The Free Internet Journal for Organic Chemistry

Paper

Archive for Organic Chemistry

Arkivoc **2019**, part v, 142-151

A new, simple and efficient method for the synthesis of tricyclic [1,3]oxazolo[3,2-*d*][1,4]benzoxazepine, [1,3]oxazino[3,2-*d*][1,4]benzoxazepine, pyrimido[1,2-*d*][1,4]benzoxazepine and their derivatives

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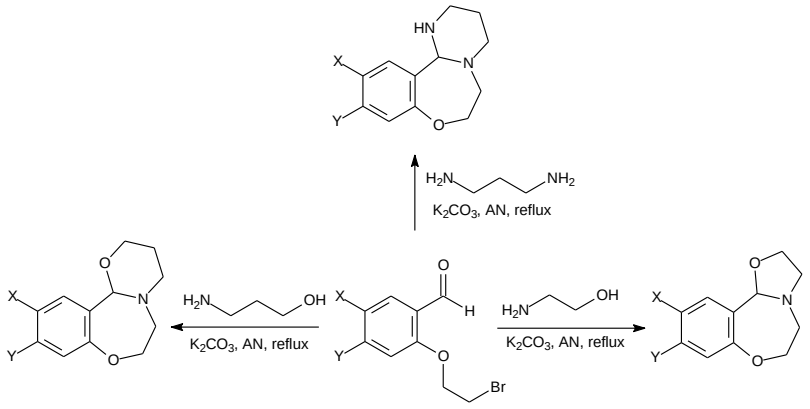
Received 10-11-2018 **Accepted** 02-03-2019 **Published on line** 03-10-2019

Abstract

A versatile and transition metal-free approach for the synthesis of a series of the novel 2,3,5,6-tetrahydro-11b*H*-[1,3]oxazolo[3,2-*d*][1,4]benzoxazepines, 3,4,6,7-tetrahydro-2*H*,12b*H*-[1,3]oxazino[3,2-*d*][1,4]benzoxazepines, 1,3,4,6,7,12b-Hexahydro-2*H*-pyrimido[1,2-*d*][1,4]benzoxazepines was developed by incorporating 1,3-oxazolidine, 1,3-oxazinane or hexahydropyrimidine rings, respectively with [1,4]benzoxazepine ring. The method depends on the condensation of 2-aminoethanol, 3-amino-1-propanol or 1,3-diaminopropane with 2-(2-bromoethoxy)benzaldehydes in acetonitrile in the presence of anhydrous potassium carbonate as base at reflux temperature. Structures of all the synthesized products were established in detail *via* NMR, HRMS spectra and single-crystal X-ray diffraction analysis.



Keywords: 1,3-oxazolidine, 1,3-oxazinane, hexahydropyrimidine, [1,4]benzoxazepine, 2-(2-bromoethoxy) benzaldehyde

Introduction

1,4-Benzoxazepines are of pharmacological interest due to their activity on the central nervous system, as enzyme inhibitors, or as analgesics and antitussives.[1] The 1,4-oxazepines are the parent core of medicinally important drugs like amoxapine, loxapine and sintamil.[2-4] It was reported that 1,4-oxazepine derivatives exhibit biological properties such as histone deacetylase inhibitors and antitumor activity.[5-6]

Most syntheses of 2,3,4,5-tetrahydro-1,4-benzoxazepines involve reduction of the carbonyl group(s) as in: 5-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine[1], 3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepines[7,8] and 3,5-dioxo-2,3,4,5-tetrahydro-1,4-benzoxazepine [9,10] or a double bond of 2,3-dihydro-1,4-benzothiazepine.[11]

Alternatively, 2,3,4,5-tetrahydro-1,4-benzoxazepines are accessible by one of the following known benzoxazepine syntheses: (i) condensation of 2-aryloxyethylamines with 2-formylbenzoic acid to form aminonaphthalides followed by cyclization: (ii) rearrangement of methyl 2-(8-methoxy-2,3-dihydro-1,4-benzoxazepin-5-yl)benzoate using Bischler-Napieralskiconditions; (iii) scandium or copper triflate-catalyzed acylaminoalkylation of α-methoxy-isoindolones with the formation of 1,4-benzoxazepines.[12-14]

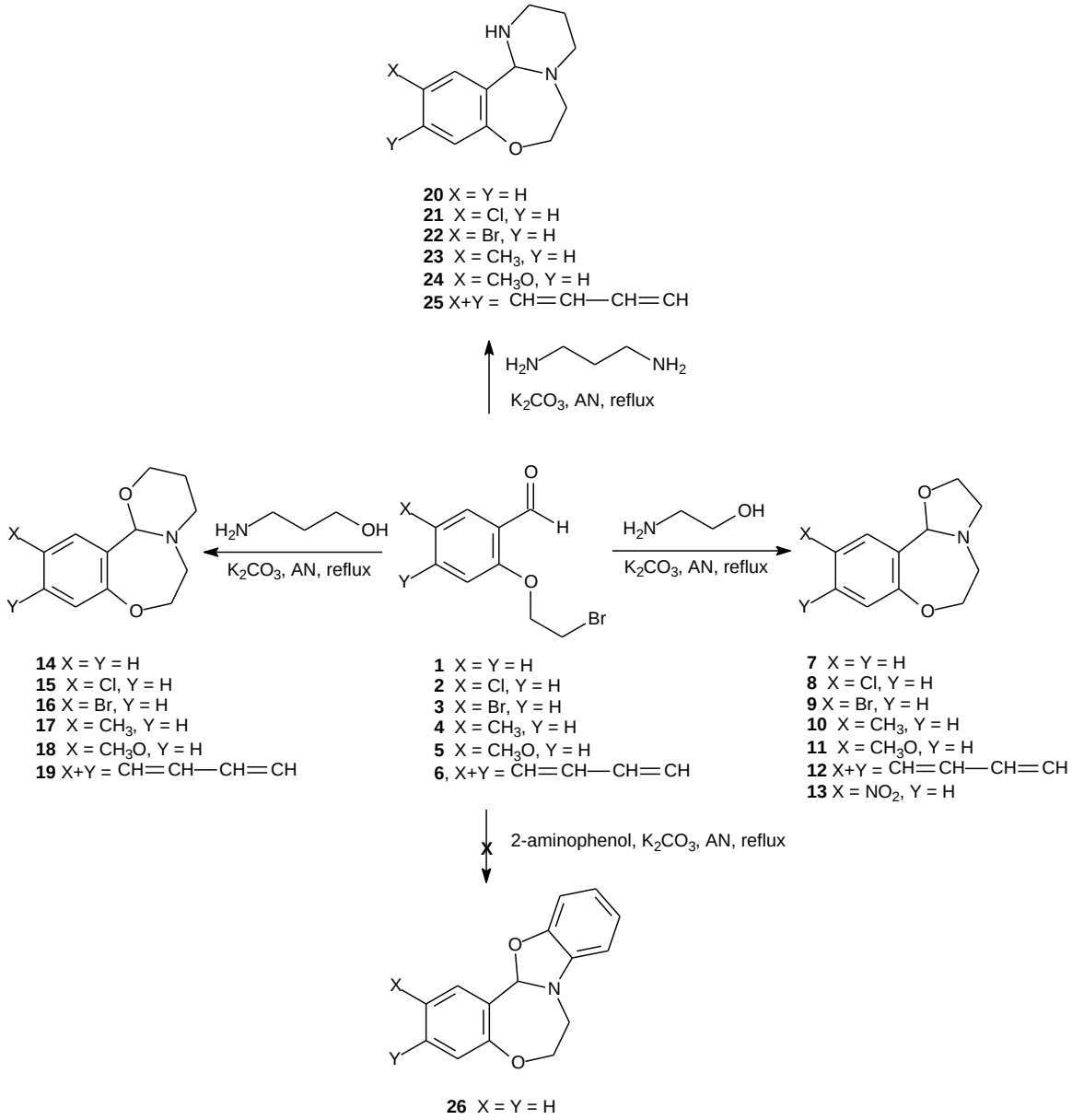
The derivatives of benzoxazepine and imidazole have been frequently synthesized and evaluated for their bioactivity. Some of the synthetic routes for fused benzoxazepine-imidazole derivatives have been reported.[12,13,15-17]In 1981, Levan *et al*. reported the isolation and characterization of unsubstituted 1,2,3,5,6,11b-hexahydroimidazo[1,2-d][1,4]benzoxazepine as a reaction byproduct.[18,19]

Results and Discussion

In 2011, we reported a new, straightforward, high-yielding and convenient synthetic method for 1,2,3,5,6,11b-hexahydroimidazo[1,2-d][1,4]benzoxazepines through a condensation of either aliphatic or aromatic 1,2-diamines with 2-(2-bromoethoxy)benzaldehydes.[20]

In continuation of our research program regarding generalization of this reaction as a useful method for the preparation of other [1,4]benzooxazepines, a new series of [1,4]benzoxazepines (**7-25**) have been prepared in high yield as shown in Scheme 1. They were obtained by the condensation of 2-aminoethanol, 3-amino-1-propanol or 1,3-diaminopropane with 2-(2-bromoethoxy)benzaldehydes (**1-6**) in presence of potassium carbonate in acetonitrile at reflux temperature. To the best of our knowledge, a general procedure for preparing these [1,4]benzoxazepines has not been reported yet. Presence of anhydrous potassium carbonate and reflux temperature are essential conditions to obtain oxazepine products. Several experimental trials to condense 2-(2-bromoethoxy)benzaldehyde **1** with 2-aminophenol to obtain compound **26** failed and only a complex mixture of inseparable products was formed. Currently, other experimental conditions are under investigation in order to obtain compound **26** and its derivatives and the results will be published in due course. The compounds **7**-**25** were characterized by ^{1}H and ^{13}C NMR spectroscopy and high resolution mass spectroscopy. The mass spectra of prepared compounds displayed the correct molecular ion peaks for which the measured high resolution (HRMS) data are in good agreement with the calculated values. Spectral data, detailed in the experimental part, are consistent with the suggested structures. ^{1}H NMR spectra of compounds **7**-**13**, as an example, have identical patterns in the chemical shift range δ ≈ 2.6-4.6 ppm. It shows seven sets of multiplets corresponding to magnetically non-equivalent methylene protons of benzoxazepine and imidazolidine rings. The signal at about δ 4.1 ppm counts for two protons. For compounds **7**-**19**, the signals of the proton and the carbon atoms of CHNN segment show up as sharp singlet signals around δ = 5 ppm and 90 ppm, respectively. On the other hand, these two signals for compounds **20**-

25 show up around 4.6 ppm and 70 ppm. Consequently, these two signals can be considered as strong evidence for the formation of the tricyclic product.



Scheme 1. Synthesis of [1,4]benzooxazepines **7**-**25**

Crystals of compound **7** were obtained from ethylacetate. The derived molecular structure of the hetero-tricyclic scaffold is shown in Figure 1. Compound **7** crystallizes in orthorhombic $P2_12_12_1$ space group. The two heterocyclic moieties are not planar, the mean deviation of atoms from the plane of the specified atom of the heterocyclic ring are 0.1559 Å and 0.2654 Å for the five and seven membered rings.

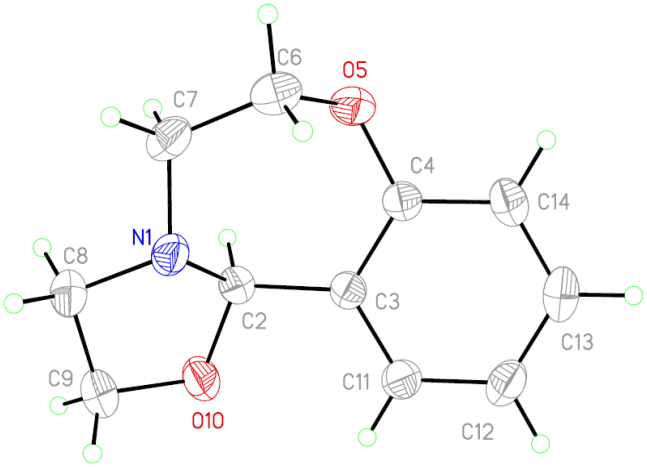
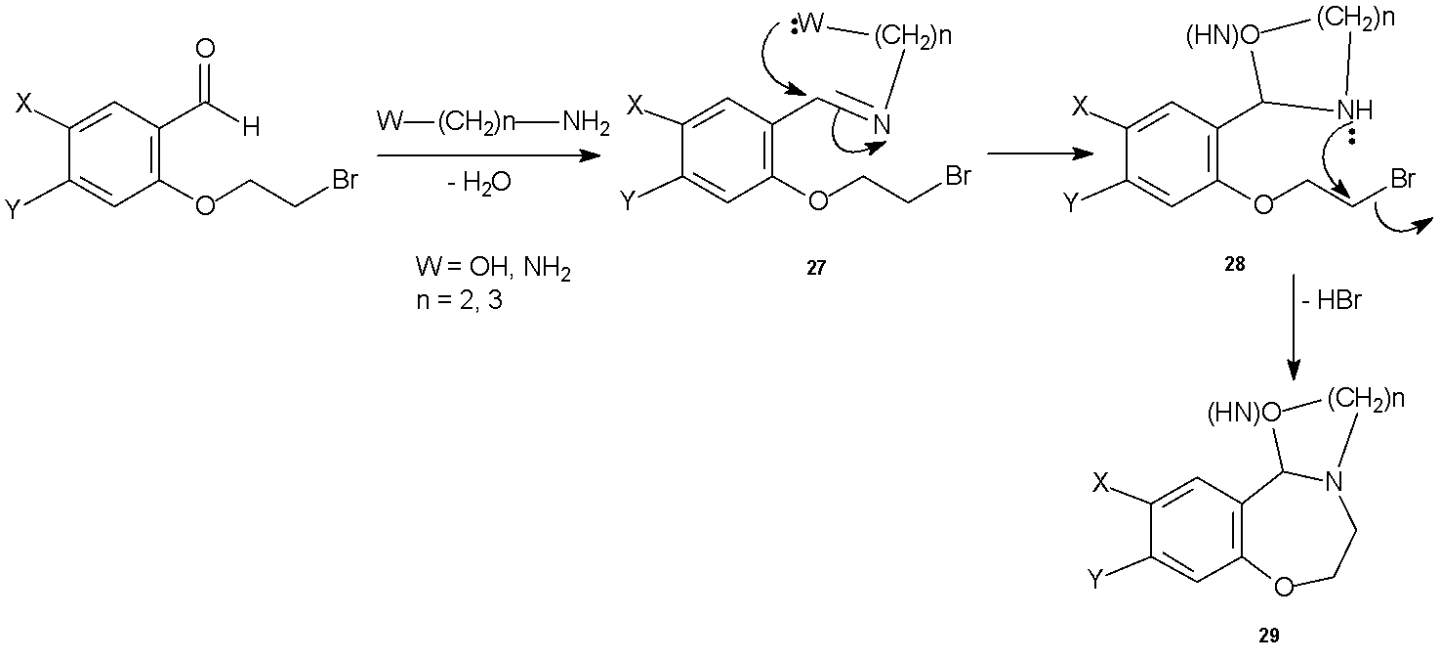


Figure 1. Crystal structure of oxazepine **7**. Thermal ellipsoids are shown at 30 % probability.

A plausible reaction mechanism that can be proposed for the formation of tricyclic scaffolds [1,4]benzoxazepines is shown in Scheme 2. As shown, the initial event is the condensation of the amino group with the aldehyde group to form imine **27**. The intermediate **28** is produced from nucleophilic attack of the hydroxyl group (or another amino group) on the imine site of **27**. Intramolecular nucleophilic substation reaction between cyclic secondary amine and alkylbromide produce the tricyclic scaffolds [1,4]benzoxazepines **29**.



Scheme 2. Proposed mechanism for the formation of tricyclic [1,4]benzoxazepine scaffolds.

Conclusions

In summary, the condensation of 2-aminoethanol or 3-amino-1-propanol or 1,3-diaminopropane with a 2-(2-bromoethoxy)benzaldehydes (**1-6**) in acetonitrile in the presence of anhydrous potassium carbonate at reflux temperature provides a new, facile and efficient route for the synthesis of 2,3,5,6-tetrahydro-11b*H*-[1,3]oxazolo[3,2-*d*][1,4]benzoxazepine, 3,4,6,7-tetrahydro-2*H*,12b*H*-[1,3]oxazino[3,2-*d*][1,4]benzoxazepine and 1,3,4,6,7,12b-hexahydro-2*H*-pyrimido[1,2-*d*][1,4]benzoxazepine and their derivatives in very good yields. The advantages of this method are high yield, readily available starting materials, simple procedure, and a straightforward purification of the products. Biological activities such as antibacterial, antifungal, cytotoxicity for these new compounds are currently under investigation and the results will be published in due course.

Experimental Section

General. Silica gel 60 for column chromatography Fluka. The progress of reactions was monitored by means of thin-layer chromatography (TLC), carried out on TLC sheets that were visualized under UV light (where appropriate). On the other hand, preparative thick layer (0.25 mm) chromatography was performed on silica gel glass plates (60 F-254, 20 cm × 20 cm, Fluka). Melting points were determined on a Stuart scientific melting point apparatus in open capillary tubes and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer (Bruker DPX-500) with TMS as the internal standard. Chemical shifts are expressed in (δ) are given in ppm, whereas *J*-values for ^{1}H–^{1}H coupling constants are given in Hertz. High-resolution mass spectra (HRMS) were obtained (in positive/or negative ion mode) using electron spray ion trap (ESI) technique with a Bruker APEX-4 (7 Tesla) instrument. Samples were dissolved in acetonitrile, diluted with a spray solution (methanol/water 1:1 v/v + 0.1% formic acid), and infused using a syringe pump with a flow rate of 2 µL/min. External calibration was conducted using arginine cluster in a mass range *m/z* 175-871. 2-(2-Bromoethoxy)benzaldehydes **1** and **6** were prepared according to the literature.[20,21] 2-(2-Bromoethoxy)benzaldehydes **2**-**5** were prepared as **1** and **6** to give after column chromatographic purification using ethyl acetate-hexane (1:4) the following pure products:

5-Chloro-2-(2-bromoethoxy)benzaldehyde (**2**). Pale-yellow solid; yield 82% ; mp 44-45 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 3.71 (t, *J* 6 Hz, 2H), 4.37 (t, *J* 6 Hz, 2H), 6.89 (d, *J* 8.85 Hz, 1H), 7.64 (dd, *J* 2.41 and 8.66 Hz, 1H),7.95 (d, *J* 2.41, 1H), 10.43 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 28.5, 68.7, 114.4, 126.1, 127.3, 128.1, 135.4 158.8, 188.2; HRMS (ESI) *m/z*: calculated for $C_9H_9ClBrO_2$ $[M + H]^+$ 262.9474, found 262.9626.

5-Bromo-2-(2-bromoethoxy)benzaldehyde (**3**). Pale-yellow solid; yield 76%; mp 61-62 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 3.72 (t, *J* 6 Hz, 2H), 4.42 (t, *J* 6 Hz, 2H), 6.88(d, *J* 8.8 Hz, 1H), 7.64 (dd, *J* 2.45 and 8.6 Hz, 1H),7.95 (d, *J* 2.45, 1H), 10.65 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 28.5, 68.6, 114.4, 114.8, 126.5, 131.1, 138.2, 159.3 188.1; HRMS (ESI) *m/z*: calculated for $C_9H_9Br_2O_2$ $[M + H]^+$ 306.8996, found 306.9011.

5-Methyl-2-(2-bromoethoxy)benzaldehyde (4). Colorless oil; yield 52%; ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H), 3.65 (t, *J* 6 Hz, 2H), 4.35 (t, *J* 6 Hz, 2H), 6.83 (d, *J* 8.45 Hz, 1H), 7.64 (dd, *J* 1.90 and 8.43 Hz, 1H), 7.61 (d, *J* 1.90, 1H), 10.47 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.3, 28.5, 68.4, 112.9, 125.0, 128.5, 131.0, 136.6 158.5, 189.8; HRMS (ESI) *m/z*: calculated for $C_{10}H_{12}BrO_2$ $[M + H]^+$ 243.0021, found 243.0019.

5-Methoxy-2-(2-bromoethoxy)benzaldehyde (5). Pale-yellow oil; yield 48%; ^{1}H NMR ($CDCl_3$): δ 3.65 (t, *J* 5.9 Hz, 2H), 3.75 (s, 3H), 4.36 (t, *J* 5.9 Hz, 2H), 6.89(d, *J* 9 Hz, 1H), 7.08 (dd, *J* 3.25 and 9 Hz, 1H),7.31 (d, *J* 3.2, 1H), 10.48 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 29.0, 55.8, 69.2, 110.4, 115.0, 123.4, 125.7, 154.3, 155.1, 189.4; HRMS (ESI) *m/z*: calculated for $C_{10}H_{11}BrNaO_3$ $[M + Na]^+$ 280.9789, found 280.9784.

General procedure for the preparation of [1,4]benzoxazepines 7-25. In a 100 mL two-necked round bottom flask equipped with a magnetic stirrer bar, a reflux condenser and a gas line to maintain a nitrogen atmosphere, 2-(2-bromoethoxy)benzaldehyde (2 mmol) and anhydrous K_2CO_3 (0.55 g, 4 mmol) were suspended in anhydrous CH_3CN (100 mL). To this well-stirred solution at room temperature was added a solution of 2-aminoethanol or 3-amino-1-propanol or 1,3-diaminopropane (2 mmol) in dry CH_3CN (10 mL) dropwise. The reaction mixture was refluxed with stirring for 24h. The reaction mixture was filtered, and the solvent was evaporated. The crude product was purified by column chromatography or thin layer chromatography using a solvent system indicated for individual reaction.

2,3,5,6-Tetrahydro-11b*H*-[1,3]oxazolo[3,2-*d*][1,4]benzoxazepine (7). The crude product was purified by column chromatography using $CHCl_3$:CH_3OH (9:1) to give light yellow solid; yield 78%; mp 73-74.5 ^oC; ^1H NMR ($CDCl_3$): δ 2.77 (m, 1H), 2.88 (m, 1H), 3.21 (m, 1H), 3.39 (m, 1H), 3.81 (m, 1H), 4.12 (m, 2H), 4.32 (m, 1H), 4.95 (s, 1H), 6.98 (d, *J* 7.9 Hz, 1H), 7.08 (t, *J* 7.4 Hz, 1H), 7.19 (t, *J* 7.4 Hz, 1H), 7.56 (d, *J* 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 54.8, 65.5, 72.2, 93.1, 120.8, 123.9, 125.5, 128.9, 133.2, 157.6; HRMS (ESI) *m/z*: calculated for $C_{11}H_{14}NO_2$ $[M + H]^+$ 192.1025, found 192.1019.

10-Chloro-2,3,5,6-tetrahydro-11b*H*-[1,3]oxazolo[3,2-*d*][1,4]benzoxazepine (8). The crude product was purified by column chromatography using $CHCl_3$:CH_3OH (9:1) to give light yellow solid; yield 86%; mp 75-76 ^oC ; ^1H NMR ($CDCl_3$): δ 2.76 (m, 1H), 2.9 (m, 1H), 3.19 (m, 1H), 3.36 (m, 1H), 3.75 (m, 1H), 4.22 (m, 2H), 4.61 (m, 1H), 4.89 (s, 1H), 6.90 (d, *J* 8.5 Hz, 1H), 7.08 (m, 1H), 7.53 (d, *J* 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 54.6, 54.7, 65.6, 72.4, 92.6, 122.3, 125.7, 128.6, 129.1, 135.1, 156.1; HRMS(ESI) *m/z*: calculated for $C_{11}H_{13}ClNO_2$ $[M + H]^+$ 226.0634, found 226.0629.

10-Bromo-2,3,5,6-tetrahydro-11b*H*-[1,3]oxazolo[3,2-*d*][1,4]benzoxazepine (9). The crude product was purified by column chromatography using $CHCl_3$:CH_3OH (9:1) to give light yellow solid; yield 82%; mp 74-75 ^oC; ^1H NMR ($CDCl_3$): δ 2.76 (m, 1H), 2.91 (m, 1H), 3.18 (m, 1H), 3.36 (m, 1H), 3.78 (m, 1H), 4.12 (m, 2H), 4.28 (m, 1H), 5.04 (s, 1H), 6.85 (d, *J* 8.5 Hz, 1H), 7.27(m, 1H), 7.69 (d, *J* 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 54.6, 54.7, 65.6, 72.3, 92.5, 116.8, 122.7, 128.7, 131.7, 135.5, 156.6; HRMS (ESI) *m/z*: calculated for $C_{11}H_{13}BrNO_2$ $[M + H]^+$ 270.0129, found 270.0124.

10-Methyl-2,3,5,6-tetrahydro-11b*H*-[1,3]oxazolo[3,2-*d*][1,4]benzoxazepine (10). The crude product was purified by column chromatography using $CHCl_3$:CH_3OH (9:1) to give light yellow oil; yield 82%; ^1H NMR ($CDCl_3$): δ 2.28, (s, 3H, CH_3), 2.74 (m, 1H), 2.87 (m, 1H), 3.17 (m, 1H), 3.36 (m, 1H), 3.80 (m, 1H), 4.14 (m, 2H), 4.28 (m, 1H), 5.07 (s, 1H), 6.86 (d, *J* 8.0 Hz, 1H), 7.03(m, 1H), 7.37 (d, *J* 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.6, 54.8, 54.9, 65.5, 72.2, 93.1, 120.7, 125.9, 129.2, 132.8, 133.2, 155.4; HRMS (ESI) *m/z*: calculated for $C_{12}H_{16}NO_2$ $[M + H]^+$ 206.1181, found 206.1176.

10-Methoxy-2,3,5,6-tetrahydro-11b*H*-[1,3]oxazolo[3,2-*d*][1,4]benzoxazepine (11). The crude product was purified by column chromatography using $CHCl_3$:CH_3OH (9:1) to give yellow semi-solid; yield 87%; ^1H NMR ($CDCl_3$): δ 2.76 (m, 1H), 2.88 (m, 1H), 3.16 (m, 1H), 3.36 (m, 1H), 3.77 (m, 1H+3H of OCH_3), 4.12 (m, 2H), 4.26 (m, 1H), 4.93 (s, 1H), 6.68 (m, 1H), 6.89 (d, *J* 8.6 Hz, 1H), 7.10 (d, *J* 3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 54.9, 55.0, 55.7, 65.5, 72.3, 92.9, 110.1, 114.2, 121.6, 134.2, 151.3, 155.9; HRMS (ESI) *m/z*: calculated for $C_{12}H_{16}NO_3$ $[M + H]^+$ 222.1130, found 222.1124.

3,5,6,13b-Tetrahydro-2*H*-naphtho[2,3-*f*]oxazolo[3,2-*d*][1,4]oxazepine (12). The crude product was purified by column chromatography using $CHCl_3$:CH_3OH (9:1) to give light red solid; yield 84%; mp 73-74 ^oC; ^1H NMR ($CDCl_3$): δ 2.76 (m, 1H), 2.97 (m, 1H), 3.21 (m, 1H), 3.42 (m, 1H), 3.88 (m, 1H), 4.20 (m, 2H), 4.43 (m, 1H), 5.11 (s, 1H), 7.40 (br, 3H), 7.71 (d, *J* 6.5 Hz, 1H), 7.81 (d, *J* 6.5 Hz, 1H), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 54.7, 55.0,

65.7, 73.0, 93.3, 117.3, 125.0, 126.3, 126.9, 128.2, 130.6, 133.4, 133.9, 155.6; HRMS (ESI) *m/z*: calculated for $C_{15}H_{16}NO_2$ $[M + H]^+$ 242.1181, found 242.1175.

10-Nitro-2,3,5,6-tetrahydro-11b*H*-[1,3]oxazolo[3,2-*d*][1,4]benzoxazepine (13). The crude product was washed with CH_3OH to give yellow solid; yield 79%; mp 145-147 °C (decomp.); ^{1}H NMR (acetone-d_6): δ 2.78 (m, 1H), 2.91 (m, 1H), 3.30 (m, 1H), 3.41 (m, 1H), 3.76 (m, 1H), 4.04 (m, 1H), 4.15 (m 1H), 4.51 (m, 1H), 4.86 (s, 1H), 7.16 (d, *J* 8.8 Hz, 1H), 8.12(m, 1H), 8.33 (d, *J* 2.5 Hz, 1H); ^{13}C NMR (acetone-d_6): δ 53.7, 54.3, 65.6, 72.9, 92.2, 121.6, 122.0, 124.3, 135.0,156.1; HRMS (ESI) *m/z*: calculated for $C_{11}H_{13}N_2O_4$ $[M + H]^+$ 237.0875, found 237.0869.

3,4,6,7-Tetrahydro-2*H*,12b*H*-[1,3]oxazino[3,2-*d*][1,4]benzoxazepine (14). The crude product was purified by TLC using ethylacetate:CH_3OH (7:3); yellow semi-solid; yield 81%; ^{1}H NMR ($CDCl_3$): δ 1.34 (m, 1H), 2.21 (m, 1H), 2.80 (m, 1H), 3.11 (m, 1H), 3.23 (m, 1H), 3.72 (m, 1H), 3.89 (m, 1H), 4.09 (m 1H), 4.24 (m, 2H), 5.19 (s, 1H), 6.85 (d, *J* 7.1 Hz, 1H), 7.0 (m, 1H), 7.18 (m, 1H), 7.32 (d, *J* 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.6, 52.0, 64.1, 68.9, 71.9, 95.0, 120.9, 123.0, 129.1, 129.7, 130.7, 157.4; HRMS (ESI) *m/z*: calculated for $C_{12}H_{16}NO_2$ $[M + H]^+$ 206.1181, found 206.1173.

11-Chloro-3,4,6,7-tetrahydro-2*H*,12b*H*-[1,3]oxazino[3,2-*d*][1,4]benzoxazepine (15). The crude product was purified by TLC using ethylacetate:hexane (8:2); yellow semi-solid; yield 77%; ^{1}H NMR ($CDCl_3$): δ 1.27 (m, 1H), 2.28 (m, 1H), 2.78 (m, 1H), 3.10 (m, 2H), 3.57 (m, 1H), 3.70 (m, 1H), 3.82 (m, 1H), 4.16 (m, 2H), 5.06 (s, 1H), 6.85 (d, *J* 8.5 Hz, 1H), 7.12 (d, *J* 8.5 Hz, 1H), 7.37 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.9, 52.6, 54.1, 68.6, 71.8, 93.6, 122.3, 128.0, 129.4, 130.1, 130.3, 155.9; HRMS (ESI) *m/z*: calculated for $C_{12}H_{15}ClNO_2$ $[M + H]^+$ 240.0791, found 240.0786.

11-Bromo-3,4,6,7-tetrahydro-2*H*,12b*H*-[1,3]oxazino[3,2-*d*][1,4]benzoxazepine (16). The crude product was purified by TLC using $CHCl_3$:CH_3OH (9:1); yellow semi-solid; yield 73%; ^{1}H NMR ($CDCl_3$): δ 1.32 (m, 1H), 2.21 (m, 1H), 2.79 (m, 1H), 3.11 (m, 2H), 3.56 (m, 1H), 3.68 (m, 1H), 3.81 (m, 1H), 4.15 (m, 2H), 5.05 (s, 1H), 6.79 (d, *J* 8.5 Hz, 1H), 7.26 (d, *J* 8.5 Hz, 1H), 7.50 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 22.3, 52.6, 54.1, 68.5, 71.8, 93.4, 115.4, 122.7, 131.3, 132.4, 133.0, 156.4; HRMS (ESI) *m/z*: calculated for $C_{12}H_{15}BrNO_2$ $[M + H]^+$ 284.0286, found 284.0281.

11-Methyl-3,4,6,7-tetrahydro-2*H*,12b*H*-[1,3]oxazino[3,2-*d*][1,4]benzoxazepine (17). The crude product was purified by TLC using ethylacetate:CH_3OH (7:3); yellow semi-solid; yield 77%; ^{1}H NMR ($CDCl_3$): δ 1.24 (m, 1H), 2.23 (s, 3H, CH_3), 2.28 (m, 1H), 2.73 (m, 1H), 3.18 (m, 1H), 3.23 (m, 1H), 3.65 (m, 2H), 3.84 (m, 1H), 4.02 (m, 1H), 4.18 (m, 1H), 5.13 (s, 1H), 6.80 (d, *J* 7.5 Hz, 1H), 6.96 (d, *J* 7.5 Hz, 1H), 7.10 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 20.9, 21.6, 51.9, 54.1, 68.9, 71.7, 95.0, 116.7, 120.7, 128.7, 130.2, 130.9, 155.1; HRMS (ESI) *m/z*: calculated for $C_{13}H_{18}NO_2$ $[M + H]^+$ 220.1338, found 220.1332.

11-Methoxy-3,4,6,7-tetrahydro-2*H*,12b*H*-[1,3]oxazino[3,2-*d*][1,4]benzoxazepine (18). The crude product was purified by TLC using ethylacetate:CH_3OH (7:3); yellow semi-solid; yield 69%; ^{1}H NMR ($CDCl_3$): δ 1.29 (m, 1H), 2.21 (s, 1H), 2.70 (m, 1H), 3.13 (m, 2H), 3.60 (m, 1H), 3.71 (s, 3H, OCH_3), 3.82 (m, 1H), 4.01 (m, 1H), 4.03 (m, 1H), 4.18 (m, 1H), 5.08 (s, 1H), 6.70 (d, *J* 8.5 Hz, 1H), 6.82 (d, *J* 8.5 Hz, 1H), 6.89 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 22.2, 52.5, 54.1, 55.7, 68.7, 71.7, 94.2, 114.7, 114.8, 121.7, 130.3, 150.9, 155.3; HRMS (ESI) *m/z*: calculated for $C_{13}H_{18}NO_3$ $[M + H]^+$ 236.1287, found 236.1281.

2,3,4,6,7,14b-Hexahydronaphtho[2,3-*f*][1,3]oxazino[3,2-*d*][1,4]oxazepine (19). The crude product was purified by TLC using ethylacetate:CH_3OH (8:2); yellow solid; yield 79%; mp 114-115 °C; ^{1}H NMR ($CDCl_3$): δ 1.23 (m, 1H), 1.41 (m, 1H), 2.33 (s, 1H), 2.79 (m, 1H), 3.15 (m, 1H), 3.23 (m, 1H), 3.73 (m, 1H), 3.90 (m, 1H), 4.22 (m, 1H), 4.28 (m, 1H), 5.32 (s, 1H), 7.36 (s, 1H), 7.40 (m, 2H), 7.67 (d, *J* 7.5 Hz, 1H), 7.76 (d, *J* 7.5 Hz, 1H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 22.64, 52.30, 53.79, 68.77, 71.58, 94.01, 116.7, 124.6, 126.5, 126.6, 128.1, 129.5, 155.8; HRMS (ESI) *m/z*: calculated for $C_{16}H_{18}NO_2$ $[M + H]^+$ 256.1338, found 256.1427.

1,3,4,6,7,12b-Hexahydro-2*H*-pyrimido[1,2-*d*][1,4]benzoxazepine (20). The crude product was purified by TLC using ethylacetate:CH_3OH (7:3)+few drops of trimethylamine (TEA); light brown semi-solid; yield 87%; ^{1}H NMR ($CDCl_3$): δ 1.43 (m, 1H), 1.70-2.20 (br, 2H, CH+NH), 2.69 (m, 1H), 2.90 (m, 1H), 3.02 (m, 2H), 3.22 (m, 1H), 3.52 (m, 1H), 4.15 (m, 2H), 4.64 (s, 1H), 6.89 (d, *J* 7.25 Hz, 1H), 7.00 (br, 1H), 7.15 (br, 1H), 7.28 (d, *J* 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 24.3, 46.0, 52.5, 54.2, 70.3, 78.1, 121.0, 123.4, 128.9, 129.1, 131.3, 156.8; HRMS (ESI) *m/z*: calculated for $C_{12}H_{17}N_2O$ $[M + H]^+$ 205.1341, found 205.1318.

11-Chloro-1,3,4,6,7,12b-hexahydro-2*H*-pyrimido[1,2-*d*][1,4]benzoxazepine (21). The crude product was purified by TLC using ethylacetate:CH_3OH (7:3)+ few drops of TFA ; light yellow semi-solid; yield 84%; ^{1}H NMR ($CDCl_3$): δ 1.49 (m, 1H), 1.70-1.97 (br, 2H, CH+NH), 2.74 (m, 1H), 2.88-3.00 (m, 3H), 3.21 (m, 1H), 3.43 (m, 1H), 4.08 (m, 1H), 4.18 (m, 1H), 4.63 (s, 1H), 6.84 (d, *J* 8.5 Hz, 1H), 7.11 (d, *J* 8.5 Hz, 1H), 7.33 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.9, 45.5, 52.9, 53.7, 70.2, 77.3, 122.4, 128.3, 128.9, 129.0, 133.0, 155.4; HRMS (ESI) *m/z*: calculated for $C_{12}H_{16}ClN_2O$ $[M + H]^+$ 239.0951, found 239.0946.

11-Bromo-1,3,4,6,7,12b-hexahydro-2*H*-pyrimido[1,2-*d*][1,4]benzoxazepine (22). The crude product was purified by TLC using ethylacetate:CH_3OH (7:3)+few drops of TEA; yellow semi-solid; yield 87%; ^{1}H NMR ($CDCl_3$): δ 1.50 (m, 1H), 1.79 (br, NH, 1H, which disappeared with D_2O shake), 1.88 (m, 1H), 2.75 (m, 1H), 2.91-3.01 (m, 3H), 3.19 (m, 1H), 3.44 (m, 1H), 4.09 (m, 1H), 4.17 (m, 1H), 4.62 (s, 1H), 6.79 (d, *J* 7.5 Hz, 1H), 7.25 (d, *J* 7.5 Hz, 1H), 7.48 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.8, 45.5, 52.8, 53.7, 70.1, 77.3, 115.9, 122.9, 131.9, 132.0, 133.4, 155.9; HRMS (ESI) *m/z*: calculated for $C_{12}H_{16}BrN_2O$ $[M + H]^+$ 283.0446, found 283.0354.

11-Methyl-1,3,4,6,7,12b-hexahydro-2*H*-pyrimido[1,2-*d*][1,4]benzoxazepine (23). The crude product was purified by TLC using ethylacetate:CH_3OH (7:3)+few drops of TEA; yellow oil; yield 91%; NMR ($CDCl_3$): δ 1.44 (m, 1H), 1.81 (br, NH, 1H, which disappeared with D_2O shake), 1.94 (m, 1H), 2.26 (s, 3H, CH_3), 2.69 (m, 1H), 2.93 (m, 1H), 3.03 (m, 2H), 3.24 (m, 1H), 3.49 (m, 1H), 4.14 (m, 2H), 4.64 (s, 1H), 6.80 (d, *J* 8.0 Hz, 1H), 6.95 (d, *J* 8.0 Hz, 1H), 7.10 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.7, 24.4, 46.1, 52.5, 54.3, 70.3, 78.3, 120.8, 129.4, 129.5, 131.0, 132.8, 154.4; HRMS (ESI) *m/z*: calculated for $C_{13}H_{19}N_2O$ $[M + H]^+$ 219.1497, found 219.1491.

11-Methoxy-1,3,4,6,7,12b-hexahydro-2*H*-pyrimido[1,2-*d*][1,4]benzoxazepine (24). The crude product was purified by TLC using ethylacetate:CH_3OH (7:3)+few drops of TEA; light yellow semi-solid; yield 79%; ^{1}H NMR ($CDCl_3$): δ 1.47 (m, 1H), 1.88 (br, NH, 1H, which disappeared with D_2O shake), 1.92 (m, 1H), 2.71 (m, 1H), 2.95 (m, 1H), 3.00 (m, 2H), 3.23 (m, 1H), 3.44 (m, 1H), 3.74 (s, 3H, OCH_3), 4.05 (m, 1H), 4.09 (m, 1H), 4.63 (s, 1H), 6.69 (d, *J* 7.0 Hz, 1H), 6.85 (d, *J* 7.0 Hz, 1H), 6.94 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.6, 45.8, 52.7, 54.0, 55.7, 70.2, 78.0, 113.9, 114.3, 121.7, 132.4, 150.4, 155.6; HRMS (ESI, negative) *m/z*: calculated for $C_{13}H_{17}N_2O_2$ $[M + H]^+$ 233.1290, found 233.1284.

2,3,4,6,7,14b-Hexahydro-1*H*-naphtho[2,3-*f*]pyrimido[1,2-*d*][1,4]oxazepine (25). The crude product was purified by TLC using ethylacetate:CH_3OH (7:3)+few drops of TEA; yellow semi-solid, yield 75%; ^{1}H NMR ($CDCl_3$): δ 1.55 (m, 1H), 1.93 (br, NH, 1H, which disappeared with D_2O shake), 1.95 (m, 1H), 2.70 (m, 1H), 3.03 (m, 2H), 3.09 (m, 1H), 3.32 (m, 1H), 3.53 (m, 1H), 4.10 (m, 1H), 4.39 (m, 1H), 4.84 (s, 1H), 7.34 (br+s, 2H), 7.40 (t, *J* 7.0 Hz, 1H), 7.67 (d, *J* 8.0 Hz, 1H), 7.76 (d, *J* 8.0 Hz, 1H), 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 25.4, 46.1, 52.4, 53.7, 69.8, 77.3, 116.9, 124.7, 126.3, 126.5, 127.4, 128.0, 130.4, 132.2, 134.1, 154.2; HRMS (ESI, negative) *m/z*: calculated for $C_{16}H_{17}N_2O$ $[M + H]^+$ 253.1340, found 253.1335.

Crystal structure determination. The crystal structure of **7** was determined at room temperature using 'Xcalibur, Eos' diffractometer (Mo Kα radiation, λ = 0.7107 Å). Data were acquired and processed to give *hkl* files using CrysAlisPro software.[22] The structure was solved and refined using SHELXTL program package.[23] Atoms (except hydrogens) were refined anisotropically, hydrogen atoms were placed in the calculated

positions using a riding model. The CIF file of **7** was deposited in Cambridge Crystallographic Data Center (CCDC # 1871357).

Acknowledgements

Many thanks for Chemistry Department at Jordan University for running the NMR, HRMS spectra and X-ray structure analysis.

Supplementary Material

Copies of ^{1}H, ^{13}C NMR for compounds **2-5**, **7-25**, HRMS spectra for compounds **7-25** and tables of crystal data and structure refinement parameters for the compound **7** and corresponding crystallographic data files (cif) can be found in the Supplementary Material.

References

1. Grunewald, G. L.; Dahanukar, V. H.; Ching, P.; Criscione, K. R. *J. Med. Chem*. **1996**, *39*, 3539-3546. https://doi.org/10.1021/jm9508292
2. Kapur, S.; Cho, R.; Jones, C.; McKay, G.; Zipursky, R. B. *Biol. Psychiatry* **1999**, *45*, 1217-1220. https://doi.org/10.1016/S0006-3223(98)00204-2
3. Umemiya, H.; Fukasawa, H.; Ebisawa, M.; Eyrolles, L.; Kawachi, E.; Eisenmann, G.; Gronemeyer, H.; Hashimoto, Y.; Shudo, K.; Kagechika, H. *J. Med. Chem*. **1997**, *40*, 4222-4234. https://doi.org/10.1021/jm9704309
4. Klunder, J. M.; Hargrave, K. D.; West, M.; Cullen, E.; Pal, K.; Behnke, M. L.; Kapadia, S. R.; McNeil, D. W.; Wu, J. C.; Chow, G. C. *J. Med. Chem*. **1992**, *35*, 1887-1897. https://doi.org/10.1021/jm00088a027
5. Fu, P.; Jamison, M.; La, S.; MacMillan, J. B. *Org. Let*t. **2014**, *16*, 5656-5659. https://doi.org/10.1021/ol502731p
6. Yoo, C. B.; Jones, P. A. *Nat. Rev. Drug Discovery* **2006**, *5*, 37-50. https://doi.org/10.1038/nrd1930
7. Walker, G. N.; Smith, R. T. *J. Org. Chem*. **1971**, *36*, 305-308. https://doi.org/10.1021/jo00801a013
8. Derieg, M. E.; Sternbach, L. H. *J. Heterocycl. Chem.* **1966**, *3*, 237-238. https://doi.org/10.1002/jhet.5570030231
9. CIBA Ltd., Belg. Patent 669 838, 1966; *Chem. Abstr*. **1966**, 65, 18604.
10. CIBA Ltd., Fr. Patent 1 463 402, 1966; *Chem. Abstr*. **1968**, 68, 49670m.
11. Toshiyuki, H. ; Takuhiro, I.; Hisao,Y. Ger. Offen. 2 014 223, 1970; *Chem. Abstr*. **1970**, 73, 120697h.
12. Pecher, J.; Waefelaer, A. *Bull. Soc. Chim. Belg*. **1978**, *87*, 911-915. https://doi.org/10.1002/bscb.19780871113

13. Heaney, H.; Shuhaibar, K. F. *Tetrahedron Lett*. **1994**, *35*, 2751-2752. https://doi.org/10.1016/S0040-4039(00)77023-7
14. El Gihani, M. T.; Heaney, H.; Shuhaibar, K. F. *Synlett* **1996**, 871-872. https://doi.org/10.1055/s-1996-5611
15. Pohlki, F.; Doye, S. *Chem. Soc Rev* **2003**, *32*, 104-114. https://doi.org/10.1039/b200386b
16. Nagata, H.; Sugimoto, Y.; Ito, Y.; Tanaka, M.; Yoshimatsu, M. *Tetrahedron* **2014**, *70*, 1306-1316. https://doi.org/10.1016/j.tet.2013.12.049
17. Li, S.; Li, Z.; Yuan, Y.; Peng, D.; Li, Y.; Zhang, L.; Wu, Y. *Org Lett* **2012**, *14*, 1130-1133. https://doi.org/10.1021/ol3000525
18. Levan, K. R.; Root, C. A. *Inorg. Chem*. **1981**, *20*, 3566-3569. https://doi.org/10.1021/ic50224a083
19. Levan, K. R.; Root, C. A. *J. Org. Chem*. **1981**, *46*, 2404-2406. https://doi.org/10.1021/jo00324a043
20. Mizyed, S. A.; Ashram M.; Awwadi, F. F. *Arkivoc* **2011** (*x*) 277-286. http://dx.doi.org/10.3998/ark.5550190.0012.a22
21. Ashram, M. *J. Chem. Soc., Perkin Trans. 2*, **2002**, 1662-1666. https://doi.org/10.1039/B205436A
22. CrysAlisPro, Oxford Diffraction Ltd., Version 1.171.35.19 (release 27-10-2011 CrysAlis171.NET).
23. SHELXTL (XPREP, X., XL, XP, XCIF), version 6.10; Bruker AXS Inc.: Madison, WI., 2002.

