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New 1,3-benzoxazin-2-ones or thiones of molluscicidal activity

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A facile synthetic approach towards 3-aryl, alkyl or β-glucopyranosyl-1,3-benzoxazin-2-ones and their thio-analogues **3** was adopted via the reaction of the easily available 3-(2-hydroxyaryl)-2-propen-1-ones **1** with a variety of isocyanates or isothiocyanates. The isolation of the open-chain carbamates **2** and then independent cyclization to the corresponding 1,3-benzoxazines **3** confirms the reaction sequence. Molluscicidal activity of the products was screened.

1. Introduction

1,3-Benzoxazines were reported to exhibit antibacterial [1, 2], antifungal [1], herbicidal [3, 4], antianginal [5–7], antihistaminic [8], antidepressant and antihypertensive [9] activities. In the light of all the above reports, it was intended in the present work to investigate the construction of various 1,3-benzoxazine derivatives from the easily available 3-(2-hydroxyaryl)-2-propen-1-ones **1** and screening their molluscicidal activity against the *Biomphalaria alexandrina* snails (the intermediate host of *Schistosoma mansoni*). Schistosomiasis is the most endemic disease in many tropic and subtropic regions. It is also a national problem in Egypt and is considered the public health enemy number one. Searching for a way to compete the intermediate host snails could be an efficient method to control that disease.

2. Investigations, results and discussion

2.1. Synthesis of the compounds

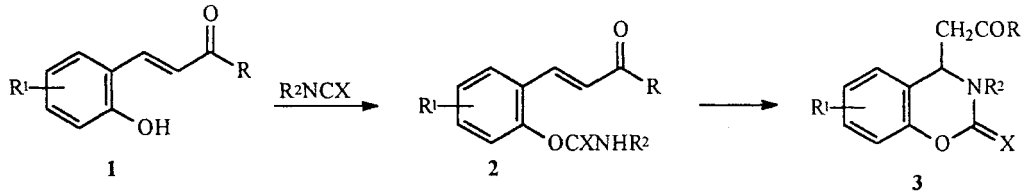
Reaction of 3-(2-hydroxyaryl)-2-propen-1-ones **1a–d** with a variety of aryl, alkyl isocyanates or their thio-analogues in dry benzene in the presence of triethylamine as a catalyst led directly to the formation of the corresponding 1,3-benzoxazin-2-ones or thiones **3a–p**. The reaction probably took place by initial formation of the open-chain carbamates **2** which spontaneously cyclized under the effect of the basic catalysis giving **3**. The structure of these compounds was established through spectroscopic and elemental analyses data. The absence of any NH stretching vibration band in the IR spectra as well as the presence of a $CHCH_2$ function in the ^{1}H-NMR spectra confirm the cyclized form structure of **3**. ^{1}H-NMR spectra of **3o**, **p** exhibit each of the methylene protons of the $C\underline{H}_2CH_3$ residue as a doublet of triplet signals. This is due to the mutual coupling with each other and in turn with the vicinal methyl protons (where $J_{vic.} \simeq ½\ J_{gem.}$).

However, reaction of **1a**, **c** with ethyl isocyanate in boiling dry benzene using triethylamine as a catalyst afforded the corresponding open-chain carbamates **2.** The latter could be cyclized to the corresponding 1,3-benzoxazine **3** under stronger basic conditions (i.e. refluxing in dry benzene in the presence of a catalytic amount of potassium hydroxide). On the other hand, **3q** could be alternatively isolated a one-step reaction of **1a** with ethyl isocyanate in the presence of potassium hydroxide as a basic catalyst.

The isolation of the open-chain carbamate **2** and its independent cyclization to the corresponding benzoxazine **3** explain not only the involvement of **2** in the reaction sequence but also the role of the basic catalysis in the cyclization.

Similarly, reaction of **1a** with 2,3,4,6-tetra-*O*-acetyl-β-glucopyranosylisothiocyanate in boiling dry denzene containing a catalytic amount of potassium hydroxide led to the formation of 3,4-dihydro-4-[2-oxo-2-(2-thienyl)ethyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-glucopyranosyl)-2 *H*-1,3-benzoxa-

Scheme



1 **2** **3**

a; R = 2-thienyl, R^1 = H
b; R = 2-thienyl, R^1 = 5-Cl
c; R = 2-thienyl, R^1 = 3-OCH_3
d; R = 2-furanyl, R^1 = H

a; R = 2-thienyl, R^1 = H, R^2 = C_2H_5, X = O
b; R = 2-thienyl, R^1 = 3-OCH_3, R^2 = C_2H_5, X = O

	R	R^1	R^2	X
a	2-thienyl	H	3,4-$Cl_2C_6H_3$	O
b	2-thienyl	5-Cl	3,4-$Cl_2C_6H_3$	O
c	2-thienyl	3-OCH_3	3,4-$Cl_2C_6H_3$	O
d	2-furanyl	H	3,4-$Cl_2C_6H_3$	O
e	2-thienyl	H	4-ClC_6H_4	O
f	2-thienyl	5-Cl	4-ClC_6H_4	O
g	2-thienyl	3-OCH_3	4-ClC_6H_4	O
h	2-thienyl	H	4-$OCH_3C_6H_4$	O
i	2-thienyl	5-Cl	4-$OCH_3C_6H_4$	O
j	2-thienyl	3-OCH_3	4-$OCH_3C_6H_4$	O
k	2-furanyl	H	4-$OCH_3C_6H_4$	O
l	2-thienyl	H	CH_3	S
m	2-thienyl	5-Cl	CH_3	S
n	2-furanyl	H	CH_3	S
o	2-thienyl	H	C_2H_5	S
p	2-furanyl	H	C_2H_5	S
q	2-thienyl	H	C_2H_5	O
r	2-thienyl	H	β-glucopyranosyl-2,3,4,6-tetraacetate	S

Table: Molluscicidal activity of the compounds

Compd.	% of snails killed at a concentration of		
	20 ppm	10 ppm	5 ppm
1a	100	100	10
1b	80	30	10
1c	100	50	–
1d	100	–	–
2a	100	90	10
2b	20	–	–
3a	30	10	10
3b	40	10	10
3c	50	10	10
3d	40	10	10
3e	20	10	10
3f	–	–	–
3g	–	–	–
3h	20	20	–
3i	–	–	–
3j	40	40	40
3k	30	10	–
3l	100	50	–
3m	100	100	100
3n	100	–	–
3o	30	10	10
3p	100	40	–
3q	100	90	10

zine-2-thione **(3r)**. The structure of **3r** was established through IR, ^{1}H-NMR and ^{1}H, ^{1}H-Cosy techniques as well as elemental analyses data (c.f. Experimental).

2.2. Molluscicidal activity screening

The toxicity of the products towards *Biomphalaria alexandrina* snails, the intermediate host of *Schistosoma mansoni* which affects the intestinal system in man was carried out according to the standard method [10–12]. The appropriate volume of acetone solution (10 ml containing 0.1 g of the test compound) was added to 1 l of water to get the required concentration. Ten snails were used in each experiment. Reference experiments were carried out using the same volume of acetone added to 1 l of water. Exposure and recovery periods were 24 h each.

Most of the compounds obtained show moderate molluscicidal activity (Table). However, the 3-alkyl benzoxazines exhibit more activity than the aryl ones. Few compounds show promising activity particularly **3m** which killed 100% of the snails at concentration down to 5 ppm. Otherwise, at a more diluted concentration (3 ppm) a milder result was obtained (30% kill of the tested snails).

3. Experimental

M.p.'s are uncorrected. IR spectra were recorded (KBr) on a JASCO FT/IR 300E spectrophotometer. ^{1}H-NMR as well as ^{1}H, ^{1}H-Cosy spectra were recorded on Varian GEMINI 200 (200 MHz). The starting propenones **1a–d** [13–15] were prepared according to reported procedures. All the results of elemental analyses were as expected within acceptable limits.

3.1. 3-[2-[[(Ethylamino)carbonyl]oxy]aryl]-1-(2-thienyl)-2-propen-1-ones **2a, b**

A mixture of equimolecular amounts of the appropriate **1** and ethyl isocyanate (5 mmol) in dry benzene (30 ml) containing triethylamine (3–5 drops) was boiled under reflux for the appropriate time. The solid separated upon concentrating the reaction mixture (to about 10 ml) was collected and crystallized from a suitable solvent affording the corresponding compounds **2a**, **b**.

3.1.1. 3-[2-[[(Ethylamino)carbonyl]oxy]phenyl]-1-(2-thienyl)-2-propen-1-one (**2a**)

Reaction time 35 h; pale yellow crystals from benzene; m.p. 139–141 °C; yield 1.1 g (73%). IR: $\nu = 3361$ cm^{-1} (NH); 1733, 1637 (CO); 1577, 1517 (C=C); 981 (*trans* C=C). ^{1}H-NMR ($CDCl_3$): δ 1.2 (t, 3 H, CH_3, J = 7.2 Hz); 3.24–3.37 (m, 2H, $C\underline{H}_2CH_3$); 5.44 (br. s, 1H, NH); 7.14 to 8.03 (m, 9H, 7 arom. H, 2 olefinic CH).
$C_{16}H_{15}NO_3S$ (301.4)

3.1.2. 3-[2-[[(Ethylamino)carbonyl]oxy]-3-methoxyphenyl]-1-(2-thienyl)-2-propen-1-one (**2b**)

Reaction time 40 h; colourless crystals from benzene; m.p. 160–162 °C; yield 1.2 g (73%). IR: $\nu = 3450$ cm^{-1} (NH); 1656, 1623 (CO); 1596, 1517 (C=C); 958 (*trans* C=C). ^{1}H-NMR ($CDCl_3$): δ 1.21 (t, 3H, CH_3, J = 7.2 Hz); 3.25–3.39 (m, 2H, $C\underline{H}_2CH_3$); 3.84 (s, 3H, OCH_3); 5.31 (br. s, 1H, NH); 6.96–8.00 (m, 8H, 6 arom. H, 2 olefinic CH).
$C_{17}H_{17}NO_4S$ (331.4)

3.2. 3,4-Dihydro-3,4-disubstituted-2H-1,3-benzoxazin-2-ones or thiones **3a–r**

A mixture of equimolecular amounts of the appropriate **1** and isocyanate or isothiocyanate (5 mmol) in dry benzene (30 ml) containing triethylamine, 3–5 drops (except in the case of **3q**, **r** where ≃ 25 mg KOH were used) was boiled under reflux for the appropriate time. The solid, separated upon concentrating the reaction mixture to half the initial volume, was collected (except in the case of **3q**, **r** where the mixture was evaporated to dryness under reduced pressure and the residue was triturated with 5 ml methanol) and crystallized from a suitable solvent affording the corresponding compounds **3a–r**.

3.2.1. 3-(3,4-Dichlorophenyl)-3,4-dihydro-4-[2-oxo-2-(2-thienyl)ethyl]-2 H-1,3-benzoxazin-2-one (**3a**)

Reaction time 90 min; colourless crystals from n-butanol; m.p. 196 to 198 °C; yield 1.8 g (86%). IR: $\nu = 1708$, 1654 cm^{-1} (CO); 1594, 1515 (C=C). ^{1}H-NMR ([D6]DMSO): δ 3.3 (dd, 1H, upfield H of CH_2, J = 5.4, 16.8 Hz); 3.76 (dd, 1H, downfield H of CH_2, J = 4.6, 16.8 Hz); 5.61 (t, 1H, $C\underline{H}CH_2$, J = 5 Hz); 7.09–7.99 (m, 10H, arom. H).
$C_{20}H_{13}Cl_2NO_3S$ (418.3)

3.2.2. 6-Chloro-3-(3,4-dichlorophenyl)-3,4-dihydro-4-[2-oxo-2-(2-thienyl)-ethyl]-2H-1,3-benzoxazin-2-one (**3b**)

Reaction time 6 h; colourless crystals from *n*-butanol; m.p. 203–205 °C; yield 2.1 g (93%). IR: $\nu = 1716$, 1648 cm^{-1} (CO); 1517, 1488 (C=C). ^{1}H-NMR ($CDCl_3$): δ 3.42 (d, 2H, $CHC\underline{H}_2$, J = 5.4 Hz); 5.43 (t, 1H, $C\underline{H}CH_2$, J = 5.4 Hz); 7.05–7.69 (m, 9H, arom. H).
$C_{20}H_{12}Cl_3NO_3S$ (452.7)

3.2.3. 3-(3,4-Dichlorophenyl)-3,4-dihydro-8-methoxy-4-[2-oxo-2-(2-thienyl)ethyl]-2H-1,3-benzoxazin-2-one (**3c**)

Reaction time 12 h; colourless crystals from *n*-butanol; m.p. 195–197 °C; yield 2.1 g (94%). IR: $\nu = 1737$, 1644 cm^{-1} (CO); 1589, 1515 (C=C). ^{1}H-NMR ($CDCl_3$): δ 3.39 (d, 2H, $CHC\underline{H}_2$, J = 6.2 Hz); 3.84 (s, 3H, OCH_3); 5.43 (t, 1H, $C\underline{H}CH_2$, J = 6.2 Hz); 6.78–7.62 (m, 9H, arom. H).
$C_{21}H_{15}Cl_2NO_4S$ (448.3)

3.2.4. 3-(3,4-Dichlorophenyl)-3,4-dihydro-4-[2-oxo-2-(2-furanyl)ethyl]-2 H-1,3-benzoxazin-2-one (**3d**)

Reaction time 12 h; colourless crystals from n-butanol; m.p. 182–184 °C; yield 1.9 g (95%). IR: $\nu = 1718$, 1662 cm^{-1} (CO); 1596, 1562 (C=C). ^{1}H-NMR ([D6]DMSO): δ 3.15 (dd, 1H, upfield H of CH_2, J = 5.8, 16.6 Hz); 3.58 (dd, 1H, downfield H of CH_2, J = 4.6, 16.6 Hz); 5.59 (t, 1H, $C\underline{H}CH_2$, J = 5.2 Hz); 6.62–7.93 (m, 10H, arom. H).
$C_{20}H_{13}Cl_2NO_4$ (402.2)

3.2.5. 3-(4-Chlorophenyl)-3,4-dihydro-4-[2-oxo-2-(2-thienyl)ethyl]-2H-1,3-benzoxazin-2-one (**3e**)

Reaction time 2.5 h; colourless crystals from *n*-butanol; m.p. 220–222 °C; yield 1.7 g (89%). IR: $\nu = 1704$, 1650 cm^{-1} (CO); 1594, 1517 (C=C). ^{1}H NMR ([D6]DMSO): δ 3.31 (dd, 1H, upfield H of CH_2, J = 5.6, 17.2 Hz); 3.69 (dd, 1 H, downfield H of CH_2, J = 4.0, 17.2 Hz); 5.52 (t, 1 H, $C\underline{H}CH_2$, J = 4.8 Hz); 7.08–7.99 (m, 11 H, arom. H).
$C_{20}H_{14}ClNO_3S$ (383.8)

3.2.6. 6-Chloro-3-(4-chlorophenyl)-3,4-dihydro-4-[2-oxo-2-(2-thienyl)ethyl]-2H-1,3-benzoxazin-2-one (**3f**)

Reaction time 10 h; colourless crystals from *n*-butanol; m.p. 226–228 °C; yield 1.9 g (91%). IR: $\nu = 1724$, 1639 cm^{-1} (CO); 1590, 1519 (C=C). ^{1}H NMR ([D6]DMSO): δ 3.32 (dd, 1 H, upfield H of CH_2, J = 5.6, 17.4 Hz); 3.76 (dd, 1 H, downfield H of CH_2, J = 4.0, 17.4 Hz); 5.52 (t, 1 H, $C\underline{H}CH_2$, J = 4.6 Hz); 7.12–8.01 (m, 10 H, arom. H).
$C_{20}H_{13}Cl_2NO_3S$ (418.3)

3.2.7. 3-(4-Chlorophenyl)-3,4-dihydro-8-methoxy-4-[2-oxo-2-(2-thienyl)-ethyl]-2 H-1,3-benzoxazin-2-one (**3g**)

Reaction time 27 h; colourless crystals from n-butanol; m.p. 174–176 °C; yield 1.6 g (78%). IR: $\nu = 1722$, 1652 cm^{-1} (CO); 1625, 1594 (C=C). ^{1}H

NMR ($CDCl_3$): δ 3.44 (d, 2H, $CHC\underline{H}_2$, J = 6.4 Hz); 3.88 (s, 3H, OCH_3); 5.47 (t, 1 H, $C\underline{H}CH_2$, J = 6.4 Hz); 6.82–7.64 (m, 10 H, arom. H).
$C_{21}H_{16}ClNO_4S$ (413.9)

3.2.8. 3,4-Dihydro-3-(4-methoxyphenyl)-4-[2-oxo-2-(2-thienyl)ethyl]-2 H-1,3-benzoxazin-2-one (**3h**)

Reaction time 30 h; colourless crystals from n-butanol; m.p. 178–180 °C; yield 1.7 g (90%). IR: ν = 1712, 1660 cm^{-1} (CO); 1596, 1560 (C=C). ^{1}H-NMR ($CDCl_3$): δ 3.44 (d, 2 H, $CHC\underline{H}_2$, J = 5.8 Hz); 3.8 (s, 3 H, OCH_3); 5.41 (t, 1 H, $C\underline{H}CH_2$, J = 6.0 Hz); 6.8–7.62 (m, 11 H, arom. H).
$C_{21}H_{17}NO_4S$ (379.4)

3.2.9. 6-Chloro-3,4-dihydro-3-(4-methoxyphenyl)-4-[2-oxo-2-(2-thienyl)-ethyl]-2H-1,3-benzoxazin-2-one (**3i**)

Reaction time 30 h; colourless crystals from *n*-butanol; m.p. 218–220 °C; yield 1.8 g (87%). IR: ν = 1722, 1646 cm^{-1} (CO); 1608, 1590 (C=C). ^{1}H NMR ($CDCl_3$): δ 3.45 (d, 2 H, $CHC\underline{H}_2$, J = 6.0 Hz); 3.8 (s, 3 H, OCH_3); 5.37 (t, 1 H, $C\underline{H}CH_2$, J = 6.0 Hz); 6.9–7.66 (m, 10 H, arom. H).
$C_{21}H_{16}ClNO_4S$ (413.9)

3.2.10. 3,4-Dihydro-8-methoxy-3-(4-methoxyphenyl)-4-[2-oxo-2-(2-thienyl)-ethyl]-2H-1,3-benzoxazin-2-one (**3j**)

Reaction time 48 h; colourless crystals from methanol; m.p. 173–175 °C; yield 1.7 g (83%). IR: ν = 1735, 1654 cm^{-1} (CO); 1623, 1606 (C=C). ^{1}H NMR ($CDCl_3$): δ 3.44 (dd, 1 H, upfield H of CH_2, J = 5.2, 11.4 Hz); 3.51 (dd, 1 H, downfield H of CH_2, J = 7.2, 11.4 Hz); 3.79 (s, 3H, OCH_3); 3.85 (s, 3 H, OCH_3); 5.41 (dd, 1 H, $C\underline{H}CH_2$, J = 5.4, 7.2 Hz); 6.81–7.63 (m, 10 H, arom. H).
$C_{22}H_{19}NO_5S$ (409.4)

3.2.11. 3,4-Dihydro-3-(4-methoxyphenyl)-4-[2-oxo-2-(2-furanyl)ethyl]-2 H-1,3-benzoxazin-2-one (**3k**)

Reaction time 40 h; colourless crystals from *n*-butanol; m.p. 179–181 °C; yield 1.7 g (94%). IR: ν = 1720, 1666 cm^{-1} (CO); 1606, 1560 (C=C). ^{1}H NMR ([D6]DMSO): δ 3.18 (dd, 1H, upfield H of CH_2, J = 6.2, 16.6 Hz); 3.48 (dd, 1H. downfield H of CH_2, J = 4.2, 16.6 Hz); 3.78 (s, 3H, OCH_3); 5.39 (dd, 1 H, $C\underline{H}CH_2$, J = 4.4, 6.0 Hz); 6.61–7.92 (m, 11 H, arom. H).
$C_{21}H_{17}NO_5$ (363.4)

3.2.12. 3,4-Dihydro-3-methyl-4-[2-oxo-2-(2-thienyl)ethyl]-2 H-1,3-benzoxazine-2-thione (**3l**)

Reaction time 90 h; colourless crystals from benzene; m.p. 138–140 °C; yield 1.3 g (86%). IR: ν = 1639 cm^{-1} (CO); 1592, 1513, 1488 (C=C, C=S). ^{1}H-NMR ($CDCl_3$): δ 3.31 (dd, 1 H, upfield H of CH_2, J = 7.6, 16.6 Hz); 3.44 (dd, 1 H. downfield H of CH_2, J = 5.2, 16.6 Hz); 3.53 (s, 3H, CH_3); 5.25 (dd, 1 H, $C\underline{H}CH_2$, J = 5.2, 7.6 Hz); 7.08–7.7 (m, 7 H, arom. H).
$C_{15}H_{13}NO_2S_2$ (303.4)

3.2.13. 6-Chloro-3,4-dihydro-3-methyl-4-[2-oxo-2-(2-thienyl)ethyl]-2 H-1,3-benzoxazine-2-thione (**3m**)

Reaction time 90 h; colourless crystals from methanol; m.p. 166–167 °C; yield 1.3 g (77%). IR: ν = 1646 cm^{-1} (CO); 1509, 1484, 1411 (C=C, C=S). ^{1}H-NMR ($CDCl_3$): δ 3.3 (dd, 1 H, upfield H of CH_2, J = 8.0, 17.0 Hz); 3.44 (dd, 1 H. downfield H of CH_2, J = 5.0, 16.8 Hz); 3.49 (s, 3 H, CH_3); 5.2 (dd, 1 H, $C\underline{H}CH_2$, J = 4.8, 8.0 Hz); 7.06–7.7 (m, 6 H, arom. H).
$C_{15}H_{12}ClNO_2S_2$ (337.8)

3.2.14. 3,4-Dihydro-3-methyl-4-[2-oxo-2-(2-furanyl)ethyl]-2 H-1,3-benzoxazine-2-thione (**3n**)

Reaction time 95 h; colourless crystals from ethanol; m.p. 146–147 °C; yield 1.2 g (84%). IR: ν = 1652 cm^{-1} (CO); 1617, 1590, 1560 (C=C, C=S). ^{1}H NMR ($CDCl_3$): δ 3.24 (dd, 1H, upfield H of CH_2, J = 7.6, 16.8 Hz); 3.37 (dd, 1 H, downfield H of CH_2, J = 5.4, 16.8 Hz); 3.51 (s, 3 H, CH_3); 5.21 (dd, 1 H, $C\underline{H}CH_2$, J = 5.4, 7.6 Hz); 6.51–7.57 (m, 7H, arom. H).
$C_{15}H_{13}NO_3S$ (287.3)

3.2.15. 3,4-Dihydro-3-ethyl-4-[2-oxo-2-(2-thienyl)ethyl]-2 H-1,3-benzoxazine-2-thione (**3o**)

Reaction time 60 h; colourless crystals from *n*-butanol; m.p. 184–186 °C; yield 0.8 g (50%). IR: ν = 1657 cm^{-1} (CO); 1595, 1515, 1459 (C=C, C=S). ^{1}H NMR ($CDCl_3$): δ 1.33 (t, 3 H, CH_3, J = 7.0 Hz); 3.32 (dd, 1H, upfield H of $CHC\underline{H}_2$, $J_{vic.}$ = 5.4, $J_{gem.}$ = 16.6 Hz); 3.42 (dd, 1 H, downfield H of $CHC\underline{H}_2$, $J_{vic.}$ = 7.6, $J_{gem.}$ = 16.6 Hz); 3.53 (dt, 1H, upfield H of $C\underline{H}_2CH_3$, J = 7.0, 14.0 Hz); 4.55 (dt, 1 H, downfield H of $C\underline{H}_2CH_3$, J = 7.2, 14.4 Hz); 5.23 (dd, 1 H, $C\underline{H}CH_2$, J = 5.4, 7.6 Hz); 7.06–7.67 (m, 7H, arom. H).
$C_{16}H_{15}NO_2S_2$ (317.4)

3.2.16. 3,4-Dihydro-3-ethyl-4-[2-oxo-2-(2-furanyl)ethyl]-2 H-1,3-benzoxazine-2-thione (**3p**)

Reaction time 90 h; colourless crystals from *n*-butanol; m.p. 186–187 °C; yield 0.8 g (53%). IR: ν = 1671 cm^{-1} (CO); 1623, 1596, 1563 (C=C, C=S). ^{1}H-NMR ($CDCl_3$): δ 1.32 (t, 3H, CH_3, J = 7.2 Hz); 3.24 (dd, 1 H, upfield H of $CHC\underline{H}_2$, $J_{vic.}$ = 5.2, $J_{gem.}$ = 16.6 Hz); 3.34 (dd, 1 H, downfield H of $CHC\underline{H}_2$, $J_{vic.}$ = 8.0, $J_{gem.}$ = 16.6 Hz); 3.51 (dt, 1H, upfield H of $C\underline{H}_2CH_3$, J = 7.2, 14.4 Hz); 4.53 (dt, 1 H, downfield H of $C\underline{H}_2CH_3$, J = 7.2, 14.4 Hz); 5.19 (dd, 1 H, $C\underline{H}CH_2$, J = 5.2, 8.0 Hz); 6.49–7.55 (m, 7H, arom. H).
$C_{16}H_{15}NO_3S$ (301.4)

3.2.17. 3,4-Dihydro-3-ethyl-4-[2-oxo-2-(2-thienyl)ethyl]-2 H-1,3-benzoxazin-2-one (**3q**)

Reaction time 20 h; colourless crystals from methanol; m.p. 138–139 °C; yield 1.1 g (73%). IR: ν = 1698, 1658 cm^{-1} (CO); 1596, 1519 (C=C). ^{1}H-NMR ($CDCl_3$): δ 1.24 (t, 3 H, CH_3, J = 7.2 Hz), 3.16 (dt, 1 H, upfield H of $C\underline{H}_2CH_3$, J = 7.2, 14.4 Hz); 3.34 (d, 2 H, $CHC\underline{H}_2$, J = 5.4 Hz); 3.9 (dt, 1 H, downfield H of $C\underline{H}_2CH_3$, J = 7.2, 14.4 Hz); 5.11 (t, 1 H, $C\underline{H}CH_2$, J = 6.0 Hz); 7.0–7.67 (m, 7 H, arom. H).
$C_{16}H_{15}NO_3S$ (301.4)

3.2.18. 3,4-Dihydro-4-[2-oxo-2-(2-thienyl)ethyl]-3-(2,3,4,6-tetra-O-acetyl-β-glucopyranosyl)-2 H-1,3-benzoxazine-2-thione (**3r**)

Reaction time 90 h; colourless crystals from methanol; m.p. 202–205 °C; yield 0.7 g (50%). IR: ν = 1749, 1716, 1654 cm^{-1} (CO); 1596, 1517, 1498 (C=C, C=S). ^{1}H-NMR ($CDCl_3$): δ 1.24 (s, 3 H, $COCH_3$); 1.9 (s, 3 H, $COCH_3$); 2.0 (s, 3 H, $COCH_3$); 2.02 (s, 3 H, $COCH_3$); 3.31 (dd, 1 H, upfield H of $CHC\underline{H}_2$, J = 8.8, 17.0 Hz); 3.63 (dd, 1 H, downfield H of $CHC\underline{H}_2$, J = 3.4, 17.0 Hz); 3.83 (ddd, 1 H, gluc. H-5, J = 2.4, 4.2, 9.8 Hz); 3.98 (dd, 1 H, upfield H of gluc. H-6, J = 4.2, 12.2 Hz); 4.16 (dd, 1 H, downfield H of gluc. H-6, J = 2, 12.4 Hz); 5.12 (t, 1 H, gluc. H-4, J = 9.4 Hz); 5.3 (t, 1 H, gluc. H-3, J = 9.2 Hz); 5.41 (dd, 1 H, hetero. H-4, J = 3.0, 8.8 Hz); 5.44 (t, 1 H, gluc. H-2, J = 9.4 Hz); 5.7 (d, 1 H, gluc. H-1, J = 9.4 Hz); 7.03–7.62 (m, 7 H, arom. H).
$C_{28}H_{29}NO_{11}S_2$ (619.6)

3.3. Cyclization of 2a

A solution of **2a** (5 mmol) in dry benzene (30 ml) containing a catalytic amount of KOH (≃ 25 mg) was boild under reflux for 9 h. The clear reaction mixture was evaporated until dryness under reduced pressure and the residue was triturated with methanol (5 ml). The separated solid was collected and crystallized from methanol (colourless crystals) affording the corresponding **3q**; m.p. 137–139 °C, yield 1.3 g (87%).

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