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Synthesis of some novel imidazolone analogues utilizing 4-((2-(4-acetanilide)-5-oxooxazol-4(5*h*)-ylidene)methyl)phenyl benzenesulfonate synthon

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Abstract: A new series of new imidazolones **3-6** have been achieved *via* the reaction of the readily obtainable 5-oxazolone **2** with 4-aminophenol, ethyl 4-aminobenzoate, 4-aminoacetophenone and 2-aminobenzoic acid as primary aromatic amines in acetic acid including freshly melted sodium acetate. Furthermore, the imidazolone **3** on reaction with ethyl 2-chloroacetate, acetic anhydride, benzoyl chloride or benzenesulfonyl chloride afforded the corresponding imidazolone derivatives **7-10**. The newly imidazolone derivatives have been established by spectral data and elemental analysis.

keywords: Oxazolones; imidazolones; 4-aminoacetophenone; 2-aminopyridine; 2-aminothiazole

1.Introduction

Imidazolone moiety is the basic core of many synthetic and natural products [1], which have remarkable biological performance [2]. Imidazolones have been reported as potent analogues of V-RAF murine [3] growth and phosphodiesterase inhibitors [4, 5]. These compounds were also antagonists of some receptors carrying neurokinin-1 [6] and the dopamine receptor [7]. Recently, the synthesis of products containing imidazolone [8-15] has been increased due to their valuable biological significance. Imidazolone is the nucleus of fluorescent probes associated with fluorescent proteins (**A**) [16-20] as well as structural fragments of active compounds against obesity-related disorders and hypertension (**B**) [21-24]. In addition, imidazolones are beneficial intermediates for the preparation of natural alkaloids, for example, compounds **A** and **C** [25]. They also found agrochemical applications such as herbicides, which are used to control weeds in pulses, grains and peanuts (**D**) [26, 27] (Fig. 1). The synthesis of azlactones by Erlenmayer has been found to be beneficial because these analogs can be suitably converted to imidazolones by an amidation/ring closure [16].

Continuing of our earlier work for the synthesis of novel biologically active heterocyclic compounds [28-30], we report in this paper a simple synthetic method for the preparation of a series of heterocyclic compounds containing imidazolone ring systems of pharmacological interest.

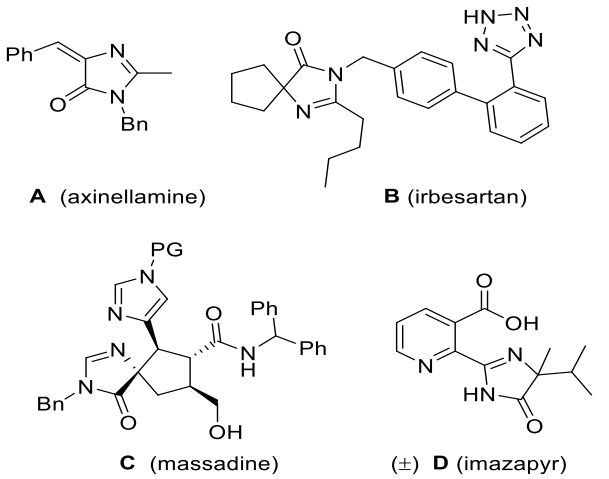
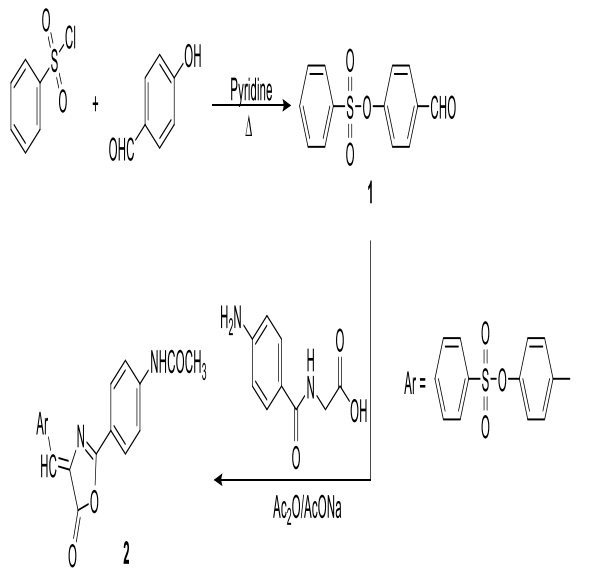


Figure 1. Structures of significant active imidazolones.

2. Results and Discussion

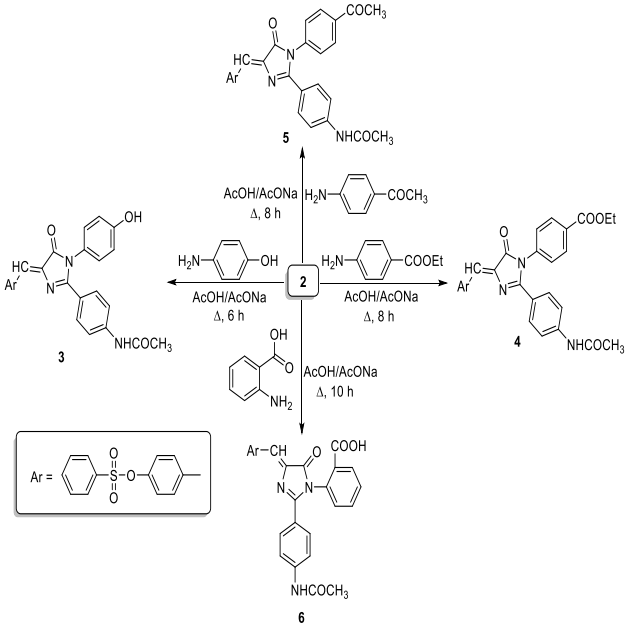
2.1. Synthetic Chemistry

The 5-oxazolone **2** was achieved in good yield *via* heating benzenesulfonyl chloride with 4-hydroxybenzaldehyde in pyridine to yield 4-formylphenyl benzenesulfonate **(1)**, which was then converted to compound **2** upon heating with benzoylglycine in acetic anhydride having freshly melted sodium acetate (Scheme 1).



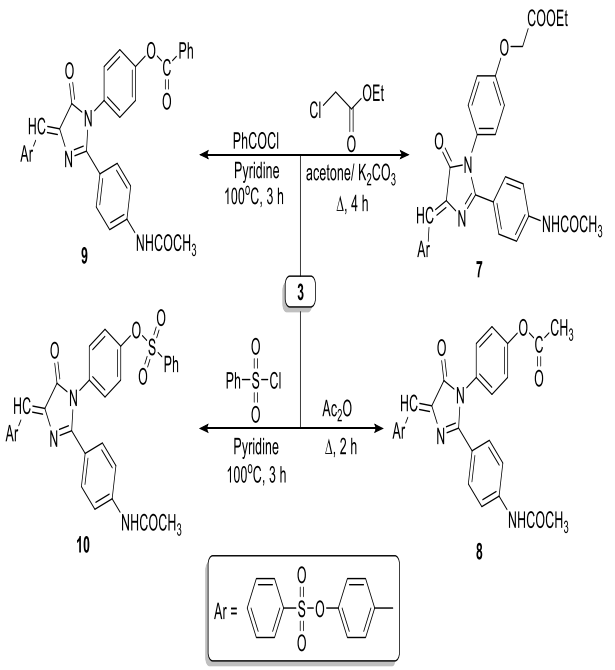
Scheme 1. Synthesis of 5-oxazolone **2**.

The 5-oxazolone **2** was utilized as a reactive precursor in reaction with various primary aromatic amines. Thus, heating **2** with 4-aminophenol, ethyl 4-aminobenzoate, 4-aminoacetophenone and 2-aminobenzoic acid in acetic acid having freshly melted sodium acetate afforded imidazol-5-ones **3-6**, respectively. The mechanism of formation of the imidazolones **3-6** was illustrated by aminolysis nucleophilic attack of amino group of aromatic amines at the carbonyl group of lactone ring involving ring opening followed by a cyclocondensation step with the elimination of water molecule. (Scheme 2).



Scheme 2. Reactions of 5-oxazolone **2** with different primary aromatic amines.

Structures of imidazolones **3-6** were established by both spectral data and elemental analysis. For example, compound **3** exhibited characteristic absorption bands at 3411, 1668 and 1642 cm^{-1} due to phenolic OH and two amidic carbonyl groups, respectively in the IR spectrum. In addition, the carbonyl ester group of compound **4** appeared at 1718 cm^{-1}. Compound **3** revealed in the ^{1}H-NMR spectrum singlet signal at δ 9.86 ppm as a result of OH proton, whereas for compound **4**, it exhibited a triplet signals at δ 1.30 ppm for the methyl protons of $COOCH_2CH_3$ group and a quartet signals at δ 4.30 ppm because of CH_2 protons of $COOCH_2CH_3$ group. Furthermore, the ^{1}H-NMR spectrum of imidazolone **5** exhibited two singlet signals at δ 2.60 and 2.42 ppm as a result of two CH_3 protons, beside the signals for the other expected protons. The mass spectra of compounds **3-6** appeared the molecular ion peaks at *m/z* = 553.32 (M^+, 12.43), 609.89 (M^+, 22.04), 579.87 (M^+, 28.75) and 581.38 (M^+, 15.55), respectively, which are in agreement with the molecular formula of the proposed structures. Heating the imidazolone **3** with ethyl 2-chloroacetate in acetone containing potassium carbonate to give the corresponding phenoxyethyl acetate **7**. In addition, acetylation of **3** by heating in acetic anhydride yielded the phenyl acetate **8**. Benzoylation of compound **3** using benzoyl chloride in pyridine gave the phenyl benzoate **9**. Sulfonylation of **3** with benzenesulfonyl chloride by heating in pyridine gave the phenyl benzenesulfonate **10** (Scheme 3). The IR spectra of imidazolones **7-10** lacked absorption band due to OH group. Imidazolone **7** disappeared a singlet signal due to OH proton in the ^{1}H-NMR spectrum and appeared a triplet signals at δ 1.20 ppm due to methyl protons of $COOCH_2CH_3$ group, a quartet signals at δ 4.16 ppm because of CH_2 protons of $COOCH_2CH_3$ group and a singlet signal at δ 4.83 ppm for -O-$\underline{CH_2}$ protons. Furthermore, imidazolone **8** appeared two singlet signals at δ 2.42 and 2.29 ppm as a result of two CH_3 protons and lacked a singlet signal due to OH proton in the ^{1}H-NMR spectrum. The mass spectra of imidazolones **7-10** evidenced the molecular ion peaks at *m/z* = 641.15 (M^++2, 21.58), 595.76 (M^+, 11.45), 657.11 (M^+, 9.67) and 693.04 (M^+, 10.14), respectively, which are in compact with the molecular formula of the proposed structures.



Scheme 3. Synthesis of the imidazolone derivatives **7**-**10**.

3. Materials and Methods

Melting points (uncorrected) were determined in degree Celsius on an electrothermal apparatus Gallenkamp (Germany). The ^{1}H-NMR spectra were run on a 400 MHz Bruker Avance III spectrophotometer (USA). The infrared spectra (KBr) (υ cm^{-1}) were measured on a Mattson 5000 FTIR Spectrometer (USA). The mass spectrum measurements were measured on Kratos Mass Spectrum (Kratos Mass Spectrum Analytical Instrument, Ramsey, NJ) instrument in EI mode with an ionizing voltage of 70 eV. Elemental analyses (C, H, and N) were achieved on Perkin-Elmer Instruments 2400, Shelton, CT).

4-((2-(4-Acetanilide)-5-oxooxazol-4(5*H*)-ylidene)methyl)phenyl benzenesulfonate (2)

To a mixture of (4-aminobenzoyl)glycine (1.94 g, 0.01 mol) in 30 mL acetic anhydride and NaOAc (0.82 g, 0.01 mol), 4-formylphenyl benzenesulfonate **(1)** (2.62 g, 0.01 mol) was added. Heat the mixture for 2 h on water bath then stand at 25^{o}C to cool and the precipitated oxazolone was separated by filtration and ethyl alcohol was used for recrystallization. Yellow crystals; yield 77%; mp 244-246^{o}C. IR (ν_{max}, cm^{-1}): 3237 (NH), 1723 (CO, lactone), 1654 (CO, amidic), 1600 (C=N), 1545 (C=C), 1370 (SO_3). ^{1}H-NMR (DMSO-d_6) δ (ppm): 10.34 (s, 1H, NH), 7.27 (s, 1H, CH=), 7.68-6.90 (m, 13H, Ar-H), 2.26 (s, 3H, CH_3). MS: (ESI) (*m/z*, %): 462.77 (M$^+$, 23.26), 433.12 (45.01), 414.22 (15.76), 375.00 (13.01), 310.46 (18.00), 257.09 (25.06), 223.12 (23.56), 176.22 (100.0), 129.11 (42.11), 95.26 (39.12). Calc. for $C_{24}H_{18}N_2O_6S$ (462.48): C, 62.33; H, 3.92; N, 6.06%; Found: C, 62.30; H, 3.90; N, 6.08%.

Preparation of imidazolones 3-6 (General procedure)

To a mixture of the 5-oxazolone **2** (2.31 g, 0.005 mol) in 20 mL acetic acid and NaOAc (0.615 g, 0.0075 mol), 4-aminophenol, ethyl 4-aminobenzoate, 4-aminoacetophenone or 2-aminobenzoic acid (0.0055 mol) was added. Reflux the mixture for 6-10 h, stand at 25^{o}C to cool and the precipitated imidazolone was separated by filtration and ethyl alcohol was used for recrystallization.

4-((2-(4-Acetamidophenyl)-1-(4-hydroxyphenyl)-5-oxo-1,5-dihydro-4*H*-imidazol-4-ylidene)methyl)phenyl benzenesulfonate (**3**). Yellow crystals; yield 55%; mp 297-299^{o}C. IR (ν_{max}, cm^{-1}): 3411, 3245 (OH, NH), 1668, 1642 (2 CO, amidic), 1612 (C=N), 1600 (C=C), 1365 (SO_3). ^{1}H-NMR (DMSO-d_6) δ (ppm): 10.22 (s, 1H, NH), 9.86 (s, 1H, OH), 7.22 (s, 1H, CH=), 7.68-6.90 (m, 17H, Ar-H), 2.38 (s, 3H, CH_3). MS: (ESI) (*m/z*, %): 553.32 (M$^+$, 12.43), 522.12 (24.89), 475.23 (34.07), 414.00 (14.12), 366.05 (44.30), 311.45 (21.86), 267.41 (33.10), 209.34 (18.08), 142.11 (100.00), 108.17 (23.18), 95.21 (76.00). Calc. for $C_{30}H_{23}N_3O_6S$ (553.59): C, 65.09; H, 4.19; N, 7.59%; Found: C, 65.06; H, 4.18; N, 7.55%.

Ehyl 4-(2-(4-acetamidophenyl)-5-oxo-4-(4-((phenylsulfonyl)oxy)benzylidene)-4,5-dihydro-1*H*-imidazol-1-yl)benzoate (**4**). Yellow crystals; yield 56%; mp 287-289^{o}C. IR (ν_{max}, cm^{-1}): 3189 (NH), 1718 (CO, ester), 1664, 1640 (2 CO, amidic), 1602 (C=N), 1588 (C=C), 1372 (SO_3). ^{1}H-NMR (DMSO-d_6) δ (ppm): 10.22 (s, 1H, NH), 8.38-7.17 (m, 17H, Ar-H), 7.29 (s, 1H, CH=), 4.30 (q, 2H, $\underline{CH_2}CH_3$), 2.42 (s, 3H, CH_3), 1.30 (t, 3H, $CH_2\underline{CH_3}$). MS: (ESI) (*m/z*, %): 609.89 (M$^+$, 22.04), 567.24 (19.32), 498.17 (45.06), 432.67 (29.09), 388.15 (42.22), 311.54 (17.62), 254.91 (11.72), 207.26 (38.13), 184.23 (100.00), 140.53 (36.10), 97.42 (34.90), 65.17 (45.30). Calc. for $C_{33}H_{27}N_3O_7S$ (609.65): C, 65.01; H,

4.46; N, 6.89%; Found: C, 65.00; H, 4.48; N, 6.85%.

4-((2-(4-Acetamidophenyl)-1-(4-acetylphenyl)-5-oxo-1,5-dihydro-4*H*-imidazol-4-ylidene)methyl)phenyl benzenesulfonate (**5**). Yellow crystals; yield 48%; mp 276-278°C. IR (ν_{max}, cm^{-1}): 3210 (NH), 1673 (CO, amidic), 1668, 1645 (2 CO, ketonic), 1611 (C=N), 1596 (C=C), 1361 (SO_3). ^{1}H-NMR (DMSO-d_6) δ (ppm): 10.18 (s, 1H, NH), 8.38-7.17 (m, 17H, Ar-H), 7.29 (s, 1H, CH=), 2.60 (s, 3H, CH_3), 2.42 (s, 3H, CH_3). MS: (ESI) (*m/z*, %): 579.87 (M^+, 28.75), 532.25 (41.90), 487.45 (31.08), 436.23 (20.33), 390.56 (29.07), 332.73 (100.00), 285.44 (45.51), 220.73 (10.11), 189.59 (14.39), 134.79 (18.82), 95.31 (53.90), 68.30 (32.45), 44.10 (53.37). Calc. for $C_{32}H_{25}N_3O_6S$ (579.63): C, 66.31; H, 4.35; N, 7.25%; Found: C, 66.30; H, 4.32; N, 7.23%.

2-(2-(4-Acetamidophenyl)-5-oxo-4-(4-((phenylsulfonyl)oxy)benzylidene)-4,5-dihydro-1*H*-imidazol-1-yl)benzoic acid (**6**). Yellow crystals; yield 48%; mp 265-267°C. IR (ν_{max}, cm^{-1}): 3411, 3240 (OH, NH), 1700 (CO, acid), 1667, 1650 (2 CO, amidic), 1619 (C=N), 1608 (C=C), 1370 (SO_3). ^{1}H-NMR (DMSO-d_6) δ (ppm): 12.01 (s, 1H, COOH), 10.18 (s, 1H, NH), 8.02-7.21 (m, 17H, Ar-H), 7.27 (s, 1H, CH=), 2.40 (s, 3H, CH_3). MS: (ESI) (*m/z*, %): 581.38 (M^+, 15.55), 427.11 (35.99), 398.34 (39.00), 280.03 (24.63), 254.30 (100.00), 171.48 (18.80), 83.76 (49.37), 72.55 (24.69). Calc. for $C_{31}H_{23}N_3O_7S$ (581.60): C, 64.02; H, 3.99; N, 7.23%; Found: C, 64.00; H, 3.97; N, 7.20%.

Ethyl 2-(4-(2-(4-acetamidophenyl)-5-oxo-4-(4-((phenylsulfonyl)oxy)benzylidene)-4,5-dihydro-1*H*-imidazol-1-yl)phenoxy)acetate (**7**).

To a mixture of imidazolone **3** (2.76 g, 0.005 mol) in acetone (20 mL) and K_2CO_3 (1.035 g, 0.0075 mol), ethyl 2-chloroacetate (0.61 g, 0.005 mol) was added. Heat the mixture for 4 h, stand at 25°C to cool. The precipitated phenoxyethyl acetate **7** was separated by filteration and ethyl alcohol was used for recrystallization. Orange needles; yield 77%; mp 274-276°C. IR (ν_{max}, cm^{-1}): 3233 (NH), 1728 (CO, ester), 1668, 1640 (2 CO, amidic), 1601 (C=N), 1575 (C=C), 1375 (SO_3). ^{1}H-NMR (DMSO-d_6) δ (ppm): 10.25 (s, 1H, NH), 8.16-7.00 (m, 17H, Ar-H), 7.39 (s, 1H, CH=), 4.83 (s, 2H, -O-$\underline{CH_2}$), 4.16 (q, 2H, $\underline{CH_2}CH_3$), 2.42 (s, 3H, CH_3), 1.20 (t, 3H, $CH_2\underline{CH_3}$). MS: (ESI) (*m/z*, %): 641.15 (M^++2, 21.58), 639.77 (M^+, 61.62), 600.60 (26.29), 526.63 (30.24), 456.40 (30.35), 321.34 (60.51), 256.74 (100.00), 221.66 (54.45), 147.16 (26.55), 70.49 (29.50). Calc. for $C_{34}H_{29}N_3O_8S$ (639.68): C, 63.84; H, 4.57; N, 6.57%; Found: C, 63.82; H, 4.55; N, 6.55%.

4-(2-(4-Acetamidophenyl)-5-oxo-4-(4-((phenylsulfonyl)oxy)benzylidene)-1*H*-4,5-dihydro-1-imidazolyl)phenyl acetate (**8**).

Imidazolone **3** (5.53 g, 0.01 mol) in 10 mL Ac_2O on heating for 2 h, then stand at 25°C to cool and cold water was used for dilution. The formed solid phenyl acetate **8** has been separated by filteration and ethyl alcohol was used for recrystallization. Yellow crystals; yield 92%; mp 234-236°C. IR (ν_{max}, cm^{-1}): 3215 (NH), 1712 (CO, ester), 1666, 1643 (2 CO, amidic), 1596 (C=N), 1578 (C=C), 1372 (SO_3). ^{1}H-NMR (DMSO-d_6) δ (ppm): 10.25 (s, 1H, NH), 8.18-7.16 (m, 17H, Ar-H), 7.28 (s, 1H, CH=), 2.42 (s, 3H, CH_3), 2.29 (s, 3H, $\underline{CH_3}$). MS: (ESI) (*m/z*, %): 595.76 (M^+, 11.45), 523.11 (32.56), 458.44 (10.46), 425.12 (35.78), 348.19 (28.90), 308.34 (100.00), 267.21 (21.08), 185.33 (19.50), 114.03 (42.09), 95.44 (65.24). Calc. for $C_{32}H_{25}N_3O_7S$ (595.63): C, 64.53; H, 4.23; N, 7.05%; Found: C, 64.50; H, 4.20; N, 7.03%.

Synthesis of the imidazolones 9 and 10 (General procedure)

To a mixture of imidazolone **3** (2.76 g, 0.005 mol) in pyridine (15 mL), benzoyl chloride or benzenesulfonyl chloride (0.006 mol) was added. The products were heated on at 100°C for 3 h, then stand to cool at 25°C and cold water was used for dilution. The formed solid imidazolone has been collected by filteration and ethyl alcohol was used for recrystallization.

4-(2-(4-Acetamidophenyl)-5-oxo-4-(4-((phenylsulfonyl)oxy)benzylidene)-4,5-dihydro-1*H*-imidazol-1-yl)phenyl benzoate (**9**). Yellow crystals; yield 60%; mp 255-257°C. IR (ν_{max}, cm^{-1}): 3234 (NH), 1718 (CO, ester), 1656, 1645 (2 CO, amidic), 1589 (C=N), 1555 (C=C), 1361 (SO_3). ^{1}H-NMR (DMSO-d_6) δ (ppm): 10.31 (s, 1H, NH), 8.32-7.12 (m, 22H,

Ar-H), 7.38 (s, 1H, CH=), 2.40 (s, 3H, CH_3). MS: (ESI) (*m/z*, %): 657.11 (M^+, 9.67), 564.14 (8.01), 511.60 (12.34), 443.19 (31.09), 375.21 (8.19), 328.22 (7.18), 255.13 (100.00), 188.56 (41.25), 134.29 (21.08), 95.21 (11.67), 64.23 (13.56). Calc. for $C_{37}H_{27}N_3O_7S$ (657.70): C, 67.57; H, 4.14; N, 6.39%; Found: C, 67.55; H, 4.13; N, 6.35%.

4-((2-(4-Acetamidophenyl)-5-oxo-1-(4-((phenylsulfonyl)oxy)phenyl)-1,5-dihydro-4*H*-imidazol-4-ylidene)methyl)phenyl benzenesulfonate (**10**). Yellow crystals; yield 45%; mp 261-263°C. IR (ν_{max}, cm^{-1}): 3266 (NH), 1673, 1649 (2 CO, amidic), 1579 (C=N), 1544 (C=C), 1375 (SO_3). ^{1}H-NMR (DMSO-d_6) δ (ppm): 10.20 (s, 1H, NH), 8.31-7.22 (m, 22H, Ar-H), 7.38 (s, 1H, CH=), 2.40 (s, 3H, CH_3). MS: (ESI) (*m/z*, %): 693.04 (M^+, 10.14), 634.34 (16.11), 496.33 (9.23), 433.23 (15.01), 367.02 (18.56), 288.06 (100.00), 188.70 (20.35), 90.21 (33.89), 74.62 (28.90). Calc. for $C_{36}H_{27}N_3O_8S_2$ (693.75): C, 62.33; H, 3.92; N, 6.06%; Found: C, 62.31; H, 3.90; N, 6.04%.

In summary, 5-oxazolone **2** is profitable precursor for easy and comfortable synthesis of a new series of imidazolone derivatives **3-10**. The imidazolone prepared are prospective to be of pharmacological usefulness.

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