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A New Expedient Protocol for the synthesis of 1, 4-Benzodiazepine derivatives (Substitute of HAART)

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A B S T R A C T

Facile expedient protocol based on the versatility and reactivity of intermediate (3) has been developed for finding potential substitutes of highly active antiretroviral therapy [HAART] as well as several molecular probes (8-11) have been developed to produce positive impact in overcoming the problem arising due to the emergence of the multidrug resistant mutants of the virus.

Keywords: Isatoic Anhydride, HAART, Etravirine, 1, 4-benzodiazepine, pyrimidine derivatives

A R T I C L E I N F O

CONTENTS

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1. Introduction

Heterocyclic compounds continue to attract considerable intrest due to their diverse biological activities. The chemistry of nitrogen heteroatom containing aromatic compounds is becoming more popular as an area of research. Isatoic anhydrideis a group of *N*-heterocycles having nitrogen and oxygen atoms. Benzodiazepines and

their analogues have been identified as the heterocyclic scaffolds, which belong to this class. [1,3a-d] Pyrimidine derivatives have been widely studied as this nucleus, has also been recognized to belong to the class of privileged ligands for a number of functionally and structurally discrete biological receptors. [4 a-d] A diarylpyrimidine-based NNRTIs the etravirine (TMC-125) [5] has emerged as one of the highly active second generation drug, which has found FDA approval for the treatment of HIV infected patients with NNRTI-resistant viruses. Federal Drug administration has allowed its application in the highly active antiretroviral therapy [HAART] [6] along with other antiretroviral agents, to adult patients showing multidrug-resistant HIV infections [7]. The treatment for HIV and AIDS target primarily the inhibition of two viral enzymes- the HIV everse transcriptase [8,9] and HIV protease. [10,11] The highly active anti-retroviral therapy 'the HAART' [12].

2. Experimental

Melting points were determined on an open capillary and are uncorrected. The IR sprectra were recorded on Schimadzu FTIR-8400S. ^{1}H-NMR spectra were recorded in $CDCl_3$ on Bruker DRX-400 MHz spectrometer using TMS as internal reference and values are expressesd in δ ppm. Mass spectra were taken on a Joel SX-102 (EI/CI/FAB) mass spectrometer at 70 eV. Purity of all the synthesized compounds were routinely checked by TLC on silica gel G in the solvent system (9:1, benzene : methanol).

Preparation of (E)-2-chloro-3H-benzo[e][1,4]diazepin-5(4H)-one (3)

A solution of **2** (0.05 mol), N, N-dimethylaniline (0.02 mol), $POCl_3$ (0.05 mol) and benzene (100 ml) was refluxed for 7 h. and then allowed to cool overnight. The reaction mixture was washed with ether and then with petroleum ether to remove the soluble impurities. Cold water was then added to the reaction mixture and brought to the neutral point by addition of $NaHCO_3$ solution. It was then extracted three times with dichloromethane to give **3** (yield: 72%); m.p: 130-132 °C; IR (KBr) cm^{-1} : 3015 [C-H str. ArH], 1720 [C=O str.], 1570 [C=C str. ArH], 1520 [C=N str.], 1090 [C-N str.], 670 [C-Cl str.]; ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.0 [s, 1H, NH], 7.63-8.13 [m , 4H, ArH], 3.4 [s, 2H, CH_2], 1.54-1.71 [m, 4H, pyrrolidine]; MS: m/z: 195 (M+,10%) ; Anal. Calcd. /found for $C_9H_7ClN_2O$: C, 55.54/ 55.49; H, 3.63/ 3.59; Cl, 18.22/ 18.17; N, 14.39/ 14.44.

Preparation of (E)-4-(5-oxo-4, 5-dihydro-3H-benzo [e] [1,4] diazepin-2-yloxy) benzonitrile (8a).

To a solution of compound 3 (0.01 mol) and 4-hydroxybenzonitrile (4a) (0.01 mol) in *N*-methyl pyrrolidone (7.5 ml) at 0-5 °C was added potassium *tert*-butoxide (0.01 mol) over a period of 6 h. The reaction was allowed to reach to room temperature and then cold water (300 ml) was added. The reaction mixture was filtered; the residue was suspended in water (150 ml) and acidified to pH 6-7 using conc. HCl. The product was filtered and washed with 15 ml of water. It was extracted by ethyl acetate (2 × 50 ml). The product obtained on evaporation of solvent was washed with 5.0 ml of chilled ethyl acetate. It was finally dried at 55- 60 °C under vacuum to give **8a** (68% yield); m.p. 256-258 °C. IR (KBr) cm-1: 2960 [C-H str. ArH], 2210 [CN str.], 1712 [C=O str.], 1560 [C=N str.], 1515 [C=C str. ArH], 1440 [C-H bending, CH3], 1220 [C-N Str.], 1050 [C-O str.];^{1}H-NMR (400 MHz, CDCl3) δ ppm: 8.2 [1H,d,CH], 8.0[1H,s,NH], 7.15[2H, m, CH], 7.68- 7.81 [5H, m, CH], 3.2 [2H, s, CH_2], MS: *m/z*: 278 (M+, 22%), Analysis: Calcd./found for $C_{16}H_{11}N_3O_2$: C, 69.31 /69.35; H, 4.00 /4.05; N, 15.15 /15.19.

Preparation of (E)-4-(5-oxo-4, 5-dihydro-3H-benzo [e] [1,4]diazepin-2-ylamino)benzonitrile (8b).

To a solution of compound 3 (0.01 mol) and 4-aminobenzonitrile (4b) (0.60 g, 0.01 mol) in *N*-methyl pyrrolidone (7.5 ml) at 0-5 °C was added potassium *tert*-butoxide (0.01 mol) over a period of 7 h. The reaction was allowed to reach to room temperature and then cold water (300 ml) was added. The reaction mixture was filtered; the residue was suspended in water (150 ml) and acidified to pH 6-7 using conc. HCl. The product was filtered and washed with 15 ml of water. It was extracted by ethyl acetate (2 × 50 ml). The product obtained on evaporation of solvent was washed with 5.0 ml of chilled ethyl acetate. It was finally dried at 55- 60 °C under vacuum to give 8b (60% yield), m.p. 254-255 °C. IR (KBr) cm^{-1}: 3320 [NH str], 2910 [C-H str. ArH], 1720 [free C=O str.], 1650 [C=O str. azepine ring], 1615 [C=C str. ArH], 1520 [NH bend.], 1550 [C=N str.], 1420 [C-H bending, CH3], 1010 [C-N str.]; ^{1}H-NMR (400 MHz, CDCl3) δ ppm: 9.8[1H,s,NH], 8.2 [1H,d,CH], 8.0[1H,s,NH], 6.80[2H, m, CH], 7.39- 7.68 [5H, m, CH], 3.2 [2H, s, CH_2], MS: *m/z*: 277 [M+, 10%], Analysis: calcd./found for $C_{16}H_{12}N_4O$: C, 69.55 /69.51; H, 4.38 /4.34; N, 20.28 /20.23.

Preparation of (E)-2-(2, 6-dichloropyrimidin-4-ylamino) -3H-benzo[e][1,4]diazepin-5(4H)-one (9).

To a solution of compound 3 (0.01 mol) and 2,6-dichloropyrimidin-4-amine (4) (0.01 mol) in *N*-methyl pyrrolidone (7.5 ml) at 0-5°C was added potassium *tert*-butoxide (0.01 mol) over a period of 6.5 h. The reaction was allowed to reach to room temperature and then cold water (300 ml) was added. The reaction mixture was filtered; the residue was suspended in water (150 ml) and acidified to pH 6-7 using conc. HCl. The product was filtered and washed with 15 ml of water. It was extracted by ethyl acetate (2 × 50 ml). The product obtained on evaporation of solvent was washed with 5.0 ml of chilled ethyl acetate. It was finally dried at 55- 60 °C under vacuum to give **9** (61% yield); m.p. 247-249°C. IR (KBr) cm-1: 3250 [NH str], 2940 [C-H str. ArH], 1710 free C=O str.], 1620 [NH bend.], 1540 [C=N str.], 1530 [C=C str.], 1460 [C-H bending, CH3], 1210 [C-N str.], 740 [C-Cl str.]; ^{1}H-NMR (400 MHz, CDCl3) δ ppm: 8.15 [1H,d,CH], 8.0[1H,s,NH], 6.45[1H, s, CH], 7.63- 7.70 [3H, m, CH],

4.0[1H,s,NH], 3.2 [2H, s, CH_2], MS: *m/z*: 323 [M+, 16%], Analysis: calcd./found for $C_{13}H_9C_{l2}N_5O$: C, 48.47 /48.43; H, 2.82 /2.86; Cl, 22.01; 22.06 N, 21.74; 21.79

Preparation of 2-[4'-[2'-chloro-6'-(4''-cyanophenoxyl)-amino-1,4]-benzodiazepin-5-[4''-ethyl-piperazinyl-carboxam (E)-4-(2-chloro-6-(5-oxo-4,5-dihydro-3H-benzo [e][1,4] diazepin-2-ylamino) pyrimidin-4-yloxy) benzonitrileide (10a).

To a solution of compound 3 (0.01 mol) and 4-(6-amino-2-chloropyrimidin-4- yloxy) benzonitrile (6a) (0.01 mol) in *N*-methylpyrrolidone (7.5 ml) at 0-5 °C was added potassium *tert*-butoxide (1.14 g, 0.01 mol) over a period of 6 h. The reaction was allowed to reach to room temperature and then cold water (300 ml) was added. The reaction mixture was filtered; the residue was suspended in water (150 ml) and acidified to pH 6-7 using conc. HCl. The product was filtered and washed with 15 ml of water. It was extracted by ethyl acetate (2 × 50 ml). The product obtained on evaporation of solvent was washed with 5.0 ml of chilled ethyl acetate. It was finally dried at 55- 60 °C under vacuum to give **10a** (61% yield); m.p. 254-256°C. IR (KBr) cm-1: 3270 [NH str], 3020 [C-H str.ArH], 2200 [CN str.], 1720 [free C=O str.], 1640 [NH bend.], 1550 [C=Cstr. ArH], 1540 [C=N str.], 1460 [C-H bending, CH3], 1120 [C-N str.], 1100 [C-O str.], 750 [C-Cl str.]; ^{1}H-NMR (400 MHz, CDCl3) δ ppm: 8.0[1H,s,NH], 7.39- 7.70 [5H, m, CH], 6.8[2H, s, CH], 5.60[1H,s,CH], 4.0[1H,s,NH], 3.2 [2H, s, CH_2], MS: *m/z*: 405 [M+, 11%]Analysis: Calcd./found for $C_{20}H_{13}ClN_6O_2$: C, 59.34;59.39 H, 3.24; 3.28 Cl, 8.76; 8.80 N, 20.76; 20.72 O, 7.90; 7.95

Preparation of (E)-4-(2-chloro-6-(5-oxo-4, 5-dihydro-3H-benzo[e][1,4]diazepin-2-ylamino)pyrimidin-4-yl amino)benzonitrile (10b).

To a solution of compound 3 (0.01 mol) and 4-(6-amino-2-chloropyrimidin-4-ylamino) benzonitrile (6b) (0.01 mol) in *N*-methylpyrrolidone (7.5 ml) at 0-5 °C was added potassium *tert*-butoxide (0.01 mol) over a period of 5.5 h. The reaction was allowed to reach to room temperature and then cold water (300 ml) was added. The reaction mixture was filtered; the residue was suspended in water (150 ml) and acidified to pH 6-7 using conc. HCl. The product was filtered and washed with 15 ml of water. It was extracted by ethyl acetate (2 × 50 ml). The product obtained on evaporation of solvent was washed with 5.0 ml of chilled ethyl acetate. It was finally dried at 55- 60 °C under vacuum to give **10b** (60% yield); m.p. 245-247 °C. IR (KBr) cm-1: 3280 [NH str], 2910 [C-H str. ArH], 2215 [CN str.], 1715 [free C=O str.], 1650 [C=C str.], 1610 [C=N str.], 1570 [NH bend.], 1525 [C=Cstr. ArH], 1430 [C-H bending, CH3], 1150 [C-N str.], 770 [C-Cl str.]; ^{1}H-NMR (400 MHz, CDCl3) δ ppm:8.4[1H,s,NH], 8.15 [1H,d,CH], 8.0[1H,s,NH], 7.39- 7.70 [5H, m, CH], 6.8[2H, s, CH], 5.22[1H,s,CH], 4.0[1H,s,NH], 3.2 [2H, s, CH_2], MS: *m/z*: 404 [M+, 25%], Analysis: calcd./found for $C_{20}H_{14}ClN_7O$: C, 59.48; 59.52 H, 3.49; 3.53 Cl, 8.78; 8.73 N, 24.28; 24.33

Preparation of (E)-4-(4-(4-cyanophenoxy)-6-(5-oxo-4,5-dihydro-3H-benzo[e][1,4]diazepin-2-ylamino)pyrimidin-2-ylamino)benzonitrile (11).

To a solution of compound 3 (0.01 mol) and 4-(6-amino-2-(4- cyanophenylamino) pyrimidin-4-yloxy) benzonitrile (7) (0.60 g, 0.01 mol) in *N*methylpyrrolidone (7.5 ml) at 0-5 °C was added potassium *tert*-butoxide (0.01 mol) over a period of 5 h. The reaction mixture was filtered; the residue was suspended in water (150 ml) and acidified to pH 6-7 using conc. HCl. The product was filtered and washed with 15 ml of water. It was extracted by ethyl acetate (2 × 50 ml). The product obtained on evaporation of solvent was washed with 5.0 ml of chilled ethyl acetate. It was finally dried at 55- 60 °C under vacuum to give **11**(64 % yield); m.p. 238-240 °C. IR (KBr) cm-1: 3310 [NH str], 3020 [C-H str. ArH], 2210 [CN str.], 1710 [free C=O str.], 1650 [C=N str.], 1620 [NH bend.], 1570 [C=C str. ArH], 1420 [C-H bending, CH3], 1220 [C-N str.], 1120 [C-O str.]; ^{1}H-NMR (400 MHz, CDCl3) δ ppm:9.45[1H,s,NH], 8.15 [1H,d,CH], 8.0[1H,s,NH], 7.39- 7.70 [5H, m, CH], 6.97[4H, s, CH], 5.22[1H,s,CH], 4.0[1H,s,NH], 3.2 [2H, s, CH_2], MS: *m/z*: 597 [M+, 10%], Analysis: calcd./found for $C_{27}H_{18}N_8O_2$: C, 66.66; 66.62 H, 3.73; 3.69 N, 23.03; 23.07

3. Applications

All the synthesized compounds gave satisfactory results for elemental analysis. IR and 1H-NMR spectral data were found to be consistent to the assigned structures.

4. Conclusion

In conclusion, we have synthesized various derivative of pyrimidine (which could find application as substitute of HAART) with good yields. The main advantage of this method is that reactions were found clean and had operational simplicity. For this, we created an efficient one step synthetic protocol to the formation of corresponding 2-(oxy and amino) substituted analogues, of the privileged nucleus of 1, 4-benzodiazepine.

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6. References

1. Evans BE, Rittle KE, Bock MG, DiPardo RM, Freidinger RM, Whitter WL, Lundell GF, Veber DF, Anderson PS, Chang RSL, Lotti VJ, Cerino DJ, Chen TB, Kling PJ, Kunkel KA, Springer JP, and Hirshfieldt J, J. Med.Chem., 1988, 31, 2235-2246.
2. Horton DA, Bourne GT and Smythe ML, Chem. Rev., **2003**, 103(3): 893-930.

3. a). Poupaert J; Carato P; Colacino E,and Yous S., Cur. Med. Chem., **2005**, 12, 877-885.
b). Triggle, DJ, Cell Mol Neurobiol., 2003, 23(3), 293-303.
c). De Simone RW; Currie KS; Mitchell SA;Darrow, JW and Pippin, DA, Comb. Chem.High. Throughput Screening, **2004**, 7 (5), 473-493.
d). Patchett AA and Nargund RP; Annu.Rep.Med. Chem., **2000**, 35, 289-298.
4. a). Yang J; Dang Q; Liu J; Wei Z; Wu J and Bai X; J. Comb. Chem., **2005**, 7, 474-482.
b). Liu J; Dang Q; Wei Z; Zhang H and Bai X, J.Comb. Chem., **2005**, 7, 627-636.
c). Dang Q and Gomez-Galeno J E; J. Org.Chem., **2002**, 67, 8703-8705.
d). Bhuyan P; Boruah R C and Sandhu J S; J. Org. chem., **1990**, 55, 568-571.
5. Summa V, Petrocchi A, Bonelli F, Crescenzi B, Donghi M, Ferra M, Fiore F, Gardelli C, Gonzalez Paz O, Hazuda, DJ, Jones P, Kinzel O, Laufer R, Montreagudo E, Murglia E, Nizi E, Orvieto F, Pace O, Pescatore G, Scarpelli R, Stillmock K, Witmer MV and Rowley M, J. Med. Chem. **2008,** 51, 5843-5855.
6. Joshi S, Maikap GC, Titirmare S, Chaudhari A and Gurjar MK, Organic Process Research & Development, **2010**, 14, 657-660.
7. Mischiati C, Finotti A, Boschetti S, Baraldi PG, Romagnoli R, Feriotto G, Jeang KT, Bianchi N, Borgatti M, and Gambari R., Biochem Pharmacol. , **2004** Feb 1, 67(3): 401-10.
8. Proudfoot JR, Patel UR, Kapadia SR,Hargrave KD, Novel non-nucleoside inhibitors of HIV-1 reverse transcriptase dipyrido [2,3-b: 2',3'-e] diazepinones, J. Med. Chem., **1995**, 36, 1406.
9. Kelly TA, Proudfoot JR, McNeil DW, Patel UR, David E, Hargrave KD, Grob PM, Cardozo M, Agarwal A, Adams J, Novel non-nucleoside inhibitors of human immunodeficiency virus type-1 reverse transcriptase 5,4-substituted; and 2,4-disubstituted analogs of nevirapine, J. Med. Chem., **1995**, 38: 4839.
10. Ronn R, Sabnis YA, Gossas T, Akerblom E, Danielson UE, Hallberg A, zohansson A, Exploration of acyl sulfonamides as carboxylic acid replacements in protease inhibitors of the hepatitis C virus full-length NS3, Bioorg. Med. Chem., **2006**, 14, 544.
11. Folkes AJ, Ahmadi K, Alderton WK, Alix S, Baker SJ, Box G, Chuckowree IS, Clarke DA, Depledge P, Eccles SA, Friedman LS, Hayes A, Hancox TC, Kugendradas A, Lensun L, Moore P, Olivero AG, Pang J, Patel S, Wilson GHP, Raynaud FI, Rabson A, Sahgir N, Salphati L, Sohal S, Ultsch MH, Valenti M, Wallweber C, Workman P, Zhyvoloup A, Zvelibil MJ, Shuttelworth SJ, The identification of 2-(1H indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-methyl)-4-morpholin -4- yl-thieno [3,2,d] pyrimidine (GDC-0941) as a potent, selective, orally bioavailable inhibitor of class I PI3 kinase for the treatment of cancer, J. Med. Chem., **2008**, 51, 5522.
12. Alcaro S, Artese A, Ceccherini F, Silberstein OF, Perno CF, Sing T, Svicher V, Molecular dynamics and free energy studies on the wild type and mutated HIV-protease complexed with four approved drugs: Mechanism of binding & drug resistance, J. Chem. Inf. Model., **2009**, 49, 1751.