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Tozer Meena Sandela
Department of Chemistry, Kakatiya University, Warangal, Telangana, India

Ch. Nageshwar Rao
Department of Chemistry, Kakatiya University, Warangal, Telangana, India

Anvitha Evangeline Lazarus
Department of Chemistry, Kakatiya University, Warangal, Telangana, India

Corresponding Author:
Tozer Meena Sandela
Department of Chemistry, Kakatiya University, Warangal, Telangana, India

Synthesis and characterization of 2-(Dimethylamino)-n-(5-(5-(Methylthio)-1,3,4-oxadiazol-2-yl benzoxazol-2-yl) acetamide

Tozer Meena Sandela, Ch. Nageshwar Rao and Anvitha Evangeline Lazarus

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Abstract
Heterocyclic compounds containing nitrogen and oxygen atoms have attracted significant pharmacological interest due to their broad spectrum of biological activities. In this study, we report the synthesis of a novel nitrogen-oxygen heterocyclic derivative using a simple and efficient synthetic approach. The structure of the compound was confirmed through UV-Vis spectroscopy, IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry.

Keywords: Benzoxazole, oxazole

Introduction
Benzoxazole (1-Oxa-3-aza-1H-indene) is a heterocyclic compound characterized by a benzene-fused oxazole ring. Oxazole (Fig. 1a) is a 1,3-azole with a pyridine-type nitrogen atom at the 3-position and an oxygen atom within the five-membered ring. First synthesized by Hantzsch in 1887, benzoxazole has a molecular formula of C_7H_5NO, a molar mass of 119.12 g·mol^{-1}, a melting point of 27-30 °C, and a boiling point of 182 °C. Benzoxazoles exhibit a wide range of biological activities, including anticancer [1], anthelmintic [2], cyclooxygenase inhibition [3], antifungal [4], antitubercular [5], 5-HT$_3$ receptor antagonism [6], anti-inflammatory, analgesic, cyclin-dependent kinase inhibition [7], 5-lipoxygenase inhibition [8], melatonin receptor agonism [9], anticancer [10], antibacterial [11], anti-HIV-1 [12], anticonvulsant [13], antiviral [14], antiparasitic [15], antiallergic [16], antipyretic [17], COX-2 inhibition [3], antihyperglycemic activity [18], dopamine D$_4$ receptor agonism [19], herbicidal [20], amyloidogenesis inhibition [21, 22], rho kinase inhibition [23], and effects on diarrhea-predominant irritable bowel syndrome [24].

Materials and Methods
Synthesis of Methyl-2-{(2-(dialkylamino) acetamido)}-benzoxazole-5-carboxylates (XII)
A solution of Methyl-2-(2-chloroacetamido) benzoxazole-5-carboxylate (V, 0.01 mol) in 20 mL of anhydrous acetone was treated with N, N-dialkylamine (0.01 mol). The reaction mixture was refluxed on a water bath for 5 hours under anhydrous conditions. Upon completion, the resulting colorless product was isolated and purified by recrystallization using appropriate solvents. The final compounds were identified as methyl-2-{(2-dialkylamino) acetamido}-benzoxazole-5-carboxylates (XII), and their structures were confirmed via spectral analysis [151].

As a representative example, dimethylamine (0.01 mol) was added to a solution of Methyl-2-(2-chloroacetamido) benzoxazole-5-carboxylate (V, 0.01mol) compound in 20 mL of dry acetone. The mixture was refluxed for 5 hours, yielding a colorless solid. Recrystallization from ethanol afforded a white crystalline product with a yield of 65% and a melting point of 164 °C.

Synthesis of 2-(Dialkylamino)-N-(5-(hydrazine carbonyl) benzoxazol-2-yl) acetamides (XIII)

A mixture of methyl-2-(2-(dialkylamino) acetamido) benzoxazole-5-carboxylate (XII, 0.01 mol) and hydrazine hydrate (99%, 0.02 mol) was dissolved in 50 mL of ethanol and refluxed on a water bath for 5 hours. Upon completion, the reaction volume was reduced to half under controlled conditions and cooled to ambient temperature. The precipitated product was collected by filtration, washed sequentially with small portions of cold ethanol followed by cold water, and dried thoroughly. Purification was achieved by recrystallization using appropriate solvents. The resulting compounds were characterized by spectral analysis.

As a representative example, methyl-2-(2-(dimethylamino) acetamido) benzoxazole-5-carboxylate (XIIa, 0.01 mol) was reacted with hydrazine hydrate (99%, 0.02 mol) under identical conditions. Recrystallization from methanol yielded a white crystalline solid with 77% yield and a melting point of 258 °C.

Synthesis of 2-(Dialkylamino)-N-(5-(5-mercapto-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamides (XIV)

Each of the 2-(dialkylamino)-N-(5-hydrazinecarbonyl) benzoxazole-2-yl) acetamides (XIII, 0.01 mol) was subjected to cyclization by reaction with carbon disulfide in alcoholic potassium hydroxide. The reaction mixture, consisting of compound XIII and carbon disulfide in ethanolic KOH, was refluxed for 3 hours. Upon completion, the resulting solid was acidified with 10% hydrochloric acid to yield a colorless product. The crude material was purified by recrystallization from alcohol. The final compounds were characterized as 2-(dialkylamino)-N-(5-(5-mercapto-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamides (XIV) based on analytical and spectral data.

As a representative example, 2-(dimethylamino)-N-(5-hydrazinecarbonyl) benzoxazole-2-yl) acetamide (XIIIa) was refluxed with alcoholic potassium hydroxide and carbon disulfide for 3 hours. The reaction caused compound XIVa, which was purified by recrystallization from ethanol to yield a crystalline solid with a melting point of 302 °C.

Synthesis of 2-(Dialkylamino)-N-(5-(5-(alkylthio)-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamides (XV)

Each compound of 2-(dialkylamino)-N-(5-(5-mercapto-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamide (XIV, 0.01 mol) was treated with 0.01 mol of methyl iodide, ethyl bromide, or n-butyl bromide in alcoholic potassium hydroxide (5%). The reaction mixtures were stirred under reflux for 4 hours. After completion, the products were isolated by standard work-up, purified by recrystallization from suitable solvents, and characterized as 2-(dialkylamino)-N-(5-(5-(alkylthio)-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamides (XV) based on satisfactory physical and spectral data.

In one case, 2-(dimethylamino)-N-(5-(5-mercapto-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamide (XIVa) was reacted with methyl iodide in alcoholic potassium hydroxide (5%). The product was purified by recrystallization from alcohol and obtained as a crystalline solid with a melting point of 265 °C.

Results and Discussion

Spectral Characterization of Synthesized Compounds

Compound: Methyl 2-{(2-dimethylamino) acetamido)}-benzoxazole-5-carboxylate (XIIb)

IR (KBr, ν, cm⁻¹): 3364 (N-H stretch), 1683 (C=O stretch), 1588 (C=N stretch), 1284 (C-O-C asymmetric stretch), 1126 (C-N stretch).

^{1}H NMR (400 MHz, DMSO-d$_6$, δ ppm): 8.60 (s, 1H, CONH), 8.10 (dd, 2H, aromatic protons), 7.80 (dd, 1H, aromatic proton), 7.70 (s, 1H, aromatic proton), 3.90 (s, 3H, OCH_3), 3.20 (s, 2H, CH_2), 2.30 (s, 6H, $N(CH_3)_2$). The compound exhibits characteristic IR absorptions corresponding to amide, heteroaromatic, and ether functionalities. The ^{1}H NMR spectrum displays well-resolved signals consistent with the proposed substitution pattern, including the dimethylaminoacetamido moiety and the methyl ester group. Collectively, the spectral data unambiguously support the structure of methyl 2-{(2-dimethylamino) acetamido)}-benzoxazole-5-carboxylate (XIIb).

2-(dimethylamino)-N-(5-hydrazinecarbonylbenzoxazol-2-yl) acetamide (XIIIa)

IR (KBr, ν, cm⁻¹): 3364 (N-H_2 stretch), 3150 (N-H stretch), 1683 (C=O stretch), 1615 (C=C stretch), 1576 (C=N stretch), 1223 (C-O-C asymmetric stretch).

^{1}H NMR (400 MHz, DMSO-d$_6$, δ ppm): 9.30 (s, 1H, NH), 8.80 (s, 1H, NH), 7.80 (s, 1H, aromatic proton), 7.50 (dd, 1H, aromatic proton), 7.30 (dd, 1H, aromatic proton), 5.40 (s, 2H, NH_2), 3.80 (s, 2H, CH_2), 2.90 (s, 6H, $N(CH_3)_2$).

The IR spectrum displays distinct absorptions corresponding to hydrazine, amide, and heteroaromatic functionalities. The ^{1}H NMR spectrum reveals well-resolved signals for the hydrazine protons, aromatic system, and dimethylaminoacetamide side chain. These spectral features are fully consistent with the proposed structure of 2-(dimethylamino)-N-(5-hydrazinecarbonylbenzoxazol-2-yl) acetamide (XIIIa).

2-(dimethylamino)-N-(5-(5-mercapto-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamide (XIVa)

IR (KBr, ν, cm⁻¹): 3146 (N-H stretch), 1708 (C=O stretch), 1626 (C=C stretch), 1528 (C=N stretch), 1428 (S-H stretch).

^{1}H NMR (400 MHz, DMSO-d$_6$, δ ppm): 8.80 (s, 1H, NH), 8.20 (s, 1H, SH), 8.00 (s, 1H, aromatic proton), 7.90 (d, 1H, aromatic proton), 7.80 (d, 1H, aromatic proton), 4.20 (s, 2H, CH_2), 2.70 (s, 6H, $N(CH_3)_2$).

The IR spectrum exhibits distinct absorptions attributable to amide, thiol, and heteroaromatic functionalities. The ^{1}H NMR spectrum confirms the presence of a free thiol proton, alongside well-defined signals for the benzoxazole core and dimethylaminoacetamide side chain. Collectively, the spectral data substantiate the structure of 2-(dimethylamino)-N-(5-(5-mercapto-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamide (XIVa).

2-(dimethylamino)-N-(5-(5-(methylthio)-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamide (XVa)

IR (KBr, ν, cm⁻¹): 3363 (N-H stretch), 1682 (C=O stretch), 1575 (C=C stretch), 1565 (C=N stretch), 1442 (C-N stretch), 1195 (C-S stretch).

^{1}H NMR (400 MHz, DMSO-d$_6$, δ ppm): 8.20 (s, 1H, NH), 7.90 (s, 1H, aromatic proton), 7.70 (d, 1H, aromatic proton), 7.60 (d, 1H, aromatic proton), 4.00 (s, 2H, CH_2), 2.80 (s, 6H, $N(CH_3)_2$), 2.40 (s, 3H, SCH_3).

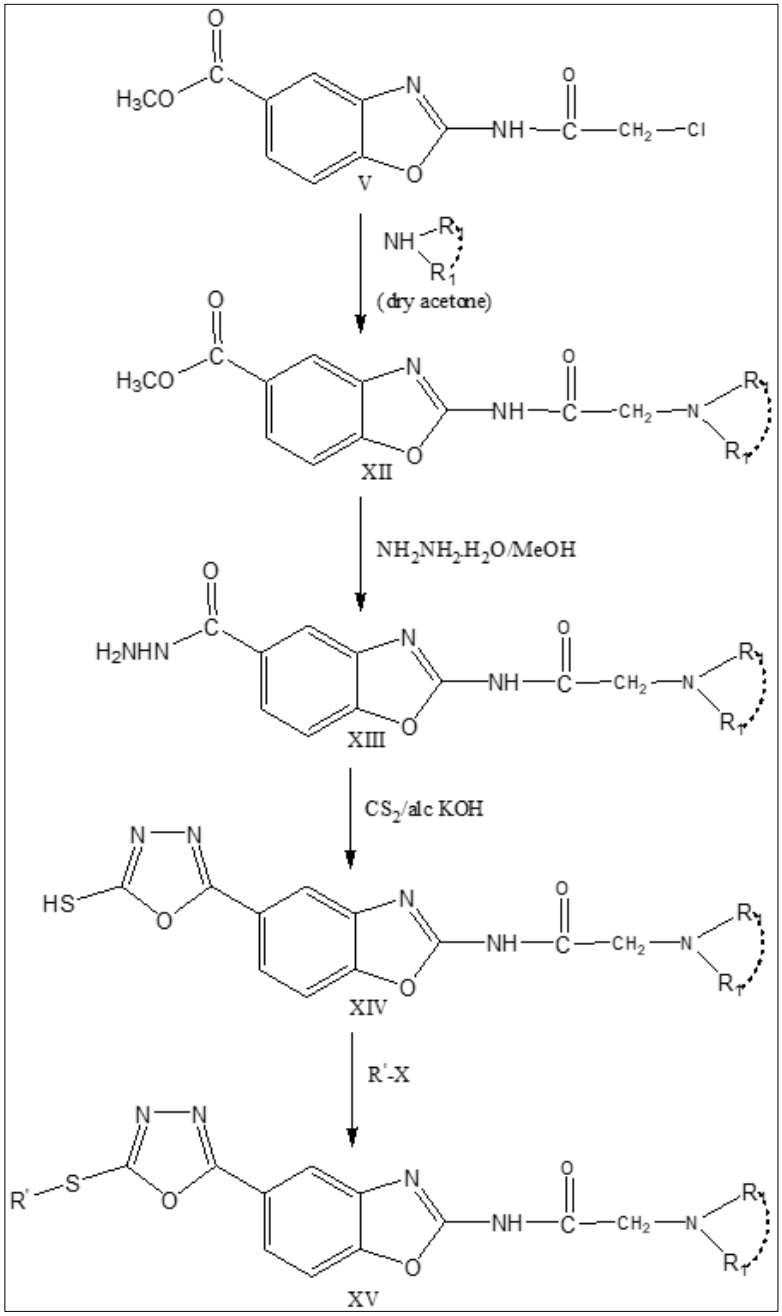
Mass Spectrometry (ESI-MS)

Molecular ion [M^+] observed at m/z 334 (18%). Fragment ion B at m/z 248.0 (10%) corresponds to the loss of the (dimethylamino)propanoyl moiety and hydrogen

abstraction.

Ion Cat m/z 332 (11%) results from proton loss from the molecularion. Ion D at m/z 305 (3%) arises from cleavage of a dimethyl radical followed by hydrogen abstraction. The IR spectrum reveals characteristic absorptions for amide, heteroaromatic, and thioether functionalities, confirming the presence of the methylthio-substituted oxadiazole ring. The ^{1}H NMR spectrum displays well-resolved singlets and doublets corresponding to the aromatic protons, methylene bridge, dimethylamino group, and methylthio substituent, supporting the proposed substitution pattern. The mass spectral fragmentation profile further substantiates the molecular framework, with key ions arising from predictable cleavage pathways involving the acetamide and thioether moieties. Taken together, the spectral and fragmentation data provide conclusive evidence for the structure of 2-(dimethylamino)-N-(5-(5-(methylthio)-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamide (XVa).

Further characterization confirmed compounds XII-XV, consistent with the proposed structures. Mass spectrometry data for XVa showed a molecular ion at m/z 334 (18%), with fragmentation patterns consistent with loss of (dimethylamino)propanoyl groups and dimethyl radicals.



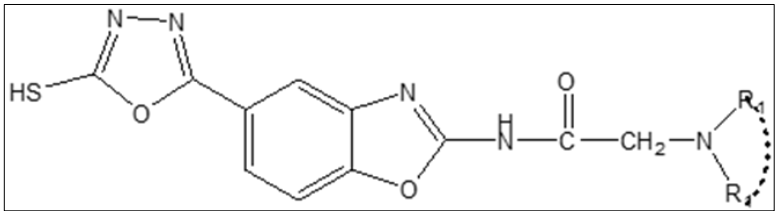
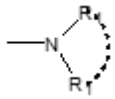
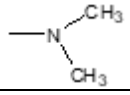
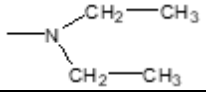
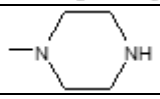
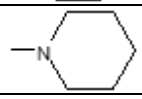
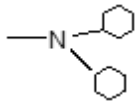
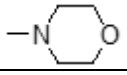


Table 1: Physical data of 2-(dialkylamino)-N-(5-(5-mercapto-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamids (XIV)

S. No	Compound		Chemical formula	Melting Point (°C)	Yield (%)
1	XIVA		$C_{13}H_{13}N_5O_3S$	302	75
2	XIVB		$C_{15}H_{17}N_5O_3S$	311	69
3	XIVC		$C_{15}H_{16}N_6O_3S$	289	64
4	XIVD		$C_{16}H_{17}N_5O_3S$	256	60
5	XIVE		$C_{23}H_{29}N_5O_3S$	288	63
6	XIVF		$C_{15}H_{15}N_5O_4S$	300	67

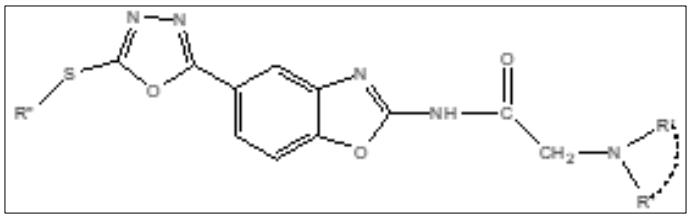
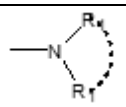
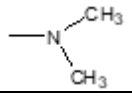
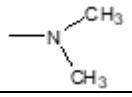
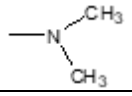
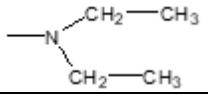
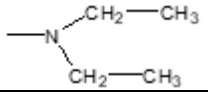
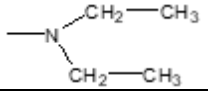
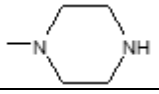
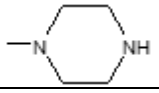
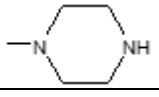


Table2: Physical data of 2-(dialkylamino)-N-(5-(5-(alkylthio)-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamides (XV)

S. No	Compound		R”	Chemical formula	Melting Point (°C)	Yield (%)
1	XVA		methyl	$C_{14}H_{15}N_5O_3S$	265	75
2	XVB		Ethyl	$C_{15}H_{17}N_5O_3S$	322	74
3	XVC		n-butyl	$C_{17}H_{21}N_5O_3S$	305	74
4	XVD		methyl	$C_{16}H_{19}N_5O_3S$	289	80
5	XVE		Ethyl	$C_{17}H_{21}N_5O_3S$	265	76
6	XVF		n-butyl	$C_{19}H_{25}N_5O_3S$	298	77
7	XVG		methyl	$C_{16}H_{18}N_6O_3S$	248	78
8	XVH		Ethyl	$C_{17}H_{20}N_6O_3S$	301	78
9	XVI		n-butyl	$C_{19}H_{24}N_6O_3S$	297	60

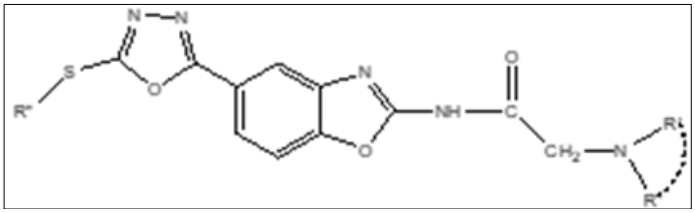
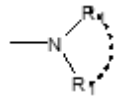
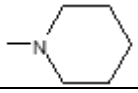
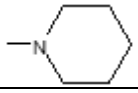
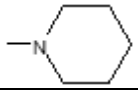
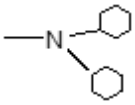
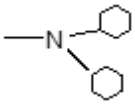
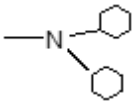
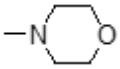
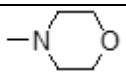
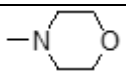


Table 3: Physical data of 2-(dialkylamino)-N-(5-(5-(alkylthio)-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl) acetamides (XV)

S. No	Compound		R"	Chemical formula	Melting Point (°C)	Yield (%)
10	XVJ		methyl	$C_{17}H_{19}N_5O_3S$	326	79
11	XVK		Ethyl	$C_{18}H_{21}N_5O_3S$	325	69
12	XVL		n-butyl	$C_{20}H_{25}N_5O_3S$	209	77
13	XVM		methyl	$C_{24}H_{31}N_5O_3S$	218	62
14	XVN		Ethyl	$C_{25}H_{33}N_5O_3S$	226	76
15	XVO		n-butyl	$C_{27}H_{37}N_5O_3S$	232	51
16	XVP		methyl	$C_{16}H_{17}N_5O_4S$	312	65
17	XVQ		Ethyl	$C_{17}H_{19}N_5O_4S$	308	70
18	XVR		n-butyl	$C_{19}H_{23}N_5O_3S$	269	72

Conclusion

A robust and reproducible synthetic route was established for the preparation of 2-(dimethylamino)-N-[5-(5-(methylthio)-1,3,4-oxadiazol-2-yl) benzoxazol-2-yl] acetamide derivatives. The methodology demonstrated high fidelity in yield and purity, with structural confirmation achieved via appropriate spectroscopic techniques. The results substantiate the efficiency of the synthetic design and provide a reliable foundation for future applications in medicinal or materials chemistry.

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