SYNTHESIS OF (SUBSTITUTED-PHENYL-1,2,4-OXADIAZOL-5-YL) METHYL-2-(3-OXO-2,3-DIHYDRO-4H-BENZO[B][1,4] OXAZIN-4-YL) ACETATE DERIVATIVES

Vijayacharan Guguloth

Department of Chemistry, Osmania University, Hyderabad-500 007, Telangana, INDIA.

*Corresponding Author: drvijayacharan77@gmail.com

ABSTRACT

A novel succession of synthesis of (substituted-phenyl-1,2,4-oxadiazol-5-yl) methyl-2-(3-oxo-2,3-dihydro-4H-benzo[b][1,4] oxazin-4-yl)acetate derivatives have been synthesized in ethical yields and was characterized by using ¹H NMR, IR and Mass spectroscopic methods and they were superior accordance with the proposed structures.

Keywords: 1,4-Bezoxazine, (*E*)-*N*¹-hydroxy-2-phenylacetimidamide, substituted phenyl-1,2,4-oxadiazoles, 1,4-benzoxazine acetates.

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INTRODUCTION

The heterocyclic compounds have been a captivating field in chemical and biological analysis. Heterocycles are constructional and essential in medical chemistry and they are routinely found in biomolecules. Heterocyclic systems are a part of a large number of drugs and biologically pertinent molecules.

The 1,4-benzoxazine-3-(4H)-one arena has been studied determinedly as significant heterocyclic systems for building natural and outlined synthetic compounds with a diverse range of biological activities¹ such as anti-proliferative, smooth muscle relaxant activity, potassium channel opening, anti-fungal, anti-microbial, platelet fibrinogen receptor antagonistic and anti-depressant activity. Exceptionally, the benzoxazine nucleus is a part of various clinically useful antibiotics such as actinocinin, actinomycin and xanthommatin, also as some of the established drug molecules as Bisoxatin, (laxative), Caroxazone SB-64,915 (2) (antagonist), Ofloxacin (3), and Paraxazone (4) (antidepressant), DIMBOA (5) (antibiotic) (Fig.-1).

Fig.-1: Some marketed Drugs containing Benzoxazinone Moiety

Oxadiazoles are a class of heterocyclic aromatic chemical compound of the azole family. 1,2,4-Oxadiazoles are the most popular platforms in medicinal chemistry and pharmaceuticals. These are bio-isomers of amides and esters and also exhibit hydrolytic, metabolic stability and strengthened pharmacokinetic properties in addition to striking biological activities, such as antimicrobial, antibiotic, anticancer and anti-inflammatory.²⁻⁷ Particularly, in the past years oxadiazole ring has been discovered

and is still being used for the forthcoming development of new drugs against numerous disease conditions.

A series of novel analogs of (substituted-3-phenyl-1,2,4-oxadiazol-benzo[*b*][1,4] oxazin acetates (**10a-f**)) have been synthesized as an aspect of our ongoing research in search of new biologically active compounds, as depicted in Schemes-1, 2 and 3.

EXPERIMENTAL

Material and Methods

To measure melting points of the compounds Sheetal precision melting point apparatus was used. Perkin Elmer-283B&Nicolet-740 was used to record IR spectra. Varian Gemini-200, Varian unit-500 and Avance 300 MHz, Avance 400 MHz, BrukerUx-NMR were used to record ¹H NMR spectra and VG Micro mass 7070H (ESI was used to record Mass spectra).

Ethyl-2-(3-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4] oxazin-4-yl) acetate (**3**)

The mixture of 4*H*-benzo [1,4] oxazin-3-one (**1**, 1.0 equiv.) and bromoethylacetate (**2**, 1.2 equiv.) was refluxed for a day in dry acetone (10 mL) and anhydrous potassium carbonate (2.0 g). This was further cooled to room temperature, was sieved and under reduced pressure, the solvent was removed. Derived solid recrystallized from ethanol to obtain ethyl-2-(3-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4] oxazin-4-yl) acetate (**3**). Yield: 80%, m. p. 75-78 °C. IR (KBr): $\nu_{\max}$ 1740 (lactone C=O) cm^{-1} . ¹H NMR (300 MHz, CDCl₃): δ 1.35-1.40 (t, 3H, -CH₃) 4.40 (q, 2H, -OCH₂-). EI-MS: m/z =235 [M⁺].

2-(3-Oxo-2,3-dihydro-4*H*-benzo[*b*][1,4] oxazin-4-yl)acetic acid (**4**)

A mixture of ethyl-2-(3-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4] oxazin-4-yl) acetate (**3**, 1.0 g) and aq. KOH (20 mL) refluxed in ethanol (30 mL) for 4h. The resultant mixture was brought to room temperature, which was neutralized thru dil. HCl and separated solid was sieved, washed with water, later dried and the rudimentary was recrystallized with ethanol to gain acid **4**, as a white solid with 82% yield, m. p. 148-150°C.

(*E*)-*N'*-hydroxy-2-phenylacetimidamide (**7a**)

The stirring solution of relevant benzonitrile (**5**, 1.0 equiv.) and hydroxylamine hydrochloride (**6**, 4.2 equiv.) in water were basified by 1M NaOH solution to pH 10. This was stirred at 30°C for an hour, then for another 2 hours under reflux to full conversion and TLC check was done. The mixture was brought to room temperature, after the completion of the reaction. The precipitate was filtered and washed with water to obtain (*E*)-*N'*-hydroxy-2-phenylacetimidamide (**7a**, 90%), which was used for the next step without further purification.

5-(Chloromethyl)-3-phenyl-1,2,4-oxadiazole (**9a**)

A solution of chloroacetyl chloride (**8**, 2.3 equiv.) in benzene (10 mL) was added drop by drop to a solution of benzamidoxime (**7a**, 1 equiv.) in benzene (100 mL) and under reflux for 10h, the mixture was heated. The reaction was monitored with the use of TLC. The reaction mixture was concentrated *in vacuo*, and flash column chromatography was used to purify crude residue by using *n*-hexane: ethyl acetate (2:1) mixture to give (5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (**9a**) as a white solid (92%).

General Procedure for (substituted-3-phenyl-1,2,4-oxadiazol-benzo[*b*][1,4]oxazin acetates (**10a-f**))

2-(3-Oxo-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)acetic acid(**4**, 1.0 equiv.), caesium carbonate (1.5 equiv.) and 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (**9a**, 1.0 equiv.) were dissolved in *N,N*-dimethylformamide and was stirred at room temperature for 16-18h. Distillation method used to remove the solvent under reduced pressure. Ethylacetate was used to extract the mixture after the addition of water to the residue. This was dried over anhydrous sodium sulphate. To get the following title compounds the solvent was removed by distillation under reduced pressure.

(3-Phenyl-1,2,4-oxadiazol-5-yl) methyl-2-(3-oxo-2,3-dihydro-4*H*-benzo [b][1,4] oxazin-4-yl)acetate (**10a**)

Yield 78%, m. p. 115-117 °C. IR (KBr): ν 2960, 1750, 1695, 1595 cm^{-1} . ¹H NMR (400 MHz, CDCl₃): δ 4.68 (s, 2H, -OCH₂-), 4.80 (s, 2H, -NCH₂-), 5.45 (s, 2H, -OCH₂-), 7.00-7.85 (m, 9H, Ar-H). ESI-MS: m/z = 366 [M+H].

(3-(2-Chlorophenyl-1,2,4-oxadiazol-5-yl) methyl-2-(3-oxo-2,3-dihydro-4H-benzo[b][1,4] oxazin-4-yl) acetate (10b)

Yield 78%, m. p. 100-103 °C. IR (KBr): ν 3015, 1755, 1690, 1590 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 4.68 (s, 2H, $-\text{OCH}_2-$), 4.82 (s, 2H, $-\text{NCH}_2-$), 5.46 (s, 2H, $-\text{OCH}_2-$), 7.05-7.80 (m, 8H, Ar-H). ESI-MS: m/z = 400 $[\text{M}+\text{H}]$, 402 $[\text{M}+2]$.

(3-(3-Chlorophenyl-1,2,4-oxadiazol-5-yl) methyl-2-(3-oxo-2,3-dihydro-4H-benzo[b][1,4] oxazin-4-yl) acetate (10c)

Yield 78%, m. p. 98-100 °C. IR (KBr): ν 3015, 1750, 1695, 1596 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 4.70 (s, 2H, $-\text{OCH}_2-$), 4.82 (s, 2H, $-\text{NCH}_2-$), 5.50 (s, 2H, $-\text{OCH}_2-$), 7.00 (s, 1H, Ar-H), 7.05-7.80 (m, 7H, Ar-H). ESI-MS: m/z = 400 $[\text{M}+\text{H}]$, 402 $[\text{M}+2]$.

(3-(4-Bromophenyl-1,2,4-oxadiazol-5-yl) methyl-2-(3-oxo-2,3-dihydro-4H-benzo[b][1,4] oxazin-4-yl) acetate (10d)

Yield 76%, m. p. 109-110 °C. IR (KBr): ν 2961, 1757, 1694, 1597 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 4.70 (s, 2H, $-\text{OCH}_2-$), 4.85 (s, 2H, $-\text{NCH}_2-$), 5.49 (s, 2H, $-\text{OCH}_2-$), 7.05 (m, 2H, Ar-H), 7.25 (m, 2H, Ar-H), 7.65 (d, 2H, Ar-H), 7.95 (d, 2H, Ar-H). ESI-MS: m/z = 443 $[\text{M}+\text{H}]$, 445 $[\text{M}+2]$.

(3-(4-Fluorophenyl-1,2,4-oxadiazol-5-yl) methyl-2-(3-oxo-2,3-dihydro-4H-benzo[b][1,4] oxazin-4-yl) acetate (10e)

Yield 72%, m. p. 101-103 °C. IR (KBr): ν 2926, 1759, 1696, 1608 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 4.70 (s, 2H, $-\text{OCH}_2-$), 4.85 (s, 2H, $-\text{NCH}_2-$), 5.50 (s, 2H, $-\text{OCH}_2-$), 7.00 (m, 3H, Ar-H), 7.10-7.20 (m, 2H, Ar-H), 8.05-8.15 (m, 3H, Ar-H). ESI-MS: m/z = 384 $[\text{M}+\text{H}]$.

(3-(4-Methoxyphenyl-1,2,4-oxadiazol-5-yl) methyl-2-(3-oxo-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl) acetate (10f)

Yield 80%, m. p. 113-114 °C. IR (KBr): ν 2965, 1755, 1695 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 3.85 (s, 3H, $-\text{OCH}_3$), 4.69 (s, 2H, $-\text{OCH}_2-$), 4.84 (s, 2H, $-\text{NCH}_2-$), 5.50 (s, 2H, $-\text{OCH}_2-$), 7.00 (m, 2H, Ar-H), 7.24 (m, 2H, Ar-H), 7.60 (d, 2H, Ar-H), 7.90 (d, 2H, Ar-H). ESI-MS: m/z = 396 $[\text{M}+\text{H}]$.

RESULTS AND DISCUSSION

The 4H-bezo[1,4]oxazine-3-one (**1**) treated thru bromoethyl acetate (**2**) in the existence of potassium carbonate in dry acetone to afford ethyl-2-(3-oxo-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)acetate (**3**) in 86% produce as a solid. A molecular ion peak at m/z = 235 $[\text{M}+\text{H}]$ appeared in the mass spectrum (EI-MS), in IR spectrum presence of ester C=O band at 1740 cm^{-1} , in ^1H NMR presence of triplet at δ 1.35 conforming to methyl protons ($-\text{CH}_3$), quartet at δ 4.35 agreeing to $-\text{OCH}_2-$ protons and a singlet at δ 4.75 consistent to $-\text{NCH}_2-$ protons confirmed the acetate derivative **3**. Which on treatment with aq. KOH in ethanol at reflux temperature gained 2-(3-oxo-2,3-dihydro-4H-benzo[b][1,4] oxazin-4-yl) acetic acid (**4**) in superior yield (Scheme-1).

Scheme 1

Substituted phenyl-1,2,4-oxadiazoles **9a-f** were prepared with the modified procedure by the reaction of *N*-hydroxybenamidines **7a-f** with chloroacetyl chloride in benzene solvent using a pinch of triethylamine at reflux temperature for 2-3 h. The precursor *N*-hydroxybenamidines **7a-f** were obtained by the reaction of various aryl cyanides **5a-f** with $\text{NH}_2\text{OH} \cdot \text{HCl}$ in methanol at reflux temperature for 2-3 h in presence of NaOH (Scheme-2).

Eventually, the besieged substituted-3-phenyl-1,2,4-oxadiazol-benzo[b][1,4]oxazin acetates (**10a-f**) accomplished in superior to exceptional yields by reaction of 2-(3-oxo-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)acetic acid (**4**) with phenyl-1,2,4-oxadiazoles **9a-f** in presence of caesium carbonate and dry *N,N*-dimethylformamide at room temperature for 16-18 h (Scheme-3).

^1H NMR, IR and Mass spectroscopic methods were used to characterize all the new synthesized derivatives **10a-f**. The spectral data of the proposed structures and the synthesized compounds were found to be in better agreement. For instance, complex **10d** was characterized by its ^1H NMR spectrum which showed characteristic $-\text{OCH}_2-$ protons of oxadiazole coupled 1,4-benzoxazine appeared as a singlet at δ 4.70 ppm and the $-\text{NCH}_2-$ protons of the 1,4-benzoxazine ring at 4.85 ppm which was further confirmed by ESI-MS having a mass ESI-MS: $m/z = 443$ $[\text{M}+\text{H}]$, 445 $[\text{M}+2]^+$ signifying the molecular formula of $\text{C}_{19}\text{H}_{14}\text{BrN}_3\text{O}_5$. Additionally, the IR spectra for the target compounds **10a-f** revealed characteristic absorption bands at 2961, 1757, 1694, 1597 cm^{-1} which corresponded to $\text{C}=\text{C}$, $\text{C}=\text{O}$, $\text{C}=\text{N}$ and $\text{C}-\text{N}$, respectively.

CONCLUSION

In conclusion, we have synthesized a novel 6-(2-amino-6-(substituted-phenyl)pyrimidin-4-yl)-4-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one derivative (**7a-c**) in better yields successfully by reaction of 2-(3-oxo-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)acetic acid (**4**) with phenyl-1,2,4-oxadiazoles **9a-f** in presence of caesium carbonate and dry *N,N*-dimethylformamide at room temperature and were characterized by using ^1H NMR, IR and Mass spectroscopic methods and they were in decent agreement with the proposed structures.

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