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Synthesis of 2-hetrylamino substituted analogues of the privileged nucleus of pyrrolo-1,5-benzothiazepines of medicinal interest

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ABSTRACT

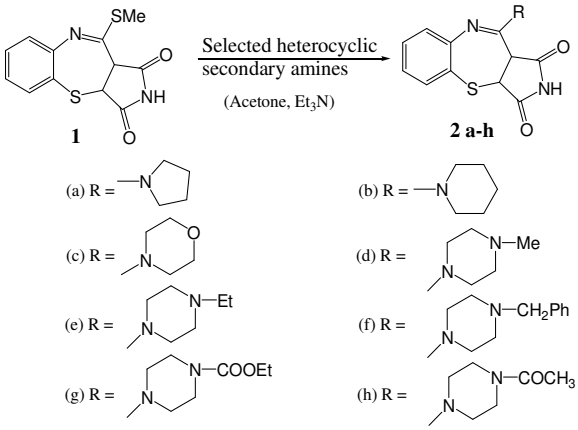
A one pot synthetic approach to the 2-hetrylamino substituted novel analogues of pyrrolo-[3,4-b][1,5]-benzothiazepin-2',5'-diones (2 a-h) has been developed from the corresponding iminothiomethylether derivative 1. The SMe group of 1 undervent smooth nucleophilic displacement reaction with a variety of heteryl amines to afford (2 a-h) in acceptable yields.

Keywords: Iminothiomethylether, Smooth, Nucleophilic and Hetervl.

1. INTRODUCTION

The quest to develop effective therapies for treatment of human immunodeficiency virus (HIV) infection has demonstrated that clinical benefits can be achieved with drugs that target the protease [1,2] or reverse transcriptase[3,4] enzymes. The currently available agents however provide only transient benefit, due to the rapid emergence of drug resistant mutants of the virus [5]. Combinations of drugs have been tried in an attempt to avoid the problem of resistance with some promising results [6,7] and combination therapy now represents the standard of care. However, there is a continuing need to identify improved agents with in each class in order to provide the optimum clinical benefits. On account of the wide range of biological properties exhibited by benzothiazepine derived compounds, benzothiazepine class of privileged scaffolds have been considered among the most important molecules for the drug discovery.

It has been observed that the incorporation of the bioactive pharmacophores such as the pyrrolidine, piperidine, morpholine, N-substituted piperazines etc in the existing drug molecules, exert a profound influence on the biological profiles of the parent molecules. Greatly encouraged by such a trend in the literature, it was planned in the present work to incorporate in 1, the structural features of pyrrolidine, piperidine, morpholine ,N-substituted piperazines, (N-methyl, N-ethyl, N -benzyl, N-carboxyethyl and N-acetylpiperazines) to afford the compound (2 a-h) respectively, following the procedure described for their incorporation on some other related structures in the literature [8,9].



Scheme 1

2. EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected.The purity of the compounds were checked by TLC on silica gel (G) plates in the solvent system (9:1, benzene:methanol). IR spectra were recorded on CE (SHIMADZU) FTIR-8400S.Before analysis all samples were dried for one hour under reduced pressure. ^{1}HNMR spectra were recorded on model AC-300F (Bruker) using $CDCl_3$/ DMSO-d_6 as solvent and TMS as an internal reference. Chemical shift are expressed in δ ppm. Mass spectra were taken on a Joel SX-102 (EI) mass spectrometer at 70 eV.

2.1. General procedure for Preparation of compound 2a - 2h

To the solution of 1 (2.4 g, 0.0085 mol) in dry acetone (10 mL) the equimolar amount of triethylamine (0.78 mL, 0.0055 mol) was added. The solution was cooled to 0°C, and the

pyrrolidine (5.0 ml) was added drop wise. The reaction mixture was stirred at room temperature for 2 h. The precipitated triethylamine hydrochloride was filtered off, the solvent was removed by distillation and the crude product was recrystallized from acetonitrile to give 2a.

Other compounds (2 b-h) were prepared following the same procedure.

3. RESULTS AND DISCUSSION

It has been reported that iminothiomethylether derivative of 1, 5-benzothiazepines are useful synthons in view of their activation for nucleophilic attack. Benzothiazepines embellished with pharmacophores such as pyrrolidine, piperidine, piperazine, etc have been the subject of several reports in the journals and patented literature on account of the positive impact which they showed by their presence in these molecules. In view of the impressive biological activities shown by the hetrylamine substituted derivatives of the 1,5-benzothiazepines, it was thought of interest in the present work to synthesize molecules which carried the indicated hetrylamine bearing substituents at C-2 of the pyrrolo-1,5-benzothiazepine nucleus based on the strategy shown in Scheme 1, which consisted of the treatment of 1 in acetone in the presence of base triethylamine with the heterylamines (such as pyrrolidine, piperidine, morpholine, N^4-(methyl, ethyl, benzyl, ethoxycarbonyl and acetyl)) substituted piperazines to produce 2-hetrylamino substituted analogues 2 (a-h) of pyrrolo-[3,4-b][1,5]-benzothiazepin-2',5'-diones respectively.

The structures of these molecules were found to be consistent to their microanalytical and spectral (IR, ^{1}HNMR and MS data).

3.1. 2-[N'-pyrrolidino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione (2a)

yield (71%), m.p: 140-142°C; IR (KBr) cm^{-1} 3400[NH str.], 1660 [C=O str.], 1630[C=N str.], 3030[C-H str. ArH], 1560 [C=C str. ArH], 690[C-S str.] ; ^{1}HNMR ($CDCl_3$) δ ppm 7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 1.7-2.4[8H,m, pyrrolidine ring], 10.0[1H,s,NH] ; MS: m/z: 301.36 (85%), 231.09(100.0%), 302.09(18.4%), 303.08(4.5%) ; Anal. Cald./found for $C_{15}H_{15}N_3O_2S$: C, 59.78/59.49; H, 5.02/4.99; N, 13.94/13.87; S, 10.64/10.69.

3.2. 2-[N'-piperidino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione (2b)

m.p: 223-225°C; IR (KBr) cm^{-1} 3390[NH str.], 1660[C=O str.], 1625[C=N str.], 3010[C-H str. ArH], 1560 [C=C str. ArH], 690[C-S str.] ; ^{1}HNMR ($CDCl_3$) δ ppm 7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 1.5-2.7[10H,m, piperidine ring], 10.0[1H,s,NH]; Anal. Cald./found for $C_{16}H_{17}N_3O_2S$: C, 60.93/60.63; H, 5.43/5.45; N, 13.32/13.38; S, 10.17/10.22.

3.3. 2-[N'-morpholino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione (2c)

m.p: 152-154°C; IR (KBr) cm^{-1} 3410[NH str.], 1660 [C=O str.] , 1630[C=N str.], 3025[C-H str. ArH], 1565 [C=C str. ArH], 700 [C-S str.]; ^{1}HNMR ($CDCl_3$) δ ppm 7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 2.9[4H,t, morpholine ring], 3.65[4H,t, morpholine ring], 10.0[1H,s,NH]; Anal. Cald./found for $C_{15}H_{15}N_3O_3S$: C, 56.77/57.05; H, 4.76/4.73; N, 13.24/13.31; S, 10.10/10.05.

3.4. Preparation of 2-[N^4-methylpiperazino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione (2d)

m.p: 135-137°C; IR (KBr) cm^{-1} 3400[NH str.], 1660 [C=O str.], 1630[C=N str.], 3030[C-H str. ArH], 1560 [C=C str. ArH], 2970 [C-H str. CH_3], 690[C-S str.]; ^{1}HNMR ($CDCl_3$) δ ppm 7.21-7.39 [4H,m,Ar-H], 3.0 [1H,d, benzothiazepine ring], 3.8 [1H,d, benzothiazepine ring], 2.13-2.65 [8H,m, piperazine ring], 2.26[3H,s,CH_3], 10.0[1H,s,NH]; Anal. Cald./found for $C_{16}H_{18}N_4O_2S$: C, 58.16/57.87; H, 5.49/5.47; N, 16.96/16.88; S, 9.70/9.74.

3.5. 2-[N^4-ethylpiperazino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione (2e)

m.p: 201-203°C; IR (KBr) cm^{-1} 3390[NH str.], 1660[C=O str.], 1625[C=N str.], 3030[C-H str. ArH], 1560 [C=C str. ArH], 2975[C-H str. CH_3], 680[C-S str.]; ^{1}HNMR ($CDCl_3$) δ ppm 7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 2.3-2.6 [8H,m, piperazine ring], 2.38[2H,q,CH_2], 1.02[3H,t,CH_3], 10.0[1H,s,NH]; Anal. Cald./found for $C_{17}H_{20}N_4O_2S$: C, 59.28/58.99; H, 5.85/5.87; N, 16.27/16.19; S, 9.31/9.36.

3.6. 2-[N^4-benzylpiperazino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione (2f)

m.p: 120-122°C; IR (KBr) cm^{-1} 3400[NH str.], 1680[C=O str.], 1630[C=N str.], 3030[C-H str. ArH], 1560 [C=C str. ArH], 2850 [C-H str. CH_2], 690[C-S str.]; ^{1}HNMR ($CDCl_3$) δ ppm 7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8 [1H,d, benzothiazepine ring], 2.37-2.65 [8H,m, piperazine ring], 3.66[2H,s,CH_2], 7.22-7.34[5H,m,Ar-H], 10.0[1H,s,NH]; Anal. Cald./found for $C_{22}H_{22}N_4O_2S$: C, 65.00/65.32; H, 5.46/5.48; N, 13.78/13.71; S, 7.89/7.85.

3.7. 2-[N^4-ethoxycarbonylpiperazino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione (2g)

m.p: 97-99°C; IR (KBr) cm^{-1} 3433[NH str.], 1660,1730 [C=O str.], 1630 [C=N str.], 3030[C-H str. ArH], 1560 [C=C str. ArH], 2957,2851[C-H str. CH_3,CH_2], 694 [C-S str.]; ^{1}HNMR ($CDCl_3$) δ ppm 7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 2.7-2.9[8H,m, piperazine ring], 4.13[2H,q,CH_2], 1.29[3H,t,CH_2], 10.0[1H,s,NH]; MS: m/z: 388.40(75%), 231.12(100.0%), 389.12(21.9%), 390.12(5.8%); Anal. Cald./found for $C_{18}H_{20}N_4O_4S$: C, 55.66/55.93; H, 5.19/5.17; N, 14.42/14.49; S, 8.25/8.21.

3.8. 2-[N⁴-acetylpiperazino][3,4-b]pyrrolo-1,5-benzothiazepin-2',5'-dione (2h)

m.p: 105-106°C; IR (KBr) cm^{-1} 3400[NH str.], 1660,1700 [C=O str.], 1630[C=N str.], 3030[C-H str. ArH], 1560 [C=C str. ArH], 2970[C-H str. CH_3], 690 [C-S str.]; ^{1}HNMR ($CDCl_3$) δ ppm 7.21-7.39[4H,m,Ar-H], 3.0[1H,d, benzothiazepine ring], 3.8[1H,d, benzothiazepine ring], 2.81-3.46[8H,m, piperazine ring], 2.32[3H,s,CH_3], 10.0[1H,s,NH]; Anal. Cald./found for $C_{17}H_{18}N_4O_3S$: C, 56.97/56.69; H, 5.06/5.08; N, 15.63/15.70; S, 8.95/8.91.

4. CONCLUSION

In view of the broad pharmacological spectrum of the pyrrolo-1,5-benzothiazepines and the hetryl amines and their affinity to various biotargets, the potential of 2-iminothiomethyl ether function of 2,3-dihydro-pyrrolo-[3,4-b]-1,5-benzothiazepin-2',5'-dione was explored to develop a one step protocol to the preparation of 2-hetryl amino substituted analogues of 2,3-dihydro-pyrrolo-[3,4-b]-1,5-benzothiazepin-2',5'-diones of medicinal interest.

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