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Synthesis and Anticancer Evaluation of 1,2,4-Oxadiazole Linked Imidazothiadiazole Derivatives[1]

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Abstract—A series of 1,2,4-oxadiazole linked imidazothiadiazole derivatives **11a–11j** have been synthesized. All derivatives were evaluated for anticancer activity against three human cancer cell lines (A375, MCF-7, and ACHN) and demonstrated activity comparable with that of doxorubicin. Three compounds **11b, 11c,** and **11j** exhibited higher anticancer activity than the positive control. The range of IC_{50} for the compounds **11b, 11c,** and **11j** is determined to be from 0.11 to 2.98 μM.

Keywords: levamisole, 1,2,4-oxadiazole and anticancer activity

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INTRODUCTION

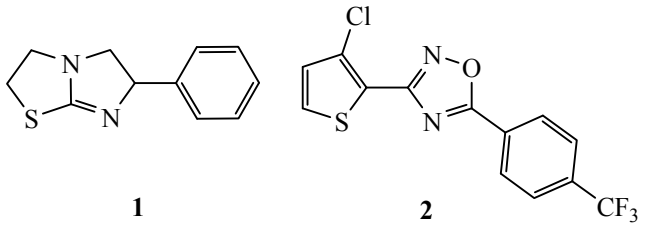
Synthesis of heterocyclic fused rings led to development of novel drugs with enhanced biological activities [1, 2] including antitumor activity against diverse human tumor cell lines [3–10]. Among such cyclic systems is imidazole fused with 1,3,4-thiadiazole moiety, imidazo[2,1-*b*]1,3,4-thiadiazoles [11], which contains a bridgehead nitrogen atom. Imidazo[2,1-*b*]-1,3,4-thiadiazoles exhibit a diverse array of biological activities, such as anticancer [12], antitubercular [13], antibacterial [14], antifungal [15], anticonvulsant, and antitumor [16, 17]. Imidazo[2,1-*b*][1,3,4]thiadiazole is somewhat structurally close to Levamisole (**1**) (see the figure) [11], a well- known potential antitumor agents and immunomodulator [18].

1,2,4-Oxadiazole is considered to be a privileged nitrogen containing heterocyclic scaffold and is used extensively in medicinal chemistry [19–22]. Among oxadiazoles, 3,5-disubstituted-1,2,4-oxadiazoles (**2**) (see the figure) are reported to demonstrate anticancer potential [23, 24].

In view of the above facts and as part of our earlier efforts to create novel biologically active agents, we report herein synthesis of 1,2,4-oxadiazole linked imidazothiadiazole derivatives and evaluation of their anticancer action on human cancer cell lines.

RESULTS AND DISCUSSION

Synthetic approach to 1,2,4-oxadiazole linked imidazothiadiazole derivatives **11a–11j** is presented in Scheme 1. Imidazothiadiazole precursor 6-chloro-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbonitrile **9** was synthesized by the reaction of 5-methyl-1,3,4-thiadiazol-2-amine **3** with bromoacetic acid **4** in

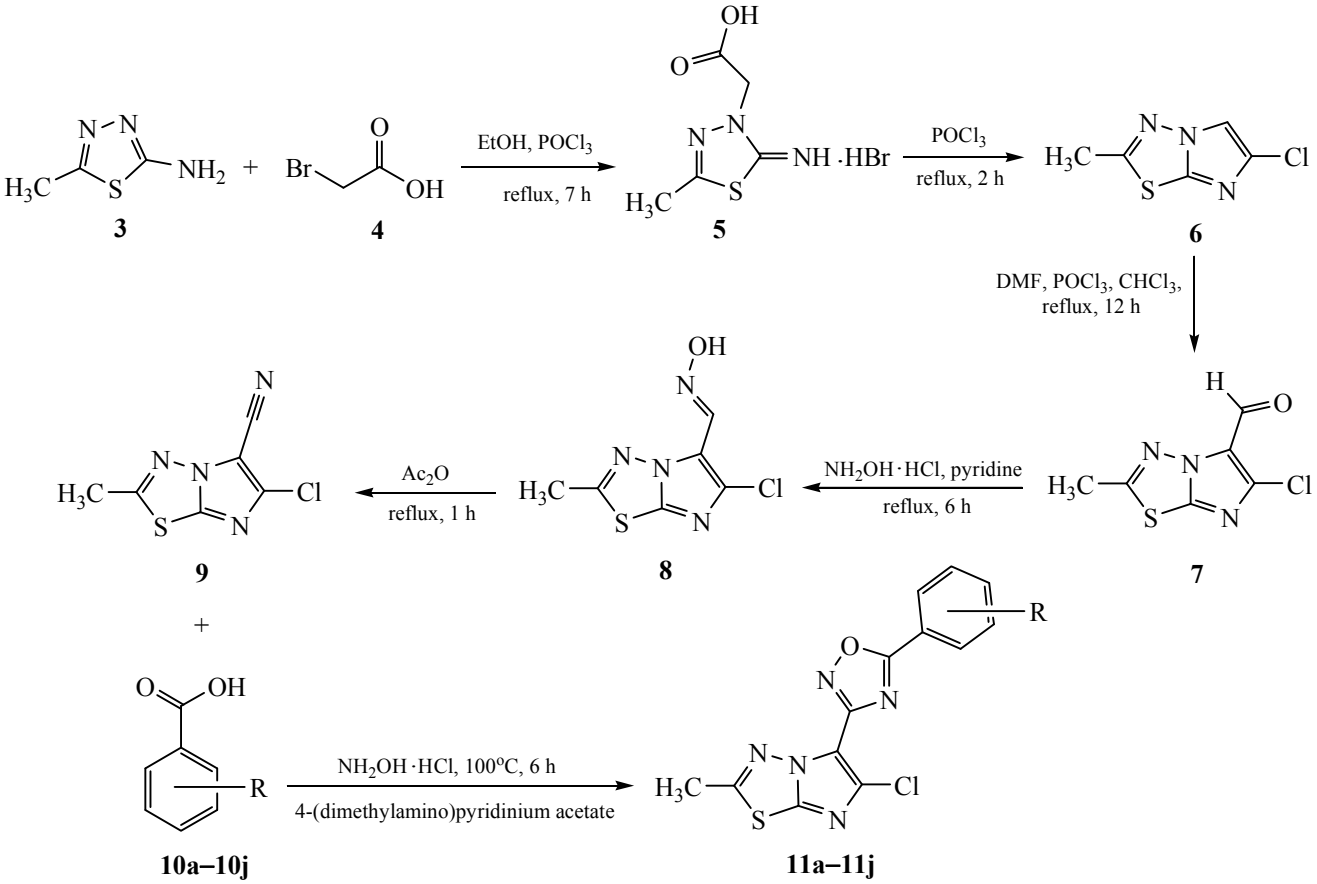


1 **2**

Structures of Levamisole (**1**) and 3,5-disubstituted-1,2,4-oxadiazoles (**2**).

[1] The text was submitted by the authors in English.

Scheme 1. Synthetic pathway to 1,2,4-oxadiazole linked imidazothiadiazole derivatives **11a–11j**.



R = H (**10a, 11a**), 3,4,5-trimethoxy (**10b, 11b**), 4-methoxy (**10c, 11c**), 4-chloro (**10d, 11d**), 4-bromo (**10e, 11e**), 4-fluoro (**10f, 11f**), 4-nitro (**10g, 11g**), 3-nitro (**10h, 11h**), 4-methyl (**10i, 11i**), 4-trifluoromethyl (**10j, 11j**).

ethanol in the presence of $POCl_3$. This was followed by refluxing the salt **5** in $POCl_3$ that gave 6-chloro-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole **6** with high yield. Formylation of the byproduct **5** with DMF, $POCl_3$ in $CHCl_3$, led to 6-chloro-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde **7**. Its reaction with $NH_2OH·HCl$ in pyridine afforded oxime **8**. Oxime **8** reaction with Ac_2O led to 6-chloro-2-methylimidazo [2,1-*b*][1,3,4]thiadiazole-5-carbonitrile **9**. This nitrile intermediate **9** underwent cyclization with substituted aromatic carboxylic acids **10a–10j** in $NH_2OH·HCl$ and in the presence of 4-(dimethylamino)pyridinium acetate giving the target 1,2,4-oxadiazole linked imidazothiadiazole derivatives **11a–11j**.

***In vitro* cytotoxicity.** The newly synthesized 1,2,4-oxadiazole linked imidazothiadiazole compounds **11a–11j** were evaluated for their *in vitro* anticancer activity against a panel of three human cancer cell lines, A375 (melanoma), MCF-7 (breast) and ACHN (renal), by employing the MTT assay (see the table). Here doxorubicin was used as a reference drug. The compound **11b** demonstrated the most potent anticancer activity higher than the positive control doxorubicin. The compound **11j** exhibit excellent activity towards melanoma cancer cell line (A375) and potent activities towards MCF-7 and ACHN.

EXPERIMENTAL

All chemicals and reagents were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254 and visualized by UV light or iodine indicator. ^1H and ^{13}C NMR spectra were measured on a Bruker UXNMR/XWIN-NMR spectrometer in $CDCl_3$ for **7, 8** and DMSO-d_6 for all other compounds using TMS as

Cytotoxicity data for compounds **11a–11j**

Compound	IC_{50} values, μM			Compound	IC_{50} values, μM		
	A375	MCF-7	ACHN		A375	MCF-7	ACHN
11a	11.4	10.2	18.5	**11g**	17.7	9.7	12.2
11b	1.22	0.23	0.11	**11h**	2.20	5.98	10.6
11c	2.98	0.70	1.89	**11i**	9.56	13.7	2.44
11d	14.6	19.1	6.47	**11j**	0.37	1.47	0.33
11e	8.20	11.2	7.7	Doxorubicin	5.51	2.02	0.79
11f	2.70	8.41	17.6				

the internal standard. ESI spectra were recorded on a Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an electrothermal melting point apparatus.

Synthesis of 6-chloro-2-methylimidazo[2,1-*b*][1,3,4]-thiadiazole (6). The appropriate 5-methyl-1,3,4-thiadiazol-2-amine **3** (2 g, 17.3 mmol) was dissolved in ethanol (30 mL) and treated with the equivalent of 2-bromoacetic acid **4** (2.4 g, 17.3 mmol). The reaction mixture was refluxed for 7 h. The resulting salt **5** was filtered off and without further purification refluxed for 2 h with 15 mL of $POCl_3$. After completion of the reaction, the solvent was evaporated under vacuum and the residue was poured onto crushed ice. The solution was basified with 20% NH_4OH. The residue was filtered off and dried to obtain the crude compound. The crude product was purified by column chromatography with hexanes–ethyl acetate (3 : 7) to afford pure compound **6**. Yield 69%, mp 129–131°C. ^{1}H NMR spectrum, δ, ppm: 2.82 s (3H), 7.26–7.30 m (1H). MS (ESI): *m/z:* 174 $[M + H]^+$.

Synthesis of 6-chloro-2-methylimidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbaldehyde (7). The Vilsmeier reagent was prepared at 0–5°C by dropping $POCl_3$ (13.5 mL, 144.5 mmol) into a stirred solution of DMF (8 mL) in $CHCl_3$. 6-Chloro-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole **6** (2.5 g, 14.4 mmol) was suspended in $CHCl_3$ (20 mL). The mixture thus obtained was added drop wise to the Vilsmeier reagent while stirring and cooling. The reaction mixture was stored for 3 h at room temperature and then refluxed for 12 h. Chloroform was removed under reduced pressure and the resulting oily liquid was poured onto crushed ice. The crude aldehyde was purified by column chromatography with hexanes–ethyl acetate (2 : 8) to obtain pure compound **7**. Yield 70%, mp 103–105°C. ^{1}H NMR spectrum, δ, ppm: 2.85 s (3H), 9.91 s (1H). MS (ESI): *m/z:* 202 $[M + H]^+$.

Synthesis of 6-chloro-2-methylimidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbaldehyde oxime (8). A mixture of 6-chloro-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde **7** (5 g, 24.8 mmol) with hydroxyl amine hydrochloride (1.8 g, 24.8 mmol) was refluxed in pyridine (15 mL) for 6 h. Upon completion of the reaction, the mixture was cooled down then poured onto crushed ice. The precipitate was filtered off, washed with water, aqueous ethanol, and dried to afford pure aldoxime **8**. Yield 86%, mp 154–156°C. ^{1}H NMR spectrum, δ, ppm: 2.87 s (3H), 8.36 s (1H), 11.56 br.s (1H). MS (ESI): 217 $[M + H]^+$.

Synthesis of 6-chloro-2-methylimidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbonitrile (9). 6-Chloro-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde oxime **8** (4 g, 18.5 mmol) was suspended in acetic anhydride (15 mL) and refluxed for 1 h, then poured into cold water and neutralized by sodium carbonate solution. The precipitated solid was filtered off, washed repeatedly with water, dried, and recrystallized from ethanol to afford pure compound **9**. Yield 74%, mp 166–168°C. ^{1}H NMR spectrum, δ, ppm: 2.87 s (3H). MS (ESI): 199 $[M + H]^+$.

Synthesis of 6-chloro-2-methyl-5-(5-phenyl-1,2,4-oxadiazol-3-yl)imidazo[2,1-*b*][1,3,4]thiadiazole (11a). In a 5-mL round-bottom flask 6-chloro-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbonitrile **9** (300 mg, 1.5 mmol), hydroxylamine hydrochloride (104 mg, 1.5 mmol) and benzoic acid **11a** (183 mg, 1.5 mmol) were added to 4-(dimethylamino) pyridinium acetate (544 mg, 3 mmol). The reaction mixture was heated to 100°C for 6 h. Then the mixture was cooled down to

room temperature, ethanol (1 mL) was added, and stirring continued for 30 min. Water (5 mL) was added to the reaction mixture. The ionic liquid was dissolved in water and filtered for separation of the products. The solid product was collected and washed with water (2×5 mL). The crude product was purified by column chromatography with hexanes–ethyl acetate (3 : 7) to afford pure compound **11a**. Yield 61%, mp 170–172°C. ^{1}H NMR spectrum: δ, ppm: 2.87 s (3H), 7.54–7.60 m (3H), 7.76 d (2H, J = 8.23 Hz). ^{13}C NMR spectrum: δ 18.7, 114.7, 126.9, 129.5, 132.5, 138.6, 142.5, 143.8, 149.6, 158.8, 159.6. MS (ESI): 318 $[M + H]^+$.

The compounds **11b–11j** were synthesized according to the above method presented for **11a**.

6-Chloro-5-[5-(3,4,5-trimethoxyphenyl)-1,2,4-oxadiazol-3-yl]-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole (11b). Yield 51%, mp 147–149°C. ^{1}H NMR spectrum, δ, ppm: 2.87 s (3H), 3.86 s (3H), 3.92 s (6H), 7.75 s (2H). ^{13}C NMR spectrum, δ, ppm: 18.7, 57.8, 61.7, 107.8, 114.6, 133.8, 142.6, 143.7, 144.6, 149.6, 158.6, 159.5. MS (ESI): 408 $[M + H]^+$.

6-Chloro-5-[5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl]-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole (11c). Yield 61%, mp 131–133°C. ^{1}H NMR spectrum, δ, ppm: 2.87 s (3H), 3.87 s (3H), 7.24 d (2H, J = 8.12 Hz), 7.76 d (2H, J = 8.12 Hz). ^{13}C NMR spectrum, δ, ppm: 18.6, 57.5, 114.6, 116.5, 118.6, 131.5, 142.6, 143.8, 149.7, 158.7, 159.5, 160.3. MS (ESI): 348 $[M + H]^+$.

6-Chloro-5-[5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl]-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole (11d). Yield 62%, mp 176–178°C. ^{1}H NMR spectrum, δ, ppm: 2.87 s (3H), 7.74 d (2H, J = 8.17 Hz), 7.77 d (2H, J = 8.17 Hz). ^{13}C NMR spectrum, δ, ppm: 18.6, 114.8, 126.5, 129.8, 134.5, 136.8, 142.6, 143.8, 149.7, 158.7, 159.6. MS (ESI): 353 $[M + H]^+$.

5-[5-(4-Bromophenyl)-1,2,4-oxadiazol-3-yl]-6-chloro-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole (11e). Yield 55%, mp 180–182°C. ^{1}H NMR spectrum, δ, ppm: 2.88 s (3H), 7.75 d (2H, J = 8.34 Hz), 7.80 d (2H, J = 8.34 Hz). ^{13}C NMR spectrum, δ, ppm: 18.9, 114.7, 124.8, 126.8, 132.6, 136.4, 142.6, 143.6, 149.7, 158.9, 159.5. MS (ESI): 397 $[M + H]^+$.

6-Chloro-5-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole (11f). Yield 67%, mp 150–152°C. ^{1}H NMR spectrum, δ, ppm: 2.86 s (3H), 7.45 d (2H, J = 8.26 Hz), 7.74 d (2H, J = 8.26 Hz). ^{13}C NMR spectrum, δ, ppm: 18.7, 114.6, 117.6, 125.7, 133.8, 142.7, 143.8, 149.9, 158.7, 159.6, 160.5. MS (ESI): 336 $[M + H]^+$.

6-Chloro-2-methyl-5-[5-(4-nitrophenyl)-1,2,4-oxadiazol-3-yl]imidazo[2,1-*b*][1,3,4]thiadiazole (11g). Yield 66%, mp 179–181°C. ^{1}H NMR spectrum, δ, ppm: 2.88 s (3H), 7.82 d (2H, J = 8.45 Hz), 7.93 d (2H, J = 8.45 Hz). ^{13}C NMR spectrum, δ, ppm: 18.8, 114.7, 123.8, 126.8, 142.6, 143.7, 143.9, 149.8, 150.6, 158.6, 159.8. MS (ESI): 363 $[M + H]^+$.

6-Chloro-2-methyl-5-[5-(3-nitrophenyl)-1,2,4-oxadiazol-3-yl]imidazo[2,1-*b*][1,3,4]thiadiazole (11h). Yield 68%, mp 183–185°C. ^{1}H NMR spectrum, δ, ppm: 2.88 s (3H), 7.77–7.83 m (2H), 7.90 d (1H, J = 8.34 Hz), 7.96 s (1H). ^{13}C NMR spectrum, δ, ppm: 18.9, 114.8, 119.7, 128.7, 129.6, 130.5, 139.6, 142.5, 143.8, 149.7, 150.4, 158.7, 159.8. MS (ESI): 363 $[M + H]^+$.

6-Chloro-2-methyl-5-(5-*p*-tolyl-1,2,4-oxadiazol-3-yl)imidazo[2,1-*b*][1,3,4]thiadiazole (11i). Yield 64%, mp 137–139°C. ^{1}H NMR spectrum, δ, ppm: 2.76 s (3H), 2.86 s (3H), 7.48 d (2H, J = 8.15 Hz), 7.75 d (2H, J = 8.15 Hz). ^{13}C NMR spectrum, δ, ppm: 18.6, 29.4, 114.6, 124.7, 129.6, 135.8, 141.6, 143.5, 144.4, 149.7, 158.6, 159.6. MS (ESI): 332 $[M + H]^+$.

6-Chloro-5-{5-[4-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole (11j). Yield 55%, mp 155–157°C. ^{1}H NMR spectrum, δ , ppm: 2.88 s (3H), 7.76 d (2H, J = 8.35 Hz), 7.80 d (2H, J = 8.35 Hz). ^{13}C NMR spectrum, δ, ppm: 18.7, 114.5, 122.4, 126.8, 128.6, 132.7, 143.5, 143.9, 144.6, 149.7, 158.6, 159.8. MS (ESI): 386 $[M + H]^+$.

MTT assay. Cytotoxic activity of the compounds was determined using the MTT assay. 1×10^4 Cells/well were seeded in 200 mL DMEM, supplemented with 10% FBS in each well of 96-well microculture plates and incubated for 24 h at 37°C in a CO_2 incubator. Compounds, diluted to the desired concentrations in culture medium, were added to the wells with respective vehicle control. After 48 h of incubation, 10 mL of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] (5 mg/mL) were added to each well and the plates were further incubated for 4 h. Then the supernatant from each well was carefully removed, formazan crystals were dissolved in 100 mL of DMSO and absorbance at 540 nm wavelength was recorded.

CONCLUSIONS

Ten derivatives of 1,2,4-oxadiazole linked imidazothiadiazoles **11a–11j** have been synthesized and tested

for their anticancer activity against human cancer cell lines (A375, MCF-7 and ACHN). All synthesized compounds exhibited variable *in vitro* anticancer activity at micro molar (μM) concentration. The compounds **11b**, 11c and **11j** demonstrated higher anticancer activity than the positive control.

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