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Research Article

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Green Synthesis, 1D and 2D NMR spectral characterization of imidazole fused with pyrimidine nucleus by using grinding techniques.

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ABSTRACT

Some novel new series of Ethyl-6-((1H-imidazol-1-yl)methyl)-1,2,3,4-tetrahydro-4-aryl-oxopyrimidine-5-carboxylates (6a-f) have been synthesized in two steps. In the first step Ethyl-6-chloromethyl-1,2,3,4-tetrahydro-4-aryl-oxopyrimidine-5-carboxylates (4a-f) ie Biginelli compounds were prepared from Chloroetylacetoacetate, urea and substituted benzaldehyde by using ZrO_2 nanopowder under microwave irradiation and the second step, the Biginelli compounds (4a-f) were treated with imidazole (5) in the presence of catalytic amount of NaOH under grinding technique. The present methodology offers several advantages, such as simple procedure with easy work-up, short reaction time, high yields and the absence of volatile organic solvents. The structure of the compounds were confirmed by IR, Mass, 1D and 2D NMR like ^1H-^1H COSY, ^1H-^{13}C HSQC spectral analysis and CHN analysis. The synthesized compounds were obeyed the Lipinski's rule of Five.

Key words: Grinding technique, Lipinski's rule, 2D NMR, imidazole, Biginelli compounds

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INTRODUCTION

Synthesis of imidazole ring system and its derivatives occupy a significant position in the field of natural and synthetic organic chemistry, because of their immense pharmacological and therapeutic potentials [1]. Such ring system serve as an integral part of many biological systems[2] *viz* histidine, histamine and biotine and also as an active back bone in existing drugs[1c]& [3] such also sartan, olmestran, eprosartan and trifenagrel. The number of this class of compounds are found to exibit promising inhibitory activities against p38 MAP kinase [4], B-Rafkinase[5] transforming growth factor β1 (TGF-β1) type1active receptor-like kinase(ALK5)[6] cyclooxygenase-2 (COX-2) [7], and also against the biosynthesis of interlukin -1 (IL-1)[8].In addition to that ,substituted imidazoles are extensively used as glucagon receptors [9] and CBI cannabinoid receptor antagonists[10], modulators of p-glycoprotein (P-gp)-mediated multidrug resistance (MDR) [11], antibacterial[12], anti-allergic [13], analgesic[14 and antitumor agents [15] and also as pesticides[16&17].Other biological activities of the imidazole pharmacophore relate to the down regulation of intracellular Ca++ and K+ fluxed and interference with translation initiation [18].Imidazole when fused to a pyrimidine ring it forms purine, which is the most widely occurring nitrogen containing heterocycle in nature [19].

Solid- state reaction without using harmful organic solvent has captured great current interest especially in the development of green chemistry [20-23] and its applications in synthetic organic chemistry [24-28]. In view of these observations in recent years, environmentally benign synthetic methods have received considerable attention, and

some solvent-free protocols have been developed [29, 30]. Grinding technique is one which has been increasingly used in organic synthesis compared to traditional methods [31, 32]. These reactions not only of interest from economical point of view, but also in many cases they offer considerable advantages in terms of yield, selectivity, and simplicity of reaction procedure with high atom efficiency. The grinding mode for solid-state reactions has been reported for some well-known reactions such as Grignard reactions [33], Reformatsky reactions [34], Aldol Condensations [35], Dieckmann condensations [36], Knoevenegal condensations [37], Reductions [38], and others [39]. Most of these reactions are carried out at room temperature in absence of solvent -free environment, using only a mortar and pestle. In grindstone technique, reaction occurs through generation of local heat by grinding of crystals of substrate and reagent. Reactions are initiated by grinding, with the transfer of very small amount of energy through friction. In some cases, a mixture and reagent turn to glassy material. Such reactions are simple to handle, reduce pollution, comparatively cheaper to operate and may regarded as economical and ecologically favorable procedure in chemistry [40, 41]. To improve these methods towards organic synthesis and reactions, increasing attention is being focused on green chemistry using environmentally benign reagent s and conditions, particularly solvent-free procedures. Thus, utilization of nontoxic chemicals, renewable materials, and solvent-free conditions is the key issue of green synthetic strategy. In view of these observations, it was thought worthwhile to synthesize ethyl 6-(1H-imidazol-1-yl)methyl-1,2,3,4-tetrahydro-4-aryl-2-oxo-4-aryl-pyrimidine-5-carboxylates from Biginelli compounds [42,43] using grinding technique as it meets the requirement of greenness [44].

EXPERIMENTAL SECTION

Melting points are uncorrected and determined in an open capillary tube. FT-IR recorded on Thermo Nicolet-Avatar-330 FT-IR spectrometer. The sample was mixed with KBr and pellet technique was adopted to record the spectra.^{1}H NMR spectra were recorded in Bruker AvanceII 400 NMR spectrometer operating at 400 MHz. ^{13}C NMR spectra were recorded in Bruker Avance II 400 NMR Spectrometer operating at 100 MHz. HOMO COSY and HSQC spectra were recorded in Bruker Avance II 400 NMR spectrometer using standard parameters. Solutions were prepared by dissolving 10-25 mg of the compound in 0.5 ml of solvent ($CDCl_3$ / DMSO $-d_6$).TMS (Trimethylsilane) was used as an internal standard. All the NMR measurements were made on 5 mm NMR tube. A mass spectrum was recorded on a Varian-Saturn 2200 GC-MS spectrometer using electron spray soft ionization technique in positive mode. Elemental analysis was carried out using Perkin Elmer-240 CHN analyser.

Typical Procedure for the synthesis of imidazolyl-pyrimidine derivatives (6a-f)

The mixture of Ethyl-6-(chloromethyl)-1,2,3,4-tetrahydro-4-aryl-oxopyrimidine-5-carboxylates (Beginelli Compounds) **4a-f** (0.01 mol) and imidazole **5** (0.01 mol) was thoroughly ground with a pestle in an open mortar at room temperature for 2 minutes, and then a catalytic amount of sodium hydroxide (0.001 mol) was added to this grinded reaction mixture. The grinding was continued for 15-20 minutes and the progress of reaction was monitored on Thin layer chromatography (TLC). The completion of reaction was indicated by in the formation of yellow colored reaction mixture. The reaction mixture was poured in to ice water in a beaker and kept aside for one overnight. Obtained solid was easily separated by using cold water and simple Buchner filtration; final purification was achieved by crystallization from ethanol. The present method reported here for synthesis of imidazolyl pyrimidine derivatives 6a-f.

Ethyl 6-(1H-imidazol-1-yl) methyl-4-(4-bromophenyl)-1, 2, 3, 4-tetrahydro-2-oxopyrimidine-5-carboxylate (6a)

Melting Point (°C): 152. Moleculat formula: $C_{17}H_{17}BrN_4O_3$. IR (ν max)cm^{-1};1693 (ester carbonyl), 1646 (amide carbonyl)3356,3233 (-NH groups), 3127 (aromatic C-H), 2975,2925 and 2854 (aliphatic C-H), 1229 (C-N), 764 and 657(aromatic ring stretching). ^{1}H NMR (δ ppm): 1.09 ppm (t, 3H, estermethyl protons) J=7.0 Hz, 4.06 ppm(quartet, 2H, estermethylene protons), 9.70 ppm(s, 1H, H-1 proton), 7.79 ppm(s,1H, H-3 proton), 5.19 ppm (d, 1 H, H4 proton) J=3.5 Hz, 5.08 ppm (d, 1H, H_a methylene proton attached to imidazole moiety) J=13.5 Hz, 5.28 ppm (d, 1H, H_b methylene proton attached to imidazole moiety), 7.88 ppm (s, 1H. H-2 proton) 7.12 ppm (s, 1H, H-5 proton)7.76-6.93 ppm (m,aromatic protons).^{13}C NMR (δ ppm);53.95 ppm (C-4 benzylic carbon of pyrimidine moiety), 60.60 ppm (estermethylene carbon), 44.72 ppm(imidazole attached tomethylene carbon), 14.35 ppm (estermethyl carbon), 101.86ppm (C-5 of pyrimidine moiety, 146.02 ppm(C-6 of pyrimidine moiety), 152.16 ppm (C-2 amide carbonyl carbon), 165.04 (estercarbonyl carbon), 135.46 ppm (C-2of imidazole moiety), 121.76 ppm (C-4 & C-5 carbon), 131.92-119.75 (aromatic carbons), 143.83 & 138.07 ppm(*ipso* carbons).

Ethyl 6-((1-H-imidazol-1-yl) methyl)-1, 2, 3, 4-tetrahydro-2-oxo-4-phenylpyrimidine-5-carboxylate (6b)
Melting point **(**°C): 168 °C. Molecular formula: $C_{17}H_{18}N_4O_3$. IR (ν max) cm^{-1}:1695 cm^{-1} (ester carbonyl), 1646 cm^{-1} (amide carbonyl), 3390, 3216 cm^{-1} (-NH groups), 3098 cm^{-1} (aromatic CH), 2930 and 2854 cm^{-1}(aliphatic CH), 1226 cm^{-1}(C-N), 796 and 665 cm^{-1}(aromatic ring stretching). ^{1}H NMR (δ ppm); 1.09 ppm (t, 3H, ester methyl protons) J=7.0 Hz, 4.06 ppm (q, 2H, ester methylene protons) , 9.65 ppm (s, 1H, H-1 proton) , 7.93 ppm (s, 1H, H-3 proton), 5.21 ppm (d, 1H, H-4proton) J=3.0 Hz, 5.13 ppm(d, 1H,H_a methylene proton attached to imidazole) J=14. 0 Hz, 5.26 ppm (d, 1H, H_b methylene proton attached to imidazole) J= 14.0 Hz,H-2 of imidazole moiety ismerged with H-3 of pyrimidine moiety, 7.15 ppm (s, 1H, H-4 & H-5 of imidazole moiety), 7.37-7.19 ppm (aromatic protons. ^{13}C NMR (δ ppm): 54.47 ppm (C-4 benzylic carbon of pyrimidine moiety), 60.52 ppm (ester methylene carbon0, 44.78 (methylene carbon attached to imidazole moiety), 14.34 ppm (ester metyl carbon), 102.34 ppm (C-5 of pyrimidine moiety), 145.69 ppm(C-6 of pyrimidine moiety), 152.35 ppm (C-2 amide carbonyl carbon), 165.20 ppm(ester carbonyl carbon), 128.89 ppm (C-2 of imidazole moiety), 126.71 ppm (C-4 & C-5 of imidazole moiety), 129.10-121.80 ppm (aromatic carbons), 144.46 ppm (*ipso* carbon).

Ethyl 6 ((1-H-imidazol-1-yl) methyl) 1, 2, 3, 4-tetrahydro-4-(4-methoxyphenyl)-2oxopyrimidine-5-carboxylate (6c)
Melting Point (°C): 139°C. Molecular formula**:** $C_{18}H_{20}N_4O_4$. IR (ν max)cm^{-1}: 1679 cm^{-1}(ester carbonyl), 1660 cm^{-1} (amide carbonyl), 3417 & 3243 cm^{-1} (-NH groups), 3117cm^{-1}(aromatic CH) , 2923 & 2854 cm^{-1}(aliphatic CH), 1225 cm^{-1} (C-N) , 761 & 670 cm^{-1} (aromatic ring stretching). ^{1}H NMR (δ ppm): 1.13ppm (t, 3H, ester methyl protons) J=6.8 ppm, 4.05 ppm (q, 2H, ester methylene proton) J=7.3 Hz, 9.56 ppm (s, 1H.H-1 proton), 7.75 ppm (s, 1H, H-1 proton), 5.15 ppm (d, 1H, H-4 proton) J=3.0 Hz, 5.10 ppm(d, 1H, H_a methylene proton attached to imidazole) J= 14.0 Hz, 5.23 ppm (d. 1H. H_b proton attached to imidazole) J=14.0 Hz, 3.72 ppm(OCH_3 of phenyl ring), 7.92 ppm (s, 1h, H-2 of imidazole moiety), 7.14 ppm (s, 1H, H-4 & H-5 of imidazole moiety), 7.23- 6.85 ppm (aromaticprotons). ^{13}C NMR (δ ppm): 53.84 ppm (C-4 benzylic carbon of pyrimidine moiety), 60.49 ppm (ester methylene carbon), 44.85 ppm (methylene carbon attached to imidazole), 14.39 ppm (ester methyl carbon), 102.85 ppm (C-5 of pyrimidine moiety), 145.51 ppm(C-6 of pyrimidine moiety), 152.34 ppm (C-2 amide carbonylcarbon), 165.25 ppm (ester carbonyl carbon),135.43 ppm (C-2 carbon of imidazole moiety), 55.53 ppm (OCH_3 of phenyl ring), 121.68 ppm (C-4 & C-5 carbon of imidazole moiety), 128.73-114.27 ppm (aromatic carbons), 159.11-138.03 ppm (*ipso* carbons).

Ethyl6-((1-H-imidazol-1-yl) methyl)-1, 2, 3, 4-tetrahydro-2-oxo-4—p-tolylpyrimidine-5-carboxylate (6d)
Melting Point (°C): 230°C. Molecular formula: $C_{18}H_{20}N_4O_3$. IR (ν max cm^{-1}): 1694 cm^{-1} (eater carbonyl), 1647 cm^{-1} (amide carbonyl), 3356 & 3232 cm^{-1}(-NH groups), 3125 cm^{-1} (aromatic CH), 2974 & 2931 cm^{-1} (aliphatic CH), 695 & 668 cm^{-1} (aromatic ring stretching). ^{1}H NMR (δ ppm):1.10 ppm (t, 3H, estermethyl protons) J=7.0 Hz, 4.00 ppm (q, 2H, ester methylene protons) J=7.3 Hz, 9.93 ppm (s, 1H, H-1 proton), 7.84 ppm (s, 1H, H-3 proton), 5.18 ppm(d, 1H, H-4 proton) J=3.5 Hz, 5.12 ppm (d, 1H, H_a methylene proton attached to imidazole) J=14.0 Hz, 5.23 ppm (d, 1H, H_b proton attached to imidazole moiety) J=14.0 Hz, 2.27 ppm (CH_3 of phenyl ring), 7.70 ppm (s, 1H, H-2 proton of imidazole moiety), 7.05 ppm (s, 1H.H-4 & H-5 of imidazole moiety), 7.21-7.09 ppm(aromatic protons). ^{13}C NMR (δ ppm):52.89 ppm (C-4 benzylic carbon of pyrimidine moiety),65.40 ppm (estermethylene carbon), 44.61 ppm(methylene carbon attached to imidazole), 14.41 ppm (ester methylcarbon), 97.09 ppm (C-5 of pyrimidine moiety), 151.37 ppm (C-6 of pyrimidine moiety), 159.37 ppm(C-2 of amide carbonyl carbon), 170.25 ppm (estercarbonyl carbon), 21.10 ppm(CH_3 at phenyl ring), 135.64 ppm (C-2 of imidazole moiety), 122.13 ppm (C-4 & C-5of imidazole moiety), 129.45- 126.97 ppm (aromatic carbons), 140.17 & 137.48 ppm(*ipso* carbons).

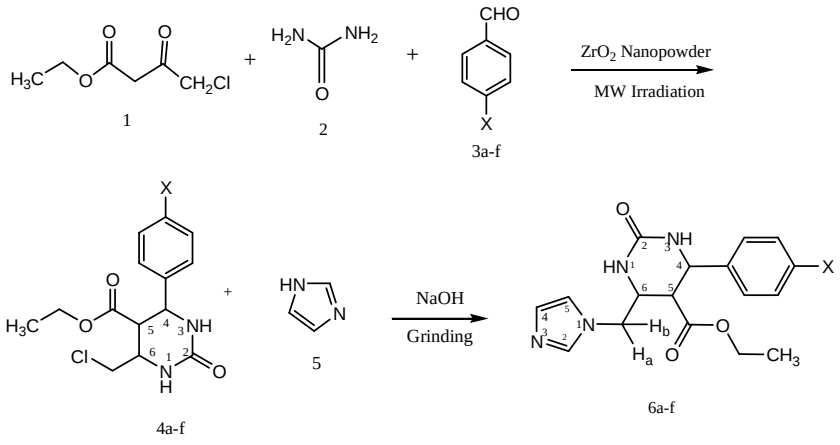
Ethyl 6-((1-H-imidazol-1yl)methyl)-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-oxopyrimidine-5-carboxylate (6e)
Melting Point (°C): 140 °C. Molecular formula: $C_{17}H_{17}ClN_4O_3$. IR (ν max cm^{-1}): 1687 cm^{-1} (ester carbonyl), 1647 cm^{-1}(amide carbonyl), 3358 & 3293 (NH groups), 3156 cm^{-1} (aromatic CH), 2986 & 2920 cm^{-1} (aliphatic CH), 1221 cm^{-1} (C-N), 763 & 669 cm^{-1} (aromatic ring stretching). ^{1}H NMR (δ ppm): 1.09 ppm (t, 3h, ester methyl protons)J=7.0 Hz, 4.06 ppm (q, 2H, ester methylene protons) J=7.0Hz, 9.71 ppm (s, 1H, H-1 proton), 7.78 ppm (s, 1H, H-3 proton), 5,21 ppm (d, 1H, H-4 proton) J=3.0 Hz, 5.09 ppm (d, 1H, H_a methylene proton attached to imidazole)J=14.0 Hz, 5.29 ppm (d, 1H, H_b methylene proton attached to imidazole) J=13.5 Hz, 7.99 ppm (s, 1H, H-2 of imidazole moiety), 7.17 ppm (H-4 & h-5 of imidazole moiety), 7.38-7.21 ppm (aromatic protons). ^{13}C NMR (δ ppm): 53.88 ppm (C-4 benzylic carbon of pyrimidine moiety), 60.59 ppm (ester methylene carbon), 44.73 ppm (methylene carbon attached to imidazole), 14.13 ppm (ester methyl carbon), 101.93 ppm (C-5 of pyrimidine moiety), 146.01 ppm (C-6 of pyrimidine moiety), 152.16 ppm (C-2amide carbonyl carbon), 165.05 ppm (ester carbonyl carbon), 135.38 ppm (C-2 of imidazole moiety), 121.57 ppm (C-4 & C-5 of imidazole moiety), 128.99-119.77 ppm (aromatic carbons), 143.42 & 138.06ppm (*ipso* carbons).

Ethyl 6-((1H-imidazol-1-yl) methyl)-4-(4-fluorophenyl)-1, 2, 3, 4-tetrahydro-2-oxopyrimidine-5-carboxylate (6f)
Melting Point (°C): 136 °C. Molecular formula: $C_{17}H_{17}FN_4O_3$. IR (ν max cm^{-1}): 1687 cm^{-1} (ester carbonyl), 1647 cm^{-1} (amide carbonyl), 3375& 3243 cm^{-1} (-NH groups), 3123 cm^{-1} (aromatic CH), 2925 & 2854 cm^{-1} (aliphatic CH), 1221 cm^{-1}(C-N), 763 & 669 cm^{-1} (aromatic ring stretching). ^{1}H NMR (δ ppm):1.10 ppm (t , 3H, ester methyl protons) J=7.0 Hz ,4.05 ppm (q, 2H, ester methylene protons) J=7.0 Hz, 7.30 ppm (s, 1H, H-1 proton), 7.90 ppm (s, 1H, H-3 proton), 5.20 ppm(d, 1H, H-4 proton) J=3.5 Hz, 5.08 ppm(d, 1H, H_a methylene proton attached to imidazole) J=14.0 Hz, 5.28 ppm (d, 1H, H_b methylene proton attached to imidazolemoiety) J=14.0 Hz, 8.16 ppm (H-2 of imidazole moiety), 7.25 ppm (H-4 & H-5 of imidazole moiety), 7.38-7.31 ppm (aromatic protons). ^{13}C NMR (δ ppm): 53.92 ppm(C-4benzylic carbon of pyrimidine moiety), 60.44 ppm (ester methylene carbon), 44.62 ppm (methylene carbon attached to imidazole), 14.33 ppm (ester methyl carbon), 102.04 ppm (C-5 of pyrimidine moiety), 146.68 ppm (C-6 of pyrimidine moiety), 152. 32 ppm (C-2 amide carbonyl carbon), 165.10 ppm(ester carbonyl carbon), 135. 25 ppm (C-2 of imidazole moiety), 121.26 ppm (C-4 & C-5of imidazole moiety), 128.83 ppm- 115.67 ppm (aromatic carbons), 162.95, 160.99, 138.02 ppm (*ipso* carbons).

RESULTS AND DISCUSSION

In continuation of our research work on organic synthesis, we wish to report herein, a simple, rapid, and highly efficient procedure for the synthesis of newly synthesized Ethyl 6-(1H-imidazol-1-yl)methyl)-1,2,3,4-tetrahydro-2-oxo-4-aryl-pyrimidine-5-carboxylates **6a-f** using catalytic amount of sodium hydroxide under solvent-free conditions using grinding technique (Scheme 1). Ethyl-6-(chloromethyl)-1,2,3,4-tetrahydro-4-aryl-oxopyrimidine-5-carboxylates (Biginelli compounds) **4a-f** were prepared by literature method [42].The present studies describe that reactions were carried out using grindstone technique simply by mixing corresponding Ethyl-6-(chloromethyl)-1,2,3,4-tetrahydro-4-aryl-oxopyrimidine-5-carboxylates (Beginelli Compounds) **4a-f** and imidazole **5.** The mixture was grinding together in mortar with pestle at room temperature for 2 minutes, and then a catalytic amount of sodium hydroxide was added to this grinded reaction mixture. The grinding was continued for 15-20 minutes and the progress of reaction was monitored on Thin layer chromatography (TLC). The completion of reaction was indicated by in the formation of yellow colored reaction mixture. The reaction mixture was poured in to ice water in a beaker and kept aside for one overnight. Obtained solid was easily separated by using cold water and simple Buchner filtration; final purification was achieved by crystallization from ethanol. The present method reported here for synthesis of imidazole fused to pyrimidine derivatives **6a-f** is simple and effective in terms of short reaction time, excellent yields, and simple reaction procedure with high atom efficiency. It is also consistent with green chemistry approach because it does not require heating or microwave irradiation. It occurs at room temperature and is completely free from organic solvents during both the reaction and separation of the product, expect for recrystallization of product 6**a-f**. All the synthesized compounds **6a-f** was established on the basis of spectral and elemental analysis. The drug ability was checked by using Lipinski's rule of Five.

Scheme:



Scheme: Synthesis of ethyl 6-((1H-imidazol-1-yl) methyl)-1,2,3,4-tetrahydro-2-oxo-4-arylpyrimidine-5-carboxylates (3a-f).

Spectral Characterization of the synthesized compounds

FT-IR Spectrum

FT-IR spectrum of compound 6a shows characteristics absorption at 1693 and 1646 cm-1 due to ester carbonyl and amide carbonyl functional groups respectively. Absorption frequencies observed at 3356 and 3233 cm-1 suggesting the presence of NH groups. The absorption frequency at 3127 cm-1 is assigned to aromatic C-H stretching vibration and the absorption frequencies at 2975, 2925 and 2854 cm-1 is assigned to aliphatic C-H stretching vibration. Absorption frequency at 1229 is due to C-N stretching vibration. Moreover, aromatic ring stretching frequencies are observed at 764 and 657 cm-1.

Mass Spectrum

Mass spectrum of the compound 6a shows that the molecular ion peak at m/z406 ($M^{+\cdot}$) which is consists with the proposed molecular formula of the compound 3a. Elemental analysis of compound 6a (C_{cal} 50.38, C_{obs} 50.11; H_{cal} 4.23, H_{obs} 4.02; N_{cal} 13.83, N_{obs} 13.51) are consistent with the proposed molecular formula ($C_{17}H_{17}BrN_4O_3$) of compound 3a.

^{1}H NMR Spectrum of compound 6a

In the ^{1}H NMR spectrum of compound 6a, a triplet observed at 1.09 ppm (J=7.0 Hz) corresponding to three protons and this signal is due to ester methyl protons. A quartet observed at 4.06 ppm corresponding to two protons and this signal is due to ester methylene protons. There are two singlets observed at 9.70 and 7.97 ppm, each corresponding to one proton. The singlet at 9.70 ppm can be assigned to H-1 proton and the signal at 7.97 ppm can be assigned to H-3 proton. The benzylic proton H-4 of pyrimidine moiety appears as a doublet at 5.19ppm (J= 3.5 Hz). The NMR signal for methylene protons attached to imidazole moiety appears as two doublets. This behavior is due to non-equivalence of the two protons of the methylene group. The spectrum belongs to AB type. A doublet observed at 5.08 ppm (J=13.5 Hz) is due to H_a methylene proton attached to imidazole moiety. Another doublet appears at 5.28 ppm (13.5 Hz) is dueto H_b methylene proton attached to imidazole moiety. The H-2 proton of imidazole moiety gives signal as a singlet at 7.88 ppm whereas the signals for H-4 and H-5 protons of imidazole moiety appear at 7.12 ppm. The aromatic protons appear as a multiplet in the range 7.76-6.93 ppm .

^{13}C NMR spectrum of compound 6a

In the ^{13}C NMR spectrum, resonance in the aliphatic range 53.95, 60.60, 44.72 and 14.35 ppm has been observed. The ^{13}C resonance at 53.95 ppm is assigned to C-4 benzylic carbon of pyrimidine moiety. Two ^{13}C resonances at 60.60 and 44.72 ppm are due to ester methylene and imidazole attached methylene carbons respectively. The ester methyl carbon resonates at 14.35 ppm. The ^{13}C resonance observed at 101.86 and 146.02 ppm are assigned to C-5 and C-6 carbons of pyrimidine moiety respectively. The signal observed at 152.16 ppm is assigned to C-2 amide carbonyl carbon, whereas the signal at 165.04 ppm is assigned to ester carbonyl carbon. C-2 carbon of imidazole moiety resonates at 135.46 ppm whereas the C-4 and C-5 carbon resonances at 121.76 ppm. The aromatic carbons are observed in the range of 131.92-11.75. The remaining ^{13}C signals at 143.83 and 138.07 ppm are due to ipso carbons.

^{1}H-^{1}H COSY spectrum of compound 6a

It is observed that the proton signal at 5.19 ppm shows cross peak with the signal at 7.97 ppm. Consequently the proton signal at 7.97ppm show cross peak with the signal at 5.19 ppm.From the above cross peaks, it reveal that the doublet at 5.19 ppm must be due to H-4 proton of pyrimidine moiety and the singlet at 7.97 ppm must be due to H-3 proton of pyrimidine moiety. A doublet obseeved at 5.08 ppm shows cross peak with the signal at 5.28 ppm and vice-versa. From this mutual correlation it reveals that the signal at 5.08 ppm is due to H_a metylene proton attached to imidazole moiety and another doublet appears at 5.28 ppm is due to H_b methylene proton attached to imidazole moiety.The H-2 proton of imidazole moiety shows correlation peak with the signal for H-4 and H-5 proton of imidazole moiety and vice-versa. From the mutual correlations it reveal that the signal at 7.88 ppm is due to H-2 proton of imidazole moiety and the signal at 7.12 ppm is due to H-4 and H-5 proton of imidazole moiety. Also, the triplet at 1.09 ppm shows cross peaks with the quartet at 4.06 ppm. Similarly, the quartet at 4.06 ppm shows cross peaks with the triplet at 1.09 ppm. From these mutual correlations, it reveals that the triplet at 1.09 ppm must be due to ester methyl protons whereas the signal at 4.06 ppm is assigned to ester methylene protons. The individual assignments can be made using ^{1}H-^{13}C HSQC spectra.

^{1}H-^{13}C HSQC spectra of compound 6a

The ^{1}H-^{13}C shows that the proton signal at 9.70 ppm and 7.97 ppm have no HSQC correlation with any carbon signal. Thus, it is obvious that this signal is due to two NH protons H-1 and H-3 protons respectively of pyrimidine moiety. Also the carbon signal at 152.16, 165.04, 101.86, 146.02, 143.83 and 138.07 ppm show no correlations with any proton signal, which do not have any proton bound to them. Obviously, the signals at 152.16 and 165.04 ppm are due to C-2 amide carbonyl carbon of pyrimidine ring and ester carbonyl carbon respectively. C-5 and C-6 carbons of pyrimidine ring carbon resonate at 101.86 and 146.02 ppm respectively whereas the carbon signal at 143.83 and 138.07 ppm are due to ipso carbons.the signal around 131.92-119.75 ppm are due to aromatic carbons. The doublet observed at 5.19 ppm shows correlations with the carbon signal at 53.95 ppm. From the observed correlations, it is clear that the doublet at 5.19 ppm is due to H-4 proton of pyrimidine ring and the carbon signal at 53.95 is due to C-4 benzylic carbon of pyrimidine moiety. The ^{13}C resonance at 60.60 ppm and 14.35 ppm shows correlations with the proton signals at 4.06 and 1.09 ppm respectively. From these correlations, it reveals that the signal at 60.60 ppm is assigned to ester methylene carbon and the signal at 4.06 ppm is assigned to ester methylene proton. Also the signal at 14.35 ppm is assigned to ester methyl carbon and the signal at 1.09 ppm is assigned to ester metyl protons. Two doublets observed at 5.08 and 5.28ppm show correlation peak with the carbon signal 44.72 ppm. From the observed correlation, it is clear that the signal at 5.08 ppm is due to H_a methylene proton attached to imidazole moiety and another doublet appears at 5.28 ppm is due to H_b methylene proton attached to imidazole moiety. Likewise, two signals observed at 7.88 and 7.12 ppm show correlation peak with the carbon signals at 135.46 and 121.76 ppm respectively. From the observed correlations, it is clear that the signal at 7.88 ppm is due to H-2 proton of imidazole ring and the signal at 135.46 ppm is due to C-2 carbon of imidazole ring. Also the signal at 7.12 ppm is due to H-4 and H-5 proton of imidazole ring and the signal 121.76 ppm is due to C-4 and C-5 carbons of imidazole ring. Therefore with reference to ^{1}H-^{1}H COSY and ^{1}H-^{13}C HSQC correlations in compound 3a, the tentative assignments made for protons and carbons are confirmed. Based on ^{1}H-^{1}H COSY and ^{1}H-^{13}C HSQC correlations of compound 3a, the ^{1}H and ^{13}C chemical shifts of 3a are assigned unambiguously.

Lipinski's Rule

The above synthesized compounds obey the rule of five, because they have not (1). No more than 5 Hydrogen bond donors (the total number of Nitrogen-Hydrogen and Oxygen-Hydrogen bonds). (2). Not more than 10 Hydrogen bond acceptors (all Nitrogen and Oxygen atoms). (3). A molecular mass of our synthesized compounds not exceeding 500 Daltons. (Molecular mass of Compound 6a -405, Compound 6b-326, Compound 6c-356, Compound 6d-340, Compound 6e- 360, Compound 6f- 344). (4). Melting point of our synthesized compounds are not exceeding 500°C (Melting point of Compound 6a-152°C, Compound 6b-168°C, Compound 6c- 139°C, Compound 6d- 230°C, Compound 6e- 140°C, Compound 6f- 136°C).(5). The log p value also not exceeding greater than 5 (log p values of Compound 6a- 1.51, Compound 6b-0.68, Compound 6c-0.55, Compound 6d-1.17, Compound 6e- 1.24, Compound 6f- 0.84). So the above synthesized compounds are obeyed the Lipinski's Rule [45] of Five. Therefore our synthesized compounds 3a-f is drug molecules. The values are shown in Table 1.

Table 1 Lipinski's Rule for Compound (6a-f)

Compound	No. of H-bond donors	No. of H-bond acceptors	Molecular mass m/z	Melting point in °C	log p
6a	<5	<10	405	152	1.51
6b	<5	<10	326	168	0.68
6c	<5	<10	356	139	0.55
6d	<5	<10	340	230	1.17
6e	<5	<10	360	140	1.24
6f	<5	<10	344	136	0.84

CONCLUSION

In this study we synthesized Ethyl-6-((1H-imidazol-1-yl)methyl)-1,2,3,4-tetrahydro-4-aryl-oxopyrimidine-5-carboxylates by using grinding technique and characterized the compounds by IR, Mass, 1D and 2D NMR spectra like HOSY and HSQC and CHN analysis. The synthesized compounds are obeyed the drug capability of Lipinski's rule of Five.

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