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Development of Some Novel Reverse Transcriptase Inhibitor

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In the present study, a series of substituted 2-aminodaryl-pyrimidine derivatives were synthesized using Schotten-Bauman and Baker-Venkatraman rearrangement principle followed by cyclization of the obtained product. The formed derivatives were characterized by spectral analysis and the purity was checked by TLC.

Key Words: Reverse transcriptase inhibitor, Antiretroviral.

INTRODUCTION

Development of AIDS[1,2] is characterized by susceptibility to various infections and malignancies. The development of the highly effective antiretroviral[3,4] agents made it possible to probe viral pathogenesis. It has been reported in many studies conducted all over the world that enzymatic incorporation of modified nucleosides or nucleotides into virus DNA can lead to inhibition of virulent activity of virus. Experiments using unnatural bases that have different hydrogen bonding pattern from Watson-Crick type have indicated that correct H-bonding is necessary for replication process. It has been reported that diaryl pyrimidines (DAPY)[5] possess antiviral properties as non-nucleoside reverse transcriptase[6,7] inhibitors (NNRTIs). Some 2- and 4-substituted DAPY[5] compounds have been reported with their biological activity. It was found that such compounds have high potency against mutant strains of HIV-1 with minimal *in vitro* toxicity. One of such compound, which is under Phase IIB clinical trial, is TMC125.

Synthesis of new NNRTI's[7] involves four synthetic steps. The first step is synthesis of ester using Schotten-Baumann principle; it involves reaction of acid chloride with an alcohol or phenol in the presence of a base like NaOH or pyridine to obtain an acid derivative. The acid chloride is generated *in situ* by reaction of substituted benzoic acid and phosphorous oxychloride in the presence of pyridine and subsequent esterification of acid chloride with *o*-hydroxy acetophenone to obtain 2-acetyl-1-(substituted benzoyloxy)-

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benzene. In case of unsubstituted compound (**1**), the compound is obtained directly from reaction of benzoyl chloride and *o*-hydroxyacteophenone. The second step uses the principle of Baker-Venkatraman rearrangement. It is carried out in the presence of a base to obtain a β-diketo derivative, which is converted into flavone by acidification with acetic acid and sulphuric acid. The obtained flavone is finally converted into 2-aminodiarylpyrimidine derivatives using guanidine hydrochloride.

EXPERIMENTAL

The melting points were determined in open capillaries, using the heating block type apparatus and are uncorrected. Analytical TLC was carried out on glass plates coated with silica gel G, activated at 110 °C for 0.5 h. The plates were developed by exposure to iodine vapours and anhydrous sodium sulphate was used as drying agent. The IR spectra were recorded on Shimadzu-8300 FTIR instrument using KBr pallets. Solvents and reagents were obtained from SD Fine, Spectrochem and Loba Chemicals.

Synthesis of 2-acetyl-1-(substituted benzoyloxy)benzene derivatives[8,9]: A cold solution of *o*-hydroxyaceto-phenone 3.74 g (0.027 mol), 6.07 g (0.044 mol), 5.31 g (0.039 mol), respectively and 3,4-dimethoxy benzoic acid 5 g (0.027 mol), furoic acid 5 g (0.044 mol) and 2-thenoic acid 5 g (0.039 mol), respectively was taken in a round bottom flask containing pyridine (25 mL). Phosphorous oxychloride (5 mL) was then added slowly to each round bottom flask. The reaction mixture was stirred at room temperature for 3 h and poured into the mixture of crushed ice and HCl. The solid so obtained was filtered, dried and recrystallized from methanol to obtain pure compounds **1-3**.

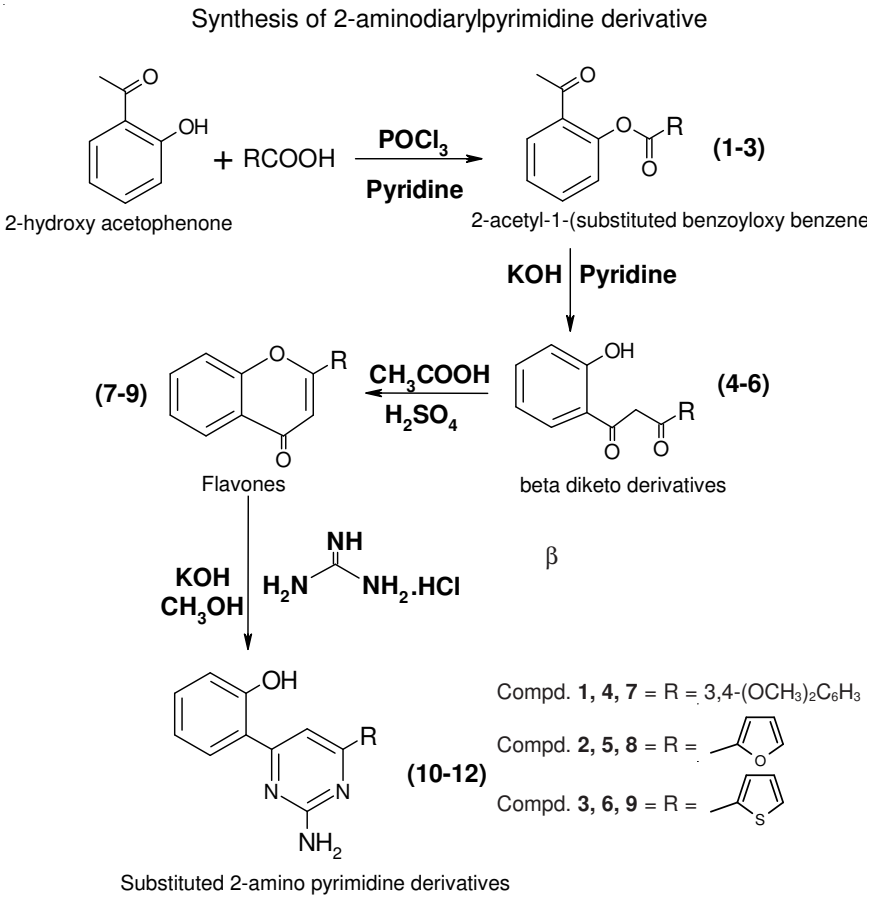
2-Acetyl-1-(3,4-dimethoxybenzoyloxy)benzene (1): Yield 3.6 g (43.68 %); m.p. 129-131 °C, R_f: 0.3 (benzene), IR (KBr, ν_{max}, cm^{-1}): 1732 (C=O *str.*) benzoate ester, 1681 (C=O *str.*)

2-Acetyl-1-(2-furancarbonyloxy)benzene (2): Yield 7 g (68.6 %); m.p. 94-96 °C, R_f: 0.5 (3 % chloroform in benzene), IR (KBr, ν_{max}, cm^{-1}): 1732 (C=O *str.*) benzoate ester, 1689 (C=O *str.*).

2-Acetyl-1-(2-thienylcarbonyloxy)benzene (3): Yield 9.6 g (100 %); m.p. 112-115 °C, R_f: 0.92 (chloroform), IR (KBr, ν_{max}, cm^{-1}): 1732 (C=O *str.*) benzoate ester, 1681 (C=O *str.*)

Synthesis of β-diketo derivatives: The mixture of 2-acetyl-1-(substituted benzoyloxy)benzene derivative 3.5 g, 6.5 g, 9 g (**1-3**), respectively and 7 g potassium hydroxide (pulverized and fused) was stirred at room temperature, in a round bottom flask containing 20 mL pyridine till a paste was obtained. This paste was poured into a mixture of crushed ice and HCl. The solid so obtained was filtered, dried and recrystallized from methanol to obtain compounds **4-6**.

In case of oily compounds, the compound obtained was poured in crushed ice, extracted with chloroform, washed with water; dried and recovered the organic layer. The oily compound obtained was used for the next step without purification.



Scheme-I

1-(3,4-Dimethoxyphenyl)-3-(2-hydroxyphenyl)-1,3-propanedione (4): Yield 1.1 g (0.31 %), R_f: 0.56 (3 % methanol in chloroform), IR (KBr, ν_{max}, cm^{-1}): 3100 (O-H *str.*), 1604 (C=O *str.*).

1-(2-furyl)-3-(2-hydroxyphenyl)-1,3-propanedione (5): Yield 5.5 g (84.6 %) ; m.p.79-81 °C, R_f: 0.8 (chloroform), IR (KBr, ν_{max}, cm^{-1}): 1616 (C=O *str.*).

1-(2-thienyl)-3-(2-hydroxyphenyl)-1,3-propanedione (6): Oily compound was obtained.

Synthesis of flavones: 1-Phenyl-3-(2-hydroxyphenyl)-1,3-propane dione derivative 1 g, 5 g, whole oily compound (**4-6**), respectively was taken and to it 15 mL glacial acetic acid and 2mL of sulphuric acid was added. The reaction mixture was heated on a water bath for 2 h. The resulting solution was poured into crushed ice and filtered to get solid compound. The compound was dried and recrystallized with methanol to obtain the pure compound **7-9**.

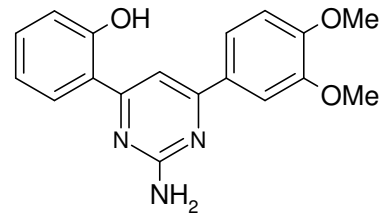
3,4-dimethoxyflavone (7): Yield 0.9 g (87.37 %); m.p. 145-147 °C, R_f: 0.63 (chloroform), IR (KBr, ν_{max}, cm^{-1}): 1653 (C=O *str.*).

2-Furan-2-yl-chromen-4-one (8): Yield 4.3 g (93.4 %); m.p.136-138 °C, R_f: 0.31 (chloroform), IR (KBr, ν_{max}, cm^{-1}): 1662 (C=O *str.*).

2-Thiophen-2-yl-chromen-4-one (9): Yield 6.8 g (81.53 %); m.p. 91-94 °C, R_f: 0.9 (chloroform), IR (KBr, ν_{max}, cm^{-1}): 1639 (C=O *str.*)

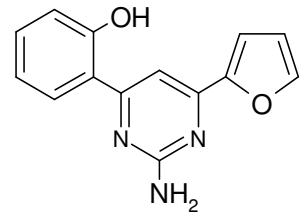
Conversion of flavones to 2-amino diaryl pyrimidine derivatives: A mixture of flavone 0.5 g, 0.5 g, 1 g of (**7-9**), respectively, guanidine hydrochloride 1 g and sodium hydroxide 1.5 g was refluxed in methanol (30 mL) for 10 h. After completion of reaction, the mixture was poured in crushed ice-acetic acid mixture. The solid so obtained was filtered, washed with water and recrystallized from methanol to obtain the final compound **10-12**.

6-(3,4-dimethoxyphenyl)-4-(2-hydroxyphenyl)-2-amino pyrimidine (10): Yield: 0.3 g (52.63 %); m.p. 221-223 °C, R_f: 0.32 (3 % methanol in chloroform).



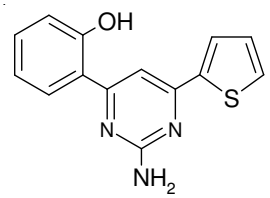
Compound **10**

6-(2-furyl)-4-(2-hydroxyphenyl)-2-amino pyrimidine (11): Yield: 0.3 g (50.84 %); m.p. 211-213 °C, R_f: 0.5 (chloroform).



Compound **11**

6-(2-Thienyl)-4-(2-hydroxyphenyl)-2-amino pyrimidine (12): Yield: 0.29 g (24.78 %); m.p. 182-184 °C, R_f: 0.28 (chloroform).



Compound **12**

RESULTS AND DISCUSSION

Compound **10** showed a characteristic peak at 3190 cm^{-1} (O-H *str.*), asymmetric and symmetric peaks at 3431 and 3313 cm^{-1} for N-H stretching, respectively and a sharp peak at 1259 cm^{-1} (OCH_3 *str.*) in the IR spectrum. The PMR spectrum displayed a sharp singlet for six protons at δ 3.85 (s, 6H, OCH_3) and 6.9 (s, 2H, NH_2). A pyrimidinyl proton and seven aryl protons appeared as multiplet at δ 6.93-8.26 (m, 8H, ArH). A broad hump was observed at δ 14.12 (br, 1H, OH).

Compound **11** showed a characteristic peak at 3283 cm^{-1} (O-H *str.*) and 3417, 3163 cm^{-1} (N-H *str.*) in the IR spectrum. The PMR spectrum displayed a sharp singlet at δ 5.3 (s, 2H, NH_2), The four heteroaryl protons and four aryl protons appeared as multiplet at δ 6.5-7.8 (m, 8H, ArH) and 14.4 (br, 1H, OH).

Compound **12** showed a characteristic peak at 3232 cm^{-1} (O-H *str.*) and 3502, 3342 cm^{-1} (N-H *str.*) in the IR spectrum. The PMR spectrum displayed a multiplet for eight aryl/heteroaryl protons (aryl 4*H* + pyrimidinyl 1*H* + thienyl 3*H*) at δ 6.9-7.8 (m, 8H, ArH), a distinctive sharp singlet appeared at δ 5.27 (s, 2H, NH_2) and broad band at 13.5 (br, 1H, OH).

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