Novel synthesis and stereochemical structure of 2*H*-2,6-methano-1,3-benzoxazocine-5-carbohydrazides

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A novel synthetic approach for 5,6-dihydro-2,4-disubstituted-2*H*-2,6-methano-1,3-benzoxazocine-5-carbohydrazides **4a–j** was achieved through the reaction of 1-aryl-3-(2-hydroxyphenyl)prop-2-en-1-ones **1a–c** with cyanoacetohydrazones **2a,b** in the presence of sufficient amount of secondary amines **3a,b**. Single crystal X-ray diffraction study of **4c** supports the established structure and reveals that the relative configuration is 2*R*,5*S*,6*R*.

Keywords: 2-propen-1-ones, cyanoacetohydrazones, 2*H*-2,6-methano-1,3-benzoxazocine-5-carbohydrazides, Michael reaction

Cyanoacetohydrazide is a well known antituberculosis active agent long time ago[1-5] and widely used by many investigators for construction of numerous heterocyclic compounds.[6-13] Reaction of cyanoacetohydrazones derived from cycloalkanones (namely, cyclopentanone or cyclohexanone) with α, β-unsaturated nitrile containing compounds afforded spiro[cycloalkane-1,2'(3'*H*)-[1,2,4]triazolo[1,5-*a*] pyridines].[14,15] However, 6-amino-2-oxo-3,5-pyridinedicarbonitriles were obtained regioselectively through the reaction of arylidenemalononitriles with cyanoacetohydrazones derived from benzo-fused cycloalkanones (namely, 1-indanone or α-tetralone).[16]

In continuation of our previous work directed towards construction of various heterocyclic systems using easily accessible starting materials and facile synthetic approaches.[16-20] It is intended in the present work to investigate the reaction of cyanoacetohydrazones derived from benzo-fused cycloalkanones **2a,b** with various 1-aryl-3-(2-hydroxyphenyl)-2-propen-1-ones **1a–c** under different basic catalytic conditions. Where the α, β-unsaturated ketone system **1** can easily interact with the active methylene of **2**. In addition, the hydroxyl group of **1** as a good nucleophilic centre may overlap in the basic catalysed reaction giving fused heterocyclic compound. The stereochemical structure of the isolated product will be also considered.

Results and discussion

Reaction of 1-aryl-3-(2-hydroxyphenyl)-2-propen-1-ones **1a–c** with cyanoacetohydrazones **2a,b** in refluxing ethanol containing sufficient amount of secondary amines **3a,b** "namely, piperidine or morpholine" afforded only one product 5,6-dihydro-2,4-disubstituted-2*H*-2,6-methano-1,3-benzoxazocine-5-carbohydrazides **4a–j**. The structure of which was established through different spectroscopic techniques (IR, ^{1}H, ^{13}C NMR) as well as elemental analyses data. The IR spectra of **4a–j** exhibit the absence of any band assignable for nitrile absorption. However, stretching vibration bands due to NH and carbonyl hydrazone functions are well recognised at ν = 3185–3170, 1671–1657 cm^{-1} regions, respectively.

^{1}H NMR spectra of **4a–j** show each of the CH_2–CH methylene protons as double doublets due to mutual coupling with each other and in turn with the vicinal methine proton "*H*-6" (at δ = 2.08–2.15, 2.30–2.36 regions). In addition to the methine *H*-5 which appears as a doublet signal at δ = 4.65–4.78 (*J* = 1.2–1.8 Hz). However, the methine *H*-6 is hidden under the secondary amine multiplet signals. Meanwhile, the appearance of the secondary amine signals (piperidinyl at δ = 1.45–1.63, 3.31–3.54; morpholinyl at δ = 3.40–3.51, 3.56–3.64 regions) adds a good support for the involvement of the used secondary amines in the reaction sequence.

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^{13}C NMR (APT) spectrum of **4c** "as a representative example" affords a conclusive evidence for the established structure. Where, three methylene carbons are appeared at δ = 27.28, 28.62, 30.51 assignable for the two indane CH_2 and H_2C–CH, in addition to the morpholinyl methylene carbons (δ = 44.92, 66.49). The heterocyclic methines *C*-6 and *C*-5 are exhibited at δ = 33.75, 46.94, respectively. Meanwhile, the quaternary *C*-2 and carbonyl carbons are recognised at δ = 86.12, 171.62, respectively.

The single crystal X-ray study of **4c** (Fig. 1) confirms the established structure.[21] It has been noticed that, none of the starting materials are chiral, so it is assumed that the isolated product is a racemic mixture. However, X-ray diffraction studies of **4c** shows that the isolated product is 2*R*,5*S*,6*R*. In addition it shows that, the hydrazone attachment takes an *E*-form configuration.

The reaction was assumed to be initiated *via* Michael addition pathway of the active methylene hydrazone function of **2** to the β-carbon of unsaturated system **1**. Then, under secondary amine nucleophilic attack at the nitrile group followed by interaction with the neighbouring carbonyl residue and subsequent water molecule elimination as a result of the hydroxyl phenolic group involvement, the reaction furnished finally **4** (Scheme 1). Many attempts have been made for either isolation or identification of any intermediate compound from the reaction mixture, but were unsuccessful. Even, when the reaction was conducted in the presence of few

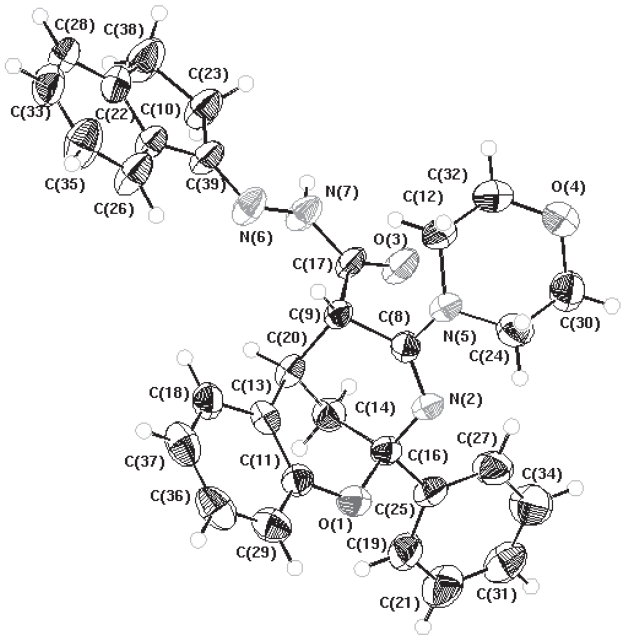
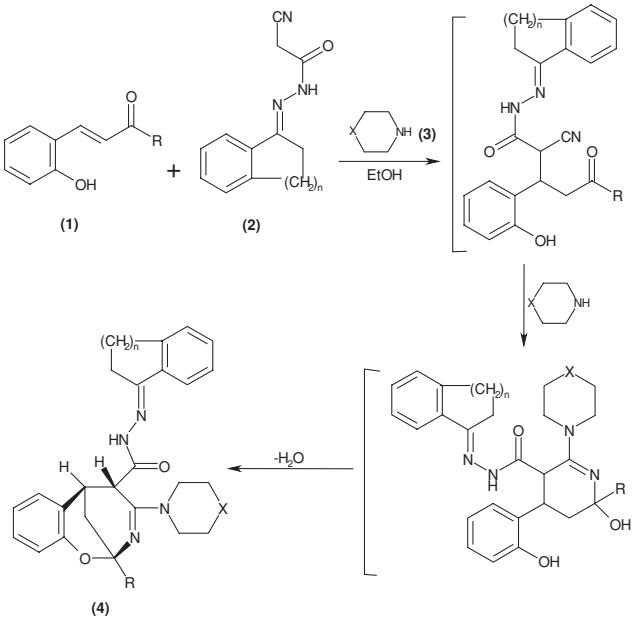


Fig. 1 Single crystal X-ray diffraction of **4c**.



1a, R = Ph
1b, R = 4-ClC_6H_4
1c, R = 4-$H_3CC_6H_4$

2a, *n* = 1
2b, *n* = 2

3a, X =CH_2
3b, X = O

4a, R = Ph, X =CH_2, *n* = 1
4b, R = Ph, X =CH_2, *n* = 2
4c, R = Ph, X = O, *n* = 1
4d, R = Ph, X = O, *n* = 2
4e, R = 4-ClC_6H_4, X =CH_2, *n* = 1
4f, R = 4-ClC_6H_4, X =CH_2, *n* = 2
4g, R = 4-ClC_6H_4, X = O, *n* = 1
4h, R = 4-ClC_6H_4, X = O, *n* = 2
4i, R = 4-$H_3CC_6H_4$, X =CH_2, *n* = 2
4j, R = 4-$H_3CC_6H_4$, X = O, *n* = 2

Scheme 1

drops of basic catalysis (**3**), where the final product **4** was also isolated in a very low yield.

Single crystal X-ray crystallographic data of **4c**: The crystallographic data were collected at $T = 298$°K on a Kappa CCD Enraf Nonius FR 590 diffractometre using a graphite monochromator with *Mo-*K_α radiation ($\lambda = 0.71073$ Å). The crystal structure was determined by SIR[22] and refined by maXus[23]. Chemical formula $C_{31}H_{30}N_4O_3$, $M_r = 506.606$, monoclinic, crystallises in space group $C_{2/c}$, Cell lengths; $a = 24.4527(6)$, $b = 11.9530(3)$, $c = 20.3239(5)$ Å, Cell angles; $\alpha = 90.00$, $\beta = 105.379(2)$, $\gamma = 90.00°$, $V = 5727.6(2)$ Å^3, $Z = 8$, $D_c = 1.175$ mg/m^3, θ values 2.99–23.54°, absorption coefficient μ (*Mo-*K_α) = 0.08 mm^{-1}, $F(000) = 2143$. The 7982 unique reflections were measured of which 2409 reflections with threshold expression $I>3\sigma(I)$ were used in the structural analysis. Convergence for 343 variable parametres by least-squares refinement on F^2 with $w = 1/[\sigma^2(F_o^2) + 0.10000\ F_o^2]$. The final agreement factors were $R = 0.093$ and $wR = 0.300$ with a goodness-of-fit of 6.889.

Experimental

Melting points are uncorrected and were recorded on an Electrothermal 9100 digital melting point apparatus. IR spectra (KBr) were recorded on a JASCO FT/IR 300E spectrophotometre. NMR spectra were recorded on a Varian MERCURY spectrometre (^{1}H: 300 MHz, ^{13}C: 75 MHz) in $CDCl_3$. The starting compounds **1a–c**[24, 25] and **2a,b**[16] were prepared according to the previously reported procedures.

Synthesis of 5,6-dihydro-2,4-disubstituted-2H-2,6-methano-1,3-benzoxazocine-5-carbohydrazides **4a–j** *General procedure*

A solution of equimolar amounts of **1a–c** and the corresponding **2a,b** (5 mmol) in absolute ethanol (20 ml) containing secondary amine **3a,b** (6 mmol) was boiled under reflux for the appropriate time. The solid separated while refluxing was collected and crystallised from *n*-butanol affording **4a–j** as colourless crystals.

5,6-Dihydro-N-(2,3-dihydro-1H-indene-1-ylidene)-2-phenyl-4-(piperidin-1-yl)-2H-2,6-methano-1,3-benzoxazocine-5-carbohydrazide (**4a**): Reaction time 12 h, m.p. 219–221 °C, yield 52 %. IR: ν 3178, 1670, 1589, 1484 cm^{-1}. ^{1}H NMR: δ 1.46–1.58 (m, 6H, piperidinyl 3CH_2), 2.13 (dd, $J = 3.9$, 13.2 Hz, 1H, upfield H of CH_2CH), 2.35 (dd, $J = 2.1$, 13.2 Hz, 1H, downfield H of CH_2CH), 2.87–2.91 (m, 2H, indane CH_2), 3.16–3.20 (m, 2H, indane CH_2), 3.32–3.53 (m, 5H piperidinyl 2NCH_2 + hetero. *H*-6), 4.71 (d, $J = 1.8$ Hz, 1H, hetero. *H*-5), 6.96–7.82 (m, 13H, arom. H), 9.45 (s, 1H, NH). Anal. Calcd. for $C_{32}H_{32}N_4O_2$ (504.61): C, 76.16; H, 6.39; N, 11.10. Found: C, 76.38; H, 6.53; N, 11.19 %.

5,6-Dihydro-N-(3,4-dihydronaphthalene-1(2H)-ylidene)-2-phenyl-4-(piperidin-1-yl)-2H-2,6-methano-1,3-benzoxazocine-5-carbohydrazide (**4b**): Reaction time 8 h, m.p. 220–222 °C, yield 66 %. IR: ν 3178, 1671, 1590, 1484 cm^{-1}. ^{1}H NMR: δ 1.46–1.56 (m, 6H, piperidinyl 3CH_2), 1.89–2.01 (m, 2H, naphthalene CH_2), 2.12 (dd, $J = 3.9$, 13.2 Hz, 1H, upfield H of CH_2CH), 2.36 (dd, $J = 2.1$, 13.2 Hz, 1H, downfield H of CH_2CH), 2.67 (t, $J = 6.3$ Hz, 2H, naphthalene CH_2), 2.83 (t, $J = 6$ Hz, 2H, naphthalene CH_2), 3.32–3.54 (m, 5H piperidinyl 2NCH_2 + hetero. H-6), 4.77 (d, $J = 1.2$ Hz, 1H, hetero. H-5), 6.88–8.27 (m, 13H, arom. H), 9.46 (br., 1H, NH). Anal. Calcd. for $C_{33}H_{34}N_4O_2$ (518.63): C, 76.42; H, 6.61; N, 10.80. Found: C, 76.61; H, 6.67; N, 10.65 %.

5,6-Dihydro-N-(2,3-dihydro-1H-indene-1-ylidene)-4-(morpholin-4-yl)-2-phenyl-2H-2,6-methano-1,3-benzoxazocine-5-carbohydrazide (**4c**): Reaction time 12 h, m.p. 212–214 °C, yield 51 %. IR: ν 3170, 1660, 1594, 1484 cm^{-1}. ^{1}H NMR: δ 2.15 (dd, $J = 3.9$, 13.2 Hz, 1H, upfield H of CH_2CH), 2.35 (dd, $J = 2.1$, 13.2 Hz, 1H, downfield H of CH_2CH), 2.87–2.91 (m, 2H, indane CH_2), 3.16–3.20 (m, 2H, indane CH_2), 3.41–3.51 (m, 5H morpholinyl 2NCH_2 + hetero. *H*-6), 3.60–3.63 (m, 4H, morpholinyl 2OCH_2), 4.67 (d, $J = 1.5$ Hz, 1H, hetero. *H*-5), 6.98–7.92 (m, 13H, arom. H), 9.70 (br., 1H, NH). ^{13}C NMR "APT": δ 27.28, 28.62, 30.51 (CH_2), 33.75 (hetero. *C*-6), 44.92 (morpholinyl NCH_2), 46.94 (hetero. *C*-5), 66.49 (morpholinyl OCH_2), 86.12 (hetero. *C*-2), 118.06, 120.31, 121.45, 125.73, 125.88, 127.28, 127.35, 127.77, 128.55, 131.12 (arom. CH), 124.77, 137.34, 146.08, 148.63, 152.98, 158.46, 159.82 (quaternary arom. C), 171.62 (C=O). Anal. Calcd. for $C_{31}H_{30}N_4O_3$ (506.58): C, 73.49; H, 5.97; N, 11.06. Found: C, 73.40; H, 5.86; N, 10.93 %.

5,6-Dihydro-N-(3,4-dihydronaphthalene-1(2H)-ylidene)-4-(morpholin-4-yl)-2-phenyl-2H-2,6-methano-1,3-benzoxazocine-5-carbohydrazide (**4d**): Reaction time 18 h, m.p. 216–218 °C, yield 54 %. IR: ν 3178, 1662, 1600, 1484 cm^{-1}. ^{1}H NMR: δ 1.89–2.03 (m, 2H, naphthalene CH_2), 2.14 (dd, $J = 3.9$, 13.2 Hz, 1H, upfield H of CH_2CH), 2.35 (dd, $J = 2.4$, 13.2 Hz, 1H, downfield H of CH_2CH), 2.67 (t, $J = 6.3$ Hz, 2H, naphthalene CH_2), 2.84 (t, $J = 6.3$ Hz, 2H, naphthalene CH_2), 3.46–3.51 (m, 5H morpholinyl 2NCH_2 + hetero. *H*-6), 3.56–3.64 (m, 4H, morpholinyl 2OCH_2), 4.72 (d, $J = 1.5$ Hz, 1H, hetero. H-5), 6.92–8.25 (m, 13H, arom. H), 9.43 (s, 1H, NH). Anal. Calcd. for $C_{32}H_{32}N_4O_3$ (520.61): C, 73.82; H, 6.20; N, 10.76. Found: C, 73.65; H, 6.12; N, 10.56 %.

2-(4-Chlorophenyl)-5,6-dihydro-N-(2,3-dihydro-1H-indene-1-ylidene)-4-(piperidin-1-yl)-2H-2,6-methano-1,3-benzoxazocine-5-carbohydrazide (**4e**): Reaction time 11 h, m.p. 231–233 °C, yield 52 %. IR: ν 3174, 1657, 1590, 1484 cm^{-1}. ^{1}H NMR: δ 1.45–1.60 (m, 6H, piperidinyl 3CH_2), 2.09 (dd, $J = 3.9$, 13.2 Hz, 1H, upfield H of CH_2CH), 2.30 (dd, $J = 2.4$, 13.2 Hz, 1H, downfield H of CH_2CH), 2.85–2.89 (m, 2H, indane CH_2), 3.16–3.20 (m, 2H, indane CH_2), 3.32–3.52 (m, 5H piperidinyl 2NCH_2 + hetero. *H*-6), 4.70 (d, $J = 1.5$ Hz, 1H, hetero. H-5), 6.95–7.81 (m, 12H, arom. H), 9.35 (br., 1H, NH). Anal. Calcd. for $C_{32}H_{31}ClN_4O_2$ (539.053): C, 71.30; H, 5.80; N, 10.39. Found: C, 71.10; H, 6.63; N, 10.50 %.

2-(4-Chlorophenyl)-5,6-dihydro-N-(3,4-dihydronaphthalene-1(2H)-ylidene)-4-(piperidin-1-yl)-2H-2,6-methano-1,3-benzoxazocine-5-carbohydrazide (**4f**): Reaction time 13 h, m.p. 219–221 °C, yield 69 %. IR: ν 3185, 1664, 1589, 1484 cm^{-1}. ^{1}H NMR: δ 1.46–1.60 (m, 6H, piperidinyl 3CH_2), 1.85–2.05 (m, 2H, naphthalene CH_2), 2.08 (dd, $J = 3.9$, 13.2 Hz, 1H, upfield H of CH_2CH), 2.31 (dd, $J = 2.4$, 13.2 Hz, 1H, downfield H of CH_2CH), 2.66 (t, $J = 6.6$ Hz, 2H, naphthalene CH_2), 2.84 (t, $J = 6$ Hz, 2H, naphthalene CH_2), 3.31–3.53 (m, 5H piperidinyl 2NCH_2 + hetero. *H*-6), 4.77 (d, $J = 1.5$ Hz, 1H, hetero. *H*-5), 6.91–8.26 (m, 12H, arom. H), 9.59 (br., 1H, NH). Anal. Calcd. for $C_{33}H_{33}ClN_4O_2$ (553.073): C, 71.66; H, 6.01; N, 10.13. Found: C, 71.78; H, 6.09; N, 10.25 %.

2-(4-Chlorophenyl)-5,6-dihydro-N-(2,3-dihydro-1H-indene-1-ylidene)-4-(morpholin-4-yl)-2H-2,6-methano-1,3-benzoxazocine-5-carbohydrazide (**4 g**): Reaction time 11 h, m.p. 240–242 °C, yield

48 %. IR: ν 3174, 1658, 1596, 1484 cm^{-1}. ^1H NMR: δ 2.11 (dd, *J* = 3.9, 13.2 Hz, 1H, upfield H of CH_2CH), 2.30 (dd, *J* = 2.1, 13.2 Hz, 1H, downfield H of CH_2CH), 2.84–2.88 (m, 2H, indane CH_2), 3.16–3.21 (m, 2H, indane CH_2), 3.40–3.50 (m, 5H morpholinyl $2NCH_2$ + hetero. *H*-6), 3.60–3.63 (m, 4H, morpholinyl $2OCH_2$), 4.65 (d, *J* = 1.5 Hz, 1H, hetero. *H*-5), 6.96–7.89 (m, 12H, arom. H), 9.30 (br., 1H, NH). Anal. Calcd. for $C_{31}H_{29}ClN_4O_3$ (541.023): C, 68.82; H, 5.40; N, 10.36. Found: C, 69.00; H, 5.49; N, 10.53 %.

2-(4-Chlorophenyl)-5,6-dihydro-N-(3,4-dihydronaphthalene-1(2H)-ylidene)-4-(morpholin-4-yl)-2H-2,6-methano-1,3-benzoxazocine-5-carbohydrazide (**4h**): Reaction time 14 h, m.p. 229–231 °C, yield 54 %. IR: ν 3185, 1658, 1598, 1484 cm^{-1}. ^1H NMR: δ 1.86–2.05 (m, 2H, naphthalene CH_2), 2.10 (dd, *J* = 3.9, 13.2 Hz, 1H, upfield H of CH_2CH), 2.30 (dd, *J* = 2.4, 13.2 Hz, 1H, downfield H of CH_2CH), 2.65 (t, *J* = 6.3 Hz, 2H, naphthalene CH_2), 2.85 (t, *J* = 6.0 Hz, 2H, naphthalene CH_2), 3.40–3.50 (m, 5H morpholinyl $2NCH_2$ + hetero. *H*-6), 3.60–3.64 (m, 4H, morpholinyl $2OCH_2$), 4.71 (d, *J* = 1.5 Hz, 1H, hetero. *H*-5), 6.93–8.24 (m, 12H, arom. H), 9.40 (br., 1H, NH). Anal. Calcd. for $C_{32}H_{31}ClN_4O_3$ (555.053): C, 69.24; H, 5.63; N, 10.09. Found: C, 69.48; H, 5.83; N, 9.97 %.

5,6-Dihydro-N-(3,4-dihydronaphthalene-1(2H)-ylidene)-2-(4-methylphenyl)-4-(piperidin-1-yl)-2H-2,6-methano-1,3-benzoxazocine-5-carbohydrazide (**4i**): Reaction time 12 h, m.p. 214–216 °C, yield 64 %. IR: ν 3185, 1668, 1592, 1484 cm^{-1}. ^1H NMR: δ 1.45–1.63 (m, 6H, piperidinyl $3CH_2$), 1.80–2.00 (m, 2H, naphthalene CH_2), 2.11 (dd, *J* = 3.6, 12.9 Hz, 1H, upfield H of CH_2CH), 2.35 (dd, *J* = 2.4, 13.2 Hz, 1H, downfield H of CH_2CH), 2.38 (s, 3H, CH_3), 2.68 (t, *J* = 6.3 Hz, 2H, naphthalene CH_2), 2.81 (t, *J* = 6.3 Hz, 2H, naphthalene CH_2), 3.32–3.54 (m, 5H piperidinyl $2NCH_2$ + hetero. *H*-6), 4.78 (d, *J* = 1.5 Hz, 1H, hetero. *H*-5), 6.90–8.27 (m, 12H, arom. H), 10.00 (br., 1H, NH). Anal. Calcd. for $C_{34}H_{36}N_4O_2$ (532.66): C, 76.66; H, 6.81; N, 10.52. Found: C, 76.61; H, 6.77; N, 10.46 %.

5,6-Dihydro-N-(3,4-dihydronaphthalene-1(2H)-ylidene)-2-(4-methylphenyl)-4-(morpholin-4-yl)-2H-2,6-methano-1,3-benzoxazocine-5-carbohydrazide (**4j**): Reaction time 13 h, m.p. 223–225 °C, yield 52 %. IR: ν 3180, 1664, 1600, 1484 cm^{-1}. ^1H NMR: δ 1.86–2.05 (m, 2H, naphthalene CH_2), 2.13 (dd, *J* = 3.9, 13.2 Hz, 1H, upfield H of CH_2CH), 2.33 (dd, *J* = 2.4, 13.2 Hz, 1H, downfield H of CH_2CH), 2.38 (s, 3H, CH_3), 2.66 (t, *J* = 6.6 Hz, 2H, naphthalene CH_2), 2.83 (t, *J* = 6.0 Hz, 2H, naphthalene CH_2), 3.40–3.50 (m, 5H morpholinyl $2NCH_2$ + hetero. *H*-6), 3.57–3.64 (m, 4H, morpholinyl $2OCH_2$), 4.70 (d, *J* = 1.5 Hz, 1H, hetero. *H*-5), 6.92–8.23 (m, 12H, arom. H), 9.50 (br., 1H, NH). Anal. Calcd. for $C_{33}H_{34}N_4O_3$ (534.63): C, 74.13; H, 6.41; N, 10.48. Found: C, 74.02; H, 6.29; N, 10.72 %.

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