

Design, synthesis, and biological activity of novel 4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxylic acid derivatives

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Abstract—Novel 4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxylic acid derivatives (**11–23**) were synthesized from 3,4-dimethoxyacetophenone (**5**) in six-step procedure. Their biological activities were evaluated in the greenhouse. Some of the compounds had shown fungicidal and insecticidal activities at 375 g ai/ha and 600 g ai/ha, respectively.

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1. Introduction

The biological activity of thiazole-related molecules has been extensively studied. Ethaboxam,¹ thifluzamide,² and metsulfosax³ are known fungicidal thiazoles used in agriculture.

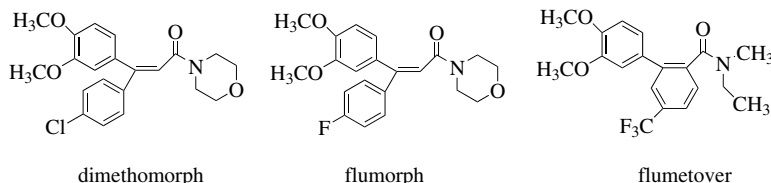
Cinnamic acid analogs^{4,5} have been studied as agricultural fungicides. Among these, dimethomorph (developed by American Cyanamid)⁶ and flumorph (developed by Shenyang Research Institute of Chemical Industry)⁷ have been commercialized. Similar compounds, such as flumetover,⁸ **1**⁹ and **2**,¹⁰ also possess fungicidal activity. All these compounds are structurally related to the natural product **3**,¹¹ and contain a common toxiphore as illustrated in structure **4**.

In this paper we report the design and synthesis of 4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxylic acid (**9**) and its novel derivatives (**11–23**), in which a thiazole ring is attached to the basic toxiphore moiety. It is conceivable that new lead compounds may be discovered for the development of potential agrochemicals.

2. Results and discussion

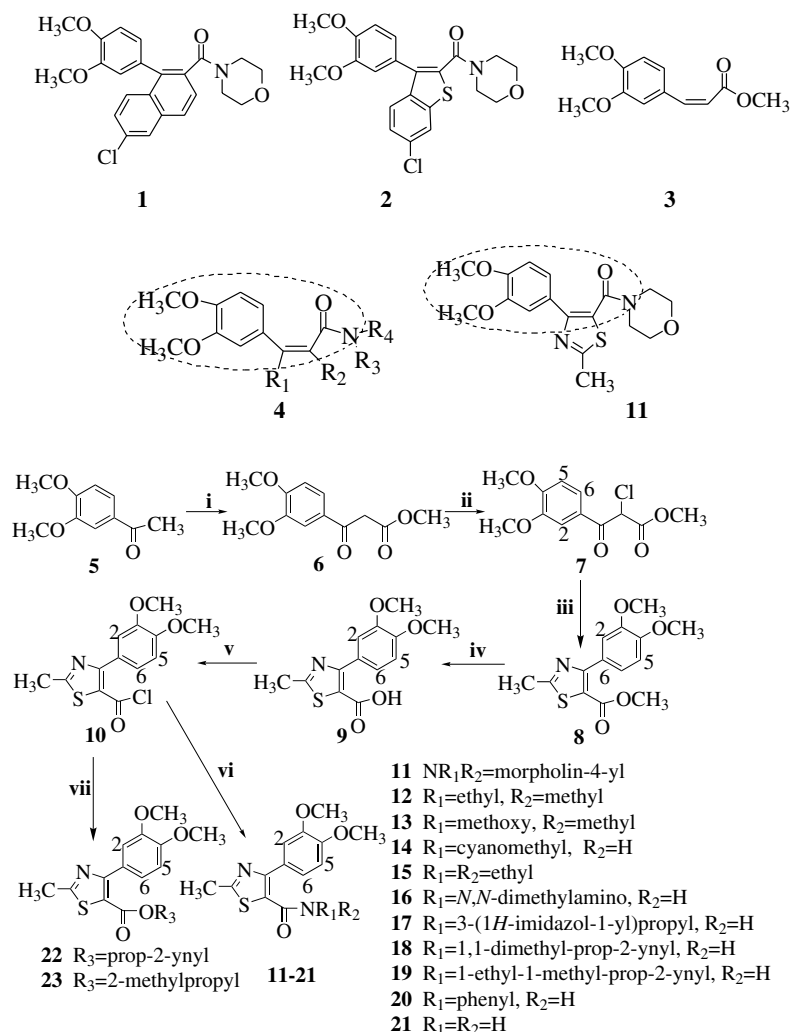
2.1. Chemistry

The synthesis of the 4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxylic acid derivatives (compounds **11–23**) was accomplished via the routes illustrated in Scheme 1.



Keywords: Thiazolecarboxylic acid derivatives; Synthesis; Biological activity.

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Scheme 1. Synthesis of the 4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxylic acid derivatives (**11–23**): (i) NaH/(CH₃O)₂CO in THF; (ii) SO₂Cl₂/CCl₄; (iii) thioacetamide/NaHCO₃ in THF; (iv) NaOH/H₂O, HCl(aq); (v) SOCl₂; (vi) R₁R₂NH/Et₃N in CH₃CN; (vii) R₃OH/Et₃N in CH₃CN.

Methyl 3-(3,4-dimethoxyphenyl)-3-oxopropionate (**6**) was prepared in 90% yield by using 3,4-dimethoxyacetophenone (**5**) as a starting material according to the literature procedure.¹² All new compounds, **7–23**, were synthesized at high yields based on published methods.¹³ Compound **6** was converted into methyl 2-chloro-3-(3,4-dimethoxyphenyl)-3-oxopropionate (**7**), which was cyclized into methyl 4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxylate (**8**) by treating with thioacetamide. Compound **8** was easily converted into 4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxylic acid (**9**), and was subsequently transformed to 4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carbonyl chloride (**10**). The key intermediate **10** was then converted into various derivatives, **11–21**, by treating it with the appropriate amine in the presence of triethylamine. Two ester compounds, **22** and **23**, were also synthesized and tested for their biological activities for the comparison with amide derivatives.

Physical, analytical, and spectral characterization of all synthesized compounds were conducted. IR, ¹H NMR, and MS spectral data, as well as elemental analyses,

were found to be fully consistent with those expected for assigned structures.

The IR spectra of all synthesized esters and amides showed a readily detectable C=O band ranging between 1725–1700 cm⁻¹ and 1665–1635 cm⁻¹, with the C=O band of the acid **9** at 1680 cm⁻¹. Compounds **14**, **18**, **19**, and **22** also have C≡C or C≡N absorption bands between 2240 and 2120 cm⁻¹.

Although GC–MS and TLC suggested that compound **12** may be a single substance, the ¹H NMR data clearly indicated that it has actually two isomers (1:1), possibly reflecting *trans* and *cis* isomers around the amide bond.¹⁴ It is also possible that a sterically hindered rotation around the C(=O)–N axis rendering that the nitrogen atom may have a chiral characteristics.¹⁵ Saturation transfer experiment spectrum (Fig. 1, same as in NOE a specific peak is irradiated, and what a peak points down means that the peak is saturated by irradiation) was carried out by specifically saturating (or irradiating) N–CH₃ peak at δ 2.61. As a result, the peak at δ 3.04 was also saturated, which indicated that these two peaks are

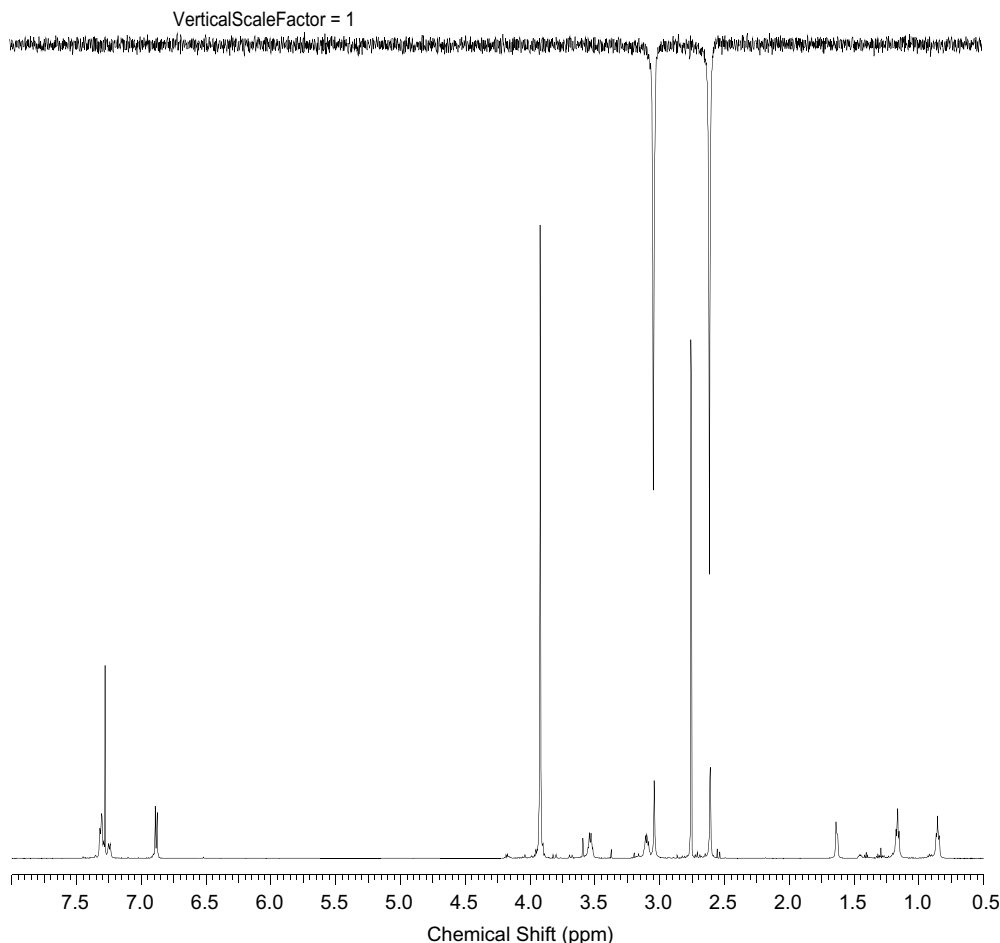
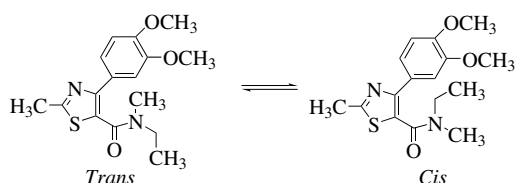
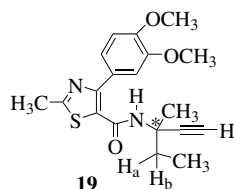


Figure 1. Saturation transfer experiment spectrum of compound 12.

in equilibrium to each other. This experiment unequivocally confirms that they are the two peaks from the two isomers of the same molecule.



^1H NMR data also show that H_a and H_b in compound 19 are different. Presumably, the CH_2 of compound 19 was affected by the adjacent CH_3 group and the chiral carbon center and therefore showed two sets of quartets.



2.2. Biological activity

Biological activity of the newly synthesized compounds was evaluated at Rohm and Haas Co. In Table 1, zero

Table 1. Biological activity of the synthesized compounds (8, 9, 11–23)

Compound	Insecticidal activity (% control)		Fungicidal activity (% control) TLB
	GPA	PLH	
8	0	40	0
9	0	20	0
11	20	20	90
12	40	40	0
13	20	20	50
14	0	0	0
15	0	40	0
16	20	60	0
17	0	0	75
18	60	40	0
19	20	0	90
20	20	40	0
21	0	20	0
22	20	20	0
23	20	20	75
Dimethomorph ^a	0	0	100
Flumorph ^a	0	0	100

^a Dose for all tests: 300 g ai/ha.

indicates no control and 100% is complete control of the insect or fungus. Several compounds at 600 g ai/ha have some insecticidal activity against green peach aphid

(GPA) and potato leafhopper (PLH), with compounds **16** and **18** having the best activities against PLH and GPA, respectively. Additionally, some of the compounds such as **11** and **19** at 375 g ai/ha possess good fungicidal activity against tomato late blight (TLB) with 90% control. All compounds showed no herbicidal activity at 1200 g ai/ha.

Though it is hard to tell the relationship of structure–activity, the test results show that compounds **14** and **17** have no activities against GPA and PLH and PLB; and compounds with higher activities against insects show less activity against fungus; compounds with higher fungicidal activities show less insecticidal activities by contraries. Moreover, ester compounds (**8**, **9**, **22**) and amide compounds (**14**, **15**, **21**) with simple substitutes have less activities.

3. Conclusions

4-(3,4-Dimethoxyphenyl)-2-methylthiazole-5-carboxylic acid derivatives described in the present study were synthesized, starting from 3,4-dimethoxyacetophenone via six steps. Preliminary biological evaluation showed that some of the compounds have fungicidal and insecticidal activity at 375 g ai/ha and 600 g ai/ha, respectively, suggesting that compounds **11**, **16**, **18**, and **19** may become useful leads for further investigation.

4. Experimental

4.1. Chemistry

Melting points were determined in a Büchi capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded with a Mercury or Gemini 300 (Varian, 300 MHz) spectrometer with CDCl_3 as the solvent and TMS as the internal standard. Infrared spectra were measured on KBr pellets using a PE-983G (Perkin–Elmer) or FTS-40 (Biorad) instrument. Mass spectra (GC–MS) and HRMS were obtained on MD-800 (Fisons) and Q-TOF Micro (Micromass), respectively. Combustion analyses for elemental composition were made with an EA 1106 analyzer (Fisons). All chemicals or reagents were purchased from standard commercial suppliers.

Methyl 3-(3,4-dimethoxyphenyl)-3-oxopropionate (**6**) was prepared according to an established procedure.¹²

4.1.1. Methyl 2-chloro-3-(3,4-dimethoxyphenyl)-3-oxopropionate (7). Sulfuryl chloride (98%, 27.5 g, 0.2 mol) was added dropwise under vigorous stirring to a solution of methyl 3-(3,4-dimethoxyphenyl)-3-oxopropionate (**6**)¹² (47.6 g, 0.2 mol) in carbon tetrachloride (150 mL) at room temperature. The mixture was stirred for 1 h at room temperature. After evaporation of the solvent, a yellow oil was obtained (23.8 g, ~100%),

which was used directly for preparation of compound **8**, ^1H NMR (CDCl_3): δ 7.63 (d, 1H, J = 8.1 Hz, phenyl-H-6), 7.52 (s, 1H, phenyl-H-2), 6.90 (d, 1H, J = 8.1 Hz, phenyl-H-5), 5.62 (s, 1H, CH), 3.97 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3).

4.1.2. Methyl 4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxylate (8).¹³ A mixture of **7** (50 g, 0.18 mol), thioacetamide (17 g, 0.22 mol), and NaHCO_3 (17 g, 0.20 mol) in THF (400 mL) was heated to reflux for 6 h and then filtered. After evaporation of the solvent, a thick oil was obtained and was then purified by column chromatography (ethyl acetate/petroleum ether 60–90; 2:3) affording the title compound (42 g, 79.6%) as a white solid, mp 87–88 °C. IR (KBr) ν 2980, 1700, 1605, 1530, 1500, 1475, 1440, 1338 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.41 (d, 1H, J = 8.4 Hz, phenyl-H-6), 7.38 (s, 1H, phenyl-H-2), 6.93 (d, 1H, J = 8.4 Hz, phenyl-H-5), 3.94 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.75 (s, 3H, CH_3); GC–MS m/z 293 M^+ (100), 278 (65), 262 (23), 250 (15), 235 (50), 218 (77), 193 (26), 178 (16), 163 (8), 149 (38), 120 (26). Anal. Calcd (%) for $\text{C}_{14}\text{H}_{15}\text{NO}_4\text{S}$: C 57.32, H 5.15, N 4.77. Found: C 57.56, H 5.08, N 4.68.

4.1.3. 4-(3,4-Dimethoxyphenyl)-2-methylthiazole-5-carboxylic acid (9).¹³ The solution of the ester **8** (35 g, 0.12 mol), 50% NaOH (28 g, 0.35 mol), and water (150 mL) in THF (500 mL) was stirred and heated to reflux for 3 h. The reaction mixture was allowed to cool room temperature and ethyl acetate (350 mL) was added. The water layer was separated and neutralized with 10% HCl to pH 4, followed by addition of ethyl acetate (300 mL). The organic layer was dried over anhydrous magnesium sulfate. After evaporation of the solvent, the carboxylic acid **9** (28 g, 83.6%) was obtained as white crystals and was used to prepare the acid chloride **10** without further purification, mp 202–204 °C (dec). IR (KBr) ν 3500, 2500, 1680, 1600, 1500 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.37 (t, 2H, phenyl-H-6+H-2), 6.90 (d, 1H, J = 8.4 Hz, phenyl-H-5), 3.94 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 2.77 (s, 3H, CH_3); GC–MS m/z 235 M^+ – CO_2 (100), 220 (78), 192 (71), 179 (30), 164 (8), 151 (60), 136 (31). Anal. Calcd (%) for $\text{C}_{13}\text{H}_{13}\text{NO}_4\text{S}$: C 55.90, H 4.69, N 5.01. Found: C 55.79, H 4.75, N 5.15.

4.1.4. 4-(3,4-Dimethoxyphenyl)-2-methylthiazole-5-carbonyl chloride (10).¹³ Thionyl chloride (98%, 24.3 g, 0.2 mol) was added dropwise under vigorous stirring to a solution of carboxylic acid **9** (27.9 g, 0.1 mol) in chloroform (100 mL). The mixture was stirred and heated to reflux for 2 h. After evaporation of the solvent, a yellow solid was obtained (29.2 g, 98%), mp 120–122 °C and was used directly for preparation of compound **11–23**. IR (KBr) ν 2950, 2840, 1765, 1605, 1535, 1485 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.41–7.43 (d, 1H, J = 8.1 Hz, phenyl-H-6), 7.34 (s, 1H, phenyl-H-2), 6.91–6.94 (d, 1H, J = 8.1 Hz, phenyl-H-5), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 2.80 (s, 3H, CH_3).

4.1.5. General method for the synthesis of 4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxylates and carboxamides (11–23). A solution of acid chloride **10** (2 mmol) in dry acetonitrile (5 mL) was added dropwise under vigorous stirring to a solution of the appropriate amine or alcohol (2.2 mmol) and triethylamine (2 mmol) in acetonitrile (10 mL). The mixture was heated to reflux for 10 min and evaporated to remove the acetonitrile, followed by addition of water (10 mL) and extraction with ethyl acetate (3 × 10 mL). The organic layer was washed with 10% HCl to remove the excess of amine, then with saturated aqueous NaHCO₃ solution, water, and brine, dried over magnesium sulfate, and evaporated to give the target compounds as an oil or a solid. Purification was performed with column chromatography (ethyl acetate/petroleum ether 60–90; 2:3).

4.1.6. 4-[4-(3,4-Dimethoxyphenyl)-2-methylthiazole-5-carbonyl]morpholine (11). Yield 93%, colorless oil. IR (KBr) ν 3000, 2920, 1625, 1435 cm⁻¹; ¹H NMR (CDCl₃): δ 7.17–7.20 (t, 2H, phenyl-H-6+H-2), 6.83 (d, 1H, J = 8.7 Hz, phenyl-H-5), 3.86 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 3.60 (m, 4H, CH₂OCH₂), 3.05 (m, 4H, CH₂NCH₂), 2.68 (s, 3H, CH₃); HRMS Calcd for C₁₇H₂₀N₂O₄S: 348.1144. Found: 348.1168. Anal. Calcd (%) for C₁₇H₂₀N₂O₄S: C 58.60, H 5.79, N 8.04. Found: C 58.80, H 5.62, N 7.90.

4.1.7. N-Ethyl-N-methyl-4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxamide (12). Yield 92%, colorless oil. IR (KBr) ν 2980, 2940, 2840, 1635, 1515 cm⁻¹; ¹H NMR (CDCl₃): δ one isomer (50%): 7.32 (m, 2H, phenyl-H-6+H-2), 6.89 (d, 1H, J = 8.7 Hz, phenyl-H-5), 3.92 (s, 6H, 2OCH₃), 3.54 (m, 2H, NCH₂), 3.04 (s, 3H, NCH₃), 2.76 (s, 3H, CH₃), 1.16 (t, 3H, CH₃); another isomer (50%): 7.32 (m, 2H, phenyl-H-6+H-2), 6.89 (d, 1H, J = 8.7 Hz, phenyl-H-5), 3.92 (s, 6H, 2OCH₃), 3.10 (m, 2H, NCH₂), 2.61 (s, 3H, NCH₃), 2.76 (s, 3H, CH₃), 0.86 (t, 3H, CH₃); GC–MS m/z 320 M⁺ (100), 305 (5), 291 (7), 278 (2), 262 (98), 247 (23), 235 (75), 220 (18), 193 (77), 178 (23), 160 (16), 148 (11), 131 (25). Anal. Calcd (%) for C₁₆H₂₀N₂O₃S: C 59.98, H 6.29, N 8.74; Found: C 59.81, H 6.40, N 8.58.

4.1.8. N-Methoxy-N-methyl-4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxamide (13). Yield 92%, colorless oil. IR (KBr) ν 3000, 2920, 1635, 1505 cm⁻¹; ¹H NMR (CDCl₃): δ 7.32 (d, 1H, J = 8.7 Hz, phenyl-H-6), 7.24 (s, 1H, phenyl-H-2), 6.88 (d, 1H, J = 8.7 Hz, phenyl-H-5), 3.93 (s, 3H, OCH₃), 3.92 (s, 3H, OCH₃), 3.57 (s, 3H, OCH₃), 3.21 (m, 4H, NCH₃), 2.76 (s, 3H, CH₃). Anal. Calcd (%) for C₁₅H₁₈N₂O₄S: C 55.88, H 5.63, N 8.69. Found: C 56.00, H 5.79, N 8.87.

4.1.9. N-Cyanomethyl-4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxamide (14). Yield 92% of white solid, mp 223–224 °C. IR (KBr) ν 3400, 3120, 2240, 1600, 1565 cm⁻¹; ¹H NMR (CDCl₃): δ 7.13 (t, 2H, phenyl-H-6+H-2), 6.98 (d, 1H, J = 8.7 Hz, phenyl-H-5),

6.15 (b s, 1H, NH), 4.17 (d, 2H, J = 6 Hz, CH₂CN), 3.95 (s, 3H, OCH₃), 3.94 (s, 3H, OCH₃), 2.75 (s, 3H, CH₃). Anal. Calcd (%) for C₁₅H₁₅N₃O₃S: C 56.77, H 4.76, N 13.24. Found: C 56.59, H 4.83, N 13.50.

4.1.10. N,N-Diethyl-4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxamide (15). Yield 92% of white solid, mp 100–101 °C. IR (KBr) ν 2975, 2935, 2840, 1635, 1515 cm⁻¹; ¹H NMR (CDCl₃): δ 7.34 (s, 1H, phenyl-H-6), 7.27 (d, 1H, J = 8.1 Hz, phenyl-H-2), 6.86 (d, 1H, J = 8.1 Hz, phenyl-H-5), 3.92 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 3.51 (q, 2H, NCH₂), 3.07 (q, 2H, NCH₂), 2.75 (s, 3H, CH₃), 1.19 (t, 3H, CH₃), 0.83 (s, 3H, CH₃); GC–MS m/z 334 M⁺ (97), 319 (1), 305 (5), 293 (1), 277 (1), 262 (100), 247 (16), 235 (88), 220 (20), 204 (4), 193 (61), 178 (18), 167 (8), 148 (10), 131 (18), 120 (16). Anal. Calcd (%) for C₁₇H₂₂N₂O₃S: C 61.05, H 6.63, N 8.38. Found: C 60.89, H 6.78, N 8.54.

4.1.11. N,N-Dimethylamino-4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxamide (16). Yield 87% of white solid, mp 142–143 °C. IR (KBr) ν 3340, 3100, 2980, 1640, 1540, 1500 cm⁻¹; ¹H NMR (CDCl₃): δ 7.18 (t, 2H, phenyl-H-6+H-2), 6.92 (d, 1H, J = 8.7 Hz, phenyl-H-5), 6.42 (b s, 1H, NH), 3.94 (s, 3H, OCH₃), 3.93 (s, 3H, OCH₃), 2.73 (s, 3H, CH₃), 2.48 (s, 6H, 2CH₃). Anal. Calcd (%) for C₁₅H₁₉N₃O₃S: C 56.06, H 5.96, N 13.07. Found: C 56.25, H 5.81, 13.26.

4.1.12. N-[3-(1H-Imidazol-1-yl)propyl]-4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxamide (17). Yield 85%, colorless oil. IR (KBr) ν 3440, 2920, 2850, 1645, 1500 cm⁻¹; ¹H NMR (CDCl₃): δ 7.25 (s, 1H, N=CH–N), 7.14 (m, 2H, phenyl-H-6+H-2), 7.01 (s, 1H, CH), 6.95 (d, 1H, J = 8.1 Hz, phenyl-H-5), 6.85 (s, 1H, CH), 5.95 (b s, 1H, NH), 3.88–3.93 (m, 8H, 2OCH₃+CH₂), 3.25 (m, 2H, CH₂), 2.72 (s, 3H, CH₃), 1.95 (m, 2H, CH₂). Anal. Calcd (%) for C₁₅H₁₉N₃O₃S: C 59.05, H 5.74, N 14.50. Found: C 58.88, H 5.90, 14.37.

4.1.13. N-(1,1-Dimethyl-prop-2-ynyl)-4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxamide (18). Yield 95% of white solid, mp 114–115 °C. IR (KBr) ν 3440, 3255, 2180, 1665, 1515 cm⁻¹; ¹H NMR (CDCl₃): δ 7.20 (d, 1H, J = 8.1 Hz, phenyl-H-6), 7.15 (s, 1H, phenyl-H-2), 6.99 (d, 1H, J = 8.7 Hz, phenyl-H-5), 5.96 (b s, 1H, NH), 3.95 (s, 3H, OCH₃), 3.94 (s, 3H, OCH₃), 2.76 (s, 3H, CH₃), 2.32 (s, 1H, C≡CH), 1.49 (s, 6H, 2CH₃); GC–MS m/z 344 M⁺ (100), 329 (18), 313 (8), 301 (8), 288 (25), 277 (42), 262 (93), 246 (13), 231 (38), 216 (9), 203 (8), 193 (43), 178 (17), 178 (17), 163 (38), 148 (12), 120 (18). Anal. Calcd (%) for C₁₈H₂₀N₂O₃S: C 62.77, H 5.85, N 8.13. Found: C 62.61, H 5.77, N 8.34.

4.1.14. N-(1-Ethyl-1-methyl-prop-2-ynyl)-4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxamide (19). Yield 96% of white solid, mp 99–100 °C. IR (KBr) ν 3395, 3300, 2975, 2930, 2180, 1650, 1500 cm⁻¹; ¹H NMR

(CDCl₃) δ 7.15 (d, 1H, J = 8.7 Hz, phenyl-H-6), 7.10 (s, 1H, phenyl-H-2), 6.92 (d, 1H, J = 8.7 Hz, phenyl-H-5), 5.91 (b s, 1H, NH), 3.94 (s, 6H, 2OCH₃), 2.72 (s, 3H, CH₃), 2.30 (s, 1H, C $\equiv$ CH), 1.82 (m, 1H, CH_aMe), 1.64 (m, 1H, CH_bMe), 1.51 (s, 3H, CH₃), 0.82 (t, 3H, CH₂). HRMS Calcd for C₁₉H₂₂N₂O₃S: 358.1351. Found: 358.1370. Anal. Calcd (%) for C₁₉H₂₂N₂O₃S: C 63.66, H 6.19, N 7.82 Found: C 63.75, H 6.27, N 7.69.

4.1.15. N-(Phenyl)-4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxamide (20). Yield 95% of white solid, mp 157–158 °C. IR (KBr) ν 3280, 2940, 2830, 1660, 1595, 1505, 1440 cm⁻¹; ¹H NMR (CDCl₃): δ 7.65 (b s, 1H, NH), 7.15–7.27 (m, 7H, phenyl-H-6+H-2+C₆H₅), 7.05 (d, 1H, J = 8.1 Hz, phenyl-H-5), 3.97 (s, 3H, OCH₃), 3.88 (s, 3H, OCH₃), 2.76 (s, 3H, CH₃). Anal. Calcd (%) for C₁₉H₁₈N₂O₃S: C 64.39, H 5.12, N 7.90; Found: C 64.55, H 5.03, N 7.73.

4.1.16. 4-(3,4-Dimethoxyphenyl)-2-methylthiazole-5-carboxamide (21). Yield 92% of white solid, mp 192–193 °C. IR (KBr) ν 3330, 3165, 2930, 2910, 1650, 1505, 1460 cm⁻¹; ¹H NMR (CDCl₃): δ 7.18 (d, 1H, J = 8.7 Hz, phenyl-H-6), 7.13 (s, 1H, phenyl-H-2), 6.95 (d, 1H, J = 8.7 Hz, phenyl-H-5), 5.80 (b s, 1H, NH_a), 5.50 (b s, 1H, NH_b), 3.94 (s, 3H, OCH₃), 3.93 (s, 3H, OCH₃), 2.74 (s, 3H, CH₃). Anal. Calcd (%) for C₁₃H₁₄N₂O₃S: C 56.10, H 5.07, N 10.06. Found: C 56.24, H 5.23, N 9.88.

4.1.17. Prop-2-ynyl 4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxylate (22). Yield 91% of white solid, mp 134–135 °C. IR (KBr) ν 3225, 2940, 2835, 2125, 1725, 1500 cm⁻¹; ¹H NMR (CDCl₃): δ 7.41 (d, 1H, J = 8.7 Hz, phenyl-H-6), 7.39 (s, 1H, phenyl-H-2), 6.94 (d, 1H, J = 8.7 Hz, phenyl-H-5), 4.81 (d, 2H, J = 2.4 Hz, CH₂ C $\equiv$ C), 3.94 (s, 3H, OCH₃), 3.93 (s, 3H, OCH₃), 2.75 (s, 3H, CH₃), 2.49 (s, 1H, C $\equiv$ CH). Anal. Calcd (%) for C₁₆H₁₅NO₄S: C 60.55, H 4.76, N 4.41 Found: C 60.79, H 4.63, N 4.30.

4.1.18. 2-Methylpropyl 4-(3,4-dimethoxyphenyl)-2-methylthiazole-5-carboxylate (23). Yield 92%, colorless oil. IR (KBr) ν 2960, 2840, 2835, 1715, 1495 cm⁻¹; ¹H NMR (CDCl₃): δ 7.38 (m, 2H, phenyl-H-6+H-2), 6.94 (d, 1H, J = 8.1 Hz, phenyl-H-5), 3.99 (d, 2H, J = 3.6 Hz, OCH₂), 3.92 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 2.74 (s, 3H, CH₃), 1.95 (m, 1H, CH), 0.92 (d, 6H, J = 6.6 Hz, 2CH₃). Anal. Calcd (%) for C₁₇H₂₁NO₄S: C 60.87, H 6.31, N 4.18. Found: C 60.68, H 6.59, N 4.01.

4.2. Biological activity assays

Evaluations of biological activities of the reported compounds were performed as previously described.^{16–19}

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