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Synthesis of 2-Nitroimidazole Derivatives with Oxazinone Moieties

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Abstract
An efficient methodology employing for the preparation of 2-nitro -imidazole derivatives containing 1,3 -oxazinone as a functional moiety by a one pot three component reaction of substituted phenol, substituted aromatic aldehydes and urea / thiourea under microwave conditions has been presented.All the synthesized products were characterized by elemental analysis and spectroscopy.Various imidazole-containing compounds have been tested for their medical usefulness in clinical trials for several disease conditions. The rapid expansion of imidazole-based medicinal chemistry suggests the promising and potential therapeutic values of imidazole-derived compounds for treating incurable diseases. Oxazinones are highly significant pharmacophoric scaffolds with a broad spectrum of biological activities, making them a vital class of compounds in medicinal chemistry. Various synthetic routes have been explored in the literature for producing aromatic oxazinones, showcasing the versatility of these compounds. Aromatic oxazinones were first synthesized in 1944 by Holly and Cope through Mannich reactions, utilizing phenols, formaldehyde, and amines. This pioneering work laid the foundation for further exploration of oxazinone derivatives in pharmaceutical applications. Over time, these heterocyclic compounds have garnered attention for their role as precursors in the synthesis of phosphinic ligands, which are widely employed in asymmetric catalysis. Given their diverse biological activities and utility in drug design, aromatic condensed oxazinone derivatives are regarded as 'Privileged structures' within the realm of pharmaceutical compounds. Their significance continues to grow, cementing their place in the development of novel therapeutic agents and catalytic processes.

Keywords: 4-(1H-imidazol-1-yl)-benzaldehyde, Substituted phenol,Microwave assisted conditions.

Introduction

The synthesis of 2-nitro imidazole derivatives containing oxazinones has gained significant attention due to their wide range of biological activities and potential applications in medicinal chemistry. 2-nitro imidazoles are well known for their use as radiosensitizers and antimicrobial agents, particularly in the treatment of hypoxic tumors[1] . Their ability to

selectively target hypoxic cells makes them important scaffolds for developing anti-cancer drugs. Oxazinones, on the other hand, are recognized as vital pharmacophoric structures with diverse biological properties, including anti-inflammatory, antimicrobial, and anti-tumor activities [2]. The combination of these two pharmacologically important moieties, 2-nitro imidazole and oxazinone, offers potential for the development of novel therapeutic agents with enhanced biological activity.

Imidazole derivatives have long been explored for their roles in drug design, with 2-nitro imidazoles being particularly noted for their efficacy in radiosensitization during cancer treatments [3]. The inclusion of the oxazinone ring in these derivatives opens new avenues in drug synthesis, as oxazinones have proven to be useful scaffolds in asymmetric catalysis and have been widely studied for their role as precursors in the formation of biologically active ligands [4,5].

The first synthesis of aromatic oxazinones was reported by Holly and Cope in 1944, where they employed a Mannich reaction involving phenols, formaldehyde, and amines [6] . Since then, numerous methods have been developed for the preparation of oxazinone derivatives, particularly due to their importance in drug discovery. These heterocyclic structures are often referred to as 'Privileged scaffolds' due to their frequent occurrence in bioactive compounds and their ability to interact with various biological targets [7]. Thus, combining the pharmacophoric attributes of both 2-nitro imidazole and oxazinones presents an exciting area of research in the development of new pharmacologically active compounds.

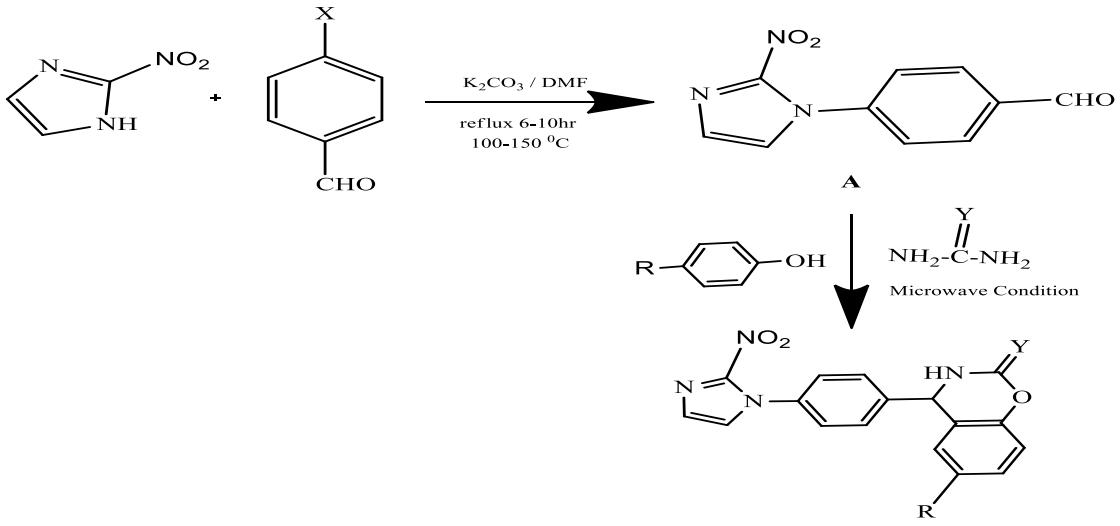
In this study, we focus on the synthesis and characterization of 2-nitro imidazole derivatives containing oxazinone rings. This work aims to explore the biological potential of these hybrid compounds, given the individual importance of both oxazinones and 2-nitro imidazoles in medicinal chemistry. The strategy for synthesizing these derivatives is based on the premise that integrating these two active pharmacophores could lead to compounds with enhanced therapeutic profiles, particularly in the context of anticancer and antimicrobial activities.

Oxazinone [8-11] sare importantpharmacophoric scaffolds with a wide range of biological activities.[12]A number of methods are known in literature for the synthesis of aromatic oxazinones.[5-6]Aromticoxazines were first synthesized in 1944 by Holly and Cope through Mannich reactions from phenols, formaldehyde and amines.[7]

This class of heterocyclic compounds has been used as precursors in the synthesis of phosphinic ligands for asymmetric catalysis.[13] Therefore aromatic condensed oxazinone derivatives scaffold can be viewed as a 'Privileged structure' among pharmaceutical compounds.[14-15] The construction of new analogues of bioactive heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry .[11]Imidazoles are an important class of heterocycles and include many substances of both biological and chemical interest. Insertion of the imidazole nucleus is an important synthetic strategy in drug discovery. Due to their broad spectrum of biological activities, naphthalene condensed 1, 3-oxazin-3-ones have been reported[16-18] to act as antibacterial agents and HIV-1 reverse transcriptase inhibitors . [19]

Generally they are synthesized by three component condensation of urea or thiourea with an aldehyde and β- naphthol, which entails the use of pTSA ,perchloric acid supported on silica , montmorillonite K10, phosphomolybdic acid , Iodine[20] and nano copper in PEG-400.

In our ongoingefforts towards the synthesis of heterocyclic moieties, nitro imidazole derivatives containing oxazinone moiety have been synthesized in the present study by one pot three component coupling of various substituted phenol with aromatic aldehydes and urea or thio urea under microwave conditions. All the synthesized products were characterized by spectral techniques like IR, ^{1}HNMR ,^{13}CNMR and mass spectroscopy.



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Scheme - 1.

Where X= Cl, Br ; Y=O,S; R= CH_3, OCH_3,$C_{10}H_8O$

Table: Synthesized 2-nitro imidazole derivatives (**1a-1j**).

Comp.	Mol.Formula	X-	R-C_6H_3OH	CH_4N_2Y	M.Point(°C) Yield(%)
1a	$C_{17}H_{12}N_4O_5$	4-Cl	4-OH	CH_4N_2O	205 60
1b	$C_{18}H_{14}N_4O_5$	4-Cl	4-OCH_3	CH_4N_2O	208 68
1c	$C_{21}H_{14}N_4O_4$	4-Cl		$C_6H_4CH_4N_2O$	230 88
1d	$C_{17}H_{12}N_4O_4S$	4-Cl	4-OH	CH_4N_2S	242 68
1e	$C_{18}H_{14}N_4O_4S$	4-Cl	4-OCH_3	CH_4N_2S	210 74
1f	$C_{21}H_{14}N_4O_3S$	4-Cl		$C_6H_4CH_4N_2S$	216 92
1g	$C_{21}H14N_4O_4$	4-Cl, 2-CH_3		$C_6H_4CH_4N_2O$	235 90
1h	$C_{21}H_{14}N_4O_3S$	4-Cl , 2-CH_3		$C_6H_4CH_4N_2S$	240 93
1i	$C_{21}H_{14}N_4O_4$	4-Cl		$C_6H_4CH_4N_2O$	232 82
1j	$C_{21}H_{14}N_4O_3S$	4-Cl		$C_6H_4CH_4N_2S$	245 87

Experimental Section

All melting points were determined in open glass capillaries on a Gallenkamp apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on a Pye-Unicam spectrophotometer type 1200 using KBr discs. ^{1}HNMR and ^{13}CNMR spectra were recorded on a Bruker Advance -II (300 MHz and 75MHz respectively) spectrometer using TMS as an internal standard and dimethyl sulphoxide (DMSO-d6) as a solvent. Chemical shifts were expressed in δ (ppm) values and mass spectra were determined on FinniganIncos 500 (70 ev). Elemental analyses were determined using a Parkin-Elmer 240C Micro analyzer.

General procedure forthe synthesis of nitro imidazole derivatives:

Firstly we have synthesized [**4-(2-nitro-1H-imidazol-1-yl) benzaldehyde**] with the help of reported method [22-23] in our lab. In the first step, a mixture of chlorobenzaldehyde(1 mmol), 2-nitro imidazole(1 mmol), potassaium carbonate(K_2CO_3) (1.5 mmol) and Dimethyl formamide(DMF) were taken in 250ml Round Bottam flask was magnetically stirred and refluxed in oil bath at 100-150 °C for 6-10 hrs. The reaction mixture after being cooled to room temperature formed yellow colour solid compound . After that the compound was washed with ethyl acetate and water. The two layers are separated by separating funnel and after the evaporation of ethyl acetate , pale yellow colour solid formed. It is recrystallized with methanol, the solid compound [4-(2-nitro-1H-imidazol-1-yl) benzaldehyde]**(A)** was obtained.

In second step , a mixture of resorcinol (1 mmol), 4-(2-nitro-1H-imidazol-1-yl) benzaldehyde (1 mmol), Urea and few drops of methanol were finely mixed together. The reaction mixture placed in air tight conical flask undergoes microwave radiation irradiated for 6 min. with a power of Medium frost Range. After cooling ,the reaction mixture was

washed with water and then recrystallized from Ethyl acetate-Hexane (1:4) to afford the pure products. The purity of synthesized compounds was performed on thin layer chromatography (TLC) by methanol: toluene(1.5:8.5) and ethyl acetate: hexane(1:4).

All the synthesized products were characterized by IR, ^{1}HNMR, and Mass Spectra .

Specteral data of synthesized products:

6-hydroxy-4-(4-(2-nitro-1H-imidazol-1-yl)phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2- one(1a):

IR (KBr, cm^{-1}): 3228(N-H) , 3312(O-H), 3148(C-H), 1748(C=O), 1620,1468 (C=C), 1560(C=N), 1490(NO_2), 1364(C-O), 1260(C-N); ^{1}H NMR (300.00MHz, DMSO-d_6): δ 8.72(s ,1H,N-H),6.18(s , 1H,C-H), 6.38(d,J=2.6Hz,1H,C-H), 8.79(d,J = 2.6 Hz,1H,CH),6.84(s1H,O-H), 7.25-8.06(m, 7H,Ar-H) ; ^{13}C NMR(75.00MHz, DMSO-d_6): δ 156.23,154.25,152.27, 142.32, 138.39,132.45,128.62 ,126.25,124.36, 114.12 ,110.45, 51.26; ESI-MS: m/z 352.04(M^+) ; Anal. calcd. For $C_{17}H_{12}N_4O_5$; C,57.95 ;H, 3.40; N ,15.90 %. Found: C,57.91; H, 3.45;N, 15.94%.

6-methoxy-4-(4-(2-nitro-1H-imidazol-1-yl)phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2- one (1b):

IR (KBr, cm^{-1}): 3230(N-H) , 3334(O-H), 3140(C-H), 1752(C=O), 1624,1485 (C=C), 1572(C=N), 1494(NO_2), 1370(C-O), 1262(C-N), 1225(O-CH_3) ; ^{1}H NMR (300.00MHz, DMSO-d_6): δ 8.81(s ,1H,N-H), 6.22(s , 1H,C-H), 6.50 (d, J=2.4Hz, 1H, C-H), 8.56(d, J=2.4Hz, 1H, CH), 6.90(s1H,O-H), 3.84(s, 3H, O-CH_3), 7.24-8.09(m, 7H,Ar-H) ; ^{13}C NMR(75.00MHz, DMSO-d_6): δ 156.24,155.26 , 152.29, 144.43 , 142.46, 137.38, 134.52, 128.36, 124.42 , 120.44 ,116.39 , 112.26, 55.34 , 52.28; ESI-MS: m/z 366.15(M^+) ; Anal. calcd. For $C_{18}H_{14}N_4O_4$; C,59.01 ;H, 3.82; N ,15.30; %. Found: C,59.08; H, 3.81;N, 15.25 %.

4-(4-(2-nitro-1H-imidazol-1-yl)phenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazin-2-one (1c):

IR (KBr, cm^{-1}): 3245(N-H) , 3158(C-H), 1792(C=O), 1650,1488 (C=C), 1572(C=N), 1485(NO_2), 1372(C-O), 1256(C-N); ^{1}H NMR (300.00MHz, DMSO-d_6): δ 8.84(s ,1H,N-H),6.34(s , 1H,C-H), 6.42(d,J=3.0Hz,1H,C-H), 8.76 (d,J = 3.0 Hz, 1H, CH), 7.10-7.86(m, 10H,Ar-H) ; ^{13}C NMR(75.00MHz, DMSO-d_6): δ 154.24, 152.28, 148.32, 146.37 , 138.41, 135.45, 130.49 , 128.43 ,125.48 ,123.52 , 118.54 ,110.29, 48.32; ESI-MS: m/z 386.07(M^+) ; Anal. calcd. For $C_{21}H_{14}N_4O_4$; C,65.28 ; H, 3.62 ; N ,14.50 %. Found: C,65.30.; H, 3.62;N, 14.48%.

6-hydroxy-4-(4-(2-nitro-1H-imidazol-1-yl)phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine- 2- thione(1d) :

IR (KBr, cm^{-1}): 3234(N-H) , 3334(O-H), 3155(C-H), 1245(C=S), 1625,1470 (C=C), 1565(C=N), 1492(NO_2), 1368(C-O), 1264(C-N); ^{1}H NMR (300.00MHz, DMSO-d_6): δ 8.75(s,1H,N-

H),6.20(s,1H,C-H),6.28(d,J=2.9Hz,1H,C-H),8.72(d,J=2.9Hz,1H,CH),6.90(s1H,O-H), 7.15-8.12(m, 7H,Ar- H) ; ^{13}C NMR(75.00MHz, DMSO-d_6): δ 172.12, 150.23,148.25,146.32, 144.35 ,140.38,137.40,134.17,128.44,125.56 , 115.62,112.59, 105.38 , 52.48; ESI-MS: m/z 368.09(M^+) ; Anal. calcd. For $C_{17}H_{12}N_4O_4S$; C,55.43 ;H, 3.26; N ,15.21; 8.69 %. Found: C,55.40; H, 3.21;N, 15.25; S,8.65 %.

6-methoxy-4-(4-(2-nitro-1H-imidazol-1-yl)phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine- 2-thione (1e) :

IR (KBr, cm^{-1}): 3240(N-H) , 3158(C-H), 1250(C=S), 1628,1488 (C=C), 1566(C=N), 1485(NO_2), 1370(C-O), 1270(C-N), 1229(O-CH_3) ; ^{1}H NMR (300.00MHz, DMSO-d_6): δ 8.83(s ,1H,N-H), 6.32(s , 1H,C-H), 6.53 (d, J=3.4Hz, 1H, C-H), 8.58(d, J=3.4Hz, 1H, CH), 3.86(s, 3H, O-CH_3), 7.28-8.19(m, 7H,Ar-H) ; ^{13}C NMR(75.00MHz, DMSO-d_6): δ 170.02, 154.12, 152.18, 145.24 , 143.28, 140.33 , 138.39, 135.43, 130.47, 128.52, 124.55 , 122.59 ,118.63 , 116.65,113.43, 54.29 , 50.14; ESI- MS: m/z 382.04(M^+) ; Anal. calcd. For $C_{18}H_{14}N_4O_4S$; C,56.54 ;H, 3.66; N ,14.65; S,8.37 %. Found: C,56.58; H, 3.68;N, 14.67; S,8.40 %.

4-(4-(2-nitro-1H-imidazol-1-yl)phenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-2-thione (1f):

IR (KBr, cm^{-1}): 3260(N-H) , 3160(C-H), 1285(C=S), 1654,1492 (C=C), 1586(C=N), 1492(NO_2), 1376(C-O), 1260(C-N); ^{1}H NMR (300.00MHz, DMSO-d_6): δ 8.86(s ,1H,N-H),6.28(s , 1H,C-H), 6.45(d,J=3.2Hz,1H,C-H), 8.86 (d,J = 3.2 Hz, 1H, CH), 7.20-7.90(m, 10H,Ar-H) ; ^{13}C NMR(75.00MHz, DMSO-d_6): δ 152.12, 150.23, 148.25, 143.18 , 140.26, 134.32, 130.38 , 129.41 ,128.46,125.49, ,123.52 , 115.58 ,108.62, 48.21; ESI-MS: m/z 402.07(M^+) ; Anal. calcd. For $C_{21}H_{14}N_4O_3S$; C,62.68 ; H, 3.48 ; N ,13.93; S,7.96 %. Found: C,62.70.; H, 3.52;N, 13.95; S,7.94%.

4-(2-methyl-4-(2-nitro-1H-imidazol-1-yl)phenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazin-2-one (1g) :

IR (KBr, cm^{-1}): 3225(N-H) , 3128(C-H), 1728(C=O), 1658,1460 (C=C), 1580(C=N), 1479(NO_2), 1374(C-O), 1260(C-N); ^{1}H NMR (300.00MHz, DMSO-d_6): δ 8.76(s ,1H,N-H),6.18(s , 1H,C-H), 8.02(d,J=7.6Hz,1H,C-H), 7.80 (d,J = 7.6 Hz, 1H, CH), 7.08-7.88(m, 10H,Ar-H) ,2.26(s, 3H,CH_3) ; ^{13}C NMR(75.00MHz, DMSO-d_6): δ 155.15, 152.21, 142.26, 137.29, 136.33, 133.38 , 128.43 ,127.47, 125.53 ,123.56 , 121.59, 110.64, 52.15, 24.19; ESI- MS: m/z 400.10(M^+) ; Anal. calcd. For $C_{22}H_{16}N_4O_4$: C,66.00 ; H, 4.02 ; N ,14.02 %. Found: C,66.08.; H, 3.93;N, 14.05%.

4-(2-methyl-4-(2-nitro-1H-imidazol-1-yl)phenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-2-thione (1h) :

IR (KBr, cm^{-1}): 3238(N-H) , 3132(C-H), 1282(C=S), 1662,1468 (C=C), 1584(C=N), 1483(NO_2), 1370(C-O), 1264(C-N) ; ^1H NMR (300.00MHz, DMSO-d_6): δ 8.78(s ,1H,N-H), 6.22(s , 1H,C-H), 7.89 (d, J=3.8Hz, 1H, C-H), 8.04(d, J=3.8Hz, 1H, CH), 3.30(s, 3H, CH_3), 7.12-8.14(m, 7H,Ar-H) ; ^{13}C NMR(75.00MHz, DMSO-d_6): δ 174.23,154.26, 152.39, 140.34 , 138.42, 135.48, 132.53, 128.55,126.59 , 124.62 , 122.66 ,121.69 , 112.36 , 50.18, 24.16 ; ESI- MS: m/z 416.12(M^+) ; Anal. calcd. For $C_{22}H_{16}N_4O_3S$: C,63.46 ; H , 3.84; N ,13.46; S,7.69 %. Found: C,63.48; H, 3.82;N, 13.49; S,7.72 %.

4-(4-(2-nitro-1H-imidazol-1-yl)phenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazin-2-one (1i):

IR (KBr, cm^{-1}): 3255(N-H) , 3162(C-H), 1798(C=O), 1658,1498 (C=C), 1589(C=N), 1490(NO_2), 1378(C-O), 1262(C-N); ^1H NMR (300.00MHz, DMSO-d_6): δ 8.88(s ,1H,N-H),6.38(s , 1H,C-H), 6.46(d,J=3.4Hz,1H,C-H), 8.78 (d,J = 3.4 Hz, 1H, CH), 7.18-7.96(m, 10H,Ar-H) ; ^{13}C NMR(75.00MHz, DMSO-d_6): δ 154.32, 152.36, 148.25, 146.29 , 138.42, 135.46, 130.38 , 128.56 ,125.59 ,123.63 , 118.26 ,110.29, 48.17; ESI-MS: m/z 386.06(M^+) ; Anal. calcd. For $C_{21}H_{14}N_4O_4$; C,65.28 ; H, 3.62 ; N ,14.50 %. Found: C,65.30.; H, 3.62;N, 14.48%.

4-(4-(2-nitro-1H-imidazol-1-yl)phenyl)-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-2-thione (1j):

IR (KBr, cm^{-1}): 3264(N-H) , 3166(C-H), 1090(C=S), 1662,1499(C=C), 1590(C=N), 1494(NO_2), 1380(C-O), 1265(C-N); ^1H NMR (300.00MHz, DMSO-d_6): δ 8.90(s ,1H,N-H),6.32(s , 1H,C-H), 6.48(d,J=3.6Hz,1H,C-H), 8.88 (d,J = 3.6 Hz, 1H, CH), 7.25-7.94(m, 10H,Ar-H) ; ^{13}C NMR(75.00MHz, DMSO-d_6): δ 174.15, 152.25, 150.23, 148.34, 143.35 , 140.38, 134.45, 130.27 , 129.32 ,128.38,125.54, ,123.59 , 115.62 ,108.48, 48.23; ESI-MS: m/z 402.07(M^+) ; Anal. calcd. For $C_{21}H_{14}N_4O_3S$; C,62.68 ; H, 3.48 ; N ,13.93; S,7.96 %. Found: C,62.70.; H, 3.52;N, 13.95; S,7.94%.

Conclusion

It can be said that a simple ,eco-friendly and efficient procedure for the synthesis of 2-nitro imidazole derivatives containing 1,3-oxazinoneas a functional moiety has been developed under micro wave assisted conditions. This new protocol has enormous potential for the preparation of large series of 1,3 -oxazin-2-one in an expeditious way in good to excellent yields from starting materials. Hence in future , there is ample scope in taking up these imidazole derivatives containing oxazinone as a functional moiety for the further studies as bioactive agents.

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Graphical abstract:-

Synthesis of 2-nitro imidazole derivatives containing oxazinones

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An efficient methodology employing for the preparation of 2-nitro-imidazole derivatives containing 1,3-oxazinone as a functional moiety under microwave conditions has been presented.