4.85 (br s, 1H, NH), 4.27 (d, $J = 14.1$ Hz, 1H, H_{18b}), 3.06–2.96 (m, 2H, $H_{aliphatic}$), 2.81 (sep, 1H, $H_{15(iPr)}$), 2.46 (d, $J = 14.1$ Hz, 1H, H_{18a}), 2.30–0.83 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 165.6, 157.5, 147.3, 145.7, 144.8, 134.2, 133.9, 131.2, 128.5, 127.1, 126.9, 124.1, 124.0, 119.1, 116.0, 114.9, 112.5, 72.6 (C2′), 54.9 (C18), 45.6, 40.4, 38.2, 37.8, 37.4, 33.5, 30.2, 25.9, 24.0, 19.5, 18.6, 18.5. HRMS (ESI) calculated for $C_{34}H_{41}N_2O_2$: 509.3163 $[M + H]^+$, found: 509.3165.

3-Hydroxy benzaldehyde derivatives (4f1, 4f2)

Total yield 60 %, diastereomeric ratio (**4f1**:**4f2** 37:63).

4f1: IR (KBr, cm^{-1}): 3,463, 2,927, 2,860, 1,633, 1,462, 1,252, 1,163. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.73 (d, $J = 7.4$ Hz, 1H, H_{Ar}), 7.19–6.62 (m, 10H, H_{Ar} and OH), 6.52 (d, $J = 7.6$ Hz, 1H, H_{Ar}), 5.71 (s, 1H, $H_{2'}$),4.92 (br s, 1H, NH), 4.46 (d, $J = 14.0$ Hz, 1H, H_{18b}), 2.94–2.84 (m, 2H, $H_{aliphatic}$), 2.81 (sep, 1H, $H_{15(iPr)}$), 2.46 (d, $J = 14.0$ Hz, 1H, H_{18a}), 2.30–0.80 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 165.7, 157.5, 147.2, 145.4, 144.8, 141.0, 135.2, 133.6, 130.2, 128.4, 127.0, 123.8, 123.6, 119.5, 117.3, 116.5, 115.9, 115.1, 113.1, 73.6 (C2′), 56.6 (C18), 45.0, 40.2, 38.1, 37.6, 36.9, 33.4, 29.7, 26.0, 24.0, 19.6, 19.3, 18.7. HRMS (ESI) calculated for $C_{34}H_{41}N_2O_2$: 509.3163 $[M + H]^+$, found: 509.3181.

4f2: IR (KBr, cm^{-1}): 3,456, 2,927, 2,854, 1,630, 1,459, 1,242, 1,161. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.73 (d, $J = 7.4$ Hz, 1H, H_{Ar}), 7.19–6.67 (m, 10H, H_{Ar} and OH), 6.49 (d, $J = 7.6$ Hz, 1H, H_{Ar}), 5.64 (s, 1H, $H_{2'}$), 4.87 (br s, 1H, NH), 4.32 (d, $J = 14.0$ Hz, 1H, H_{18b}), 2.99–2.89 (m, 2H, $H_{aliphatic}$), 2.82 (sep, 1H, $H_{15(iPr)}$), 2.46 (d, $J = 14.0$ Hz, 1H, H_{18a}), 2.30–0.80 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 165.6, 157.4, 147.4, 145.4, 144.6, 141.4, 134.5, 133.5, 130.1, 128.5, 126.9, 124.5, 124.0, 119.1, 117.1, 116.2, 116.1, 116.0, 112.8, 73.1 (C2′), 56.6 (C18), 45.0, 40.2, 38.1, 37.6, 36.9, 33.4, 29.7, 26.0, 24.0, 19.6, 19.3, 18.7. HRMS (ESI) calculated for $C_{34}H_{41}N_2O_2$: 509.3163 $[M + H]^+$, found: 509.3167.

4-Bromo benzaldehyde derivatives (4g1, 4g2)

Total yield 80 %, diastereomeric ratio (**4g1**:**4g2** 46:54).

4g1: IR(KBr, cm^{-1}): 3,317, 2,931, 2,863, 1,640, 1,494, 1,460, 1,164. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.92 (d, $J = 7.8$ Hz, 1H, H_{Ar}), 7.44–6.79 (m, 9H, H_{Ar}), 6.57 (d, $J = 8.1$ Hz, 1H, H_{Ar}), 5.67 (s, 1H, $H_{2'}$), 5.33 (br s, 1H, NH), 4.38 (d, $J = 13.9$ Hz, 1H, H_{18b}), 2.98–2.88 (m, 2H, $H_{aliphatic}$), 2.84 (sep, 1H, $H_{15(iPr)}$), 2.32 (d, $J = 13.9$ Hz, 1H, H_{18a}), 2.29–0.76 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 164.7, 147.2, 145.5, 144.3, 139.1, 135.2, 133.5, 132.0, 128.6, 127.28, 127.0, 123.9, 123.7, 122.7, 119.6, 117.1, 115.2, 73.0 (C2′), 56.3 (C18), 45.1, 40.2, 38.1, 37.6, 37.0, 33.4, 30.4, 26.1, 24.0, 19.6, 19.2, 18.7. HRMS (ESI) calculated for $C_{34}H_{40}^{79}BrN_2O$:

571.2319 $[M + H]^+$, found: 571.2327 and calculated for $C_{34}H_{40}^{81}BrN_2O$: 573.2298 $[M + H]^+$, found: 573.2348.

4g2: IR(KBr, cm^{-1}): 3,315, 2,932, 2,865, 1,638, 1,497, 1,461, 1,163. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.96 (d, $J = 7.6$ Hz, 1H, H_{Ar}), 7.43–6.69 (m, 9H, H_{Ar}), 6.56 (d, $J = 8.1$ Hz, 1H, H_{Ar}), 5.66 (s, 1H, $H_{2'}$), 4.92 (br s, 1H, NH), 4.38 (d, $J = 14.0$ Hz, 1H, H_{18b}), 3.08–2.98 (m, 2H, $H_{aliphatic}$), 2.88 (sep, 1H, $H_{15(iPr)}$), 2.40 (d, $J = 13.9$ Hz, 1H, H_{18a}), 2.33–0.81 (m, 21H, $H_{aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 164.9, 147.3, 145.7, 144.1, 139.2, 134.2, 133.6, 132.1, 128.6, 127.6, 126.9, 124.2, 124.1, 122.8, 119.6, 116.7, 115.2, 72.2 (C2′), 55.1 (C18), 45.8, 40.4, 38.2, 37.8, 37.5, 33.5, 30.3, 25.8, 24.0, 19.5, 18.6, 18.5. HRMS (ESI) calculated for $C_{34}H_{40}^{79}BrN_2O$: 571.2319 $[M + H]^+$, found: 571.2302 and calculated for $C_{34}H_{40}^{81}BrN_2O$: 573.2298 $[M + H]^+$, found: 573.2321.

Analysis of diastereomers by HPLC

A Knauer liquid chromatography apparatus consisting of a 1,000 smartline pump, a 5,000 smartline manager solvent organizer and a 2,800 smartline photo-diode array (PDA) detector was used for the HPLC analysis. Injection was through a 3,900 smartline autosampler injector equipped with a 100 µl loop. The temperature control of the column was made with a jet stream two plus oven (Knauer, advanced scientific instrument, Berlin, Germany). Separation was achieved on Eurospher 100-5 RP-C18 (25 cm × 4.6 mm, 5 µm particle size), analytical column with pre-column provided by Knauer (Berline, Germany). Data acquisition and integration was performed with EZ-chrom Elite software. Acetonitrile (100 %) was employed as an isocratic mobile phase with the flow-rate of 1 ml/min. Peaks were monitored at the λ_{max} of each diastereomers (Table 1). Injection volume was 20 µl.

Antioxidant assays

The free radical-scavenging activity of different samples was investigated by two different antioxidant methods, i.e., DPPH and β-carotene bleaching assays.

DPPH assay

DPPH assay was assessed using the method described earlier [23, 24]. Thus, 200 µl of 0.5 mM of DPPH in methanol and different amounts of the synthesized compounds and DHA in DMSO were mixed in a 96-well microplate assay. After 30 min shake and incubation at 25 °C (Heidolph titramax 1000 and incubator 1000, Germany), the absorbance was read against a blank at 517 nm in a Powerwave XS2 microplate spectrophotometer. The inhibition of $DPPH^{\bullet}$, in percent (In%) was calculated by the following equation;

$$\text{In}\% = \frac{(A_{\text{blank}} - A_{\text{sample}})}{A_{\text{blank}}} \times 100$$

where A_{blank} is the absorbance of the control reaction (containing all reagents except the test compound), and A_{sample} is the absorbance of the test compound. Sample concentration providing 50 % inhibition (IC_{50}) was calculated from the graph plotted of inhibition percentage against samples concentration. Tests were carried out in triplicate.

β-Carotene bleaching test

The antioxidant activity of samples was evaluated by the β-carotene-linoleic acid model with some modifications [25]. A stock solution of β-carotene-linoleic acid was prepared by dissolving 0.5 mg of β-carotene in 1 ml of chloroform, then 25 µl of linoleic acid and 200 mg of Tween 40 were added. Chloroform was subsequently evaporated using a rotary evaporator. Then, 100 ml of distilled water saturated with oxygen was added with vigorous shaking. Aliquots (35 µl) portion of the samples (2 g/l in ethanol) were transferred to each well, and 250 µl of the prepared reaction mixture was added before incubating for 48 h at room temperature. The same procedure was repeated with BHT at the same concentration and a blank containing only 35 µl of ethanol. After incubation for 48 h, the absorbance of the mixtures was measured at 490 nm. Antioxidant capacities of different samples and DHA were compared with those of BHT and the blank according to the below equation:

$$\text{Relative antioxidant activity (RAA \%)} = \frac{A_{\text{Sample}}}{A_{\text{BHT}}} \times 100$$

Antibacterial assay

In vitro antibacterial activity of products was assessed against two Gram-positive, *Staphylococcus aureus* ATCC 25923, *Bacillus cereus* PTCC 1015 and one Gram-negative, *Escherichia coli* ATCC 25922 bacteria. The antibacterial activity was evaluated by Broth dilution susceptibility tests according to the standard protocol [26]. Serial dilutions of samples were made in a concentration ranging from 0.06 to 128 µg/ml in sterile plastic micro-dilution trays containing Mueller–Hinton broth supplemented by 0.5 % Tween 80. Minimum inhibitory concentrations (MICs) were recorded after 22 h incubation at 37 °C. Each experiment was done in duplicate. Chloramphenicol was used as an antibiotic standard.

Conclusion

The incorporation of dehydroabietylamine and 2,3-dihydroquinazolin-4(1*H*)-one cores was made by a three-component reaction of DHA, isatoic anhydride and aromatic aldehydes which led to a novel series of compounds. The products were investigated for their antioxidant activities and found to exhibit very good inhibitory effect in β-carotene bleaching method relative to starting material DHA and also BHT. Most of the synthesized compounds showed a better antibacterial activity than DHA against *B. cereus*.

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