Artigo

EFFICIENT SYNTHESIS OF BENZOTHIAZINE AND ACRYLAMIDE COMPOUNDS

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This article describes the synthesis of the new (2*Z*)-2-(4-methoxybenzylidene)-6-nitro-4*H*-benzo[1,4]thiazin-3-one, (2*Z*)-2-(4-methoxybenzylidene)-4-methyl-6-nitro-4*H*-benzo[1,4]thiazin-3-one, (2*Z*)-6-amino-2-(4-methoxybenzylidene)-4*H*-benzo[1,4] thiazin-3-one, (2*Z*)-6-butylamino-2-(4-methoxybenzylidene)-4-methyl-4*H*-benzo[1,4]-thiazin-3-one and (2*E*)-*N*-alkyl-*N*-(2-hydroxy-5-nitrophenyl)-3-phenylacrylamides and the spectroscopic data. The arylidenebenzothiazine compounds were prepared using the Knoevenagel condensation with substituted benzaldehydes in the presence of sodium methoxide in DMF. The presence of a nitro substituent in the 4-position, water and a slightly acid reaction medium in this condensation caused the rupture of the benzothiazine ring and subsequent formation of the phenylacrylamide compounds. A crystallographic data was presented for (2*E*)-3-(4-bromophenyl)-*N*-dodecyl-*N*-(2-hydroxy-5-nitrophenyl) acrylamide.

Keywords: benzothiazines; acrylamides; X-ray crystallography.

INTRODUCTION

1,4-Benzothiazine derivatives exhibit a wide range of pharmacological properties, including antifungal, immunostimulating, anti-aldoso-reductase, anti-rheumatic, anti-allergic, vasorelaxant, anti-arrhythmic, anti-hypertensive, neuroprotective and cytotoxic activities. These properties indicate that 1,4-benzothiazine is a template that may be potentially useful in medicinal chemistry research and therapeutic applications.[1]

Gupta and Ojha[2] reviewed the chemical and pharmacological properties of phenothiazines and 1,4-benzothiazines. Some of the latter showed microbiological and antitumor activities.[3,4] The synthesis, spectroscopic properties and microbiological activities of several 6-alkylacylamino-4-methyl-4*H*-benzo[1,4]thiazin-3-ones have also been reported.[5] Moreover, the reactivity of a methylene group activated by a carbonyl substituent or a thioxo has been studied by Guarda and Silva.[6,7] Condensation of 1,4-benzothiazin-3-ones with arylaldehydes or Michael addition on cyanoacrylates leads to the formation of 2-arylidene-4*H*-benzo[1,4]thiazin-3-one compounds.[8]

RESULTS AND DISCUSSION

The present study describes the synthesis of substituted (2*E*)-*N*-alkyl-*N*-(2-hydroxy-5-nitrophenyl)-3-phenylacrylamides, (**4-6**), (2*Z*)-2-(4-methoxybenzylidene)-6-nitro-4*H*-benzo[1,4]thiazin-3-one, (**7**), (2*Z*)-2-(4-methoxybenzylidene)-4-methyl-6-nitro-4*H*-benzo[1,4]thiazin-3-one (**8**) and (2Z)-6-amino-2-(4-methoxybenzylidene)-4*H*-benzo[1,4] thiazin-3-one (**9**) or (2*Z*)-6-butylamino-2-(4-methoxybenzylidene)-4-methyl-4*H*-benzo[1,4]thiazin-3-one (**12**), Figure 1. The intermediary 6-nitro-4*H*-benzo[1,4]-oxazin-3-one, which were not isolated, were obtained as a result of the Knoevenagel condensation of activated 4-alkyl-6-nitro-4*H*-benzo[1,4]thiazin-3-one **2-3** with 4-methoxy or 4-bromobenzaldehydes in the presence of sodium methoxide in DMF.[9]

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The (2*Z*)-2-(4-methoxybenzylidene)-4-methyl-6-nitro-4*H*-benzo[1,4]thiazin-3-one **8** was first condensed in position 2; subsequently, alkylation was carried out at position 4.[10] Methylation followed by condensation did not yield good results. The reduction of the nitro group to a primary amine with tin chloride in concentrated hydrochloric acid produced (2*Z*)-6-amino-2-(4-methoxybenzylidene)-4*H*-benzo[1,4] thiazin-3-one **9** or 6-amino-4-methyl-4*H*-benzo[1,4]thiazin-3-one **10**.[11]

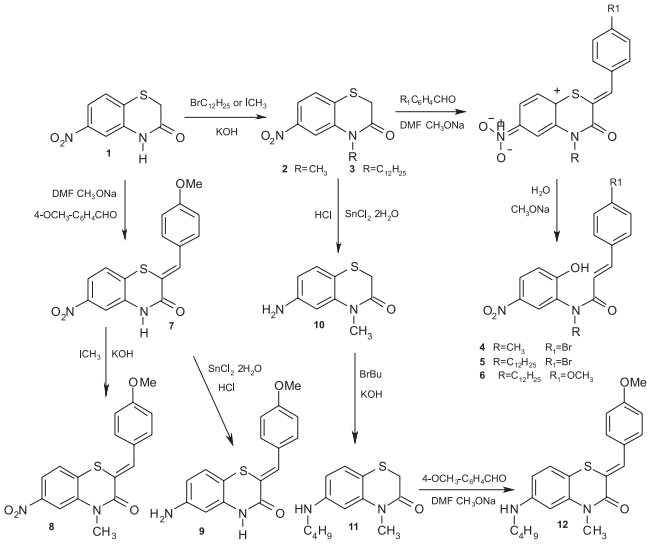

Figure 1. *Benzothiazine and acrylamide derivatives: synthetic pathways*

The arylidenebenzothiazines (**7**,**12**) described in this work were isolated in a single isomeric form. It has been previously demonstrated[12] that the *Z* isomer is the main derivative that is obtained from the standard Knoevenagel condensation of benzaldehydes with benzylidene-4*H*-benzo[1,4]thiazin-3-ones in an alkaline medium. The study was carried out using coupled NMR ^{13}C-H spectrometry. The value of the coupling

constant between the ethylene proton and the carbon of the carbonyl group in position 3 verifies the existence of the *Z* isomer.

The (2*E*)-*N*-alkyl-*N*-(2-hydroxy-5-nitrophenyl)-3-phenylacrylamides **4**-**6** were formed due to the presence of the nitro group in the *para*-position, water and the excess of heat lead in a slightly acid reaction medium to the formation of the intermediary 6-nitro-4*H*-benzo[1,4]-oxazin-3-one and posterior rupture, figure 2. The chemical shifts and coupling constants in the ^{1}H NMR of ethylenic protons and the crystallographic data show that the *N*-alkyl-*N*-(2-hydroxy-5-nitro-phenyl)-3-phenylacrylamides (**4**-**6**) that formed have the *E* configuration.

The spectroscopic characteristics and IR, ^{1}H NMR and MS spectroscopic data of the arylidenebenzothiazines and acrylamides that were prepared are given in the experimental section.

Crystallographic data

The crystal data, collection procedures, structure determination methods and refinement results for the (2*E*)-3-(4-bromo-phenyl)-*N*-dodecyl-*N*-(2-hydroxy-5-nitro-phenyl)acrylamide (**5**) are summarized in Table 1. We used the following programs: for the cell determination and data collection,[13] data reduction,[14] data collection,[15] structure resolution,[16] refinement,[17] graphic presentation[18] and material to publication.[19]

The structure was solved by direct methods and refined by a full-matrix least squares calculations. The refinement was conducted until all atomic parameter shifts were smaller than their standard deviations. All H atoms were located by geometrical considerations. In the final difference Fourier map there are no peaks greater than 0.34 Å^{-3}. The asymmetrical unit consists of two independent molecules, which are not related one to the other by symmetry.

Table 1. Crystal data and structure refinement

Empirical formula	$C_{27}H_{35}O_4N_2Br$
Formula weight	531.48
Temperature	120(2) K
Wavelength	0.71070 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 11.0421(5) Å
b = 7.3059(3) Å	β= 91.51(2)°
c = 32.3832(16) Å	
Volume	2611.5(2) Å^3
Z	4
Density (calculated)	1.352 Mg/m^3
Absorption coefficient	1.608 mm^{-1}
F(000)	1112
Crystal size	0.12 x 0.10 x 0.10 mm
Theta range for data collection	1.26 to 25.0°
Index ranges	$-12 \le h \le 13$, $-8 \le k \le 8$, $-38 \le l \le 38$
Reflections collected	15287
Independent reflections	8677 [R(int) = 0.0163]
Absorption correction	Multiscan
Refinement method	Full-matrix least-squares on F^2
Data / parameters	5425 / 615
Goodness-of-fit on F^2	1.046
Final R indices [I>2σ(I)]	R1 = 0.061, wR2 = 0.1191

In both independent molecules, no conformational differences are observed. Bond lengths and angles agree well, within the experimental accuracy, with values found in literature, Figure 2.

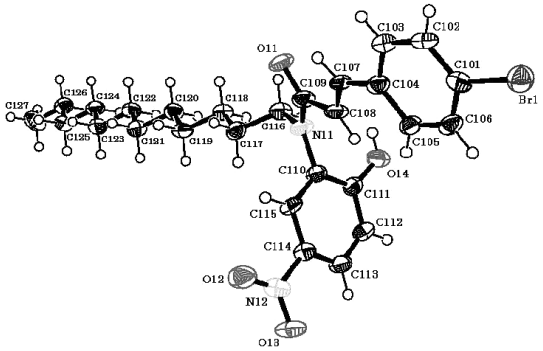

Figure 2. *Perspective view of one molecule from the asymmetric unit of the acrylamide* ***5*** *with atom-labeling. Displacement of ellipsoids plotted at the 30% probability level are shown for the non-H atoms*

CONCLUSION

The study of the reactivity of 1,4-benzothiazine heterocyclic ring activated in position 3 by carbonyl substituent leads by Knoevenagel condensation with arylaldehydes to the formation of arylidenebenzothiazines compounds in the form of a single isomer in good yields. Phenylacrylamide derivatives were also obtained by rupture of the benzothiazine ring.

EXPERIMENTAL

Melting points were measured on a Quimis Q340D apparatus with an oil bath in capillary tubes. Thin layer chromatography was performed on Merck 60F$_{254}$ silica gel plates with a 0.2 mm thickness. Compounds were powdered, mixed with KBr at 1% concentration and pressed into pellets before infrared spectra were recorded on a FT-IFS 66 Bruker spectrometer; the wavelengths are expressed in cm^{-1}. Nuclear magnetic resonance spectra were recorded on a Varian Unity Plus spectrometer ^{1}H NMR at 300 MHz; the chemical shifts (δ) are expressed in parts per million (ppm) and the coupling constants (*J*) in Hertz (Hz). DMSO-d$_6$ was used as the solvent and SiMe$_4$ as the reference. Electronic impact (70 eV) mass spectra were recorded on an HP G1019A, coupled to a CPG HP 5890 spectrometer; for compounds (**5**) and (**6**) chemistry ionization was performed in ammonia and isobutane and recorded on a Waters ZQ apparatus. The intensities of the molecular peaks are presented relative to the most intense peak M$^+$(%). The synthesis and the spectroscopic characteristics of 6-nitro-4*H*-benzo[1,4]thiazin-3-one (**1**), 4-methyl-6-nitro-4*H*-benzo[1,4]thiazin-3-one (**2**), 6-amino-4-methyl-4*H*-benzo[1,4]thiazin-3-one (**10**) and 6-butylamino-4-methyl-4*H*-benzo[1,4]thiazin-3-one (**11**) have been already described.[5]

4-Dodecyl-6-nitro-4*H*-benzo[1,4]thiazin-3-one (3)

A suspension of 6-nitro-4*H*-benzo[1,4]thiazin-3-one (**1**) 0.5 g (2.38 mmol) in DMSO/EtOH 50% was treated with potassium hydroxide 0.27 g (4.8 mmol). The reaction mixture was maintained under strong agitation for 10 min at room temperature. Dodecylbromide (1.18 mL, 4.76 mmol) was added dropwise while stirring. The reaction mixture was then maintained under agitation at 55 °C for 15 h. The crude product was extracted with ethyl acetate. After solvent evaporation, the compound was purified using flash chromatography on silica 60 (230-400 Mesh) using toluene as the eluent. The product appeared as a viscous oil that crystallized after a few days in a desiccator. $C_{20}H_{30}N_2O_3S$, 0.57 g (64%), mp 37-39 °C; TLC silica gel plates type 60F$_{254}$, R$_f$ (C_6H_6) 0.58; IR (potassium bromide) ν_{max} cm^{-1}: 2916, 2849, 1681, 1524, 1342 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 0.85 (t, 3 H, CH_3) *J* 6.9Hz, 1.21 (s, 16 H, CH_2), 1.51 (m, 2 H, CH_2CH_3), 3.3 (m, 2 H, βCH_2), 3.63 (s, 2 H, SCH_2), 4.06 (t, 2 H, αCH_2) *J* 7.3 Hz, 7.71 (d, 1 H, H8 benzothiazine)

J 8.4 Hz, 7.89 (dd, 1 H, H7 benzothiazine) *J* 8.4 and 2.4 Hz, 8.02 (d, 1 H, H5 benzothiazine) *J* 2.4 Hz.; MS, *m/z*(%): 378(M^+ 7.86), 331(100), 332(9.7), 329(21.9), 211(12.7), 209(3), 195(17.2), 181(27.4).

General procedure for (2*E*)-N-alkyl-N-(2-hydroxy-5-nitrophenyl)-3-phenylacrylamides compounds (4-6)

A mixture of 6-nitro-4-alkyl-4*H*-benzo[1,4]thiazin-3-one (0.26 mmol) and substituted benzaldehyde (0.26 mmol) in 3 mL of DMF was treated with sodium methoxide in excess. The solution was refluxed at 125 °C for 6 h. After cooling, the isolated precipitate was washed with water. The compounds were of acceptable purity and were analyzed without further recrystallization.

(2*E*)-3-(4-Bromophenyl)-*N*-(2-hydroxy-5-nitrophenyl)-*N*-methylacrylamide (4)

$C_{16}H_{13}BrN_2O_4$, 0.042 g (43%), mp 150-152 °C; TLC silica gel plates type $60F_{254}$, R_f ($CHCl_3$: EtOH 99.5:0.5) 0.48; IR (potassium bromide) ν_{max} cm^{-1}: 3429, 3079, 1656, 1584, 1511, 1340, 1320, 817; ^1H NMR (300 MHz, DMSO-d_6): δ 3.19 (s, 3 H, CH_3), 6.4 (d, 1 H, H2 ethylene) *J* 15 Hz, 7.13 (d, 2 H, H2"6" phenyl) *J* 9.6 Hz, 7.4 (d, 1 H, H3' phenyl) *J* 7.5 Hz, 7.49 (d, 2 H, H3"5" phenyl) *J* 8.4 Hz, 7.5 (d, 1 H, H3 ethylene) *J* 15.6 Hz, 8.17 (s, 1 H, H6' phenyl), 8.18 (d, 1 H, H4' phenyl) *J* 7.2 Hz; MS, *m/z*(%): 376(M^+ 2.52), 209(100), 210(15.5), 211(88.1), 181(19.6), 102(79.8).

(2*E*)-3-(4-bromophenyl)- *N*-dodecyl-*N*-(2-hydroxy-5-nitrophenyl)acrylamide (5)

$C_{27}H_{35}BrN_2O_4$, 0.062 g (45%), mp 117 °C; TLC silica gel plates type $60F_{254}$, R_f (C_6H_6: AcOEt 8:2) 0.62; IR (potassium bromide) ν_{max} cm^{-1}: 2924, 2853, 1642, 1599, 1530, 1341, 1305; ^1H NMR (300 MHz, DMSO-d_6): δ 0.84 (t, 3 H, CH_3) *J* 7.2 Hz, 1.21 (s, 16 H, CH_2), 1.44 (m, 2 H, CH_2CH_3), 3.51 (m, 2 H, βCH_2), 3.76 (m, 2 H, αCH_2), 6.34 (d, 1 H, H2 ethylene) *J* 15.6 Hz, 7.09 (d, 1 H, H3' phenyl) *J* 9.3 Hz, 7.38 (d, 2 H, H2"6" phenyl) *J* 8.7 Hz, 7.48 (d, 1 H, H3 ethylene) *J* 15 Hz, 7.51 (d, 2 H, H3"5" phenyl) *J* 8.4 Hz, 8.06 (d, 1 H, H6' phenyl) *J* 3 Hz, 8.17 (dd, 1 H, H4' phenyl) *J* 9.3 and 2.6 Hz; DCI, NH_3/isobutane: 531(MH^+ 100), 532(M+2 39.39), 533(MH^++2 64.49), 397(3.9), 323(21.4), 209(19), 211(15.3), 167(7.2), 130(5.5).

(2*E*)- *N*-dodecyl-*N*-(2-hydroxy-5-nitrophenyl)-3-(4-methoxyphenyl)acrylamide (6)

$C_{28}H_{38}N_2O_5$, 0.055 g (44%), mp 130-132 °C; TLC silica gel plates type $60F_{254}$, R_f (C_6H_6:AcOEt 8:2) 0.67; IR (potassium bromide) ν_{max} cm^{-1}: 2926, 2854, 1645, 1604, 1513, 1336, 1250, 828; ^1H NMR (300 MHz, DMSO-d_6): δ 0.84 (t, 3 H, CH_3) *J* 6.6Hz, 1.22 (s, 16 H, CH_2), 1.42 (m, 2 H, CH_2CH_3), 3.32 (m, 2 H, βCH_2 hidden for the water), 3.74 (s, 3 H, OCH_3), 3.79 (m, 2 H, αCH_2), 6.2 (d, 1 H, H2 ethylene) *J* 15.6 Hz, 6.63 (d, 1 H, H3' phenyl) *J* 9.9 Hz, 6.88 (d, 2 H, H3"5" phenyl) *J* 9 Hz, 7.31 (d, 2 H, H2"6" phenyl) *J* 8.7 Hz, 7.4 (d, 1 H, H3 ethylene) *J* 15.6 Hz, 7.86 (d, 1 H, H6' phenyl) *J* 3 Hz, 7.96 (dd, 1 H, H4' phenyl) *J* 9.1 and 2.8 Hz; MS, m/z(%) DCI, NH_3/isobutane: 483(MH^+ 0.95), 409(46.6), 384(22.5), 328(20.5), 295(51.2), 273(100), 247(29.4), 191(58), 163(68.3).

(2*Z*)-2-(4-Methoxybenzylidene)-6-nitro-4*H*-benzo[1,4]thiazin-3-one (7)

An equimolar mixture of 6-nitro-4*H*-benzo[1,4]thiazin-3-one (**1**) (250 mg, 1.19 mmol) and 4-methoxy-benzaldehyde (162 mg) in 2 mL of anhydrous DMF was treated with sodium methoxide in excess and refluxed at 125 °C for 3 h under nitrogen pressure. After cooling, the obtained precipitate was purified by washing with toluene. $C_{16}H_{12}N_2O_4S$, 0.269 g (69%), mp 261-263 ºC; TLC silica gel plates type $60F_{254}$, R_f (C_6H_6:AcOEt 7:3) 0.72; IR (potassium bromide) ν_{max} cm^{-1}: 2956, 1665, 1604, 1512, 1343, 1255, 737. ^1H NMR (300 MHz, DMSO-d_6): δ 3.83 (s, 3 H, OCH_3), 7.09 (d, 2 H, H3'5' phenyl) *J* 9 Hz, 7.68 (d, 2 H, H2'6' phenyl) *J* 8.7 Hz, 7.6 (d, 1 H, H8 benzothiazine) *J* 8.7 Hz, 7.81 (s, 1 H, CH ethylene), 7.82 (dd, 1 H, H7 benzothiazine) *J* 8.7 and 2.4 Hz, 7.89 (d, 1 H, H5 benzothiazine) *J* 2.4 Hz, 11.24 (s, 1 H, NH); MS, *m/z*(%): 328(M^+ 100), 313(3.94), 295(84.9), 296(50.7), 281(14.1), 249(20).

(2*Z*)-2-(4-Methoxybenzylidene)-4-methyl-6-nitro-4*H*-benzo[1,4]thiazin-3-one (8)

A solution of (2*Z*)-2-(4-methoxybenzylidene)-6-nitro-4*H*-benzo[1,4]thiazin-3-one **7** (400 mg, 1.22 mmol) in DMSO/MEOH (5/6 mL) and potassium hydroxide (164 mg, 2.9 mmol) was stirred at room temperature for 10 min. Methyl iodide (0.18 mL, 2.43 mmol) was added dropwise under stirring. The mixture was stirred at 55 ºC for 15 h. After cooling, the crude was extracted with ethyl acetate. After the solvent evaporated, the compound was washed with acetone. $C_{17}H_{14}N_2O_4S$, 0.267 g (64%), mp 147-150 °C; TLC silica gel plates type $60F_{254}$, (C_6H_6) 0.59, IR (potassium bromide) ν_{max} cm^{-1}: 2925, 1649, 1601, 1511, 1342, 1254, 1021, 821; ^1H NMR (300 MHz, DMSO-d_6): δ 3.56 (s, 3 H, CH_3), 3.83 (s, 3 H, OCH_3), 7.09 (d, 2 H, H3'5' phenyl) *J* 8.7 Hz, 7.68 (d, 2 H, H2'6' phenyl) *J* 9 Hz, 7.69 (d, 1 H, H8 benzothiazine) *J* 8.1 Hz, 7.84 (s, 1 H, CH ethylene), 7.94 (dd, 1 H, H7 benzothiazine) *J* 10.5 and 2.1 Hz, 7.96 (d, 1 H, H5 benzothiazine) *J* 1.8 Hz; MS, *m/z*(%): 342(M^+ 24,85), 314(5.75), 310(58.9), 308(100), 306(30.7), 296(9.5), 292(14.6).

(2*Z*)-6-Amino-2-(4-methoxybenzylidene)-4*H*-benzo[1,4]thiazin-3-one (9)

Over a period of 15 min, 100 mg (0.3 mmol) of compound (**7**) was added stepwise to a cold, stirring solution of 324 mg (0.3 mmol) of stannous dihydrate in 35 µL of concentrated HCl. The mixture was then left for 15 min at room temperature and refluxed for 2 h. After cooling, the precipitate was suspended in water and a 20% sodium hydroxide solution was added (pH 10) to produce the corresponding amine, which was collected and washed with 10% sodium hydroxide and water. $C_{16}H_{14}N_2O_2S$, 0.061 g (68%), mp 210-213 ºC; TLC silica gel plates type $60F_{254}$, R_f ($CHCl_3$:EtOH 9:1) 0.58; IR (potassium bromide) ν_{max} cm^{-1}: 3387, 3302, 3017, 2958, 2835, 1659, 1604, 1509, 1253, 1173, 801. ^1H NMR (300 MHz, DMSO-d_6): δ 3.81 (s, 3 H, OCH_3), 5.24 (s, 2 H, NH_2), 6.26 (d, 1 H, H5 benzothiazine) *J* 2.1 Hz, 6.28 (d, 1 H, H7 benzothiazine) *J* 8.4 Hz, 6.90 (d, 1 H, H8 benzothiazine) *J* 8.1 Hz, 7.05 (d, 2 H, H3'5' phenyl) *J* 9 Hz, 7.63 (d, 2 H, H2'6' phenyl) *J* 9 Hz, 7.67 (s, 1 H, CH ethylene); MS, *m/z*(%): 299(MH^+ 14.34), 297(84.7), 265(100), 250(22.9), 237(13.1), 222(17.3).

(2*Z*)-6-Butylamino-2-(4-methoxybenzylidene)-4-methyl-4*H*-benzo[1,4]thiazin-3-one (12)

We successfully used the method of condensation described for (**7**). $C_{21}H_{24}N_2O_2S$, 0.055 g (50%), mp 102-104 ºC; TLC silica gel plates type $60F_{254}$, R_f ($CHCl_3$:EtOH 9:1) 0.47; IR (KBr) ν_{max} cm^{-1}: 3371, 2958, 2926, 1635, 1601, 1507, 1257, 1143, 827. ^1H NMR (300 MHz, DMSO-d_6): δ 0.91 (t, 3 H, CH_3 δ) *J* 7.2 Hz, 1.31-1.44 (m, 2 H, CH_2 β), 1.48-1.57 (m, 2 H, CH_2 γ), 2.98-3.04 (m, 2 H, CH_2 α), 3.41 (s, 3 H, NCH_3), 3.81 (s, 3 H, OCH_3), 5.79 (t, 1 H, NH) *J* 5.6 Hz, 6.33 (dd,

1 H, H7 benzothiazine) *J* 8.4 and 2.1 Hz, 6.43 (d, 1 H, H5 benzothiazine) *J* 2.1 Hz, 7.02 (d, 1 H, H8 benzothiazine) *J* 8.7 Hz, 7.05 (d, 2 H, H3'5' phenyl) *J* 9 Hz, 7.63 (d, 2 H, H2'6' phenyl) *J* 9 Hz, 7.69 (s, 1 H, CH ethylene); MS, *m/z*(%): 368(M^+ 43.89), 367(100), 335(28), 334(20.1), 326(13.3), 312(10.2), 309(11.6), 256(8.5).

SUPPLEMENTARY INFORMATION

Supplementary crystallographic data have been deposited in the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 242133. Copies of the available material can be obtained, free of charge, by contacting the Director at CCDC, 12 Union Road, Cambridge CH21EZ, UK (fax: +44-1223-336-033 or by e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk.

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