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Research Article

SYNTHESIS OF 4-(1*H*-BENZO[*d*] IMIDAZOL-2-YL) ANILINE DERIVATIVES OF EXPECTED ANTI-HCV ACTIVITY

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ABSTRACT

Starting from 4-(1*H*-benzo[*d*]imidazol-2-yl)aniline (**1**), derivatives of expected anti-HCV activity were prepared. Reaction of compound **1** with maleic anhydride yielded the α,β-unsaturated carboxylic acid **2** which was cyclized using hydrazine hydrate, phenylhydrazine or 4-nitrophenylhydrazine to give the pyrazole derivatives **3**, **4** & **5** respectively. Condensation of compound **1** with the pyrazolecarbaldehydes **6**, **7**, **8** & **9** afforded the corresponding schiff's bases **11**, **12**, **13** & **14** respectively. The structures of the new compounds were confirmed by their spectral data and microanalyses.

INTRODUCTION

An estimated 170 million persons worldwide (WHO) are infected with hepatitis C virus (HCV) which causes chronic liver disease. HCV is a positive stranded RNA virus and is a member of the Flaviviridae family of viruses[1,2]. Current standard therapies consist of combinations of pegylated IFN-a and ribavirin which are only effective in 50-60% of infected individuals and is associated with serious side effects such as depression, flu- like symptoms, fatigue and hemolytic anemia caused by ribavirin[3,4].

There is an unmet need for potent and selective inhibitors of HCV replication. Significant research efforts are currently directed towards targeting viral enzymes especially NS3-4A serine protease[5-10] and NS5B RNA-dependant RNA polymerase which are both required for virus propagation[11-14]. The benzimidazole scaffold is common in different anti-HCV agents with different modes of actions. 2-Aryl benzimidazole-5-carboxylic acids represent a class of HCV NS5B RNA polymerase inhibitors [14]. The first NNI of HCV that entered clinical trials were JTK-109 (**Fig 1**)[14,18] and JTK-003 (**Fig 2**)[18] (Japan Tobacco). These inhibitors act as allosteric inhibitors and block the polymerase before elongation. Co-crystallization studies suggest that these compounds bind on the surface of the thumb domain[19,20].

2-Heteroarylbenzimidazole-5-carboxamides e.g. compound **I** (**Fig 3**) is an inhibitor with optimized right-hand side having IC_{50}= 0.027 μM[21].

Derivatives of bis-benzimidazolemethane were discovered to be highly potent reversible and selective serine protease inhibitors e.g. CRA-6336 (**Fig. 4**)[16,17].

Based on the previous findings, our target in this manuscript was to synthesize benzimidazole derivatives bearing a substituted phenyl group at position 2 which might be potent against hepatitis C virus.

CHEMISTRY

The starting material 4-(*1H*-benzo[*d*]imidazol-2-yl)aniline (**1**), previously prepared by Xu et al.[22], was reacted with maleic anhydride in toluene to yield the α,β-unsaturated carboxylic acid **2**. The structure of compound **2** was proved by its spectral data and microanalysis. The IR spectrum of compound **2** showed the NH band at 3300 cm^{-1}, H-bonded OH & NH broad band at 3107-2370 cm^{-1}, the carboxylic C=O at 1714 cm^{-1} and the amidic C=O at 1644 cm^{-1}. The ^{1}HNMR spectrum of compound **2**

revealed the presence of the two vicinal protons at δ 6.32 and 6.47 ppm as well as the D_2O exchangeable OH signal at δ 10.57 ppm. The ^{13}CNMR exhibited the signals of the amidic C=O at δ 164.06 ppm and the carboxylic C=O at δ 167.58 ppm.

Cyclization of the carboxylic acid **2** using hydrazine hydrate, phenylhydrazine or 4-nitrophenylhydrazine in DMF and ethanol yielded the pyrazole derivatives **3**, **4** & **5** respectively. Cyclization took place via Michael addition of the hydrazine to the olefinic double bond of compound **2** followed by cyclocondensation. Cyclization was confirmed on the basis of the spectral data of the three pyrazole derivatives **3**, **4** & **5** and their microanalyses. The ^{1}HNMR spectra of the three compounds **3**, **4** & **5** revealed the absence of the CH=CH pattern and the presence of the singlet of the pyrazole proton at δ 6.78 for compounds **3** & **5** and at δ 6.81 for compound **4**. (**Scheme 1**).

3-methyl-1-phenyl-5-(piperazin-1-yl)-*1H*-pyrazole-4-carbaldehyde (**7**) was prepared via nucleophilic substitution of the chlorine atom of 5-chloro-3-methyl-1-phenyl-*1H*-pyrazole-4-carbaldehyde (**6**)[23,24] using piperazine in DMF and potassium carbonate as basic medium (**Scheme 2**). The structure of compound **7** was confirmed by its spectral data and microanalysis. The IR spectrum showed the NH band at 3436 cm^{-1} and the ^{1}HNMR spectrum exhibited the piperazine protons as two multiplets at δ 3.05 & 3.31. The pyrazoles **8**[25], **9**[26] & **10**[27] (**Fig 5**) were synthesized according to the previously reported methods. Condensation of 4-(*1H*-benzo[*d*]imidazol-2-yl)aniline (**1**) with the aldehydes **6**, **7**, **8** & **9** in glacial acetic acid yielded the corresponding schiff's bases **11**, **12**, **13** & **14** respectively.(**Scheme 3**). The ^{1}HNMR spectra of compounds **11-14** revealed the presence of CH=N proton at δ 8.65, 8.62, 10.17 & 10.08 respectively. The IR spectra of compounds **11-14** showed the C=N bands at 1668, 1663, 1671 & 1664 cm^{-1} respectively. When the same reaction was carried out with the aldehyde **10**, fission of the pyrazole ring took place to give an unidentified product (**15**). The ^{1}HNMR of compound **15** showed that the protons of the phenyl ring at position 1 of the pyrazole were absent in the ^{1}HNMR spectrum, as well as its mass spectrum gave a M^+ peak at 397 which is different from the molecular weight of the expected product.

EXPERIMENTAL

Compounds used as starting materials and reagents were obtained from Sigma, Aldrich Chemical Co., and utilized without further purification. The IR spectra (4000-400 cm^{-1}) were recorded using KBr pellets in a Jasco FT/IR 300E Fourier transform infrared spectrophotometer on a Perkin Elmer FT-IR 1650 (spectrophotometer). The ^{1}H and ^{13}C NMR spectra were recorded using Joel EX-500 MHz NMR spectrophotometers. Chemical shifts (*δ*) are reported in parts per million (ppm) from the tetramethylsilane resonance in the indicated solvent. Coupling constants (*J*) are reported in Hertz (*Hz*); spectral splitting partners are designed as follow: singlet (s); doublet (d); triplet (t); multiplet (m).The mass spectra were carried out using Finnigan mat SSQ 7000 (Thermo. Inst. Sys. Inc., USA) spectroscopy at 70 ev. Melting points were determined in open capillary tubes on electrothermal SMP30 digital melting point apparatus and were uncorrected.

4.1.1. 4-(1*H*-Benzo[*d*]imidazol-2-yl)aniline (1)[22]

A mixture of *p*-aminobenzoic acid (12.34 g, 90 mmol) and *o*-phenylenediamine (6.48 g, 60 mmol) was refluxed in *o*-phosphoric acid (60 mL) at (180-200) °C for 4h. The reaction mixture was then partially cooled (to about 50°C), poured onto crushed ice and neutralized with 10% NaOH solution (140 mL). The precipitated product was collected by vacuum filtration, washed with excess 10% NaOH solution and then water dried and recrystallized from ethanol. M.p.: 235-237 °C (lit. m.p. 237-240 °C, yield= 66%, R_f= 0.38 [EtAc/Pet. ether (40-60), 2:1]. IR (KBr) υ_{max}/cm^{-1}: 3430 (NH benzimidazole); 3350, 3217 (NH_2 aminophenyl); 3061 (CH arom); 1629 (C=N); 1605 (C=C arom). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ *ppm*): 5.58 (s, NH_2 aminophenyl, D_2O exchangeable), 6.63 (d, 2H, *J* = 8.4 *Hz*, $H_{2`}$, $H_{6`}$ aminophenyl moiety), 7.08 (m, 2H, H_5, H_6 benzimidazole moiety), 7.46 (m, 2H, H_4, H_7 benzimidazole moiety), 7.79 (d, 2H, *J* = 8.4 *Hz*, $H_{3`}$, $H_{5`}$ aminophenyl moiety), 12.46 (br.s, NH benzimidazole, D_2O exchangeable). ^{13}C NMR (500 MHz, DMSO-d_6): 113.05, 114.14, 123.50, 129.32, 135.78, 151.59, 152.68. MS, m/z (%): 210 (M^+ +1, 17%); 209 (M^+, 100%); 208 (M^+ -1, 48%); 181 (12%); 118 (16%). Anal. Calcd for $C_{13}H_{11}N_3$ (FW: 209.10): C, 74.62; H, 5.30; N, 20.08. Found: C, 74.63; H, 5.31; N, 20.08.

4.1.3. 4-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenylamino)-4-oxobut-2-enoic acid (2).

A mixture of compound **1** (2.09 g, 10 mmol) and maleic anhydride (1.08g, 11 mmol) in dry toluene was refluxed for 6h. After reaction completion, the formed solid was collected by vacuum filtration, washed with diethyl ether

and recrystallized from ethanol. M.p.: 255-257 °C, yield= 91%, R_f = 0.62 [Methylene chloride/Pet. ether (40-60)/Ethanol, 3:1:0.5]. IR (KBr) υ_{max}/cm^{-1}: 3430 (NH benzimidazole); 3300 (NH aminophenyl); 3107-2370 (H-bonded OH and NH); 3067, 2992 (CH olefinic & arom); 1714 (C=O carboxylic); 1644 (C=O amidic); 1606 (C=N); 1589 (C=C arom). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ *ppm*): 6.32 (*d*, 1H, *J* = 12.25 *Hz*, olefinic =CH); 6.47 (*d*, 1H, *J* = 12.25 *Hz*, olefinic =CH); 7.19 (m, 2H, H_5, H_6 benzimidazole moiety); 7.56 (m, 2H, H_4, H_7 benzimidazole moiety); 7.78 (d, 2H, *J* = 8.4 *Hz* $H_{2`}$, $H_{6`}$ aminophenyl moiety); 8.10 (d, 2H, *J* = 8.4 *Hz*, $H_{3`}$, $H_{5`}$ aminophenyl moiety); 10.57 (s, 1H, NH aminophenyl, D_2O exchangeable); 12.09 (br., 1H, NH benzimidazole, D_2O exchangeable), 13.09 (br., OH carboxylic, D_2O exchangeable). ^{13}C NMR (500 MHz, DMSO-d_6):110.26, 113.86, 114.18, 115.28, 120.05, 124.93, 127.95, 129.84, 131.13, 133.54, 134.89, 138.85, 141.04, 151.27, 153.91 (Ar-C and olefinic-C), 164.06 (C=O, amidic), 167.58 (C=O, COOH). MS, m/z (%): 307 (M^+, 10%); 306 (M^+ -1, 21%); 289 (19%); 262 (92%); 208 (100%). Anal. Calcd for $C_{17}H_{13}N_3O_3$ (FW: 307.10): C, 66.44; H, 4.26; N, 13.67. Found: C, 66.38; H, 4.31; N, 13.73.

5-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenylamino)-1*H*-pyrazole-3-carboxylic acid (3).

A mixture of compound **3** (0.92 g, 3 mmol) and hydrazine hydrate (4mmol) in ethanol (40 mL) was refluxed for 3 h. Completion of the reaction was monitored by TLC. The excess solvent was evaporated under reduced pressure, poured onto ice. The formed solid was collected by vacuum filtration, washed with diethyl ether and recrystallized from ethanol. M.p.: 180:182 °C, yield= 84%, R_f= 0.63 (EtAc/Pet. ether (40-60)/MeOH, 3:1:0.5), IR (KBr) υ_{max}/cm^{-1}: 3445 (NH benzimidazole); 3330, 3287(NH(s)); 3048 (CH arom); 3110-2412 (H bonded OH and NH); 1689 (C=O carboxylic); 1629, 1607 (C=N(s)); 1538 (C=C arom.). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ *ppm*): 6.78 (s, 1H, CH_4 pyrazolyl moiety), 7.10 (m, 4H, $H_{2`}$, $H_{6`}$ aminophenyl and H_5, H_6 benzimidazole moieties), 7.46 (m, 2H, H_4, H_7 benzimidazole moiety), 7.81 (d, 2H, *J* = 7.65 *Hz*, $H_{3`}$, $H_{5`}$ aminophenyl moiety), 9.03 (s, 1H, NH, D_2O exchangeable); 9.59 (s, 1H, NH, D_2O exchangeable); 12.46 (br.s, NH benzimidazole, D_2O exchangeable); 12.82 (br., OH carboxylic, D_2O exchangeable). MS, m/z (%): 319 (M^+, 48%); 318 (M^+-1, 11%); 274 (35%); 248 (64%); 209 (100%). Anal. Calcd for $C_{17}H_{13}N_5O_2$ (FW: 319.11): C, 63.94; H, 4.10; N, 21.93. Found: C, 63.89; H, 4.08; N, 21.96.

General procedure for the preparation of 5-(4-(1*H*-benzo[*d*]imidazol-2-yl)phenylamino)-1*H*-pyrazole-3-carboxylic acid derivatives (4,5).

A mixture of compound **3** (0.92 g, 3 mmol) and phenylhydrazine or 4-nitrophenylhydrazine (3mmol) and K_2CO_3 (0.41 g, 3mmol) in 40 mL ethanol and 5 mL DMF was refluxed. Completion of the reaction was monitored by TLC. The excess solvent was evaporated under reduced pressure, poured onto ice and the pH was adjusted to pH (6:8). The formed solid was collected by vacuum filtration. The crude solid was purified by column chromatography , eluent: EtAc/Pet. ether (40-60), 7:3 to give compounds **4** & **5**.

5-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenylamino)-1-phenyl-1*H*-pyrazole-3-carboxylic acid (4).

M.p.: 216:218 °C, yield= 52%, R_f=0.58 (EtAc/Pet. ether (40-60)/MeOH, 3:1:0.5). IR (KBr) υ_{max}/cm^{-1}: 3420 (NH benzimidazole); 3378 (NH aminophenyl); 3080, 3020 (CH arom); 3050-2398 (H bonded OH and NH); 1699 (C=O carboxylic); 1626, 1603 (C=N(s)); 1538 (C=C arom). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ *ppm*); 6.81(s, 1H, CH_4 pyrazolyl moiety), 7.16 (m, 4H, $H_{2`}$, $H_{6`}$ aminophenyl and H_5, H_6 benzimidazole moieties), 7.54 (m, 5H, H_4, H_7 benzimidazole and H_{3a}, H_{4a}, H_{5a} phenyl moieties), 7.73 (m, 2H, H_{2a}, H_{6a} phenyl moiety), 8.05 (d, 2H, *J* = 7.65 *Hz*, $H_{3`}$, $H_{5`}$ aminophenyl moiety), 10.09 (s, 1H, NH aminophenyl, D_2O exchangeable), 12.46 (br., NH benzimidazole, D_2O exchangeable), 12.93 (br., OH carboxylic, D_2O exchangeable). MS, m/z (%): 396 (M^+ +1, 7%); 395 (M^+, 20%); 318 (45%); 273 (65%); 247 (58%); 208 (100 %). Anal. Calcd for $C_{23}H_{17}N_5O_2$ (FW: 395.14): C, 69.86; H, 4.33; N, 17.71. Found: C, 69.90; H, 4.32; N, 17.73.

5-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenylamino)-1-(4-nitrophenyl)-1*H*-pyrazole-3-carboxylic acid(5).

M.p.: 326:328 °C, yield= 85%, R_f= 0.42 (EtAc/Pet. ether (40-60)/MeOH, 3:1:0.5). IR (KBr) υ_{max}/cm^{-1}: 3445 (NH benzimidazole); 3339 (NH aminophenyl); 3150-2400 (H bonded OH and NH); 3048 (CH arom), 1693 (C=O carboxylic); 1629, 1607 (C=N(s)); 1576 (C=C arom); 1538 (υ_{as} NO_2); 1403 (υ_s NO_2). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ *ppm*); 6.78 (s, 1H, CH_4 pyrazolyl moiety), 7.12 (m, 4H, $H_{2`}$, $H_{6`}$ aminophenyl and H_5, H_6 benzimidazole moieties), 7.54 (m, 2H, H_4, H_7 benzimidazole moiety), 7.73 (d, 2H, *J* = 7.82 *Hz*, $H_{2``}$, $H_{6``}$ nitrophenyl moiety), 8.05 (d, 2H, *J* = 7.65 *Hz*, $H_{3`}$, $H_{5`}$ aminophenyl moiety), 8.23 (d, 2H, *J* =

7.82 *Hz*, $H_{3``}$, $H_{5``}$ nitrophenyl moiety), 10.26 (s, 1H, NH aminophenyl, D_2O exchangeable), 12.13 (br.s, NH benzimidazole, D_2O exchangeable), 13.04 (br.s, OH carboxylic, D_2O exchangeable). MS, m/z (%): 440 (M^+, 65%); 394 (22%); 349 (41%); 273 (26%); 209 (100%). Anal. Calcd for $C_{23}H_{16}N_6O_4$ (FW: 440.12): C, 62.72; H, 3.66; N, 19.08. Found: C, 62.68; H, 3.70; N, 19.11.

3-methyl-1-phenyl-5-(piperazin-1-yl)-*1H*-pyrazole-4-carbaldehyde (7)

A mixture of compound **6** (4.41 g, 20 mmol), piperazine (1.72 g, 20 mmol) and K_2CO_3 (5.4 g, 40 mmol) in 25 mL DMF was refluxed for 16h. After reaction completion, the reaction mixture poured onto ice and the pH was adjusted to 6. The formed solid was collected by vacuum filtration, washed with pet. ether and recrystallized from ethanol. M.p.: 169-171 °C, yield= 74%, R_f = 0.78 [Pet. ether (40-60)/ethyl acetate, 1:1]. IR (KBr) υ_{max}/cm^{-1}: 3436 (NH); 3032 (CH arom); 2965, 2921 (CH aliph); 2846 (CHO); 1664 (C=O); 1595 (C=N); 1538 (C=C arom). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ *ppm*): 2.32 (s, 3H, CH_3); 3.05 (m, 4H, CH_2); 3.31 (m, 4H, CH_2); 7.46 (m, 5H, phenyl moiety); 9.88 (s, 1H, CHO); 11.71 (s, 1H, NH, D_2O exchangeable). MS, m/z (%): 270 (M^+, 26%); 255 (63%); 240 (57%); 193 (41%); 186 (37%); 77 (92%). Anal. Calcd for $C_{15}H_{18}N_4O$ (FW: 270.15): C, 66.64; H, 6.71; N, 20.73; O, 5.92. Found: C, 66.70; H, 6.77; N, 20.79; O, 5.94.

General procedure for synthesis of compounds 11-15

A mixture of compound **1** (2.09 g, 10 mmol), pyrazolone derivative (10 mmol) and K_2CO_3 (4.11 g, 30 mmol) in 30 mL glacial acetic acid was refluxed. Completion of the reaction was monitored by TLC. The excess solvent was evaporated, poured onto ice and the pH was adjusted to pH (6:8). The formed solid was collected by vacuum filtration, washed with pet. ether and recrystallized from ethanol..

4-(*1H*-benzo[*d*]imidazol-2-yl)-*N*-((5-chloro-3-methyl-1-phenyl-*1H*-pyrazol-4-yl) methylene) aniline (11)

M.p.: 183-185 °C, yield= 41%, R_f= 0.62 [EtAc/Pet. ether (40-60), 2:1]. IR (KBr) υ_{max}/cm^{-1}: 3397 (NH benzimidazole); 3106, 3067 (CH arom); 2984 (CH aliph); 1668 (C=N); 1631, 1602 (C=C arom). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ *ppm*): 1.87 (s, 3H, CH_3); 7.19 (m, 3H, phenyl moiety); 7.38 (m, 2H, phenyl moiety); 7.57 (m, 2H, H_5, H_6 benzimidazole moiety); 7.74 (d, 2H, *J* = 8.4 *Hz*, $H_{2`}$, $H_{6`}$ aminophenyl moiety), 7.96 (m, 2H, H_4, H_7 benzimidazole moiety), 8.20 (d, 2H, *J* = 8.4 *Hz*, $H_{3`}$, $H_{5`}$ aminophenyl moiety); 8.65 (s, 1H, CH=N); 11.40 (br., 1H, NH benzimidazole, D_2O exchangeable). MS, m/z (%): 413 (M^+ +2, 11%); 411 (M^+, 47%); 375 (23%); 219 (34%); 209 (71%); 185 (29%). Anal. Calcd for $C_{24}H_{18}ClN_5$ (FW: 411.13): C, 69.98; H, 4.40; Cl, 8.61; N, 17.00. Found: C, 70.01; H, 4.39; Cl, 8.65; N, 17.06.

4-(*1H*-benzo[*d*]imidazol-2-yl)-*N*-((3-methyl-1-phenyl-5-(piperazin-1-yl)-*1H*-pyrazol-4-yl) methylene) aniline (12)

M.p.: 255-257 °C, yield= 68%, R_f= 0.47 [EtAc/Pet. ether (40-60), 1:1]. IR (KBr) υ_{max}/cm^{-1}: 3422 (NH benzimidazole); 3185 (NH piperazine); 3102, 3074 (CH arom); 2977 (CH aliph); 1663 (C=N); 1601, 1544 (C=C arom). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ *ppm*): 2.06 (s, 3H, CH_3); 3.26 (t, 4H, CH_2); 3.51 (t, 4H, CH_2); 7.16 (m, 3H, phenyl moiety); 7.51 (d, 2H, *J* = 8.4 *Hz*, $H_{2`}$, $H_{6`}$ aminophenyl moiety); 7.60 (m, 2H, H_5, H_6 benzimidazole moiety); 7.72 (m, 2H, phenyl moiety); 7.98 (m, 2H, H_4, H_7 benzimidazole moiety), 8.20 (d, 2H, *J* = 8.4 *Hz*, $H_{3`}$, $H_{5`}$ aminophenyl moiety); 8.62 (s, 1H, CH=N); 10.19 (s, 1H, NH piperazine, D_2O exchangeable); 12.86 (br., 1H, NH benzimidazole, D_2O exchangeable). MS, m/z (%): 461 (M^+, 39%); 384 (55%); 376 (46%); 220 (51%); 78 (91%). Anal. Calcd for $C_{28}H_{27}N_7$ (FW: 461.23): C, 72.86; H, 5.90; N, 21.24. Found: C, 72.91; H, 5.94; N, 21.26.

4-(*1H*-benzo[*d*]imidazol-2-yl)-*N*-((3-methyl-5-morpholino-1-phenyl-*1H*-pyrazol-4-yl) methylene) aniline (13)

M.p.: 241-242 °C, yield= 54%, R_f= 0.52 [EtAc/Pet. ether (40-60), 3:1]. IR (KBr) υ_{max}/cm^{-1}: 3486 (NH benzimidazole); 3111, 3058 (CH arom); 2981 (CH aliph); 1671 (C=N); 1602, 1547 (C=C arom). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ *ppm*): 2.05 (s, 3H, CH_3); 3.48 (t, 4H, CH_2); 3.60 (t, 4H, CH_2); 7.14 (m, 3H, phenyl moiety); 7.52 (m, 2H, H_5, H_6 benzimidazole moiety); 7.70 (m, 2H, phenyl moiety); 7.86 (d, 2H, *J* = 8.4 *Hz*, $H_{2`}$, $H_{6`}$ aminophenyl moiety); 7.98 (m, 2H, H_4, H_7 benzimidazole moiety), 8.06 (d, 2H, *J* = 8.4 *Hz*, $H_{3`}$, $H_{5`}$ aminophenyl moiety); 10.17 (s, 1H, CH=N); 12.81 (br., 1H, NH benzimidazole, D_2O exchangeable). MS, m/z (%): 462 (M^+, 60%); 385 (21%); 376 (71%); 220 (82%); 78 (100%). Anal. Calcd for $C_{28}H_{26}N_6O$ (FW: 462.22): C, 72.71; H, 5.67; N, 18.17; O, 3.46. Found: C, 72.69; H, 5.62; N, 18.22; O, 3.51.

2-(4-((4-(*1H*-benzo[*d*]imidazol-2-yl)phenylimino)methyl)-3-methyl-1-phenyl-*1H*-pyrazol-5-ylthio) ethanol (14)

M.p.: 284-285 °C, yield= 83%, R_f= 0.43 [EtAc/Pet. ether (40-60), 4:1]. IR (KBr) u_{max}/cm^{-1}: 3399 (NH benzimidazole); 3470-2700 (H-bonded OH); 3108, 3058 (CH arom); 2981, 2926 (CH aliph); 1664 (C=N); 1601, 1544 (C=C arom). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ *ppm*): 2.08 (s, 3H, CH_3); 3.31 (t, 2H, SCH_2, J= 6.9); 3.64 (t, 2H, CH_2OH, J= 6.9);); 7.16 (m, 3H, phenyl moiety); 7.38 (m, 2H, H_5, H_6 benzimidazole moiety); 7.53 (m, 2H, phenyl moiety); 7.73 (m, 2H, H_4, H_7 benzimidazole moiety); 7.96 (d, 1H, *J* = 8.4 *Hz*, $H_{2'}$ aminophenyl moiety); 8.05 (d, 2H, *J* = 8.4 *Hz*, $H_{3'}$, $H_{5'}$ aminophenyl moiety); 7.96 (d, 1H, *J* = 8.4 *Hz*, $H_{6'}$ aminophenyl moiety); 10.08 (s, 1H, CH=N); 12.48 (br., 1H, NH benzimidazole, D_2O exchangeable); 13.16 (s, 1H, OH, D_2O exchangeable). MS, m/z (%): 455 (M^++2, 3%); 453 (M^+, 41%); 436 (57%); 422 (32%); 376 (44%); 220 (58%); 209 (100%). Anal. Calcd for $C_{26}H_{23}N_5OS$ (FW: 453.16): C, 68.85; H, 5.11; N, 15.44; O, 3.53; S, 7.07. Found: C, 68.91; H, 5.18; N, 15.45; O, 3.51; S, 7.11.

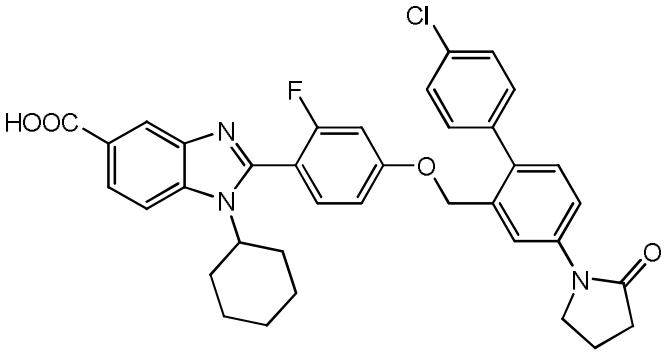


Fig. 1 (JTK-109)

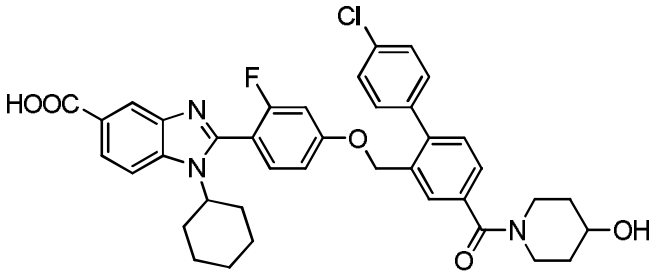


Fig. 2: JTK-003 (Japan Tobacco)

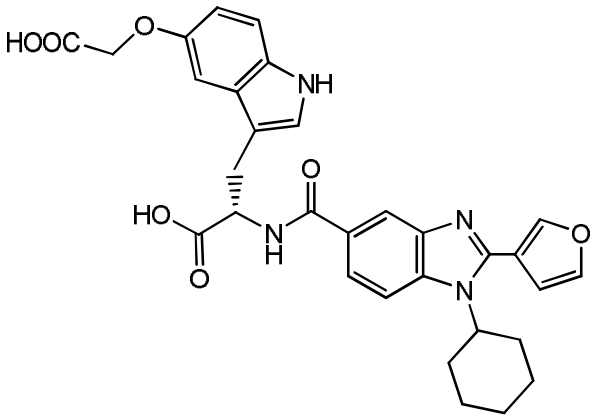


Fig. 3: Compound I

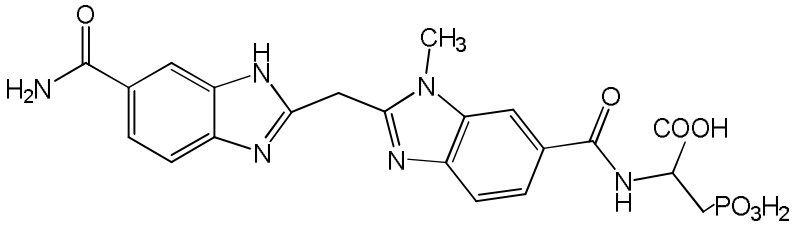
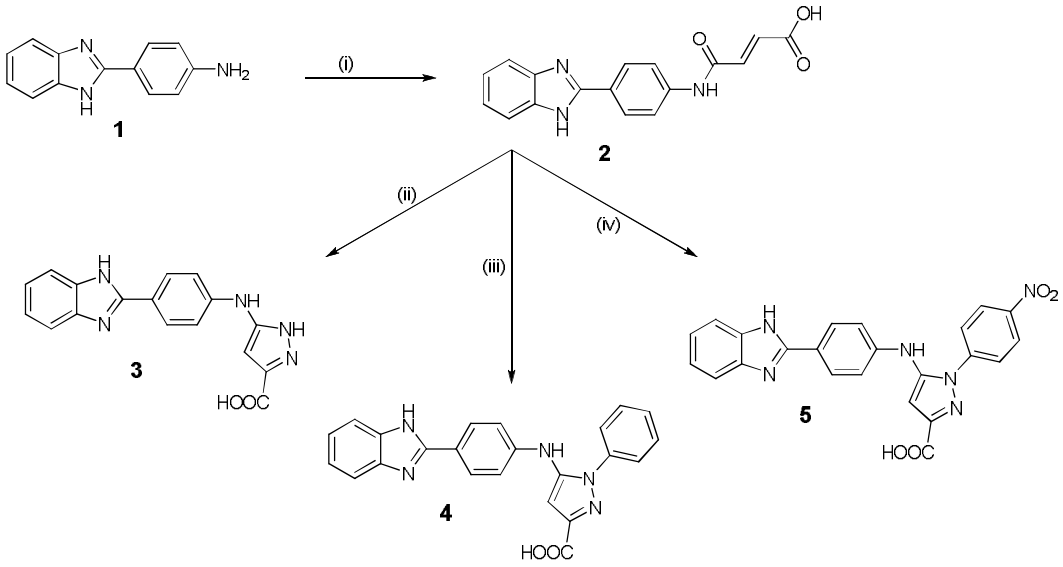
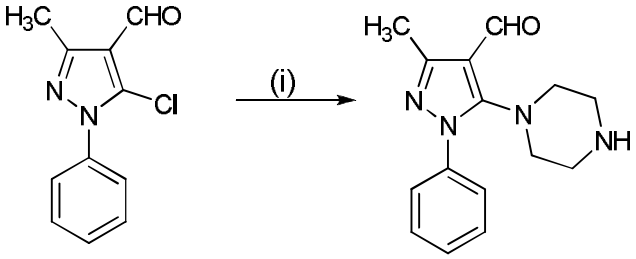


Fig. 4: (CRA-6336)



Scheme 1

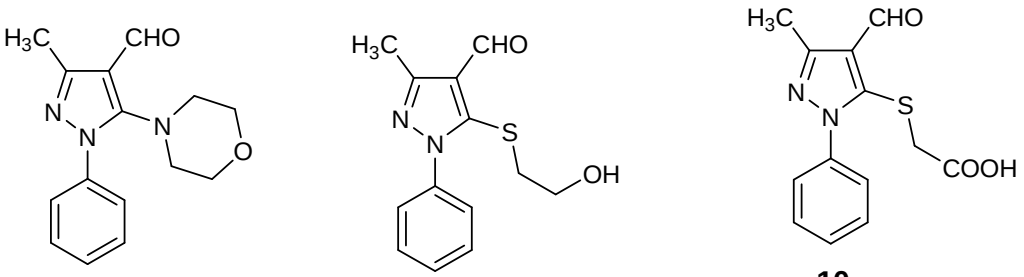
Reagents and conditions: (i) Maleic anhydride, toluene, reflux 6h. (ii) Hydrazine hydrate, ethanol, DMF, reflux 4h. (iii) Phenylhydrazine, ethanol, DMF, reflux 8h. (iv) 4-Nitrophenylhydrazine, ethanol, DMF, reflux 5h.



6 **7**

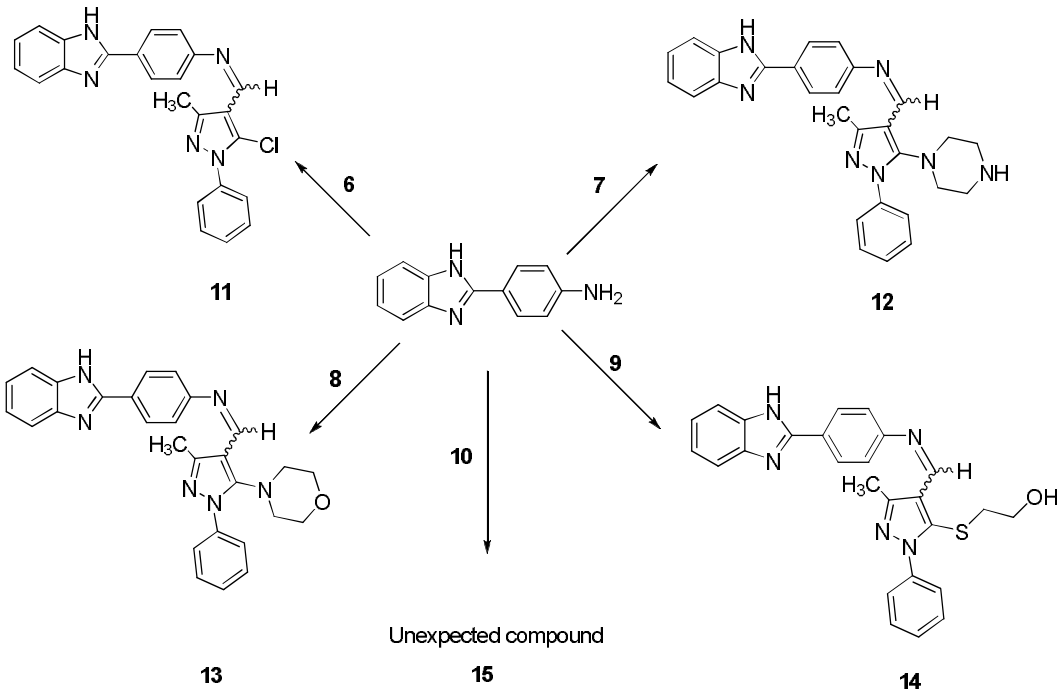
Scheme 2

Reagents and conditions: (i) Piperazine, K_2CO_3, DMF, reflux 16h.



8 **9** **10**

Fig. 5



Scheme 3

Reagents and conditions: The appropriate aldehyde, glacial acetic acid.

CONCLUSION

Successfully, via various routes, different new 4-(1*H*-benzo[*d*]imidazol-2-yl)aniline derivatives were prepared. Their activity against hepaptitis C virus will be tested in the future.

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