Research Article

Design and Synthesis of Two Oxazine Derivatives Using Several Strategies

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Several oxazine derivatives have been synthesized; nevertheless, expensive reagents and special conditions are required. Therefore, in this study, two oxazine derivatives (2-chloro-3-{{2-[-(3-chloro-2-oxo-cyclobutyl)-(2,3-dimethoxy-9,10-dihydrostrychnid-10-yl)-amino]-ethyl}-[1,5-dimethyl-4-(1*H*-naphtho[1,2-*e*][1,3-oxazin-2-yl)-2-phenyl-2,3-dihydro-1*H*-pyrazol-3-yl]-amino}-cyclobutanone and 2-chloro-3-{{2-[(3-chloro-2-oxo-cyclobutyl)-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-ethyl}-[1,5-dimethyl-4-(1*H*-naphtho[1,2-*e*][1,3]oxazin-2-yl)-2-phenyl-2,3-dihydro-1*H*-pyrazol-3-yl]-amino}-cyclobutanone) were synthesized using several strategies. The structure of compounds obtained was confirmed by elemental analysis, spectroscopy, and spectrometry data. In conclusion, the methods used offer some advantages such as good yields, simple procedure, low cost, and ease of workup.

1. Introduction

Oxazine derivatives are very important heterocyclic compounds with several biological activities [1, 2]. Several years ago, some oxazine derivatives have been synthesized; for example, the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-one using the three-component system (β -naphthol, benzaldehyde, and urea) in presence of $\text{HClO}_4\text{-SiO}_2$ [3]. Other report [4] showed the preparation of dirithromycin (9-*N*-11-*O*-oxazine derivative) by condensation of 9(*S*)-erythromycylamine with 2-(2-methoxy-ethoxy)acetaldehyde. Other studies showed the condensation of 2-naphthol with heteroarylaldehydes or substituted benzaldehydes in the presence of ammonia [5]. In addition, a study [6] showed

the synthesis of 3,4-dihydro-3-substituted-2*H*-naphtho[2,1-*e*][1,3]oxazine derivatives catalyzed by zirconium (IV) chloride. Other data [7] showed the reaction of substituted aryl and heteroarylaldehydes to give a series of 8-bromo-1,3-diarly-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines. Also another oxazine derivative (1,3-diphenyl-1*H*-naphtho[1,2-*e*][1,3]oxazine) was developed by the reaction of *N*-arylidene-1-(α -aminoarylbenzyl)-2-naphthol with iodobenzene diacetate [8]. All these experimental results show several procedures which are available for synthesis of several oxazine derivatives; nevertheless, expensive reagents and special conditions are required. Therefore, in this study two oxazine derivatives were synthesized using some strategies.

2. Experimental

The N¹-(2,3-dimethoxystrychnidin-10-yliden)-ethane-1,2-diamine (**7**) was synthesized according to a previously reported method [9]. The other compounds evaluated in this study were purchased from Sigma-Aldrich Co. Ltd. The melting points for the different compounds were determined on an electrothermal (900 model). Infrared spectra (IR) were recorded using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ¹H and ¹³C NMR spectra were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz in CDCl₃ using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace GCPolaris Q. spectrometer. Elemental analysis data were acquired from a Perkin Elmer Ser. II CHNS/O 2400 elemental analyzer.

2.1. 1,5-Dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-(3H)-yl)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (3). A solution of naphthol (100 mg, 0.69 mmol) and 4-aminoantipyrine (141 mg, 0.69 mmol) formaldehyde (1 mL) in 10 mL of methanol was stirred for 72 h at room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure; the residue was purified by crystallization from methanol: water (3:1) yielding 80% of product, m.p. 176–178°C; IR ($V_{\max}$, cm⁻¹): 1718, 1228, 1140; ¹H NMR (300 MHz, CDCl₃) δ_{H} : 2.10 (s, 3H), 2.80 (s, 3H), 5.20–5.70 (m, 4H), 7.01 (m, 1H), 7.10 (m, 1H), 7.30 (m, 1H), 7.40 (m, 2H), 7.44 (m, 2H), 7.58 (m, 2H), 7.60–7.66 (m, 3H) ppm. ¹³C NMR (75.4 MHz, CDCl₃) δ_{C} : 15.02, 34.20, 47.42, 81.88, 110.12, 110.20, 118.22, 120.90, 123.26, 126.30, 126.42, 127.90, 128.11, 128.25, 128.40, 133.84, 133.90, 134.18, 134.38, 151.80, 166.30 ppm. EI-MS m/z : 371.10 (M⁺10). Anal. Calcd., for C₂₃H₂₁N₃O₂: C, 74.39; H, 5.70; N, 11.31; O, 8.61. Found: C, 74.36; H, 5.68.

2.2. N-1-[1,5-Dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-yl)-2-phenyl-1,2-dihydro-pyrazol-3-ylidene]-ethane-1,2-diamine (4). A solution of **3** (100 mg, 0.27 mmol), ethylenediamine (100 μ L, 1.50 mmol), and boric acid (90 mg, 1.45 mmol) in 10 mL of methanol was stirred for 72 h at room temperature. The reaction mixture was evaporated to a smaller volume, after the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure; the residue was purified by crystallization from methanol: water (2:1) yielding 62% of product, m.p. 102–104°C; IR ($V_{\max}$, cm⁻¹): 3382, 1228, 1140; ¹H NMR (300 MHz, CDCl₃) δ_{H} : 1.10 (s, 3H), 2.02 (s, 3H), 3.06 (s, 3H), 3.18 (t, 2H, J = 6.44 Hz), 3.70 (t, 2H, J = 6.44 Hz), 4.34 (broad, 2H), 5.20–5.76 (m, 4H), 6.98–7.04 (m, 3H), 7.30–7.48 (m, 3H) 7.52 (m, 2H), 7.60–8.06 (m, 3H) ppm. ¹³C NMR (75.4 MHz, CDCl₃) δ_{C} : 15.50, 34.70, 40.24, 47.24, 54.92, 81.38, 105.28, 109.66, 119.30, 121.68, 121.80, 123.30, 123.90, 126.30, 126.80, 127.91, 128.40, 131.90, 133.80, 134.18, 139.50, 142.60, 151.48 ppm. EI-MS m/z : 413.20 (M⁺10). Anal. Calcd. for C₂₅H₂₇N₅O: C, 72.61; H, 6.58; N, 16.94; O, 3.87. Found: C, 72.60; H, 6.56.

2.3. N-[1,5-Dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-yl)-2-phenyl-1,2-dihydro-pyrazol-3-ylidene]-2,3-dimethoxystrychnidin-10-ylidene-ethane-1,2-diamine (6)

Method A. A solution of **4** (100 mg, 0.24 mmol), brucine (95 mg, 0.24 mmol), and boric acid (30 mg, 0.48 mmol) in 10 mL of methanol was stirred for 72 h at room temperature. The reaction mixture was evaporated to a smaller volume, after the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure; the residue was purified by crystallization from methanol: water (3:2) yielding 80% of product, m.p. 158–160°C; IR ($V_{\max}$, cm⁻¹): 3322, 1228, 1140; ¹H NMR (300 MHz, CDCl₃) δ_{H} : 1.40–1.84 (m, 3H), 2.02 (s, 3H), 2.22–3.10 (m, 7H), 3.12 (s, 3H), 3.26–3.69 (m, 6H), 3.80 (s, 3H), 3.90 (t, 2H, J = 6.54 Hz), 3.91 (s, 3H), 3.92 (t, 2H, J = 6.54 Hz), 4.70 (m, 1H), 5.20–5.78 (m, 4H), 5.83–5.88 (m, 2H), 7.00–7.04 (m, 3H), 7.32–7.44 (m, 3H), 7.52 (m, 2H), 7.55 (m, 1H), 7.60–8.04 (m, 3H) ppm. ¹³C NMR (75.4 MHz, CDCl₃) δ_{C} : 15.48, 27.37, 29.20, 34.52, 34.75, 40.90, 45.82, 47.26, 50.74, 53.02, 53.09, 55.95, 56.20, 56.60, 63.20, 64.62, 65.02, 79.26, 81.70, 99.23, 105.30, 109.70, 119.34, 120.89, 121.69, 121.76, 123.26, 123.30, 123.90, 126.22, 126.82, 127.87, 127.90, 128.38, 130.60, 131.98, 133.82, 134.12, 139.59, 140.30, 142.65, 145.48, 145.78, 147.70, 151.50 ppm. EI-MS m/z : 789.38 (M⁺10). Anal. Calcd., for C₄₈H₅₁N₇O₄: C, 72.98; H, 6.51; N, 12.41; O, 8.10. Found: C, 72.96; H, 6.50.

Method B. A solution of **3** (100 mg, 0.24 mmol), brucine derivative (105 mg, 0.24 mmol), and boric acid (30 mg, 0.48 mmol) in 10 mL of methanol was stirred for 48 h at room temperature. The organic phase was evaporated to dryness under reduced pressure; the residue was purified by crystallization from methanol: water yielding 50% of product, m.p. 158–160°C; ¹H and ¹³C NMR data were similar to method A product.

2.4. 2-Chloro-3-{[2-[-(3-chloro-2-oxo-cyclobutyl)-(2,3-dimethoxy-9,10-dihydrostrychnid-10-yl)-amino]-ethyl]-[1,5-dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-yl)-2-phenyl-2,3-dihydro-1H-Pyrazol-3-yl]-amino}-cyclobutanone (9). A solution of **6** (100 mg, 0.10 mmol), chloroacetyl chloride (35 μ L, 0.44 mmol), and triethylamine (60 μ L, 0.43 mmol) in 10 mL of methanol was stirred for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, after the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure; the residue was purified by crystallization from methanol: water (3:2) yielding 65% of product, m.p. 74–76°C; IR ($V_{\max}$, cm⁻¹): 3410, 1716, 1228, 1150, 1140; ¹H NMR (300 MHz, CDCl₃) δ_{H} : 1.12–1.46 (m, 2H), 1.54 (m, 2H), 1.85 (m, 1H), 1.86–1.87 (m, 2H), 1.96 (s, 3H), 2.04–2.70 (m, 5H), 2.70 (s, 3H), 2.82–2.86 (m, 4H), 2.87 (m, 1H), 2.90–3.42 (m, 3H), 3.54 (m, 1H), 3.62–3.78 (m, 3H), 3.80 (s, 3H), 3.90 (m, 1H), 3.93 (s, 3H), 3.98 (m, 1H), 4.02 (m, 1H), 4.38 (m, 1H), 4.62 (m, 2H), 5.16–5.70 (m, 4H), 5.88–5.97 (m, 2H), 6.90 (m, 1H), 6.95 (m, 1H), 7.00 (m, 2H), 7.04 (m, 1H),

FIGURE 1: Synthesis of N-1-[1,5-dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-yl)-2-phenyl-1,2-dihydro-pyrazol-3-ylidene]-ethane-1,2-diamine (4). The first stage involves the reaction of naphthol (1) with 4-aminoantipyrine (2) to form the compound 1,5-dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-(3H)-yl)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (3) in presence of formaldehyde (i). The second stage was achieved by the reaction of 3 with ethylenediamine (ii) to form 4.

7.20 (m, 1H), 7.30 (m, 2H), 7.38–7.80 (m, 5H) ppm. ^{13}C NMR (75.4 MHz, CDCl_3) δ_{C} : 15.02, 27.34, 31.88, 32.40, 32.66, 34.28, 34.32, 40.86, 46.50, 47.72, 50.30, 50.38, 50.72, 50.74, 55.95, 56.20, 56.29, 62.90, 63.20, 64.16, 66.32, 70.72, 71.00, 73.10, 74.29, 78.30, 82.20, 96.38, 100.40, 108.30, 109.20, 113.70, 114.66, 118.60, 119.30, 119.90, 121.06, 121.60, 123.28, 126.30, 127.80, 127.90, 128.11, 128.40, 132.70, 132.90, 134.89, 140.30, 143.40, 146.30, 146.78, 150.54, 203.44, 204.20 ppm. EI-MS m/z : 997.40 (M^+ 10). Anal. Calcd. for $\text{C}_{56}\text{H}_{61}\text{Cl}_2\text{N}_7\text{O}_6$: C, 67.33; H, 6.15; Cl, 7.10, N, 9.81; O, 9.61. Found: C, 67.30; H, 6.12.

2.5. N-[1,5-Dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-yl)-2-phenyl-1,2-dihydro-pyrazol-3-ylidene]-N'-(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylidene)ethane-1,2-diamine (II). A solution of 4 (100 mg, 0.24 mmol), 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (40 mg, 0.26 mmol), and boric acid (30 mg, 0.48 mmol) in 10 mL of methanol was stirred for 48 h at

room temperature. The reaction mixture was evaporated to a smaller volume, after the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure; the residue was purified by crystallization from methanol : water (4 : 1) yielding 75% of product, m.p. 90–92°C; IR (V_{max} , cm^{-1}): 3320, 1228, 1138; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 0.80 (s, 3H), 0.84 (s, 6H), 1.12–1.74 (m, 4H), 2.04 (s, 3H), 2.08–2.70 (m, 3), 3.12 (s, 3H), 3.72 (t, 2H, $J = 6.54$ Hz), 3.84 (t, 2H, $J = 6.54$ Hz), 5.20–5.74 (m, 4H), 7.01–7.06 (m, 3H), 7.32–7.46 (m, 3H), 7.52 (m, 2H), 7.60–8.04 (m, 3H) ppm. ^{13}C NMR (75.4 MHz, CDCl_3) δ_{C} : 11.20, 15.48, 19.04, 19.40, 27.40, 31.18, 34.70, 38.66, 43.70, 47.24, 47.40, 49.90, 52.50, 53.35, 81.72, 105.31, 109.60, 119.38, 121.66, 121.78, 123.30, 123.88, 126.22, 126.80, 127.90, 128.40, 131.98, 133.86, 134.10, 139.57, 142.62, 151.50, 172.02 ppm. EI-MS m/z : 547.30 (M^+ 10). Anal. Calcd. for $\text{C}_{35}\text{H}_{41}\text{N}_5\text{O}$: C, 76.75; H, 7.54; N, 12.79; O, 2.92. Found: C, 76.74; H, 7.52.

FIGURE 2: Synthesis of N-[1,5-dimethyl-4-(1*H*-naphtho[1,2-*e*][1,3]oxazin-2-yl)-2-phenyl-1,2-dihydro-pyrazol-3-ylidene]-2,3-dimethoxytrychnidin-10-ylidene-ethane-1,2-diamine (**6**). Reaction of N-1-[1,5-dimethyl-4-(1*H*-naphtho[1,2-*e*][1,3]oxazin-2-yl)-2-phenyl-1,2-dihydro-pyrazol-3-ylidene]-ethane-1,2-diamine (**4**) with brucine (**5**) to form the compound **6**. iii: boric acid/rt.

2.6. 2-Chloro-3-{2-[(3-chloro-2-oxo-cyclobutyl)-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-ethyl}-[1,5-dimethyl-4-(1*H*-naphtho[1,2-*e*][1,3]oxazin-2-yl)-2-phenyl-2,3-dihydro-1*H*-pyrazol-3-yl]-amino}-cyclobutanone (**12**). A solution of **11** (100 mg, 0.18 mmol), chloroacetyl chloride (35 μ L, 0.44 mmol), and triethylamine (60 μ L, 0.43 mmol) in 10 mL of methanol was stirred for 48 h at room temperature. The reaction mixture was evaporated to a smaller volume, after the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure; the residue was purified by crystallization from methanol: water (2:1) yielding 75% of product, m.p. 98–100°C; IR ($V_{\max}$, cm^{-1}): 1716, 1228, 1196, 1138; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 0.68 (s, 3), 0.72 (s, 3H), 0.81 (s, 3H), 1.12–1.28 (m, 4H), 1.58 (m, 1H), 1.68–1.70 (m, 2H), 1.71 (m, 1H), 1.75 (m, 1H), 1.86 (m, 2H), 1.98 (s, 3H), 1.99 (m, 1H), 2.60 (m, 1H), 2.62–2.68 (t, 2H, $J = 6.51$ Hz), 2.74 (s, 3H), 2.83–2.84 (t, 2H, $J = 6.51$ Hz), 3.64–4.04 (m, 2H), 4.38 (m, 1H), 4.62 (m, 2H), 5.16–5.70 (m, 4H), 6.90–7.00 (m, 3H), 7.09 (m, 1H), 7.30 (m, 2H), 7.38–7.78 (m, 5H) ppm. ^{13}C NMR (75.4 Hz,

CDCl_3) δ_{C} : 13.36, 15.06, 19.86, 20.20, 26.40, 32.66, 32.70, 34.30, 36.50, 36.72, 44.40, 47.12, 47.78, 50.66, 51.40, 53.88, 61.70, 62.92, 71.00, 72.22, 73.10, 82.24, 100.40, 109.20, 113.70, 114.66, 118.60, 119.90, 121.09, 123.30, 126.28, 127.90, 128.12, 128.40, 132.76, 134.80, 140.86, 150.50, 202.02, 203.40 ppm. EI-MS m/z : 755.30 (M^+10). Anal. Calcd. for $\text{C}_{43}\text{H}_{51}\text{Cl}_2\text{N}_5\text{O}_3$: C, 68.24; H, 6.79; Cl, 9.37; N, 9.25; O, 6.34. Found: C, 68.20; H, 6.78.

3. Results and Discussion

In this study were synthesized two oxazine derivatives using some strategies; it is important to mention that there are reports which indicate that condensation of naphthol with formaldehyde and amino groups result in naphthoxazines [10, 11]. Therefore, in the first stage was synthesized the compound 1,5-dimethyl-4-(1*H*-naphtho[1,2-*e*][1,3]oxazin-2-(3*H*)-yl)-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**3**) by the reaction of naphthol, 4-aminoantipyrine, and formaldehyde (Figure 1). The ^1H NMR spectrum of **3** show signals at 2.10

FIGURE 3: Synthesis of N-[1,5-dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-yl)-2-phenyl-1,2-dihydro-pyrazol-3-ylidene]-2,3-dimethoxystrychnidin-10-ylidene-ethane-1,2-diamine (**6**). Reaction of 1,5-dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-(3H)-yl)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (**3**) with N¹-(2,3-dimethoxystrychnidin-10-yliden)-ethane-1,2-diamine (**7**) to form the compound **6**. iv: boric acid/rt.

and 2.80 ppm for methyl groups; at 5.00–5.70 ppm for oxazine ring; at 7.01, 7.30, 7.44, and 7.60–7.66 ppm for naphthalene group bound to oxazine ring; at 7.10, 7.40, and 7.58 ppm for phenyl group. The ¹³C NMR spectrum of **3** contains peaks at 15.02 and 34.20 ppm for methyl groups; at 110.12 and 134.38 ppm for carbons involved in the cyclopentene ring; at 47.42, 81.88, 110.20, and 151.80 ppm for oxazine ring; at 118.52–126.30, 127.90, 128.40, and 133.90–134.18 ppm for naphthalene group; at 126.42, 128.11–128.25, and 133.84 ppm for phenyl group; at 166.30 ppm for ketone group. Finally, the presence of compound **3** was further confirmed from mass spectrum which showed a molecular ion at *m/z* 371.10.

The second stage was achieved by reaction of the compound **3** with ethylenediamine (Figure 1) resulting in imino bond formation involved in the compound **4** (N-1-[1,5-dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-yl)-2-phenyl-1,2-dihydro-pyrazol-3-ylidene]-ethane-1,2-diamine). Many

procedures for the synthesis of imino groups are described in the literature [12–14]; nevertheless, in this study boric acid was used as a catalyst, because it is not an expensive reagent and no special conditions for its use are required [15]. The results of ¹H NMR spectrum of **4** show signals at 2.02 and 3.06 ppm for methyl groups; at 3.18 and 3.70 ppm for methylene groups involved in the arm bound to cyclopentene ring; at 4.34 ppm for amino group; at 5.20–5.76 ppm for oxazine ring; at 6.98–7.04 and 7.52 for phenyl group; at 7.30–7.48 and 7.60–8.06 ppm for naphthalene group. The ¹³C NMR spectrum of **4** contains peaks at 15.50 and 34.70 ppm for methyl groups; at 40.24 and 54.92 ppm for methylene groups involved in the arm bound to cyclopentene ring; at 47.24, 81.38–81.38, 109.66, and 151.48 ppm for oxazine ring; at 105.28 and 121.68 ppm for methylene groups of cyclopentene ring; at 119.30, 121.80–123.30, 126.30, 127.91–128.40, and 133.80–134.18 ppm for naphthalene group; at 123.90, 126.80, 131.90,

FIGURE 4: Synthesis of 2-chloro-3-{2-[-(3-chloro-2-oxo-cyclobutyl)-(2,3-dimethoxy-9,10-dihydrostrychnid-10-yl)-amino]-ethyl}-[1,5-dimethyl-4-(1*H*-naphtho[1,2-*e*][1,3]oxazin-2-yl)-2-phenyl-2,3-dihydro-1*H*-pyrazol-3-yl]-amino}-cyclobutanone (**9**). Reaction of *N*-[1,5-dimethyl-4-(1*H*-naphtho[1,2-*e*][1,3]oxazin-2-yl)-2-phenyl-1,2-dihydro-pyrazol-3-ylidene]-2,3-dimethoxystrychnidin-10-ylidene-ethane-1,2-diamine (**6**) with chloroacetyl chloride (**8**) to form the compound **9**. v: triethylamine/rt.

and 142.60 ppm for phenyl group; at 139.50 ppm for imino group. Finally, the presence of compound **4** was further confirmed from mass spectrum which showed a molecular ion at m/z 413.20.

In the third stage two different methods for synthesis of the oxazine-brucine derivative (**6**) were employed; the first step was achieved by reaction of the compound **4** with brucine to form the oxazine-brucine derivative (**6**) using boric acid as catalyst (method A, Figure 2). The results of ^1H NMR spectrum of **6** show signals at 2.02 and 3.12 ppm for methyl groups bound to cyclopentene ring; at 1.40–1.84, 2.22–3.10, 3.26–3.69, 4.70, 5.83–5.88, and 7.55 ppm for brucine nucleus; at 3.90 and 3.92 ppm for methylene groups involved in arm bound to cyclopentene ring; at 3.80–3.91 for methyl groups of brucine; at 5.20–5.78 for protons of oxazine ring; at 7.00–7.04 and 7.52 ppm for phenyl group; at 7.32–7.44 and 7.60–8.04 ppm for naphthalene group. The ^{13}C NMR spectrum of **6** contains peaks at 15.48 and 34.75 ppm for methyl

groups bound to cyclopentene ring; at 27.37–34.52, 40.90–45.82, 56.20, 63.20–79.26, 99.23, 123.26, 127.87, 130.60, 140.30, and 145.48–147.70 ppm for brucine nucleus; at 47.26, 81.70, 109.70–109.74, and 151.50 ppm for oxazine ring; at 55.02–55.09 for arm bound both imino groups; at 105.30, 121.69, and 139.59 ppm for cyclopentene ring; at 119.34, 121.76, 123.30–126.22, 127.90–128.38, and 133.82–134.12 ppm for naphthalene group; at 123.90, 126.82, 131.98, and 142.65 ppm for phenyl group; at 55.95 and 56.60 for methyl groups of brucine. Finally, the presence of compound **6** was further confirmed from mass spectrum which showed a molecular ion at m/z 789.38. The second step was achieved by reaction of the compound **3** with **7** to form the compound **6** using boric acid as catalyst (Figure 3). Similar ^1H and ^{13}C NMR data were obtained compared with method A product. However, it is noteworthy that with this method the yield was low as compared to method A; this phenomenon possibly is due to time of reaction required with this methodology.

FIGURE 5: Synthesis of N-1-[5-dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-yl)-2-phenyl-1,2-dihydro-pyrazol-3-ylidene]-N'-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylidene)ethane-1,2-diamine (**11**). Reaction of N-1-[5-dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-yl)-2-phenyl-1,2-dihydro-pyrazol-3-ylidene]-ethane-1,2-diamine (**4**) with 1,7,7-trimethyl bicyclo[2.2.1]heptan-2-one (**10**) to form the compound **11**. vi: boric acid/rt.

On the other hand, the compound **9** was synthesized (Figure 4); this compound has two chlorocyclobutane groups bound to both amino groups involved in their chemical structure. It is important to mention that there are several reports for preparation of chlorocyclobutenones using several techniques [16–19]; nevertheless, expensive reagents and special conditions are required. Therefore, in this study a new chlorocyclobutenone was formed in the chemical structure of **9** using chloroacetyl chloride in presence of triethylamine. The results of ^1H NMR spectrum of **9** show signals at 1.12–1.46, 1.85, 2.04–2.70, 2.87–3.42, 3.62–3.78, 3.90, 3.98, 5.88–5.97, and 7.20 ppm for brucine fragment; at 1.54, 1.86–1.87, 3.54, 4.02, and 4.62 ppm for cyclobutanone groups; at 1.96 and 2.74 ppm for methyl groups bound to cyclopentene ring; at 2.82–2.86 for methylene bound to both amino groups; at 3.80 and 3.93 ppm for methyl groups of brucine fragment; at 4.38 ppm for cyclopentene ring; at 5.16–5.70 ppm for

oxazine group; at 6.90–7.00 and 7.30 ppm for phenyl group; at 7.04 and 7.38–7.80 ppm for naphthalene group. The ^{13}C NMR spectrum of **9** contains peaks at 15.02 and 34.28 ppm for methyl groups bound to cyclopentene ring; at 27.34–31.88, 34.32–46.50, 50.72–50.74, 56.20, 63.20–66.32, 74.29–78.30, 96.38, 108.30, 121.06, 132.90, and 140.30–146.30 ppm for brucine nucleus; at 32.40–32.66, 62.90, 70.72–71.00, 203.44, and 204.20 ppm for cyclobutanone groups; at 47.72, 82.20, and 109.20 ppm for oxazine group; at 50.30 and 50.38 for methylene groups bound to both amino groups; at 55.95 and 56.29 ppm for methyl groups of brucine fragment; at 73.10, 100.40, and 114.66 ppm for cyclopentene ring; at 113.70, 119.30, 128.11, and 146.78 ppm for phenyl group; at 118.60, 119.90, 121.60–126.30, 127.90, 128.40–132.70, 134.89, and 150.54 ppm for naphthalene group. Finally, the presence of compound **9** was further confirmed from mass spectrum which showed a molecular ion at m/z 997.40.

FIGURE 6: Synthesis of 2-chloro-3-{[2-[(3-chloro-2-oxo-cyclobutyl)-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-ethyl]-[1,5-dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-yl)-2-phenyl-2,3-dihydro-1H-pyrazol-3-yl]-amino}-cyclobutanone (**12**). Reaction of N-[1,5-dimethyl-4-(1H-naphtho[1,2-e][1,3]oxazin-2-yl)-2-phenyl-1,2-dihydro-pyrazol-3-ylidene]-N'-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylidene)ethane-1,2-diamine (**11**) with chloroacetyl chloride (**8**) to form the compound **12**. v: triethylamine/rt.

The fourth stage was achieved by the reaction of **4** with 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one to form the compound **11** using boric acid as catalyst (Figure 5). The ^1H NMR spectrum of **11** shows signals at 0.80 and 0.84 ppm for methyl groups for bicyclic ring; at 1.12–1.74, 2.08–2.70 ppm for protons of bicyclic ring; at 2.04 and 3.12 ppm for methyl groups bound to cyclopentene ring; at 3.72 and 3.84 ppm for methylene groups bound to both imino groups; at 5.20–5.74 ppm for oxazine ring; at 7.01–7.06 and 7.52 ppm for phenyl group; at 7.32–7.46 and 7.60–8.04 ppm for naphthalene group. The ^{13}C NMR spectrum of **11** contains peaks at 11.20 and 19.04–19.40 ppm for methyl groups bound to bicyclic ring; at 15.48 and 34.70 ppm for methyl groups bound to cyclopentene ring; at 27.40, 31.18, 38.66–43.70, 47.40, 49.90, and 172.02 ppm for bicyclic ring; at 47.24, 81.72, and 109.60 ppm for carbons involved in oxazine ring; at 105.31, 121.66, and 139.57 ppm for cyclopentene ring; at 52.50 and 53.35 ppm for arm bound to both imino groups; at 119.38, 121.78–123.30, 126.22, 127.90–128.40, 133.86–134.10, and 151.54 ppm for naphthalene group; at 123.88, 126.80, 131.98, and 142.62 ppm for phenyl group. In addition, the presence of compound **11**

was further confirmed from mass spectrum which showed a molecular ion at m/z 547.30.

Finally, the compound **12** (Figure 6) was developed by the reaction of **11** with chloroacetyl chloride using triethylamine as catalyst. The ^1H NMR spectrum of **12** shows signals at 0.68, 0.72, and 0.81 ppm for methyl groups bound to bicyclic ring; at 1.12–1.28, 1.68–1.70, 1.75, and 2.60 ppm for bicyclic ring; at 1.58, 1.71, 1.86, 1.99, 3.64–4.04, and 4.62 ppm for protons involved in cyclobutanone groups; at 1.98 and 2.74 ppm for methyl groups bound to cyclopentene ring; at 2.62–2.68 and 2.83–2.84 ppm for methylene groups bound to both amino groups; at 4.38 ppm for proton of cyclopentene ring; at 5.16–5.70 ppm for oxazine ring; at 7.09 and 7.38–7.78 ppm for naphthalene group; at 6.90–7.00 and 7.30 ppm for phenyl group. The ^{13}C NMR spectrum of **12** contains peaks at 13.36, 19.86, and 20.20 ppm for methyl groups bound to bicyclic ring; at 15.06 and 34.30 methyl groups bound to cyclopentene ring; at 26.40, 36.50, 47.12 and 53.88–61.70 ppm for carbons of bicyclic ring; at 73.10, 100.40, and 114.66 ppm for cyclopentene ring; at 47.78, 82.24, 109.20, and 150.50 ppm for oxazine ring; at 50.66 and 51.40 ppm for methylene groups bound to both

amino groups; at 32.66, 32.70, 62.92, and 71.00–72.22 ppm for cyclobutanone groups; at 118.60, 121.09–127.90, and 128.40–134.80 ppm for naphthalene group; at 113.70, 119.90, and 128.12–146.86 ppm for phenyl group; at 202.02 and 203.40 ppm for ketone groups. Finally, the presence of compound **12** was further confirmed from mass spectrum which showed a molecular ion at m/z 755.30.

4. Conclusions

In this study two oxazine derivatives were synthesized using some strategies; the methods used offer some advantages such as good yields, simple procedure, low cost, and ease of workup.

Conflict of Interests

The authors declare that they do not have any financial relations with any of the commercial entities mentioned in the paper that could lead to a conflict of interests.

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