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Synthesis of carboxamide and sulfonyl carboxamide linked heterocycles under green conditions

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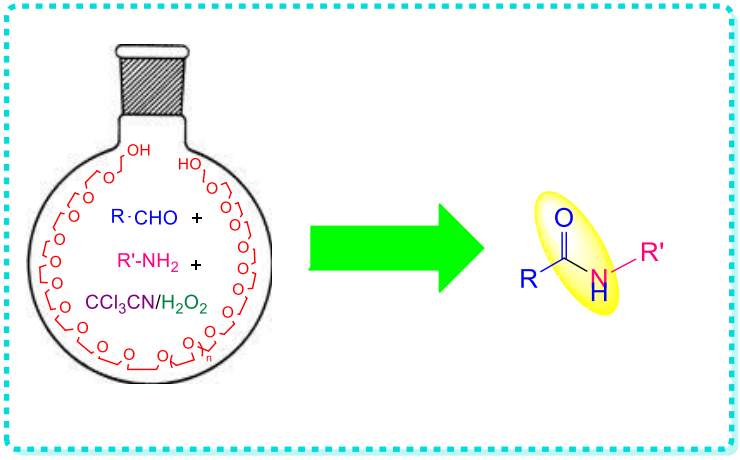
Abstract

Direct coupling of heteroaldehydes with heteroaryl amines / sulfonylamines is performed under green conditions using PEG-400 in the presence of oxidant CCl_3CN/H_2O_2. The presence of electron withdrawing substituents on heteroaldehydes increased the yield. Further heteroaryl amines favor the reaction when compared with heteroaryl sulfonylamines.



Keywords: Heteroaldehydes, heteroaryl amines , sulfonylamines, oxidant, PEG-400, amidation

Introduction

Amide moiety represents a privileged structural motif and it plays an important role in the composition of polymers, proteins, natural products and pharmaceuticals.[1,2] Various approaches were explored for efficient construction of this significant skeleton.[3,4] The most common synthetic route relies on the reactions of activated carboxylic acids and their derivatives with amines.[5-7] However, this method has innate drawbacks, for instance, a large amount of byproducts are generated leading to lower yields. As a result, alternative methods for amide synthesis have been developed *viz*., Beckmann rearrangement,[8] azide based modified Staudinger-Vilarrasa reaction,[9] amidation of aryl halides,[10] oxidative amidation of aldehydes[11] or alcohols[12] and amidation of alkynyl bromide with amines.[13] Most of these reactions require relatively harsh conditions such as light, expensive oxidant, strong bases, transition-metal complexes *viz.,* Cu, Zn, Zr, Ru, Pd, Hg,[14] high temperature *etc*. As such there is a quest for efficient and economically viable methods to construct amide bond. In continuation of our interest on green-reaction conditions for organic transformations[15] we herein report a simple and efficient protocol for the synthesis of carboxamide and sulfonyl carboxamide linked heterocycles using PEG-400 in the presence of an oxidant CCl_3CN/H_2O_2 as eco-friendly and recyclable medium.

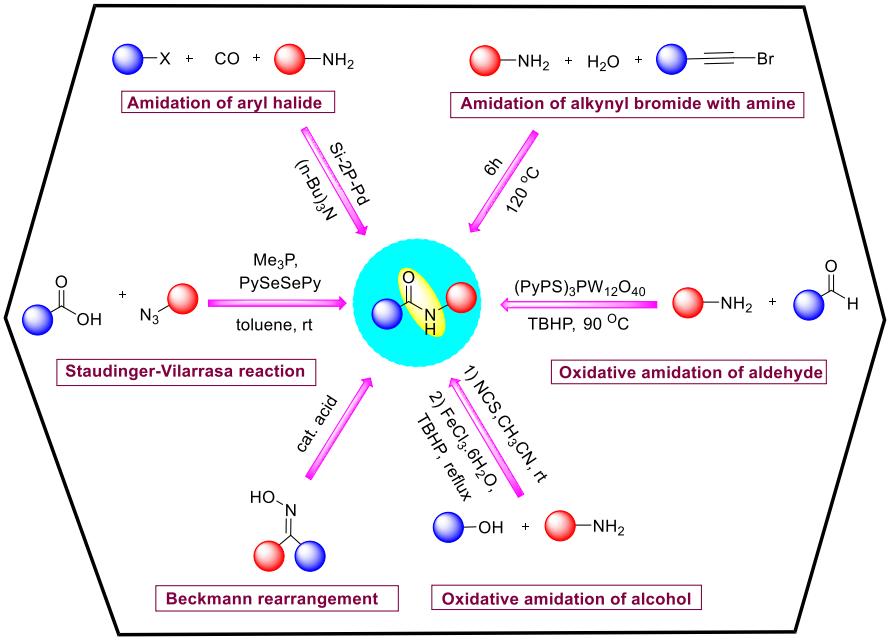


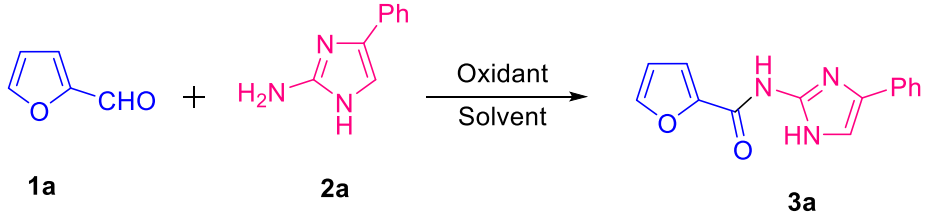
Figure 1. The most common reactions for amide bond synthesis.

Results and Discussion

For the last couple of years we have been actively engaged on the development of functionalized heterocycles linked by amide and sulfonamide moieties. In fact, we have reported the reaction between heteroaryl acids and heteroaryl amines to develop amide linkage using 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU)/ *N*,*N*-diisopropylethylamine (DIPEA)/ *N*,*N*-dimethylformamide (DMF),[16] *N*,*N*′-dicyclohexylcarbodiimide (DCC)/ 4-dimethylaminopyridine (DMAP)/ Dioxane,[17,18] 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxidehexafluorophosphate (HATU)/ DIPEA/DMF.[19] In this communication we have adopted simple, eco-friendly methodology for the development of amide and sulfonamide linked heterocycles

directly by amidation and sulfonamidation of heteroaldehydes with heteroaryl amines and sulfonylamines. Furan-2-carbaldehyde (**1a**), 1*H*-pyrrole-2-carbaldehyde (**1b**), thiophene-2-carbaldehyde (**1c**), isonicotinaldehyde (**1d**), 3,5-dichloroisonicotinaldehyde (**1e**) were purchased from Sigma-Aldrich and used as such. 2,4-Dichlorooxazole-5-carbaldehyde (**1f**), 2,4-dichlorothiazole-5-carbaldehyde (**1g**) were prepared by the reaction of urea and thiourea with chloroacetic acid in the presence of conc. HCl followed by treatment with $POCl_3$ in DMF.[20] 4-Phenyl-1*H*-imidazol-2-amine (**2a**) was obtained by the treatment of phenacyl bromide with acetyl guanidine in DMF followed by hydrolysis in the presence of dil. H_2SO_4.[17] 4-Phenylthiazol-2-amine (**2b**) was prepared by the reaction of phenacyl bromide with thiourea in methanol.[17] *N*-(5-(Aminosulfonyl)-4-phenyl-1*H*-imidazol-2-yl)benzamide (**4**) was prepared by the reaction of 4-phenyl-1*H*-imidazol-2-amine with benzoyl chloride followed by chlorosulfonylation with sulfuryl chloride under ultrasonication in DMF at 0 °C. The resultant *N*-(5-(chlorosulfonyl)-4-phenyl-1*H*-imidazol-2-yl)benzamide on further treatment with 25% NH_4OH gave **4**.[21] Initially, in our attempt to develop amide linkage directly from aldehydes and amines, we have chosen **1a** and **2a** to carry out the pilot reaction in the presence of different oxidants *viz*., *m*-CPBA in dichloromethane, H_2O_2 in dimethyl carbonate (DMC) and CCl_3CN/H_2O_2 in dichloromethane. From the data given in Table 1 it was found that CCl_3CN/H_2O_2 is the best oxidant resulting in the formation of product in 66%. In recent years, the use of green reaction solvents such as ionic liquids and polyethylene glycol (PEG-400) has gained importance.[22-24]

Table 1. Oxidative amidation of **1a** with **2a** under different conditions



1a **2a** **3a**

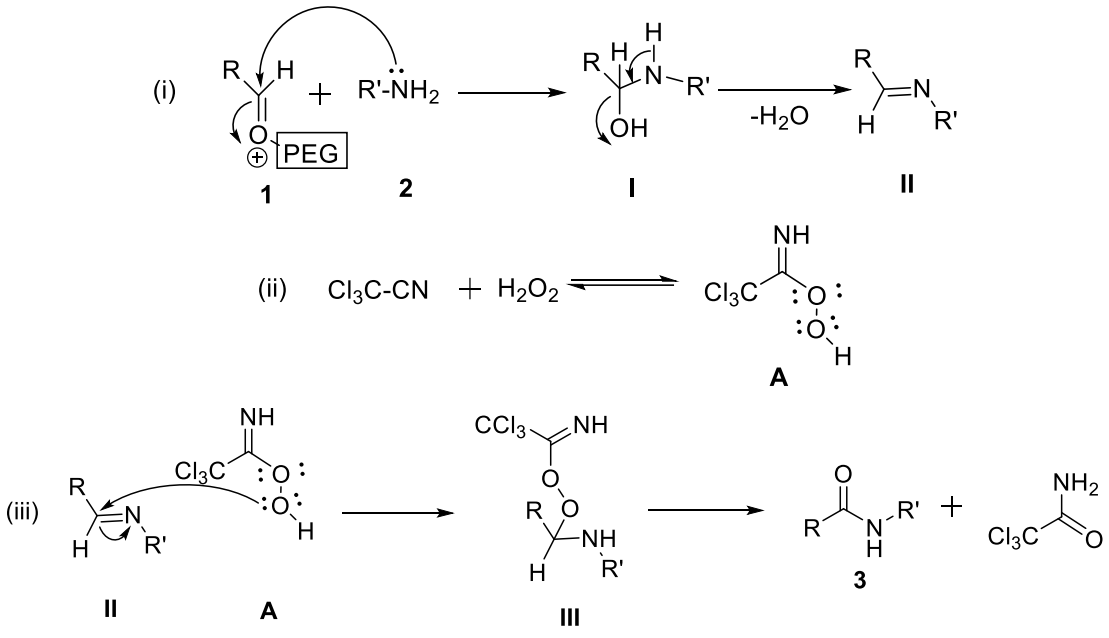
Entry	Oxidant	Solvent	Time (h)	Yield (%)
1	*m*-CPBA	CH_2Cl_2	15	57
2	H_2O_2	DMC	16	50
3	CCl_3CN/H_2O_2	CH_2Cl_2	13	66

Though phase transfer catalysis is an alternative technique, it is not always possible because of sensitivity of the reactants to aqueous conditions.[25] In this context, PEG-400 has become an alternative reaction media to perform organic synthesis due to its inherent advantages over toxic solvents. Moreover, PEG-400 is inexpensive, easy to handle, thermally stable, non-toxic and recyclable. In order to increase the yield, the reaction between **1a** and **2a** was carried out using PEG-400 in the presence of different oxidants *m*-CPBA, H_2O_2 and CCl_3CN/H_2O_2. It was noticed that CCl_3CN/H_2O_2 in PEG-400 is the most favourable reaction conditions for direct amidation of aldehydes with amines (Table 2). The mechanism for amidation of aldehydes with amines was proposed as shown in scheme 1. The mechanism for oxidative amidation of aldehydes with amines is proposed as shown in scheme **1**. The addition of trichloromethylperoxyimidic acid (A) generated by the oxidation of trichloroacetonitrile with hydrogen peroxide to imine followed by the elimination of trichloromethyl amide resulted in **3a**. The scope and generality of this reaction was subsequently examined using different heteroaldehydes and heteroaryl amines and the products were obtained in excellent yield (Table 3). The presence of electron withdrawing chloro substituent on heteroaldehydes increased the yield.

This methodology was extended to prepare sulfonyl carboxamide linked heterocycles by the reaction of heteroaldehydes with heteroaryl sulfonylamines (Table 4). Based on the obtained yield of the products it was noticed that heteroaryl amines favors the reaction with the formation of products in high yield when compared with heteroaryl sulfonylamines. This may be due to electron withdrawing effect of sulfonyl group.

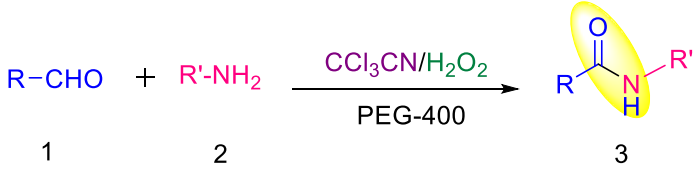
Table 2. Oxidative amidation of **1a** with **2a** in PEG-400

Entry	Oxidant	Solvent	Time (h)	Yield (%)
1	*m*-CPBA	PEG-400	12	62
2	H_2O_2	PEG-400	14	58
3	CCl_3CN/H_2O_2	PEG-400	10	84



Scheme 1. Plausible mechanism for the synthesis of amide by using CCl_3CN/H_2O_2/PEG-400.

Table 3. Synthesis of heteroaryl amides from heteroaldehydes and heteroaryl amines



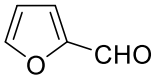
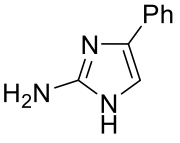
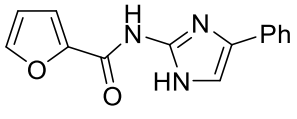
Entry	Aldehyde	Amine	Product	Yield (%)
1	 (**1a**)	 (**2a**)		84 (**3a**)

Table 3. Continued

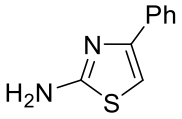
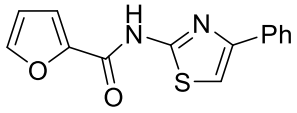
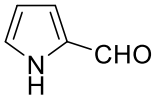
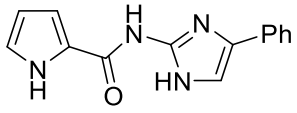
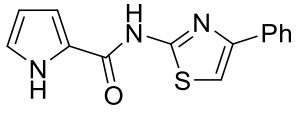
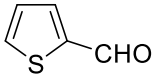
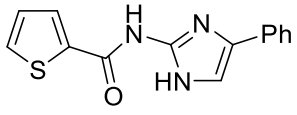
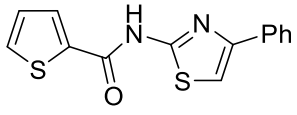
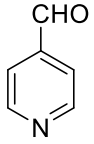
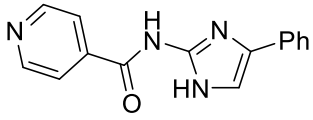
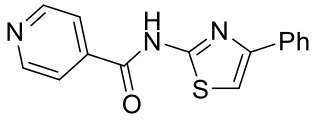
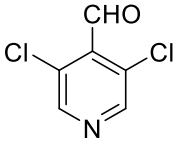
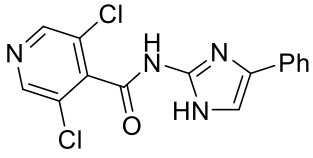
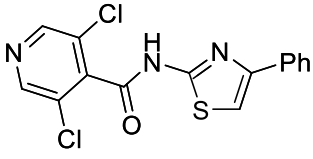
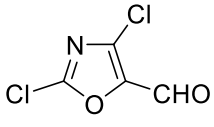
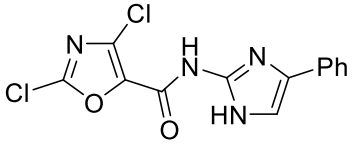
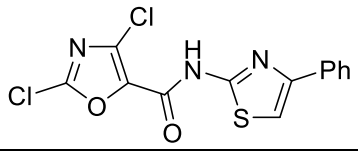
Entry	Aldehyde	Amine	Product	Yield (%)
2	**1a**	 (**2b**)		82 (**3b**)
3	 (**1b**)	**2a**		85 (**3c**)
4	**1b**	**2b**		84 (**3d**)
5	 **(1c)**	**2a**		83 (**3e**)
6	**1c**	**2b**		82 (**3f**)
7	 (**1d**)	**2a**		82 (**3g**)
8	**1d**	**2b**		83 (**3h**)
9	 (**1e**)	**2a**		91 (**3i**)
10	**1e**	**2b**		84 (**3j**)
11	 (**1f**)	**2a**		92 (**3k**)
12	**1f**	**2b**		90 (**3l**)

Table 3. Continued

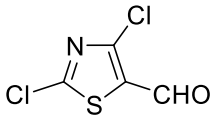
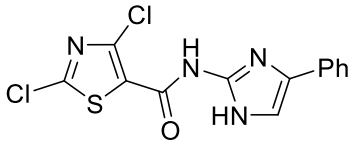
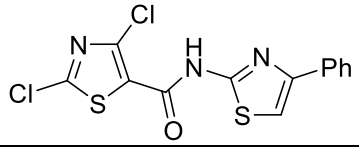
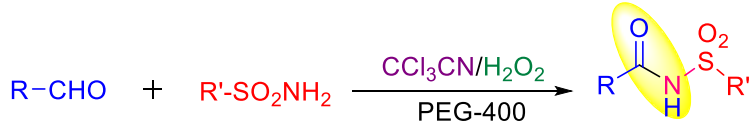
Entry	Aldehyde	Amine	Product	Yield (%)
13	 (**1g**)	**2a**		91 (**3m**)
14	**1g**	**2b**		89 (**3n**)

Table 4. Synthesis of heteroaryl sulfonyl carboxamides from heteroaldehydes and heteroaryl sulfonylamines



1 4 5

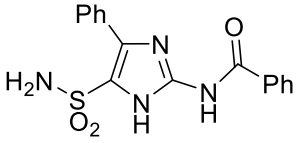
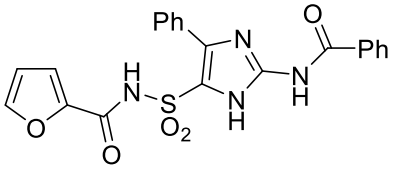
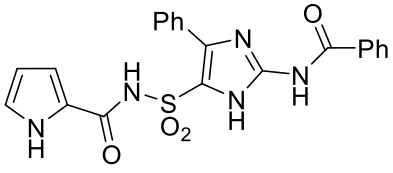
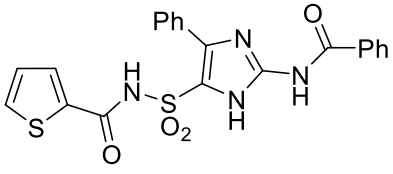
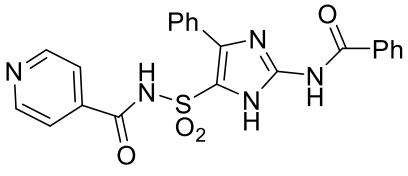
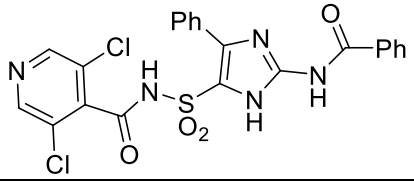
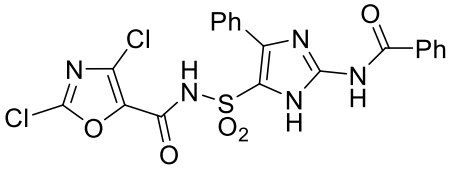
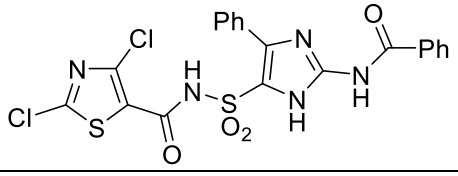
Entry	Aldehydes	Sulfonylamines	Products	Yield (%)
1	**1a**	 (**4**)		69 (**5a**)
2	**1b**	**4**		68 (**5b**)
3	**1c**	**4**		67 (**5c**)
4	**1d**	**4**		70 (**5d**)
5	**1e**	**4**		76 (**5e**)

Table 4. Continued

Entry	Aldehydes	Sulfonylamines	Products	Yield (%)
6	**1f**	**4**		74 (**5f**)
7	**1g**	**4**		75 (**5g**)

Conclusions

In conclusion we have reported a green protocol for direction amidation of heteroaldehydes with heteroaryl amines / sulfonylamines in the presence of oxidant CCl_3CN/H_2O_2 in PEG-400. The presence of electron withdrawing substituents on heteroaldehydes increased the yield. Further heteroaryl amines favor the reaction when compared with heteroaryl sulfonylamines.

Experimental Section

General. Melting points were determined in open capillaries on a Mel Temp apparatus and are uncorrected. The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were mentioned in cm^{-1}. The ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Jeol JNM spectrometer operating at 400 and 100 MHz. All chemical shifts are reported in δ(ppm) using TMS as an internal standard. High-Resolution Mass spectra were recorded on Micromass Q-TOF mass spectrometer using electrospray ionization. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The progress of the reaction was monitored by TLC using silica gel plates and components were visualized under UV light (254 and 365 nm).

General procedure for synthesis of amide from the reaction of aldehyde with amine. To a stirred solution of aldehyde (1 mmol), amine (1 mmol), CCl_3CN (2 mmol) in PEG-400 (5mL) at 0 °C, a solution of H_2O_2 (30%) (3mmol) was added drop wise. Then the reaction mixture was stirred at room temperature for 8-12 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into ice water (50 mL). The solid obtained was filtered, washed with water and crude product was purified by column chromatography (silica gel, 60-120 mesh) using hexane/ethylacetate (6:4) as eluent.

***N*-(4-Phenyl-1*H*-imidazol-2-yl)furan-2-carbo xamide (3a).** White solid. mp 215-217 °C. IR (KBr, ν_{max}, cm^{-1}): 1576 (C=N), 1609 (C=C), 1659 (CONH), 3357 (NH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.58 (t, 1H, C_4-H, *J* 5.2 Hz), 7.10 (s, 1H, $C_{5'}$-H), 7.38 (d, 1H, C_3-H, *J* 5.2 Hz), 7.62-7.83 (m, 5H, Ar-H), 7.98 (d, 1H, C_5-H, *J* 5.2 Hz), 8.96 (bs, 1H, O=C-NH), 12.44 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 112.5 (C-4), 114.1 (C-3), 121.3 (C-5'), 127.2, 128.5, 128.9, 133.2 (aromatic carbons), 141.2 (C-4'), 141.8 (C-5), 146.8 (C-2'), 147.2 (C-2), 157.4 (C=O). HRMS:

(*m/z*) 276.0760 $[M+Na]^+$. Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.46; H, 4.41; N, 16.66.

***N*-(4-Phenylthiazol-2-yl)furan-2-carboxamide (3b).** White solid. mp 219-221 °C. IR (KBr, ν_{max}, cm^{-1}): 1573 (C=N), 1603 (C=C), 1652 (CONH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.40 (t, 1H, C_4-H, *J* 4.6 Hz), 7.19 (s, 1H, $C_{5'}$-H), 7.45 (d, 1H, C_3-H, *J* 4.6 Hz), 7.52 (d, 1H, C_5-H, *J* 4.6 Hz), 7.54-7.87 (m, 5H, Ar-H), 10.28 (bs, 1H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 108.6 (C-5'), 111.9 (C-4), 113.6 (C-3), 127.8, 128.1, 130.3, 134.5 (aromatic carbons), 144.6 (C-5), 148.2 (C-2), 150.4 (C-4'), 156.2 (C-2'), 157.2 (C=O). HRMS: (*m/z*) 293.0372 $[M+Na]^+$. Anal. Calcd. for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36. Found: C, 62.29; H, 3.68; N, 10.48.

***N*-(4-Phenyl-1*H*-imidazol-2-yl)-1*H*-pyrrole-2-carboxamide (3c).** White solid. mp 214-216 °C. IR (KBr, ν_{max}, cm^{-1}): 1575 (C=N), 1605 (C=C), 1648 (CONH), 3349, 3335 (NH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.38 (t, 1H, C_4-H, *J* 4.8 Hz), 7.11 (s, 1H, $C_{5'}$-H), 7.45 (d, 1H, C_3-H, *J* 4.8 Hz), 7.49 (d, 1H, C_5-H, *J* 4.8 Hz), 7.52-7.65 (m, 5H, Ar-H), 9.73 (bs, 1H, CONH), 11.02 (bs, 1H, NH-pyrrole), 12.50 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 109.7 (C-4), 111.8 (C-3), 121.5 (C-5'), 122.8 (C-5), 125.9 (C-2), 127.5, 128.7, 129.2, 133.5 (aromatic carbons), 141.7 (C-4'), 147.1 (C-2'), 157.5 (C=O). HRMS: (*m/z*) 275.0919 $[M+Na]^+$. Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.58; H, 4.72; N, 22.34.

***N*-(4-Phenylthiazol-2-yl)-1*H*-pyrrole-2-carboxamide (3d).** White solid. mp 211-213 °C. IR (KBr, ν_{max}, cm^{-1}): 1568 (C=N), 1607 (C=C), 1646 (CONH), 3346 (NH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.41 (t, 1H, C_4-H, *J* 5.4 Hz), 7.18 (s, 1H, $C_{5'}$-H), 7.48 (d, 1H, C_3-H, *J* 5.4 Hz), 7.55 (d, 1H, C_5-H, *J* 5.4 Hz), 7.62-7.75 (m, 5H, Ar-H), 11.06 (bs, 1H, NH-pyrrole), 13.24 (bs, 1H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 108.1 (C-5'), 110.2 (C-4), 112.1 (C-3), 123.4 (C-5), 126.3 (C-2), 128.7, 129.7, 130.5, 134.5 (aromatic carbons), 150.8 (C-4'), 155.9 (C-2'), 157.7 (C=O). HRMS: (*m/z*) 292.0529 $[M+Na]^+$. Anal. Calcd. for $C_{14}H_{11}N_3OS$: C, 62.44; H, 4.12; N, 15.60. Found: C, 62.36; H, 4.08; N, 15.69.

***N*-(4-Phenyl-1*H*-imidazol-2-yl)thiophene-2-carboxamide (3e).** White solid. mp 226-228 °C. IR (KBr, ν_{max}, cm^{-1}): 1566 (C=N), 1599 (C=C), 1642 (CONH), 3342 (NH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.13 (s, 1H, $C_{5'}$-H), 7.16 (t, 1H, C_4-H, *J* 5.0 Hz), 7.53-7.68 (m, 5H, Ar-H), 7.97 (d, 1H, C_5-H, *J* 5.0 Hz), 8.28 (d, 1H, C_3-H, *J* 5.0 Hz), 9.18 (bs, 1H, CONH), 12.61 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 121.8 (C-5'), 127.7, 128.2, 128.9, 129.3, 129.7, 130.2, 133.9 (aromatic carbons, C-4, C-5, C-3), 139.7 (C-2), 140.7 (C-4'), 146.2 (C-2'), 157.1 (C=O). HRMS: (*m/z*) 292.0530 $[M+Na]^+$. Anal. Calcd. for $C_{14}H_{11}N_3OS$: C, 62.44; H, 4.12; N, 15.60. Found: C, 62.37; H, 4.16; N, 15.71.

***N*-(4-Phenylthiazol-2-yl)thiophene-2-carboxamide (3f).** White solid. mp 223-225 °C. IR (KBr, ν_{max}, cm^{-1}): 1562 (C=N), 1595 (C=C), 1638 (CONH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.19 (t, 1H, C_4-H, *J* 4.4 Hz), 7.21 (s, 1H, $C_{5'}$-H), 7.56-7.81 (m, 5H, Ar-H), 8.01 (d, 1H, C_5-H, *J* 4.4 Hz), 8.32 (d, 1H, C_3-H, *J* 4.4 Hz), 10.27 (bs, 1H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 122.8 (C-5'), 128.4, 129.1, 130.4, 131.2, 131.7, 132.1, 133.2 (aromatic carbons, C-4, C-5, C-3), 140.1 (C-2), 140.9 (C-4'), 146.5 (C-2'), 157.8 (C=O). HRMS: (*m/z*) 309.0124 $[M+Na]^+$. Anal. Calcd. for $C_{14}H_{10}N_2OS_2$: C, 58.72; H, 3.52; N, 9.78. Found: C, 58.80; H, 3.57; N, 9.68.

***N*-(4-Phenyl-1*H*-imidazol-2-yl)isonicotinamide (3g).** White solid. mp 218-220 °C. IR (KBr, ν_{max}, cm^{-1}): 1578 (C=N), 1612 (C=C), 1664 (CONH), 3364 (NH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.15 (s, 1H, $C_{5'}$-H), 7.61-7.69 (m, 5H, Ar-H), 8.02 (d, 2H, C_3-H, C_5-H, *J* 5.6 Hz), 8.84 (d, 2H, C_2-H, C_6-H, *J* 5.6 Hz), 10.88 (bs, 1H, CONH), 12.53 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 121.6 (C-3, C-5), 122.1 (C-5'), 128.8, 129.6, 130.4, 134.1 (aromatic carbons), 140.6 (C-4), 142.7 (C-4'), 147.9 (C-2'), 149.8 (C-2, C-6), 164.3 (C=O). HRMS: (*m/z*) 287.0920 $[M+Na]^+$. Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.24; H, 4.56; N, 21.29.

***N*-(4-Phenylthiazol-2-yl)isonicotinamide (3h).** White solid. mp 225-227 °C. IR (KBr, ν_{max}, cm^{-1}): 1569 (C=N), 1610 (C=C), 1658 (CONH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.18 (s, 1H, $C_{5'}$-H), 7.49-7.75 (m, 5H, Ar-H), 8.05 (d, 2H, C_3-H, C_5-H, *J* 5.2 Hz), 9.06 (d, 2H, C_2-H, C_6-H, *J* 5.2 Hz), 12.74 (bs, 1H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 122.1 (C-3, C-5), 123.4 (C-5'), 129.5, 129.8 130.2, 134.4 (aromatic carbons), 141.4 (C-4), 143.1 (C-4'), 148.1 (C-2'), 148.7

(C-2, C-6), 164.6 (C=O). HRMS: (*m/z*) 304.0533 $[M+Na]^+$. Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94. Found: C, 64.15; H, 3.98; N, 14.81.

3,5-Dichloro-*N*-(4-phenyl-1*H*-imidazol-2-yl)isonicotinamide (3i). White solid. mp 234-236 °C. IR (KBr, ν_{max}, cm^{-1}): 1582 (C=N), 1619 (C=C), 1672 (CONH), 3366 (NH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.17 (s, 1H, $C_{5'}$-H), 7.60-7.73 (m, 5H, Ar-H), 9.28 (s, 2H, C_2-H, C_6-H), 11.05 (bs, 1H, CONH), 12.57 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 122.4 (C-5'), 128.2, 129.6, 131.8, 132.7 134.3 (aromatic carbons, C-3, C-5), 142.3 (C-4), 143.4 (C-4'), 148.2 (C-2, C-6), 148.6 (C-2'), 164.8 (C=O). HRMS: (*m/z*) 355.0122 $[M+Na]^+$. Anal. Calcd. for $C_{15}H_{10}Cl_2N_4O$: C, 54.08; H, 3.03; N, 16.82. Found: C, 54.02; H, 3.00; N, 16.93.

3,5-Dichloro-*N*-(4-phenylthiazol-2-yl)isonicotinamide (3j). White solid. mp 238-240 °C. IR (KBr, ν_{max}, cm^{-1}): 1579 (C=N), 1617 (C=C), 1666 (CONH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.24 (s, 1H, $C_{5'}$-H), 7.66-7.88 (m, 5H, Ar-H), 9.31 (s, 2H, C_2-H, C_6-H), 13.04 (bs, 1H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 109.1 (C-5'), 129.2, 130.1, 130.9, 133.3, 134.9 (aromatic carbons, C-3, C-5), 142.8 (C-4), 148.5 (C-2, C-6), 151.9 (C-4'), 157.1 (C-2'), 165.0 (C=O). HRMS: (*m/z*) 344.0341 $[M+Na]^+$. Anal. Calcd. for $C_{15}H_9Cl_2N_3O$: C, 51.44; H, 2.59; N, 12.00. Found: C, 51.52; H, 2.64; N, 11.91.

2,4-Dichloro-*N*-(4-phenyl-1*H*-imidazol-2-yl)oxazole-5-carboxamide (3k). White solid. mp 213-215 °C. IR (KBr, ν_{max}, cm^{-1}): 1588 (C=N), 1629 (C=C), 1672 (CONH), 3391 (NH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.20 (s, 1H, $C_{5'}$-H), 7.61-7.78 (m, 5H, Ar-H), 9.27 (bs, 1H, CONH), 12.62 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 122.9 (C-5'), 124.9 (C-4), 127.4, 128.5, 129.9, 134.7 (aromatic carbons), 138.4 (C-5), 144.5 (C-4'), 149.7 (C-2'), 151.3 (C-2), 165.4 (C=O). HRMS: (*m/z*) 344.9929 $[M+Na]^+$. Anal. Calcd. for $C_{13}H_8Cl_2N_4O_2$: C, 48.32; H, 2.50; N, 17.34. Found: C, 48.37; H, 2.54; N, 17.24.

2,4-Dichloro-*N*-(4-phenylthiazol-2-yl)oxazole-5-carboxamide (3l). White solid. mp 229-231 °C. IR (KBr, ν_{max}, cm^{-1}): 1584 (C=N), 1627 (C=C), 1667 (CONH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.29 (s, 1H, $C_{5'}$-H), 7.68-7.87 (m, 5H, Ar-H), 12.68 (bs, 1H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 109.9 (C-5'), 125.3 (C-4), 129.5, 130.4, 130.9, 135.2 (aromatic carbons), 138.9 (C-5), 151.7 (C-2), 152.8 (C-4'), 158.3 (C-2'), 165.7 (C=O). HRMS: (*m/z*) 361.9543 $[M+Na]^+$. Anal. Calcd. for $C_{13}H_7Cl_2N_3O_2S$: C, 45.90; H, 2.07; N, 12.35. Found: C, 45.98; H, 2.10; N, 12.43.

2,4-Dichloro-*N*-(4-phenyl-1*H*-imidazol-2-yl)thiazole-5-carboxamide (3m). White solid. mp 233-235 °C. IR (KBr, ν_{max}, cm^{-1}): 1587 (C=N), 1625 (C=C), 1664 (CONH), 3382 (NH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.25 (s, 1H, $C_{5'}$-H), 7.67-7.83 (m, 5H, Ar-H), 9.23 (bs, 1H, CONH), 12.68 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 123.7 (C-5'), 128.9, 130.3, 131.4, 134.9, 135.4 (aromatic carbons, C-4), 144.6 (C-4'), 149.1 (C-5), 150.1 (C-2'), 153.4 (C-2), 161.4 (C=O). HRMS: (*m/z*) 360.9687 $[M+Na]^+$. Anal. Calcd. for $C_{13}H_8Cl_2N_4OS$: C, 46.03; H, 2.38; N, 16.52. Found: C, 46.08; H, 2.42; N, 16.40.

2,4-Dichloro-*N*-(4-phenylthiazol-2-yl)thiazole-5-carboxamide (3n). White solid. mp 221-223 °C. IR (KBr, ν_{max}, cm^{-1}): 1581 (C=N), 1621 (C=C), 1660 (CONH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.37 (s, 1H, $C_{5'}$-H), 7.72-7.91 (m, 5H, Ar-H), 12.64 (bs, 1H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 111.1 (C-5'), 130.1, 130.9, 131.4, 134.5, 135.7 (aromatic carbons, C-4), 149.2 (C-5), 152.9 (C-4'), 153.6 (C-2), 157.8 (C-2'), 161.7 (C=O). HRMS: (*m/z*) 377.9317 $[M+Na]^+$. Anal. Calcd. for $C_{13}H_7Cl_2N_3OS_2$: C, 43.83; H, 1.98; N, 11.80. Found: C, 43.75; H, 1.92; N, 11.89.

***N*-((2-Benzamido-4-phenyl-1*H*-imidazol-5-yl)sulfonyl)furan-2-carboxamide (5a).** Pale yellow solid. mp 245-247 °C. IR (KBr, ν_{max}, cm^{-1}): 1120, 1318 (SO_2), 1594 (C=N), 1640 (C=C), 1651, 1668 (CONH), 3382 (NH). ^1H NMR (400 MHz, DMSO-d_6): δ_H 6.63 (t, 1H, C_4-H, *J* 4.8 Hz), 7.46 (d, 1H, C_3-H, *J* 4.8 Hz), 7.56-7.66 (m, 10H, Ar-H), 8.01 (d, 1H, C_5-H, *J* 4.8 Hz), 11.04 (bs, 1H, CONH), 11.19 (bs, 1H, $NHSO_2$), 12.52 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 113.2 (C-4), 114.4 (C-3), 127.1, 127.8, 128.1, 129.1. 129.5, 130.3, 130.7, 133.3, 135.5 (aromatic carbons, C-5'), 138.5 (C-4'), 142.5 (C-5), 147.8 (C-2), 152.9 (C-2'), 160.1 (CONH), 161.3 ($CONHSO_2$). HRMS: (*m/z*) 459.0731 $[M+Na]^+$. Anal. Calcd. for $C_{21}H_{16}N_4O_5S$: C, 57.79; H, 3.70; N, 12.84. Found: C, 57.85; H, 3.76; N, 12.91.

***N*-((2-Benzamido-4-phenyl-1*H*-imidazol-5-yl)sulfonyl)-1*H*-pyrrole-2-carboxamide (5b).** Pale yellow solid. mp 241-243 °C. IR (KBr, ν_{max}, cm^{-1}): 1123, 1321 (SO_2), 1591 (C=N), 1635 (C=C), 1654, 1663 (CONH), 3354, 3368 (NH). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.42 (t, 1H, C_4-H, *J* 5.2 Hz), 7.49 (d, 1H, C_3-H, *J* 5.2 Hz), 7.58 (d, 1H, C_5-H, *J* 5.2 Hz), 7.64-8.01 (m, 10H, Ar-H), 11.07 (bs, 1H, NH-pyrrole), 11.11 (bs, 1H, CONH), 12.32 (bs, 1H, $NHSO_2$), 12.55 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 110.6 (C-4), 112.1 (C-3), 123.4 (C-5), 126.3 (C-2), 127.5, 127.9, 128.6, 128.9, 129.4, 131.2, 131.5, 133.1, 134.7 (aromatic carbons, C-5'), 138.9 (C-4'), 153.6 (C-2'), 160.5 (CONH), 162.8 ($CONHSO_2$). HRMS: (*m/z*) 458.0890 $[M+Na]^+$. Anal. Calcd. for $C_{21}H_{17}N_5O_4S$: C, 57.92; H, 3.94; N, 16.08. Found: C, 57.99; H, 4.00; N, 16.15.

***N*-((2-Benzamido-4-phenyl-1*H*-imidazol-5-yl)sulfonyl)thiophene-2-carboxamide (5c).** Pale yellow solid. mp 239-241 °C. IR (KBr, ν_{max}, cm^{-1}): 1131, 1325 (SO_2), 1589 (C=N), 1631 (C=C), 1658, 1661 (CONH), 3361 (NH). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.19 (t, 1H, C_4-H, *J* 5.6 Hz), 7.61-7.85 (m, 10H, Ar-H), 7.99 (d, 1H, C_5-H, *J* 5.6 Hz), 8.31 (d, 1H, C_3-H, *J* 5.6 Hz), 11.15 (bs, 1H, CONH), 11.78 (bs, 1H, $NHSO_2$), 12.65 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 126.9 (C-3), 127.3, 127.9, 128.3, 128.7, 129.1, 130.3, 130.9, 131.2, 132.7, 133.5, 134.2 (aromatic carbons, C-4, C-5, C-5'), 138.7 (C-4'), 140.5 (C-2), 153.1 (C-2'), 159.7 (CONH), 161.4 ($CONHSO_2$). HRMS: (*m/z*) 475.0519 $[M+Na]^+$. Anal. Calcd. for $C_{21}H_{16}N_4O_4S_2$: C, 55.74; H, 3.56; N, 12.38. Found: C, 55.79; H, 3.61; N, 12.43.

***N*-((2-Benzamido-4-phenyl-1*H*-imidazol-5-yl)sulfonyl)isonicotinamide (5d).** Pale yellow solid. mp 246-248 °C. IR (KBr, ν_{max}, cm^{-1}): 1134, 1327 (SO_2), 1598 (C=N), 1641 (C=C), 1662, 1670 (CONH), 3389 (NH). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.70-8.02 (m, 10H, Ar-H), 8.05 (d, 2H, C_3-H, C_5-H, *J* 5.3 Hz), 8.89 (d, 2H, C_2-H, C_6-H, *J* 5.3 Hz), 11.18 (bs, 1H, CONH), 11.85 (bs, 1H, $NHSO_2$), 12.61 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 123.1 (C-3, C-5), 127.4, 127.9, 128.0, 128.1, 129.8, 131.5, 132.4, 133.4, 134.9 (aromatic carbons, C-5'), 140.3 (C-4'), 141.8 (C-4), 150.4 (C-2, C-6), 154.5 (C-2'), 165.2 (CONH), 166.7 ($CONHSO_2$). HRMS: (*m/z*) 470.0881 $[M+Na]^+$. Anal. Calcd. for $C_{22}H_{17}N_5O_4S$: C, 59.05; H, 3.83; N, 15.65. Found: C, 59.11; H, 3.80; N, 15.73.

***N*-((2-Benzamido-4-phenyl-1*H*-imidazol-5-yl)sulfonyl)-3,5-dichloroisonicotinamide (5e).** Pale yellow solid. mp 264-266 °C. IR (KBr, ν_{max}, cm^{-1}): 1129, 1332 (SO_2), 1601 (C=N), 1645 (C=C), 1668, 1679 (CONH), 3390 (NH). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.74-8.11 (m, 10H, Ar-H), 9.32 (s, 2H, C_2-H, C_6-H), 11.24 (bs, 1H, CONH), 11.88 (bs, 1H, $NHSO_2$), 12.67 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 127.5, 127.9, 128.2, 128.6, 128.9, 129.5, 130.0, 131.9, 133.7, 134.1, 134.5 (aromatic carbons, C-3, C-5, C-5'), 141.1 (C-4'), 143.9 (C-4), 148.7 (C-2, C-6), 156.1 (C-2'), 165.6 (CONH), 167.1 ($CONHSO_2$). HRMS: (*m/z*) 538.0128 $[M+Na]^+$. Anal. Calcd. for $C_{22}H_{15}Cl_2N_5O_4S$: C, 51.17; H, 2.93; N, 13.56. Found: C, 51.24; H, 2.99; N, 13.50.

***N*-((2-Benzamido-4-phenyl-1*H*-imidazol-5-yl)sulfonyl)-2,4-dichlorooxazole-5-carboxamide (5f).** Pale yellow solid. mp 258-260 °C. IR (KBr, ν_{max}, cm^{-1}): 1142, 1342 (SO_2), 1608 (C=N), 1648 (C=C), 1678, 1685 (CONH), 3398 (NH) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.76-8.13 (m, 10H, Ar-H), 11.23 (bs, 1H, CONH), 11.94 (bs, 1H, $NHSO_2$), 12.70 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 126.8 (C-4), 127.6, 127.9, 128.6, 129.1, 129.6, 130.7, 134.6, 134.9, 135.4 (aromatic carbons, C-5'), 140.2 (C-5), 142.6 (C-4'), 153.3 (C-2), 153.9 (C-2'), 166.1 (CONH), 167.9 ($CONHSO_2$). HRMS: (*m/z*) 527.9921 $[M+Na]^+$. Anal. Calcd. for $C_{20}H_{13}Cl_2N_5O_5S$: C, 47.44; H, 2.59; N, 13.83. Found: C, 47.51; H, 2.55; N, 13.89.

***N*-((2-Benzamido-4-phenyl-1*H*-imidazol-5-yl)sulfonyl)-2,4-dichlorothiazole-5-carboxamide (5g).** Pale yellow solid. mp 270-272 °C. IR (KBr, ν_{max}, cm^{-1}): 1139, 1335 (SO_2), 1605 (C=N), 1642 (C=C), 1680, 1681 (CONH), 3395 (NH). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.85-8.07 (m, 10H, Ar-H), 11.28 (bs, 1H, CONH), 12.05 (bs, 1H, $NHSO_2$), 12.74 (bs, 1H, NH-imidazole). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 127.3, 127.9, 128.2, 128.6, 129.0, 129.4, 130.9, 131.8, 135.1, 135.5 (aromatic carbons, C-5, C-5'), 139.2 (C-4), 139.4 (C-4'), 145.7 (C-2), 153.9 (C-2'), 162.8 (CONH), 164.2 ($CONHSO_2$). HRMS: (*m/z*) 543.9693 $[M+Na]^+$. Anal. Calcd. for $C_{20}H_{13}Cl_2N_4O_5S_2$: C, 45.99; H, 2.51; N, 13.41. Found: C, 45.94; H, 2.57; N, 13.46.

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Supplementary Material

^{1}H NMR, ^{13}C NMR and HRMS Spectra for compounds *N*-(4-phenyl-1*H*-imidazol-2-yl)furan-2-carboxamide (**3a**), *N*-(4-phenyl-1*H*-imidazol-2-yl)isonicotinamide (**3g**), *N*-((2-benzamido-4-phenyl-1*H*-imidazol-5-yl)sulfonyl)furan-2-carboxamide (**5a**) and *N*-((2-Benzamido-4-phenyl-1*H*-imidazol-5-yl)sulfonyl)-2,4-dichlorothiazole-5-carboxamide (**5g**) can be found using the link "Supplementary Material" in the journal issue contents page.

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