A FACILE AND CONVENIENT ACCESS FOR THE SYNTHESIS OF PHARMACOLOGICALLY RELEVANT IMIDAZOLYL BENZAMIDES CONTAINING UREA

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Abstract: In this paper, we report an efficient protocol for the synthesis of some pharmacologically relevant imidazolyl benzamides containing urea. The reaction of Boc protected ethylene diammine with imidazolyl benzoic acid and its subsequent treatment with different isocyanates in dichloromethane (DCM) as solvent rendered the desired products in excellent yields. The salient features of the developed methodology include high yield, no hectic purification processes and room temperature reaction conditions.

Index Terms **- Imidazole, benzamide, urea.**

I. INTRODUCTION

The origin of discovery of new leads in a drug designing program is the synthesis of different series of molecules, which are novel yet resemble known biologically active molecules by the virtue of existence of some critical structural features in them. Several small heterocyclic molecules may act as highly functionalized scaffolds and are known pharmacophores for the development of medicinally relevant molecules [1]. As a result of this, the synthesis of diverse heterocyclic compounds has been the main area of research for the last six decades. Nevertheless, there exist many unexplored areas in this field so far even after modern technological advancements which reveal the need for continuous research and development in this arena [2].

The chemistry of heterocyclic compounds is one of the most complex and attractive branch of medicinal chemistry, of equal interest on account of its theoretical implications as well as its significance in pharmacological and industrial applications [3]. Since the last 40 years, rapid progress in medicinal chemistry is associated with the quest for new target compounds with desired pharmaceutical applications. Among these, the heterocyclic compounds form the largest of the classical division of organic chemistry and are of tremendous biological and industrial importance. The heterocyclic systems serve as important pharmacophores in the development of drugs for various diseases. Hence, the synthesis and examination of biological activities of novel heterocyclic compounds is increasingly becoming important in medicinal chemistry [4]. Among the various heterocyclic molecules, imidazole based compounds are widely reported to be active as antibacterial, antifungal, antihistamine, antitubercular and antiviral agents [5]. In the design and development of novel drugs, the role of amides and urea as linkers are well documented in literature [6]. For example, the o-acetamide substituted 4-hydroxy and 7-hydroxy coumarins are reported to possess anti-acetyl cholinesterase activity that is considered as a promising approach for the treatment of Alzheimer's disease [7,8]. Furthermore, the

carboxamide derivatives of coumarins and imidazoles are reported to possess significant antibacterial and anticancer activity [9,10].

In recent days, molecular hybridization is a very effective strategy developed by organic chemists for the development of novel therapeutic agents. Molecular hybridization involves the combination of two-three biologically relevant or active organic fragments into a single drug like molecule by employing modern synthetic methodologies [11]. By this approach, the overall activity of the new hybrid molecule will be improved considerably by virtue of the presence of two or three inherently active substituents in it. Since the combination of two or more pharmacophores on the same scaffold is a well established approach to more potent drugs and inspired by the profound activity profile of imidazoles, urea and amides, we focused our attention in the synthesis of some pharmacologically relevant imidazolyl benzamides containing urea as a linker. In this paper, we report our convenient and efficient approach towards the synthesis of some novel pharmacologically relevant imidazolyl benzamides linked with urea.

II. MATERIALS AND METHODS

2.1. General considerations

All chemicals and analytical reagents were purchased from commercial suppliers and used directly as delivered, unless otherwise noted. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively using an internal deuterium lock, the chemical shifts are reported in parts per million (ppm) and coupling constants in Hertz (Hz). Tetramethylsilane (TMS) (δ = 0.00 ppm) served as internal standard for recording. Molecular weights of unknown compounds were analyzed by High Resolution Mass Spectrometry (HRMS) in Q-TOF (Micromass) spectrometer by employing electron spray ionization method. Melting points of the compounds were determined on Buchi melting point apparatus.

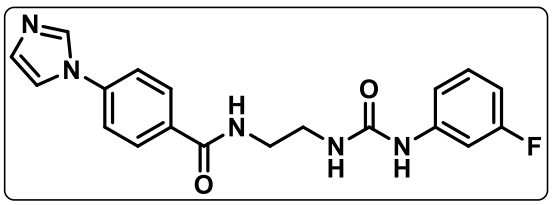
2.2. Procedure for the synthesis of intermediate 2

To the weighed quantity of 4-(1H-imidazol-1-yl)benzoic acid **1** (1 equiv.) in DCM (5 mL), HATU (1.1 equiv.), Diisopropyl ethyl amine (DIPEA) (1.5 equiv.) and Boc protected ethylene diamine (1.2 equiv.) was added and the reaction mixture was stirred at RT for 3 hours. The reaction completion was monitored by TLC. After the complete consumption of starting material, HCl in dioxane was added at 0°C and the reaction mixture was stirred for another 2 hours. The temperature of the reaction vessel was gradually brought down to RT. After 2h, the solvent was distilled under reduced pressure and the obtained salt/solid **2** was used for next step without any purification.

2.3. Procedure for the synthesis of final products 3a-e

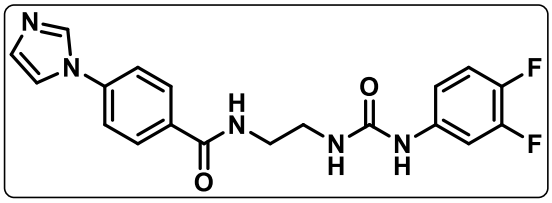
To the weighed quantity of amine salt **2** (1 equiv.) in DCM (3 mL), different isocyanates (1.2 equiv.) was added at inert atmosphere and the reaction mixture was stirred at RT for 12 hours. The completion of the reaction was monitored by TLC from time to time. After the completion of reaction, the reaction mixture was washed with water, sodium bicarbonate solution and brine. The organic layer was distilled under reduced pressure and is recrystallized from ethanol to furnish the titled compounds **3a-e**.

2.3.1. N-(2-(3-(3-Fluorophenyl)ureido)ethyl)-4-(1H-imidazol-1-yl)benzamide (3a)



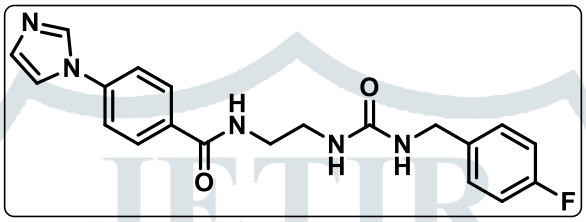
White solid: mp 154-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.52, t,2H,CH_2; δ 4.01, t,2H,CH_2; δ 7.00, d, *J*=8 Hz,1H,ArH; δ 7.12-7.18, m,2H,ArH; δ 7.20-7.26, m,2H,ArH; δ 7.38-7.48, m,3H,ArH; δ 7.95, s,1H,ArH; δ 8.02, d, *J*=8 Hz,2H,ArH; δ 8.18, br,1H,NH; δ 8.33, br,1H,NH;δ 10.46, br,1H,NH; ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.5, CH_2, δ 39.1, CH_2, δ 97.8, δ 117.9, δ 118.4, δ 120.7, δ 128.8, δ 129.1, δ 131.0, δ 133.2, δ 139.2, δ 141.4, δ 150.9, δ 152.5, δ 157.2, δ 158.5, δ 161.8, CO, δ 164.2, CO, δ 166.4,CF; HRMS: Calculated 368.1523 (M+H), Observed 368.151.

2.3.2. N-(2-(3-(3,4-difluorophenyl)ureido)ethyl)-4-(1H-imidazol-1-yl)benzamide (3b)



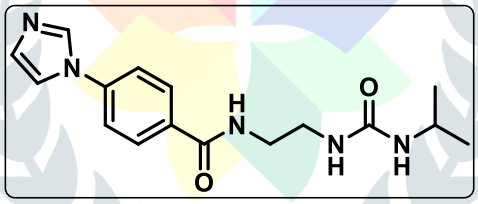
Off white solid: mp 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.54, t,2H,CH_2; δ 4.02, t,2H,CH_2; δ 7.13-7.22, m,2H,ArH; δ 7.21-7.25, m,2H,ArH; δ 7.41-7.49, m,3H,ArH; δ 7.98, s,1H,ArH; δ 8.03, d, *J*=8 Hz,2H,ArH; δ 8.19, br,1H,NH; δ 8.35, br,1H,NH;δ 10.49, br,1H,NH; ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.6, CH_2, δ 39.3, CH_2, δ 98.0, δ 117.9, δ 118.7, δ 120.9, δ 128.9, δ 129.3, δ 131.2, δ 133.5, δ 139.3, δ 141.7, δ 151.1, δ 152.6, δ 158.7, δ 159.5, δ 161.9, CO, δ 164.4, CO, δ 166.7,CF; HRMS: Calculated 386.1429 (M+H), Observed 386.1425.

2.3.3. N-(2-(3-(4-Fluorobenzyl)ureido)ethyl)-4-(1H-imidazol-1-yl)benzamide (3c)



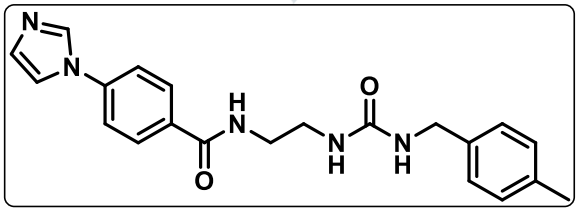
Light yellow solid: mp 159-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.51, t,2H,CH_2; δ 3.99, t,2H,CH_2; δ 4.33, s,2H,CH_2; δ 7.09-7.14, m,3H,ArH; δ 7.19-7.23, m,2H,ArH; δ 7.38-7.44, m,3H,ArH; δ 7.99, s,1H,ArH; δ 8.01, d, *J*=8 Hz,2H,ArH; δ 8.16, br,1H,NH; δ 8.31, br,1H,NH;δ 10.42, br,1H,NH; ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.2, CH_2, δ 39.0, CH_2, δ 44.3, CH_2, δ 98.2, δ 117.8, δ 120.6, δ 128.5, δ 129.1, δ 133.4, δ 139.2, δ 141.4, δ 151.0, δ 152.2, δ 158.3, δ 159.3, δ 161.6, CO, δ 164.2, CO, δ 166.4,CF; HRMS: Calculated 382.1679 (M+H), Observed 382.1677.

2.3.4. 4-(1H-Imidazol-1-yl)-N-(2-(3-isopropylureido)ethyl)benzamide (3d)



Light green solid: mp 133-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 1.54, d,6H,CH_3; δ 3.53, t,2H,CH_2; δ 4.04, t,2H,CH_2; δ 4.32, m,1H,CH; δ 7.15-7.23, m,4H,ArH; δ 7.20-7.23, m,2H,ArH; δ 7.93, s,1H,ArH; δ 8.16, br,1H,NH; δ 8.32, br,1H,NH;δ 10.45, br,1H,NH; ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.6, CH_3, δ 36.5, CH_2, δ 39.4, CH_2, δ 42.7, CH, δ 98.6, δ 118.2, δ 121.3, δ 129.2, δ 131.4, δ 139.3, δ 141.2, δ 151.3, δ 152.2, δ 161.7, CO, δ 164.1, CO; HRMS: Calculated 316.1773 (M+H), Observed 316.1775.

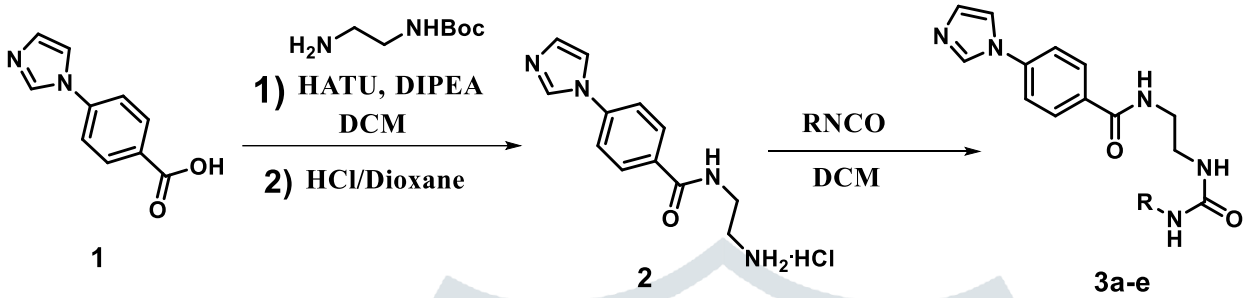
2.3.5. 4-(1H-Imidazol-1-yl)-N-(2-(3-(4-methylbenzyl)ureido)ethyl)benzamide (3e)



Brown solid: mp 150-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.42, s,3H,CH_3; δ 3.52, t,2H,CH_2; δ 4.01, t,2H,CH_2; δ 4.31, s,2H,CH_2; δ 7.11-7.16, m,3H,ArH; δ 7.17-7.20, m,2H,ArH; δ 7.35-7.40, m,3H,ArH; δ 8.02, s,1H,ArH; δ 8.03, d, *J*=8 Hz,2H,ArH; δ 8.18, br,1H,NH; δ 8.32, br,1H,NH; δ 10.44, br,1H,NH; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.2, CH_3, δ 36.4, CH_2, δ 39.1, CH_2, δ 44.7, CH_2, δ 98.4, δ 117.9, δ 120.8, δ 123.3, δ 128.3, δ 129.4, δ 133.1, δ 139.6, δ 141.7, δ 151.2, δ 152.5, δ 158.6, δ 159.8, δ 161.7, CO, δ 164.4, CO; HRMS: Calculated 378.1930 (M+H), Observed 378.1932.

III. RESULTS AND DISCUSSION

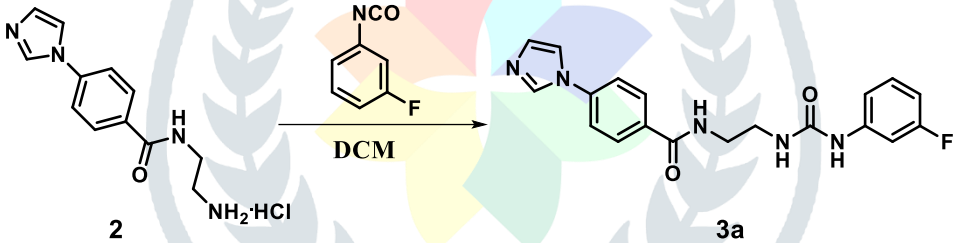
The synthetic route for the targeted compounds was initiated by taking 1H-imidazolyl-4-benzoic acid **1** as the starting material that was purchased commercially from external vendors (**Scheme 1**). The starting material **1** was subjected to peptide coupling reaction with Boc protected ethylene diamine by taking HATU as the coupling reagent and diisopropyl ethyl amine (DIPEA) as base in Dichloromethane (DCM). The deprotection of the Boc group was done in the same reaction vessel by adding HCl in dioxane to the reaction mixture to procure the amide intermediate **2** as HCl salt. The amide intermediate **2** was then planned to treat with different isocyanates in view of synthesizing some imidazolyl benzamides of considerable pharmacological relevance.



Scheme 1: Synthesis of imidazolyl benzamides **3a-e**

As a model reaction, we screened the reaction of *m*-fluoro phenyl isocyanate with the amine intermediate **2** in order to optimize the best reaction conditions that will furnish the final product **3a** in excellent yield (Table 1). We screened different solvents at varying reaction times and identified that DCM is a better solvent that DMF and dioxane (Table 1, Entries 1-3). The optimum time for the reaction was found to be 12 hours (Table 1, Entry 5).

Table 1: Optimization of reaction conditions[a]

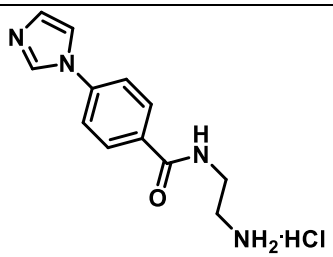
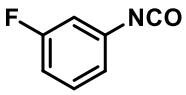
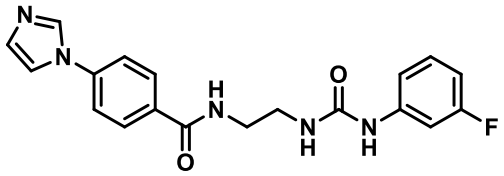
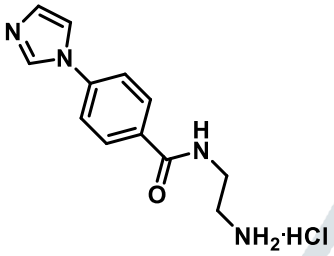
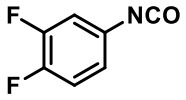
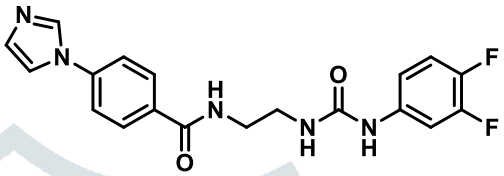
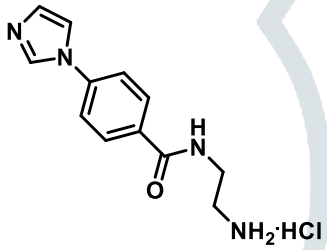
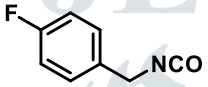
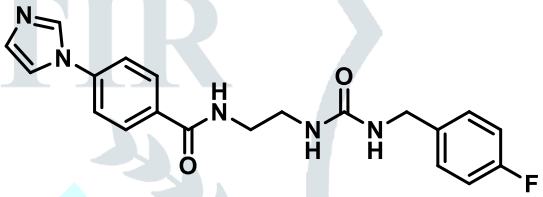
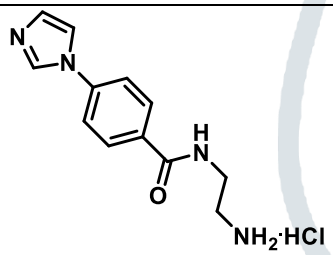
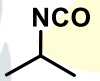
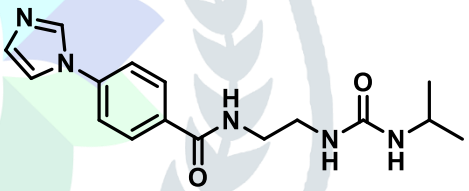
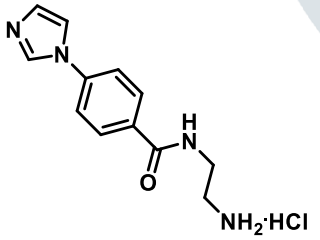
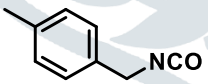
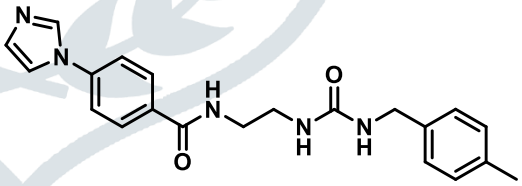


Entry	Solvent	Time (h)	Yield[b] 3a (%)
1	DMF	6	40
2	Dioxane	6	42
3	DCM	6	78
4	DCM	9	85
5	DCM	12	92

[a]Reaction conditions: Amine salt **2** (1 mmol), m-fluoro phenyl isocyanate (1.1 mmol), solvent (3 mL), RT.
[b] Isolated yield.

After establishing the optimum conditions for the reaction, our next attention was to identify the scope of the developed protocol. Keeping this in mind, we screened the reaction different isocyanates with amine intermediate **2** in DCM as solvent for 12 hours (Table 2). To our delight, all the isocyanates reacted well to render the final products **3a-e** in good to excellent yields. The aromatic isocyanates reacted well efficiently to procure the final imidazolyl benzamides in excellent yields (Table 2, Entrie 1,2,3 and 5). Aliphatic isocyanate reacted a little sluggishly to furnish the corresponding product (Table 2, Entry 4). All the newly synthesized compounds were characterized by Nuclear Magnetic Resonance (NMR) spectroscopy and High Resolution Mass Spectrometry (HRMS).

Table 2: Structure of intermediates and final compounds **3a-e**[a]

Sl. No	Substrate	Isocyanate	Product	Yield[b] (%)
1			 **3a**	92
2			 **3b**	95
3			 **3c**	97
4			 **3d**	87
5			 **3e**	93

[a] Reaction conditions: Amine intermediate **2** (1 mmol), isocyanate (1.1 mmol), DCM, 12h, RT.
[b] Isolated yield.

The ^{1}H and ^{13}C NMR spectrum of **3a** was taken in a mixture of duteriated $CDCl_3$ and DMSO as solvent at room temperature by using Tetramethyl silane (TMS) as the internal standard. In the ^{1}H NMR spectrum of **3a**, the methylene protons (CH_2) were found as triplets at chemical shift (δ) 3.52 and 4.01 ppm respectively. The 13 aromatic protons were observed between δ 6.99 and 8.03 ppm and the two NH groups of urea were found as singlet at δ 8.33 and 8.18 ppm respectively. The proton corresponding to benzamide (CONH) resonated as singlet at δ 10.46 ppm. In the ^{13}C NMR spectrum of **3a**, the methylene carbons (CH_2) were observed at δ 36.5 and 39.1 ppm respectively. The aromatic carbon atoms resonated between δ 97.8 and 158.5 ppm and the three carbonyl (CO) groups of urea and benzamide were found at δ 161.8, 164.2 and 166.4 ppm respectively.

IV. CONCLUSION

In summary, we have developed a rapid and convenient access for the synthesis of some pharmacologically relevant imidazolyl benzamides containing urea. The utilization of different isocyanates in DCM was proved to be the key for success of the reaction. This method reduces the risk of high temperature reactions and hence the mild protocol reported here can be extended for the synthesis of other urea containing amides in future.

V. ACKNOWLEDGEMENTS

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