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Synthesis and Biological Screening of Thiazole-5-Carboxamide Derivatives

Pravin C. Mhaske, Kamlesh S. Vadgaonkar†, Rahul P. Jadhav†, and Vivek D. Bobade†,*
Department of Chemistry, S. P. College, Pune, India-411 030
†Department of Chemistry, HPT Arts and RYK Science College, Nashik India-422 005.
**E-mail: v_bobade31@rediffmail.com*
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Thiazole derivatives have been studied extensively because of their ready accessibility, diverse chemical activity. The chemistry of thiazole continues to draw the attention of synthetic organic chemists due to their varied biological activities,[1-5] such as antibacterial, antitubercular, anti-cancer, antifungal and anti-inflammatory activities.[6-9] Also 4-(4-aminophenyl)-thiazoles have been reported to exhibit antitubercular activity.[10] 5-azole carboxamide derivatives show antianoxic activity.[11] The aryl imidazolyl carboxamide derivatives were shown to be cannabinoid CB_1 receptor antagonist.[12,13] Based on these observations, substituted thiazole carboxamides were synthesized and subjected to microbial screening.

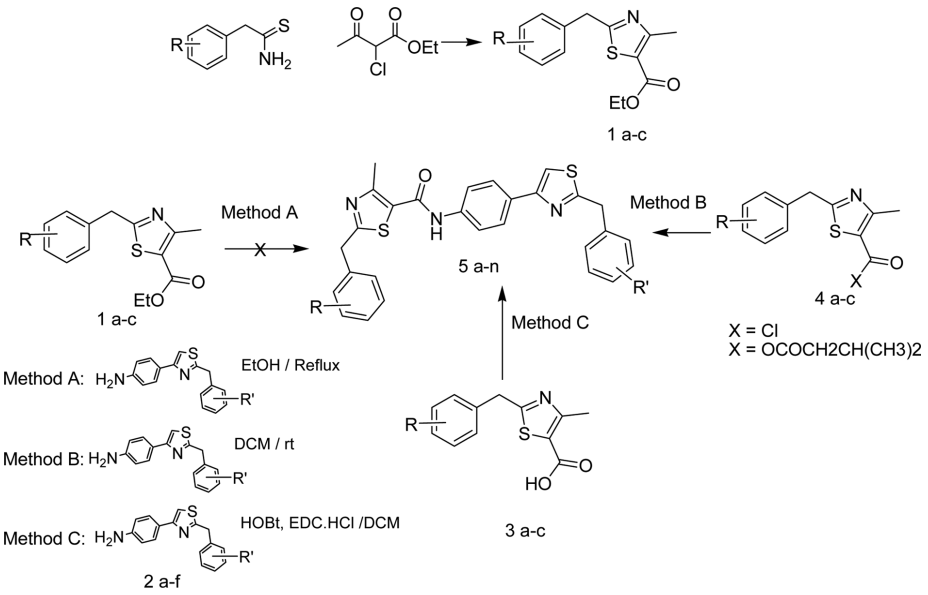
Here in, we report a simple efficient and effective protocol for the synthesis of N-(4-(2-benzylthiazol-4-yl)phenyl)-2-benzyl-4-methylthiazole-5-carboxamide derivatives using EDC-HOBt coupling in DMF and their antimicrobial activities. The target compounds **5a-n** were synthesized by reaction of 2-benzyl-4-methylthiazole-5-carboxylic acid **3a-c** with 2-methyl/substitutedbenzyl-4-(4-aminophenyl) thiazoles **2a-f** in the presence of EDC- HOBt in DMF in good yields (*Scheme* 1). The yields, melting points and molecular formula of carboxamide derivatives **5a-n** are listed in *Table* 1. The reaction failed when ethyl 2-benzyl-4-methylthiazole-5-carboxylate **1a-c** was refluxed with 2-methyl/substitutedbenzyl-4-(4-aminophenyl) thiazole **2a-f** in absolute ethanol for 24 h. When the same reaction was carried out with acid chloride or mixed anhydride activation of the carboxylic acid, the yields were poor. The amino phenyl thiazole derivatives **2a-f** were synthesized using literature protocol.[10,14] The target compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis and all the spectral data are in accordance with the assumed structures. In additions to the signals for aromatic protons ^{1}H NMR spectra of the compounds **5a-n** reveal singlet at 2.73-2.78 ppm for thiazole-CH_3 protons. Furthermore, the spectra show singlet for methylene protons of benzylic carbon atoms in the range 3.73- 4.41 ppm.

These compounds were found to be effective against the Gram-positive bacteria *S. aureu and B. Subtilis* and Gram-negative bacteria *E. coli and P. aeruginosa*. The zones of inhibition in mm, for the bioactive compounds against microorganisms tested are reported in *Table* 2. N-(4-(2-(4-chlorobenzylthiazol-4-yl)phenyl)-2-(4-chlorobenzyl)-4-methylthiazole-5-carboxamide (**5k**) is active against both gram positive and gram negative stains but looses activity on adding one chlorine at 3-position as in N-(4-(2-(3,4-dichlorobenzylthiazol-4-yl)phenyl)-2-(4-chlorobenzyl)-4-methylthiazole-5-carboxamide (**5l**). When chlorine in the first benzyl ring in **5l**, was replaced by fluorine as in N-(4-(2-(3,4-dichlorobenzylthiazol-4-yl)phenyl)-2-(4-fluorobenzyl)-4-methylthiazole-5-carboxamide (**5i**), it showed antibacterial activity.

N-(4-(2-(4-fluorobenzylthiazol-4-yl)phenyl)-2-(4-chlorobenzyl)-4-methylthiazole-5-carboxamide (**5m**) showed antifungal activity, but when one chlorine atom is added at 2-position as in N-(4-(2-(4-fluorobenzyl)thiazol-4-yl)phenyl)-2-(2,4-dichlorobenzyl)-4-methylthiazole-5-carboxamide (**5c**), it showed antibacterial activity with loss of antifungal activity. 2-methyl substituted carboxamide derivatives (**5a, 5f**) showed only antibacterial activity. The dimethoxy derivative **5n** was found to be inactive against all stains.

EXPERIMENTAL

Melting points were determined in an open capillary on Veego melting point apparatus and are uncorrected. The purity of the compounds was checked on silica gel-G plates. The compounds **5a-n** were purified on silica gel (100-200) column chromatography using ethyl acetate: hexane as eluent. Infrared spectra (cm^{-1}) were recorded in



***Scheme* 1.**

***Table* 1.** Yields and physical data of compounds **5a-n**

Compound	R	R^1	Mp (ºC)	Yield (%)	Molecular Formula
5a	2,4-di Cl_2	H	179	72	$C_{22}H_{17}Cl_2N_3OS_2$
5b	2,4-di Cl_2	4-BrC_6H_4	141	78	$C_{28}H_{20}BrCl_2N_3OS_2$
5c	2,4-di Cl_2	4-FC_6H_4	119	73	$C_{28}H_{20}Cl_2FN_3OS_2$
5d	2,4-di Cl_2	3,4-di $Cl_2C_6H_3$	142	73	$C_{28}H_{19}Cl_4N_3OS_2$
5e	2,4-di Cl_2	3,4-di $OMeC_6H_3$	113	65	$C_{30}H_{25}Cl_2N_3O_3S_2$
5f	4-F	H	152	79	$C_{22}H_{18}FN_3OS_2$
5g	4-F	4-ClC_6H_4	171	82	$C_{28}H_{21}ClFN_3OS_2$
5h	4-F	4-FC_6H_4	140	72	$C_{28}H_{21}F_2N_3OS_2$
5i	4-F	3,4-di $Cl_2C_6H_3$	158	70	$C_{28}H_{20}Cl_2FN_3OS_2$
5j	4-Cl	H	142	74	$C_{22}H_{18}ClN_3OS_2$
5k	4-Cl	4-ClC_6H_4	186	81	$C_{28}H_{21}Cl_2N_3OS_2$
5l	4-Cl	3,4-di. $Cl_2C_6H_3$	170	70	$C_{28}H_{20}Cl_3N_3OS_2$
5m	4-Cl	4-FC_6H_{4s}	155	71	$C_{28}H_{21}ClFN_3OS_2$
5n	4-Cl	3,4-di $OMeC_6H_3$	160	68	$C_{30}H_{26}ClN_3O_3S_2$

***Table* 2.** Antimicrobial data of bioactive molecules (Zone diameter of growth inhibition in mm)

Compounds[a]	Microorganisms					
	B. subtilis	S. aureus	E. coli	P. aeruginosa	C. albicans	A. niger
5a	10	9	9	-	-	-
5b	-	-	7	8	-	-
5c	-	-	9	9	-	-
5f	-	-	7	8	-	-
5i	9	8	-	-	-	-
5k	12	11	9	11	-	-
5m	-	-	-	-	7	8
Ciprofloxacin[a]	26	28	25	37	NA	NA
Nystation[a]	NA	NA	NA	NA	20.5	22.1

[a]Ciprofloxacin (10 μg/disc), Nystatin (100 U/disc) was used as reference; synthesized compounds (100 μg/disc); NA = Not Applicable; (-) = Inactive.

KBr on a Shimadzu Model FTIR-435 spectrophotometer. ^{1}H-NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 solution on a Varian Mercury YH-300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts are expressed relative to tetramethylsilane (TMS) and were reported as δ (ppm). Carbon, Hydrogen and Nitrogen analysis were performed with Perkin-Elmer 2400 series II instrument. Mass spectral (MS) measurements were made on a Jeol-JMS-DX 303 mass spectrometer. The isotopic peak at M+2 was observed in the mass spectrum of all the compounds due to S, Br and/or Cl.

The in vitro antibacterial activity was performed against Gram-positive bacteria including *Staphylococcus aureus* (NCIM 2079), *Bacillus Subtilis* (NCIM 2250) and Gram-negative bacteria including *Escherichia coli* (NCIM 2109), *Pseudomonas aeruginosa* (NCIM 2036). Yeast including *Candida albicans* (NCIM 3471) and fungi *Aspergillus niger* (NCIM 545) were used to test antifungal activity. Known antibiotics like Ciprofloxacin (the reference anti bacterial drugs) and Nystatin (the reference antifungal drug) were used for comparison.

General procedure for the synthesis of substituted 2-benzyl-4-methylthiazole-5-carboxylic acid. 1a-c. Mixture of 2-chloro-3-oxo ethylbutanoate (0.05 mol) and substituted benzyl thioamides (0.055 mol) in 50 mL of methanol was refluxed for 5-6 hours. After completion of the reaction, as monitored on TLC, 20 mL of 2N NaOH was added and refluxed further for 4 hours. Methanol was distilled off and the mixture acidified with 4N HCl to pH 2. The precipitated product was filtered, washed with water and recrystallized from aqueous ethanol.

Synthesis of amino phenylthiazole derivatives 2a-f. These compounds were prepared using the literature protocol.[10,14]

General procedure for the synthesis of N-(4-(2-methyl/benzylthiazol-4-yl) phenyl)-2-benzyl-4-methylthiazole-5-carboxamide 5a-n. A mixture of 2-benzyl-4-methylthiazole-5-carboxylic acid (**1a-c)** (1 mmol), DIPEA (0.35 mL, 2 mmol), HOBt (0.14 g, 1 mmol) in DMF (10 mL) was cooled to 0 ºC. To this 2-methyl/benzyl-4-(4-aminophenyl) thiazole (**2a-f)** (1mmol) was added followed by EDC. HCl (0.19 g, 1 mmol) at 0 ºC and stirred overnight at room temperature. The reaction was quenched with water and the product was filtered, washed with water. The spectral data of the purified compounds are as below:

N-(4-(2-Methylthiazol-4-yl)phenyl)-2-(2,4-dichlorobenzyl)-4-methylthiazole-5-carboxamide (5a). Solid, m.p. 179 ºC, IR(KBr, cm^{-1}) 3440, 3262 (NH); 1646 (CO); 1593 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.74 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 4.39 (s, 2H, CH_2-Ph), 7.26-7.28 (m, 2H, Ar-H, Thiazole-H), 7.32 (d, J=8.3 Hz, 1H, Ar-H), 7.34 (bs, 1H, NH-CO), 7.45 (d, J=2Hz, 1H, Ar-H), 7.57 (d, J=8.6 Hz, 2H, Ar-H), 7.85 (d, J=8.6 Hz, 2H, Ar-H). LCMS: 474 (M+1). Anal. Calcd. for $C_{22}H_{17}Cl_2N_3OS_2$: C, 55.70; H, 3.61; N, 8.86. Found: C, 55.31; H, 3.50; N, 8.84.

N-(4-(2-(4-Bromobenzyl)thiazol-4-yl)phenyl)-2-(2,4-dichlorobenzyl)-4-methylthiazole-5-carboxamide (5b). Solid, m.p. 141 ºC, IR(KBr, cm^{-1}) 3448, 3292 (NH); 1652 (CO); 1598 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.75 (s, 3H, CH_3), 4.33 (s, 2H, CH_2-Ph), 4.41 (s, 2H, CH_2-Ph), 7.23-7.49 (m, 9H, Ar-H, Thiazole-H, NH-CO), 7.59 (d, J=8.5 Hz, 2H, Ar-H), 7.87 (d, J=8.5 Hz, 2H, Ar-H). Anal. Calcd. for $C_{28}H_{20}BrCl_2N_3OS_2$: C, 53.43; H, 3.20; N, 6.68. Found: C, 53.08; H, 3.13; N, 6.33.

N-(4-(2-(4-Fluorobenzyl)thiazol-4-yl)phenyl)-2-(2,4-dichlorobenzyl)-4-methylthiazole-5-carboxamide (5c). Solid, m.p. 119 ºC, IR(KBr, cm^{-1}) 3462, 3252 (NH); 1641 (CO); 1596 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.75 (s, 3H, CH_3), 4.27 (s, 2H, CH_2-Ph), 4.32 (s, 2H, CH_2-Ph), 7.03-7.46 (m, 9H, Ar-H, Thiazole-H, NH-CO), 7.58 (d, J=8.5 Hz, 2H, Ar-H), 7.86 (d, J=8.5 Hz, 2H, Ar-H), ^{13}C NMR ($CDCl_3$): δ 17.3 (Thiazole-CH_3), 36.9 (CH_2-Ar), 38.9 (CH_2-Ar), 112.5- 160.2 (24-C, Aromatic-C), 168.3 (CO-NH). Anal. Calcd. for $C_{28}H_{20}Cl_2FN_3OS_2$: C, 59.15; H, 3.55; N, 7.39. Found: C, 59.08; H, 3.33; N, 7.28.

N-(4-(2-(3,4-Dichlorobenzyl)thiazol-4-yl)phenyl)-2-(2,4-dichlorobenzyl)-4-methylthiazole-5-carboxamide (5d). Solid, m.p. 142 ºC, IR(KBr, cm^{-1}) 3478, 3259 (NH); 1654 (CO); 1603 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.73 (s, 3H, CH_3), 4.38 (s, 2H, CH_2-Ph), 4.46 (s, 2H, CH_2-Ph), 7.21-7.45 (m, 8H, Ar-H, Thiazole-H, NH-CO) 7.57 (d, J=9 Hz, 2H, Ar-H), 7.85 (d, J=9 Hz, 2H, Ar-H), Anal. Calcd. for $C_{28}H_{19}Cl_4N_3OS_2$: C, 54.29; H, 3.09; N, 6.38. Found: C, 54.08; H, 3.03; N, 6.35.

N-(4-(2-(3,4-Dimethoxybenzyl)thiazol-4-yl)phenyl)-2-(2,4-dichlorobenzyl)-4-methylthiazole-5-carboxamide (5e). Solid, m.p. 113 ºC, IR(KBr, cm^{-1}) 3455, 3248 (NH); 1642 (CO); 1595 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.75 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.32 (s, 2H, CH_2-Ph), 4.41 (s, 2H, CH_2-Ph), 6.84-7.47 (m, 8H, Ar-H, Thiazole-H, NH-CO) 7.68 (d, J=8.7 Hz, 2H, Ar-H), 7.88 (d, J=8.7 Hz, 2H, Ar-H). Anal. Calcd. for $C_{30}H_{25}Cl_2N_3O_3S_2$: C, 59.01; H, 4.13; N, 6.88. Found: C, 58.72; H, 3.94; N, 6.58.

N-(4-(2-Methylthiazol-4-yl)phenyl)-2-(4-fluorobenzyl)-4-methylthiazole-5-carboxamide (5f). Solid, m.p. 152 ºC, IR(KBr, cm^{-1}) 3444, 3256 (NH); 1660 (CO); 1599 (C=N);

^{1}H NMR ($CDCl_3$): δ 2.74 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 4.26 (s, 2H, CH_2-Ph), 7.03-7.35 (m, 6H, Ar-H, Thiazole-H, NH-CO), 7.56 (d, J=8.6 Hz, 2H, Ar-H), 7.84 (d, J=8.6 Hz, 2H, Ar-H), LCMS: 423.8 (M+1). Anal. Calcd. for $C_{22}H_{18}FN_3OS_2$: C, 62.39; H, 4.28; N, 9.92. Found: C, 61.99; H, 3.95; N, 9.61.

N-(4-(2-(4-Chlorobenzylthiazol-4-yl)phenyl)-2-(4-fluorobenzyl)-4-methylthiazole-5-carboxamide (5g). Solid, m.p. 171 ºC, IR(KBr, cm^{-1}) 3449, 3232 (NH); 1651 (CO); 1595 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.73 (s, 3H, CH_3), 4.25 (s, 2H, CH_2-Ph), 4.33 (s, 2H, CH_2-Ph), 7.02-7.33 (m, 9H, Ar-H, NH-CO), 7.45 (s, IH, Thiazole-H), 7.57 (d, J=8.7 Hz, 2H, Ar-H), 7.85 (d, J=8.7 Hz, 2H, Ar-H), ^{13}C NMR ($CDCl_3$): δ 17.31 (Thiazole-CH_3), 39.01 (2 x CH_2-Ar), 112.58-169.64 (24-C, Aromatic-C), 170.69 (CO-NH), LCMS: 423.8 (M+1). Anal. Calcd. for $C_{28}H_{21}ClFN_3OS_2$: C, 62.97; H, 3.96; N, 7.87. Found: C, 62.59; H, 3.87; N, 7.53.

N-(4-(2-(4-Fluorobenzylthiazol-4-yl)phenyl)-2-(4-fluorobenzyl)-4-methylthiazole-5-carboxamide (5h). Solid, m.p. 140 ºC, IR(KBr, cm^{-1}) 3441, 3242 (NH); 1647 (CO); 1601 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.75 (s, 3H, CH_3), 3.73 (s, 2H, CH_2), 4.34 (s, 2H, CH_2), 7.00-7.32 (m, 10H, Ar-H, Thiazole-H, NH-CO), 7.49 (d, J=8.4 Hz, 2H, Ar-H), 7.82 (d, J=8.4 Hz, 2H, Ar-H). Anal. Calcd. for $C_{28}H_{21}F_2N_3OS_2$: C, 64.97; H, 4.09; N, 8.12. Found: C, 64.69; H, 3.97; N, 8.01.

N-(4-(2-(3,4-Dichlorobenzylthiazol-4-yl)phenyl)-2-(4-fluorobenzyl)-4-methylthiazole-5-carboxamide (5i). Solid, m.p. 158 ºC, IR(KBr, cm^{-1}) 3472, 3264 (NH); 1641 (CO); 1598 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.74 (s, 3H, CH_3), 4.34 (s, 2H, CH_2-Ph), 4.40 (s, 2H, CH_2-Ph), 7.02-7.60 (m, 9H, Ar-H, Thiazole-H, NH-CO), 7.58 (d, J=9.0 Hz, 2H, Ar-H), 7.86 (d, J=9.0 Hz, 2H, Ar-H), ^{13}C NMR ($CDCl_3$): δ 17.3 (Thiazole-CH_3), 36.9 (CH_2-Ar), 38.9 (CH_2-Ar), 112.5- 159.7 (24-C, Aromatic-C), 168.4 (CO-NH). Anal. Calcd. for $C_{28}H_{20}Cl_2FN_3OS_2$: C, 59.15; H, 3.55; N, 7.39. Found: C, 58.88; H, 3.38; N, 7.28.

N-(4-(2-Methylthiazol-4-yl)phenyl)-2-(4-chlorobenzyl)-4-methylthiazole-5-carboxamide (5j). Solid, m.p. 142 ºC, IR(KBr, cm^{-1}) 3439, 3255 (NH); 1644 (CO); 1596 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.75 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 4.26 (s, 2H, CH_2-Ph), 7.25-7.42 (m, 6H, Ar-H, Thiazole-H, NH-CO), 7.58 (d, J=8.7 Hz, 2H, Ar-H), 7.85 (d, J=8.7 Hz, 2H, Ar-H). Anal. Calcd. for $C_{22}H_{18}ClN_3OS_2$: C, 60.06; H, 4.12; N, 9.55. Found: C, 59.86; H, 3.92; N, 9.43.

N-(4-(2-(4-Chlorobenzylthiazol-4-yl)phenyl)-2-(4-chlorobenzyl)-4-methylthiazole-5-carboxamide (5k). Solid, m.p. 186 ºC, IR(KBr, cm^{-1}) 3472, 3222 (NH); 1655 (CO); 1594 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.78 (s, 3H, CH_3), 4.30 (s, 2H, CH_2-Ph), 4.37 (s, 2H, CH_2-Ph), 7.29-7.39 (m, 10H, Ar-H, Thiazole-H, NH-CO), 7.62 (d, J=8.7 Hz, 2H, Ar-H), 7.90 (d, J=8.7 Hz, 2H, Ar-H). Anal. Calcd. for $C_{28}H_{21}Cl_2N_3OS_2$: C, 62.97; H, 3.96; N, 7.87. Found: C, 62.65; H, 3.78; N, 7.81.

N-(4-(2-(3,4-Dichlorobenzylthiazol-4-yl)phenyl)-2-(4-chlorobenzyl)-4-methylthiazole-5-carboxamide (5l). Solid, m.p. 170 ºC, IR(KBr, cm^{-1}) 3471, 3233 (NH); 1649 (CO); 1589 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.75 (s, 3H, CH_3), 4.27 (s, 2H, CH_2-Ph), 4.47 (s, 2H, CH_2-Ph), 7.22-7.46 (m, 9H, Ar-H, Thiazole-H, NH-CO), 7.58 (d, J=8.5 Hz, 2H, Ar-H), 7.86 (d, J=8.5 Hz, 2H, Ar-H). Anal. Calcd. for $C_{28}H_{20}Cl_3N_3OS_2$: C, 62.97; H, 3.96; N, 7.87. Found: C, 62.59; H, 3.87; N, 7.53.

N-(4-(2-(4-Fluorobenzylthiazol-4-yl)phenyl)-2-(4-chlorobenzyl)-4-methylthiazole-5-carboxamide (5m). Solid, m.p. 155 ºC, IR(KBr, cm^{-1}) 3449, 3258 (NH); 1651 (CO); 1594 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.75 (s, 3H, CH_3), 4.27 (s, 2H, CH_2-Ph), 4.35 (s, 2H, CH_2-Ph), 7.01-7.38 (m, 10H, Ar-H, Thiazole-H, NH-CO), 7.58 (d, J=8.7 Hz, 2H, Ar-H), 7.87 (d, J=8.7 Hz, 2H, Ar-H). Anal. Calcd. for $C_{28}H_{21}ClFN_3OS_2$: C, 62.97; H, 3.96; N, 7.87. Found: C, 62.69; H, 3.84; N, 7.79.

N-(4-(2-(3,4-Dimethoxybenzylthiazol-4-yl)phenyl)-2-(4-chlorobenzyl)-4-methylthiazole-5-carboxamide (5n). Solid, m.p. 160 ºC, IR(KBr, cm^{-1}) 3448, 3268 (NH); 1647 (CO); 1597 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.76 (s, 3H, CH_3), 3.87 (s, 3H, O-CH_3), 3.89 (s, 3H, O-CH_3) 4.28 (s, 2H, CH_2-Ph), 4.32 (s, 2H, CH_2-Ph), 6.84-7.37 (m, 9H, Ar-H, Thiazole-H, NH-CO), 7.59 (d, J=8.5 Hz, 2H, Ar-H), 7.88 (d, J=8.5 Hz, 2H, Ar-H), LCMS: 575 (M^+), 577 (M+2). Anal. Calcd. for $C_{30}H_{26}ClN_3O_3S_2$: C, 62.54; H, 4.55; N, 7.29. Found: C, 62.35; H, 4.23; N, 7.33.

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