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Synthesis, Characterization of Various Substituted (E)-2-(2-butyl-5-chloro-4-((phenylimino)methyl)-1H-imidazol-1-yl)-N-(4-(3-oxomorpholino) phenyl)acetamide

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Abstract

A highly efficient, convergent approach to the synthesis of various substituted (E)-2-(2-butyl-5-chloro-4-((phenylimino)methyl)-1H-imidazol-1-yl)-N-(4-(3-oxomorpholino)phenyl) acetamide analogues is described. Directed vilsmeyer formylation of methyl pentanimidate with glycine provides the key intermediate 2-butyl-5-chloro-1H-imidazole-4- carbaldehyde (INT-01). BCFI (INT-01) is a major active metabolite and the most significant intermediate of Losartan. Therefore, BCFI moiety has scope for good application in medicine. Morpholin-3-one derivative reacts with chloroacetyl chloride in presence of acetonitrile provides 2-chloro-N-(4-(3-oxomorpholino)phenyl)acetamide (INT-02). Reflux INT-01 with INT-02 in presence of acetonitrile and potassium carbonate allowed the preparation of the 2-(2-butyl-5-chloro-4-formyl-1H-imidazol-1-yl)-N-(4-(3-oxomorpholino) phenyl)acetamide with good yield. The reaction of 2-(2–butyl -5-chloro-4-formyl-1H-imidazol-1-yl)-N-(4-(3-oxomorpholino)phenyl)acetamide with substituted anilines in methanol and glacial acetic acid at room temperature gives a key intermediate for the synthesis of the M2-29V analogs with good yield. Novel analogs were characterized by 1H NMR, 13C NMR Mass Spectroscopy, and elemental analyses. Spectroscopic identification of intermediates and final products taken and favors the synthesis of M2-2901 to M2-2912.

Keywords: 1H-imidazol-1-yl; 2-butyl-5-chloro-1H-imidazole-4-carbaldehyde; Morpholin-3-one; ^{1}H NMR & ^{13}C NMR spectroscopy; Mass spectroscopy; Losartan.

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1. Introduction

The Present study applied the synthesis of losartan-like derivatives having imidazole moiety. However, potential biological active and medicinal uses have long been the justification for research in imidazole-related compounds. Losartan is commercially available, and it was the first orally active drug approved by the FDA in 1995 for the treatment of hypertension, and it was released to the market in April 1995. Losartan was one of seven other commercially available derivatives that were classified as sartans.

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The imidazole ring is a prominent five-membered, nitrogen-containing heterocyclic scaffold. Interestingly, imidazole-based molecules have become a critical component of pharmaceutical and medical chemistry [1–8]. Imidazole derivatives have a wide range of industrial demands. It is the perfect building block for nonlinear optical materials because of its great electron-withdrawing potential and good co-planarity [9–11]. Various uses for imidazolium salts include coating metal nanoparticles to offer antimicrobial action, producing oriented liquid crystals, and removing metal ions from aqueous solutions [12]. Imidazoles are common scaffolds in highly significant biomolecules, including the essential amino acid histidine, histamine, pilocarpine alkaloids [13,14], and other alkaloids, which have been shown to exhibit interesting biological activities such as antimicrobial[15-17], anti-inflammatory [18,19], histamine H3 antagonist [18,20], antioxidant [18,21], farnesyltransferase and geranylgeranyltransferase-I inhibitor [18,22], antiproliferative [23], antihelmintic [24], antileishmanial agents [25], antigiardial activity [26], antidiabetic activities [27], and cytotoxic agents against glioma (C6) and liver (HepG2) cancer cell lines[28].

Derivatives of imidazole have many pharmacological properties and are widely implicated in biochemical processes. Members of this class are also known to possess nitric oxide (NO) synthase inhibition [14], active against anaerobic bacteria [29], antimycotic agent [30], histamine H2-receptor antagonist [31], antimalarial [32,33], anti-ulcerative activities [14], and analgesic [34] and include compounds, which are inhibitors of 5-lipoxygenase [14,35] and substances with CB1 and CB2 (Cannabinoid) receptors [14,36,37], vascular endothelial growth factor (VEGF) receptor I and II [14, 38], and neuropeptide Y antagonistic activities [14,39]. 2-butyl-5-chloro-1H-imidazole-4-carbaldehyde (BCFI) moiety is a presence that is not only a major active metabolite but also the most important intermediate of Losartan [40]. Therefore, the synthesis of compound (BCFI) conveniently has received considerable attention. In the past decade, most documents reported the synthesis of compound (BCFI) from 2-butyl-3H-imidazole-4-methanol via both chlorination–oxidation and oxidation–chlorination protocols or 2-butyl-2-imidazolin-5-one via Vilsmeier reagents [41].

The derivatives of 1, 3-diazole show different biological activities like antibacterial [42], antimycobacterial [43], antiviral [44], anti-allergic [45], Antipyretic, antioxidant, anti-amoebic [46], antifungal, anticonvulsant [47], alpha-blockers [48], anticancer agents [49], antitubercular activity [50-53] and urease activities [54], etc. On the other hand, nitrogen heterocycles having pharmaceutical activities are widely occurring in nature in the form of alkaloids, vitamins, and pigments and as a constituent of plant and animal cells.

Hence, the realization of this objective has indeed led to a better understanding of the structural requirements for a diversity of physiological activities and sub-sequentially led to the synthesis and alteration of several losartan derivatives and imidazole-related compounds and analogs.

The scope of this study covers various reactions, which are to develop a rapid and convenient synthetic method for the syntheses of various Losartan-like derivatives having

Imidazole moiety. For this research, BCFI [41,55] and morpholin-3-one [56] derivatives in acetonitrile were subjected to the removal of hydrogen using potassium carbonate as a mild basic reaction condition to yield the M2-29 imidazole derivative [40,41]. Further reaction with various substituted anilines yields final M2-2901 – M2-2912 imidazole derivatives [41,57]. Structure elucidation of the pure compounds was carried out using several spectroscopic methods, including Mass Spectroscopy, Elemental Analysis, ^{1}H, and ^{13}CNMR. Imidazole's numerous substituted derivatives can be made with this efficient synthetic route.

2. Experimental

All analysis reactions were distributed by Sigma–Aldrich and Loba Chemie chemicals. The progress of reactions was monitored by thin-layer chromatography (TLC) on pre-coated silica gel GF254 plates from E-Merck Co., India and compounds pictured by exposure to UV light. Melting points of synthesized compounds were found in open capillaries. The IR spectra of compounds were captured on FTIR spectrophotometer using the KBr pellet technique and tetramethylsilane (TMS) used as an internal standard in 1H NMR spectra of synthesized compounds were captured on Bruker 400-MHz NMR spectrometer in DMSO-d6 solvent with mass spectra were recorded on GC-MS.

2.1. *Synthesis of Methyl Pentanimidate*

100 g (1.20 mol) valeronitrile was charged in 58 mL of methanol and cooled to −5 to −10° C. Hydrogen chloride gas was slowly passed through the solution for about 15-18 h. After that addition of 55 mL methanol and stirring for more 60 min. The reaction mass was then transferred to a methanolic ammonia solution (12-15 wt%) and stirred for 3 h at 20-30 °C. while maintaining the pH at 8-9. The precipitated compound was then filtered and washed with 25 mL of methanol. The filtrate was concentrated until the complete removal of methanol by distillation under reduced pressure (650-700 mm Hg) at a temperature not exceeding 90 °C. Upon cooling the intermediate (methyl pentanimidate) was obtained, a yield of 140 g (1.15 mol; 96 %) as a semi-solid.

2.2. *General synthesis of 2-butyl-5-chloro-3H- imidazole- 4-carbaldehyde - BCFI (INT-1)*

50 g (0.666 mol) of glycine was added to freshly made methanolic sodium hydroxide solution (sodium hydroxide 26.64 g (0.666 mol) in 250 mL of methanol) at 0 °C. and stirred for another 15 min. 80 g (0.70 mol) of the methyl pentanimidate prepared according to the above was added over 10-15 min to the above suspension at 0-5 °C. and stirring was continued for 16 h at room temperature. The solvent was then distilled under a vacuum below 50 °C. 500 mL of toluene was added to the above reaction mass, followed by 320 g (2.08 mol) of phosphorous oxychloride was added to this reaction mixture in 60 min, followed by 150 g (2.05 mol) N,N-dimethylformamide in 2 h. The reaction mixture was heated to 100 °C. and stirred for 2 h, then cooled to 30 °C. and

quenched in 260 mL of cooled deionized water (temperature below 25 °C). 30 g of filter aid (hi-flow) was added and the pH adjusted to 1.2 using 440 mL of 30 % aqueous sodium hydroxide solution.

After the filtration and washing with 100 mL of toluene, the layers were separated. The toluene layer was washed two times with deionized water (400 mL each time). 8 g of activated carbon was accounted for the toluene, and the layer was stirred for 30 min at 30-35 °C, followed by filtration and washing with 100 mL of toluene. All toluene layers were combined and concentrated to 50 vol% under a vacuum below 55 °C. The concentrated toluene solution was then chilled to 0-5 °C. and stirred for 2 h, followed by filtration of the precipitated product and washing with 25 mL of chilled toluene to yield a wet compound, which upon drying at 50-55 °C. to constant weight resulted in 89 g (0.47 mol) of crystalline 2-butyl-4-chloro-5-formylimidazole (~yield 70 %).

2.3. *General synthesis of INT-02*

Into a solution of 4-(4-aminophenyl)morpholin-3-one (1 equi) in acetone, chloroacetyl chloride (1.1 equi) was added drop by drop and the resulting mixture was stirred for 2-3 s at 0 °C temperature. The reaction mixture was then dumped into crushed ice, and the solid intermediate product was separated, filtered and washed with water. Dried it and used it in the next step without further purification.

2.4. *General synthesis of (M2-29)*

INT-02(1 equivalent) was added to a 100 mL RBF containing INT-01(1 equivalent) and acetonitrile solvent (2V) Followed by the addition of potassium carbonate (K_2CO_3) (1.2 equivalent) as a base. The reaction mixture was further stirred at room temperature for 10-15 min. Then reflux, the reaction mixture for 3-4 hr. after completion of the reaction monitored by TLC, was cooled and filtered solid product and washed with cooled acetonitrile solvent followed by water wash to yield title compound M2-29.

2.5. *General synthesis of (M2-2901 to M2-2912)*

In a 100 mL round bottom flask containing methanol as solvent, M2-29 (1 equivalent) was added and stirred for a further 5 min. To this catalytic amount of glacial acetic acid was added and stirred further for 5 min. After that, various substituted aniline (1 equivalent) was added at room temperature and refluxed for 3-4 hr. After the reaction's completion, cool the reaction mixture and filter the precipitated product. Washed with cooled methanol and dried it.

3. Reaction Scheme

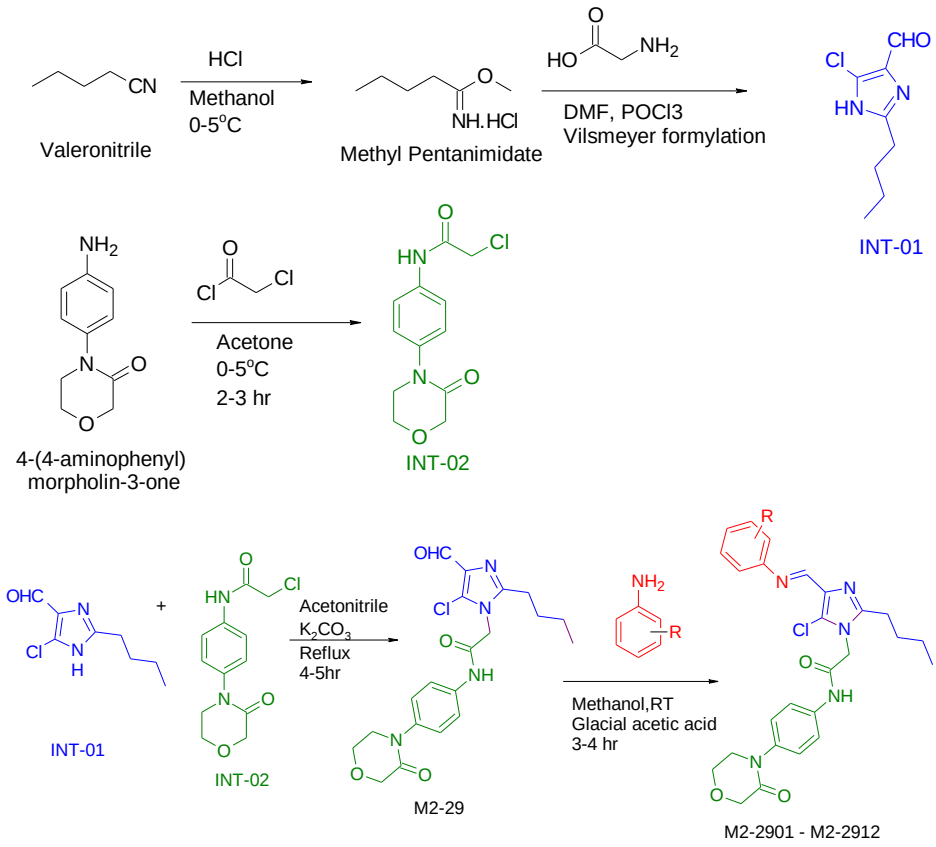

Fig. 1. Scheme M2-29V (V=01 to 12).

4. Spectral Data

2-(2-butyl-5-chloro-4-formyl-1H-imidazol-1-yl)-N-(4-(3-oxomorpholino)phenyl) acetamide(M2-29): Light yellow, **^{1}H NMR** (400 MHz, DMSO-d6) ppm: 10.45-10.50 (s, 1H), 9.62-9.67 (s, 1H), 7.63 – 7.55 (d, 2H), 7.31 – 7.39 (d, 2H), 5.17-5.22 (s, 2H), 4.17-4.22 (s, 2H), 3.93-4.01 (t, 2H), 3.67-3.74 (t, 2H), 2.66-2.74 (t, 2H), 1.59-1.71 (quin, 2H), 1.30-1.43 (sext, 2H), 0.86-0.94 (t, 3H); **Mass**: Obs. (m/z) 419.00, calcd. (m/z) 418.14; **Elemental Analysis (%)**: C, 57.35; H, 5.53; Cl, 8.46; N, 13.38; O, 15.28; Found; C, 57.32; H, 5.55; Cl, 8.45; N, 13.40; O, 15.28

(E)-2-(2-butyl-5-chloro-4-(((3,4-dimethylphenyl)imino)methyl)-1H-imidazol-1-yl)-N-(4-(3-oxomorpholino)phenyl)acetamide(M2-2901): Off white, **^{1}H NMR** (400 MHz, DMSO-*d*6) ppm:10.44-10.22 (s, 1H), 8.45-8.29 (s, 1H), 7.69-7.45 (d, 2H), 7.39-7.25 (d, 2H), 7.16-7.04 (d, 1H), 7.03-6.95 (d, 1H), 6.95-6.82 (s, 1H), 5.50-5.22 (s, 2H), 4.25-4.12 (s, 2H), 4.01-3.90 (t, 2H), 3.76-3.60 (t, 2H), 2.73-2.64 (t, 2H), 2.26-2.10 (s, 6H), 1.72-1.62

(quin ,2H), 1.45-1.31 (sext ,2H), 1.01-0.82 (t ,3H); **^{13}C NMR** (101 MHz, DMSO) δ = 165.82, 165.35, 152.87, 148.26, 145.18, 136.98, 136.89, 136.82, 134.62, 134.17, 130.04, 125.83, 123.09, 122.26, 119.27, 117.75, 67.68, 63.43, 48.99, 48.66, 28.87, 25.47, 21.61, 19.27, 18.81, 13.61; **Mass**: Obs. (*m/z*) 522.0, calcd. (*m/z*) 521.22; **Elemental Analysis (%)**: C, 64.42; H, 6.18; Cl, 6.79; N, 13.42; O, 9.19; Found; C, 64.39; H, 6.17; Cl, 6.80; N, 13.44; O, 9.20.

(E)-2-(2-butyl-5-chloro-4-(((4-chlorophenyl)imino)methyl)-1H-imidazol-1-yl)-N-(4-(3-oxomorpholino)phenyl)acetamide(M2-2902): Off white, **^{1}H NMR** (400 MHz, DMSO-*d*6) ppm: 10.58-10.39 (s, 1H), 8.47-8.35 (s, 1H), 7.73-7.51 (d, 2H), 7.51-7.30 (dd, 4H), 7.30-7.15 (d, 2H), 5.53-5.29 (s, 2H), 4.34-4.11 (s, 2H), 4.08-3.87 (t, 2H), 3.84-3.61 (t, 2H), 2.79-2.69 (t, 2H), 1.72-1.50 (quin, 2H), 1.50-1.31 (sext, 2H), 1.11-0.83 (t, 3H); **^{13}C NMR** (101 MHz, DMSO) δ 165.77, 165.15, 153.34, 149.41, 147.01, 136.86, 136.76, 135.63, 130.11, 128.97, 125.74, 122.89, 122.53, 119.33, 67.63, 63.37, 48.92, 48.51, 28.72, 25.41, 21.52, 13.49; **Mass**: Obs. (*m/z*) 528.0, calcd. (*m/z*) 527.15; **Elemental Analysis (%)**: C, 59.10; H, 5.15; Cl, 13.42; N, 13.25; O, 9.08; Found; C, 59.14; H, 5.14; Cl, 13.42; N, 13.23; O, 9.07.

(E)-2-(2-butyl-5-chloro-4-(((4-methoxyphenyl)imino)methyl)-1H-imidazol-1-yl)-N-(4-(3-oxomorpholino)phenyl)acetamide(M2-2903): White, **^{1}H NMR** (400 MHz, DMSO-*d*6) ppm: 10.58-10.39 (s, 1H), 8.45-8.36 (s, 1H), 7.68-7.55 (d, 2H), 7.37-7.17 (dd, 4H), 6.97-6.86 (d, 2H), 5.49-5.31 (s, 2H), 4.23-4.14 (s, 2H), 4.02-3.91 (t, 2H), 3.72-3.66 (s, 3H), 2.79-3.72 (t, 2H), 2.74-2.66 (t, 2H), 1.72-1.61 (quin, 2H), 1.49-1.32 (sext, 2H), 0.96-0.85 (t, 3H); **^{13}C NMR** (101 MHz, DMSO) δ 165.81, 165.34, 157.90, 152.69, 144.25, 143.45, 136.90, 136.82, 134.30, 125.80, 123.09, 122.05, 119.31, 114.36, 67.66, 63.41, 55.23, 48.96, 48.54, 28.81, 25.44, 21.59, 13.58; **Mass**: Obs. (*m/z*) 522.9, calcd. (*m/z*) 523.20; **Elemental Analysis (%)**: C, 61.89; H, 5.77; Cl, 6.77; N, 13.36; O, 12.21; Found; C, 61.92; H, 5.78; Cl, 6.75; N, 13.35; O, 12.20

Table 1. Physiochemical data of synthesized library.

Compound Code	Mol. Wt. (g/mole)	Substitution					Yield (%)	Melting Point ℃
		R1	R2	R3	R4	R5		
M2-2901	521	H	CH3	CH_3	H	H	71	180-182
M2-2902	527	H	H	CL	H	H	69	170-172
M2-2903	523	H	H	OCH_3	H	H	71	176-178
M2-2904	493	H	H	H	H	H	70	164-166
M2-2905	561	H	CL	CL	H	H	72	160-162
M2-2906	538	NO_2	H	H	H	H	71	170-172
M2-2907	538	H	NO_2	H	H	H	73	168-170
M2-2908	538	H	H	NO_2	H	H	75	170-172
M2-2909	572	H	NO_2	CL	H	H	76	178-180
M2-2910	529	F	H	F	H	H	69	164-166
M2-2911	527	CL	H	H	H	H	70	172-174
M2-2912	527	H	CL	H	H	H	65	174-176

5. Results and Discussion

In this study, 2-butyl-5-chloro-1H-imidazole-4-carbaldehyde (BCFI) treated with 2-chloro-N-(4-(3-oxomorpholino) phenyl)acetamide and yielded Intermediate 2-(2-butyl-5-chloro-4-formyl-1H-imidazol-1-yl)-N-(4-(3-oxomorpholino)phenyl) acetamide (M2-29) which further reacts with the various substituted anilines to yield a series of M2-2901 to M2-2912. All twelve compounds are stable at room temperature. As our final compounds M2-2901 to M2-2912 have a similar structure to Losartan drugs, they have the potential for medicinal application, and the presence of imidazole moiety can lead to good antifungal, antibacterial and antimicrobial activity. In Fig. 1, The scheme is given. In Table 1 physiochemical data of various substituted M2-29 are given.

All the synthesized compounds yield in the range of 65-75 %. We made an efficient methodology for the synthesis series of substituted imidazole derivatives by the reaction of 2-(2-butyl-5-chloro-4-formyl-1H-imidazol-1-yl)-N-(4-(3-oxomorpholino)phenyl) acetamide with various substituted anilines.

6. Conclusion

In summary, we have developed a novel, efficient methodology for the synthesis of a series of substituted imidazole derivatives by the reaction of 2-(2-butyl-5-chloro-4-formyl-1H-imidazol-1-yl)-N-(4-(3-oxomorpholino)phenyl)acetamide with various substituted anilines. As the structure is similar to losartan drug and has a moiety like BCFI shows good scope for biological and pharmacological application. The advantages of this currently developed method are possible synthesis in Simple conditions, higher yields, low costs, and environmental safety. Suitable reaction condition for the synthesis of targeted compounds was studied. All the compounds are well characterized by various analytical techniques.

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