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Synthesis of Tetrazolo, Triazolo and Quinazolino Annulated Analogues of the Privileged Nucleus of Pyrrolo-[1, 5]-Benzothiazepines of Medicinal Interest

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ABSTRACT

The nucleophilic displacement of 2-iminothiomethylether derivative of pyrrolo-1,5-benzothiazepines was elegantly exploited in its reaction with bidentate nucleophiles such as NH_2-NH_2 (followed by reaction with HNO_2), acetahydrazide, isatoic anhydride, amino benzonitrile to allow the facile annulation of this molecule with triazole, tetrazole and quinazoline nucleus.

KEYWORDS: Benzothiazepine, pharmacophore, nucleophilic, bidentate, annulations

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INTRODUCTION

1,5-Benzothiazepine is an important seven membered heterocyclic ring system[1] that features in a number of clinically used drugs[2] due to their potential to provide an active pharmacophore for de novo exploration[3]. The wide array of clinical importance and commercial success associated with pharmacologically active benzothiazepines have led to their recognition in the medicinal community as structures of particular significance.Successful introduction of diltiazem and clentiazem for angina pectoris, hypertension, arrhythmias and other related cardiac disorders proved potential of 1,5-benzothiazepine moiety[2]. The 1,5-Benzothiazepine derivatives are of particular interest for lead discovery because they have been found active against different families of targets[4]. The 1,5-Benzothiazepine scaffold has been used as cardiovascular modulator[5] such as vasodilator[6,7]and antiarrythmic[8], protease inhibitors, elastase[9]/ACE inhibitors[10], antagonists of several G-protein coupled receptors such as cholecystokinin (CCK) receptor as interleukin-1b converting enzyme inhibitors/the angiotensin II receptor (ACE) inhibitors[11]. Recently, anticancer activity[12], haemodynamic effects[13,14], antiulcer activity[15,16]and spasmolytic activities[17-19]have also been reported.Some of the 1,5-benzothiazepine derivatives were also used clinically for CNS disorders which includes thiazesim, and quetiapine fumarate[20,21] .

A literature survey reveals the enhanced bioactivity of annulated 1,5-benzothiazepines[22]. The recent demonstration that some of their derivatives can serve as potential agents in the control and treatment of AIDS has stimulated further interest in these compounds from yet another perspective.

MATERIAL AND METHODS

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.IR spectra were recorded on CE (SHIMADZU) FTIR-8400S.Before analysis all samples were dried for one hour under reduced pressure.Physical and spectral data for all the compounds are given in **Table I and II**. ^{1}H NMR 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.

Preparation of (Z)-1H-benzo[b]pyrrolo[3,4-f]tetrazolo[1,5-d][1,4]thiazepine-10,12(9aH,11H)-dione (1.2)

A mixture of **1.1**, (1.40g, 0.005 mol) and hydrazine hydrate (3.0 mL, 0.06mol) and ethanol (50 mL) was heated at refluxed temperature for 45 h. After this time,the reaction mixture was concentrated to dryness. The residue was taken in N-acetic acid (25 mL) and heated at 45℃ and then the reaction

mixture was cooled and the solid obtained was recrystallized from acetone-water to give **1.2**, Yield 68%, m.p. 145-147℃.

Preparation of (E)-3-methyl-1H-benzo[b]pyrrolo[3,4-f][1,2,4]triazolo[4,3-d][1,4]thiazepine-10,12(9aH,11H)-dione(1.3)

A mixture of **1.1** (1.40g, 0.005 mol), acetohydrazide (0.37g,0.005 mol) and absolute ethanol (50 mL) was refluxed for 65 h. The mixture was concentrated to dryness and recrystallized from ethanol to give **1.3**, Yield 71%, m.p. 186-188℃.

Preparation of (Z)-2,3-benzo[b]pyrimido[1,2-d]pyrrolo[3,4-f][1,4]thiazepine-4,11,13(1H,10aH,12H)-trione (1.4)

A mixture of **1.1** (1.40g, 0.005mol), methyl anthranilate (0.91 g, 0.006 mol) and acetic acid (5 drops) was refluxed for 34 h. After the completion of reaction, the mixture was cooled and extracted with ether. The extracts washed, dried (magnesium sulphate), were concentrated to dryness and recrystallize from methanol to give **1.4**, Yield 69%, m.p. 101-103℃.

Preparation of (Z)-4-amino-2,3-benzo[b]-10a,12dihydrobenzo[b]pyrimido[1,2-d]pyrrolo[3,4-f][1,4]thiazepine-11,13(1H,4H)-dione (1.5)

A mixture of **1.1**, (1.40g, 0.005 mol), o-amino benzonitrile (0.6g,0.005) and acetic acid (4 drops) was refluxed for 42h. After the completion of reaction mixture was cooled and extracted with ether. The extracts were washed with water, dried (magnesium sulphate), concentrated to dryness, the residue was recrystallized from ethanol to give **1.5**, Yield 74%, m.p. 154-155℃.

RESULTS AND CONCLUSION

Infrared spectra

Infrared spectrum of **1.2** showed absorption at 1506 cm^{-1} for (N=N str.), at 3030 cm^{-1} for the (C-H str of aromatic) and 1575 cm^{-1} for the (C=C str of aromatic). It also exhibited band at 680 cm^{-1} for the (C-S str) and at 1660 cm^{-1} for (C=O str). In addition to this,**1.2** also showed the presence of bands at 1285 cm^{-1} for (N-N=N-) and 1110 and 1135 cm^{-1} for (tetrazole ring). This corroborated strongly the formation of tetrazole ring in the compound from its precursor. Similar, IR interpretation was applied on **1.3** to ascertain its formation from **1.1**. In addition to this, compound **1.3** showed the presence of a band at 1475 cm^{-1} for C-H str for CH_3. In the same manner, compound **1.4** showed absorption at 3210, 3350

cm^{-1} for secondary amine, 1660, 1675 cm^{-1} for C=O group, 3040 cm^{-1} for aromatic C-H str and 680 cm^{-1} for C-S str and **1.5** showed the presence of bands at 3430 and 3330 cm^{-1} for primary amine.

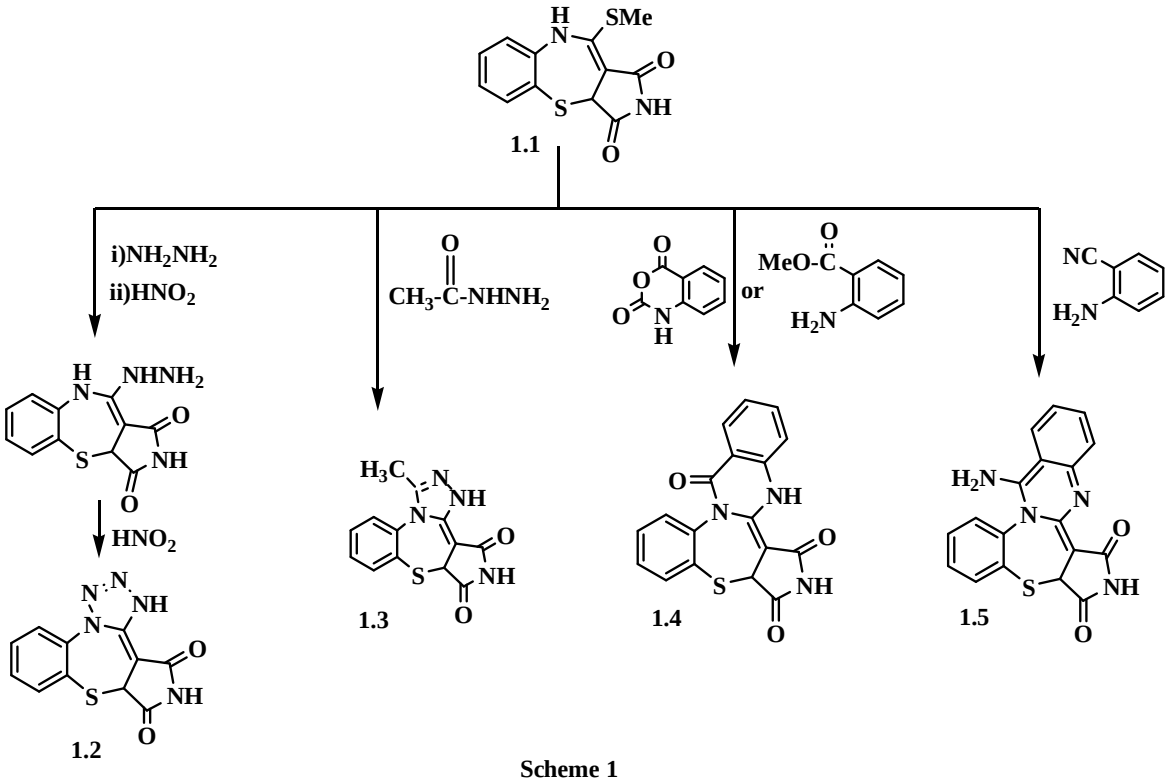
^{1}H-NMR spectra

The ^{1}HNMR spectrum of **1.2** exhibited a singlet at δ 4.16 for one proton of CH of pyrrolo ring. Also a singlet appeared at δ 10.0 which accounts for one proton of NH of pyrrolo ring.Multiplet at δ 6.53-7.14 was attributed to the protons of benzene ring of benzothiazepine. It also showed a singlet for one proton at δ 2.0 for NH of tetrazole ring. Similarly, the ^{1}HNMR spectrum of compound **1.3** showed one additional singlet at δ 2.17 for the CH_3 group which was attached to the triazole ring and a singlet for NH of triazole ring appeared at δ 7.0.^{1}HNMR spectrum of **1.4** exhibited a multiplet for eight protons at δ 7.19-8.80 of aryl hydrogen. A singlet for one proton which appeared at δ 4.0 was attributed to NH of quinazoline ring. Similarly, the ^{1}HNMR spectrum of compound **1.5** showed one additional singlet at δ 6.49 for the NH_2 group.

Mass spectra

Mass spectrum of **1.2** displayed peaks at m/z 273.27 (M^+ 85%), 273.03(100.0%), 274.04(12.1%), 275.03(4.9%).The M^+ peak which appeared at m/z 273.27 (M^+ 85%) was consistent to its molecular weight. Mass spectrum of **1.3** displayed peaks at m/z 286.31 (M^+ 81%), 271(100.0%), 287.06(14.3%), 288.05(4.7%). The M^+ peak which appeared at m/z 286.31 (M^+ 81%) provided a strong evidence to its molecular weight. The base peak at m/z 271(100.0%) appeared by the loss of CH_3 group, substantiated further the structure assigned to this molecule. Mass spectrum of **1.4** exhibited peaks at m/z 349.3(M^+ 79%),333.05(100.0%), 350.06(19.7%), 351.05(4.9%) and compound **1.5** displayed molecular ion peak at m/z 348.38 and base peak at m/z 332.07 which appeared by the loss of NH_2 group.

In anticipation of obtaining medicinally potent novel agents from pyrrolo-1,5-Benzothiazepine nucleus, herein, we describe, the application of facile protocols tothe synthesis of several heteroring annulated derivatives of pyrrolo-1,5-Benzothiazepines.The proposed synthesis was based on the established trend on the reactivity of iminothiomethyl ether function to participate actively in nucleophilic displacement reaction to effect the cyclocondensation of **1.1** with the bidendate nucleophiles, such as NH_2-NH_2 (followed by reaction with HNO_2), acetahydrazide, isatoic anhydride, and amino benzonitrile to form the tetrazolo, triazolo, and quinazolino annulated analogues of pyrrolo-1,5-benzothiazepines **1.2-1.5**respectively as shown in **Scheme-1.**



Scheme 1

Table 1: Spectral data of compound 1.2-1.5

S.No	Compound	IR(KBr)cm^{-1}	^{1}HNMR
1	1.2	3310(N-H str), 1660(C=O str), 3030(Ar-H), 1575(aro.C=C),1506(N=N),1285(N-N=N-), 1110 and 1135 (tetrazole ring) 680(C-S)	6.53-7.14(4H,m,Ar-H),2.0(1H,s,NH of tetrazole ring), 4.16(1H,s,CH of pyrrolo ring)10.0(1H,s,NH)
2	1.3	3320(N-H str), 1660(C=O str), 3035(Ar-H), 1570 (aro. C=C), 1645(C=N), 1475 (C-H str. CH_3),680(C-S)	6.71-7.01(4H,m,Ar-H),7.0(1H,s,NH of triazolering),4.16(1H,s,CH of pyrrolo ring)10.0(1H,s,NH),2.17(3H,s,CH_3)
3	1.4	3350(N-H str), 1660(C=O str),3040(Ar-H), 1580 (aro.C=C), 3210 (NH sec. amine), 1675(C=O),680(C-S)	7.19-8.80(8H,m,Ar-H),4.0(1H,s,NH of quinazoline ring),4.16(1H,s,CH of pyrrolo ring)10.0(1H,s,NH)
4	1.5	3345(N-H str), 1660(C=O str), 3040(Ar-H), 1575(aroC=C),1630(C=N),3430,3330(NH_2), 690(C-S str)	5.84-6.49(8H,m,Ar-H),6.49(2H,s,NH_2),4.16(1H,s,CH of pyrrolo ring)10.0(1H,s,NH)

Table 2: Physical and analytical data of the compounds 1.2-1.5

S. No	Compound No.	Molecular Formula	M.W.	M.P. (°C)	Yield (%)	Elemental Analysis % calculated/found			
						C	H	N	S
1.	**1.2**	$C_{11}H_7N_5O_2S$	273.27	145-147	68	48.35/48.31	2.58/2.59	25.63/25.54	11.73/11.71
2.	**1.3**	$C_{13}H_{10}N_4O_2S$	286.31	186-188	71	54.54/54.19	3.52/3.49	19.57/19.51	11.20/11.03
3.	**1.4**	$C_{18}H_{11}N_3O_3S$	349.36	101-103	69	61.88/61.73	3.17/3.11	12.03/11.76	9.18/9.05
4.	**1.5**	$C_{18}H_{12}N_4O_2S$	348.38	154-155	74	62.06/62.02	3.47/3.35	16.08/16.03	9.20/9.12

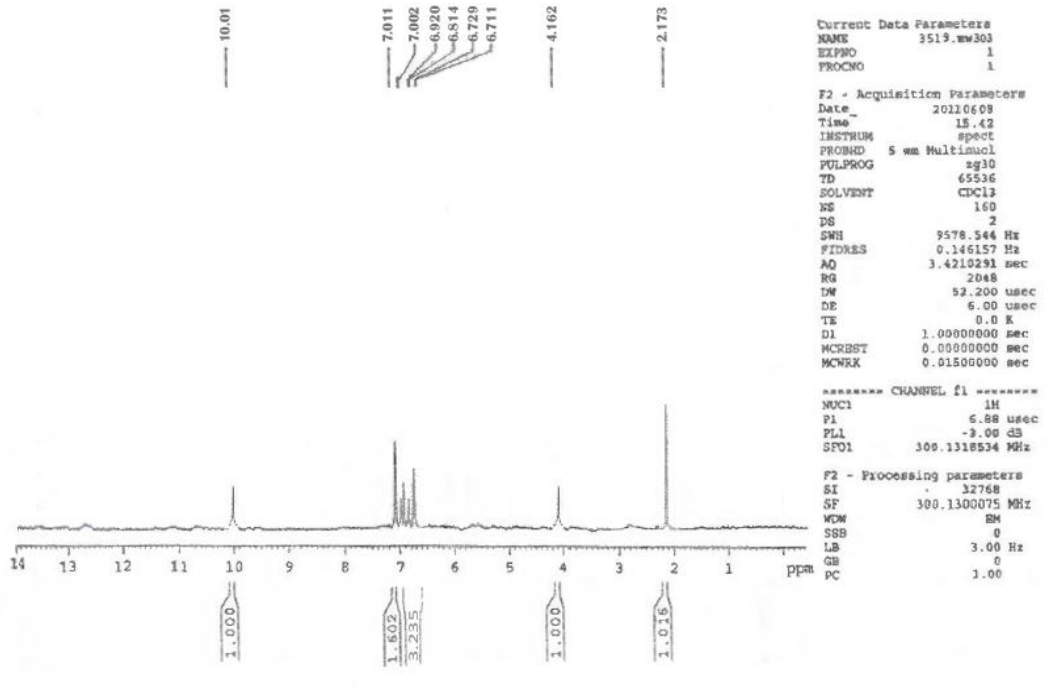


Figure 1: ^{1}HNMR spectra of (*E*)-3-Methyl-1H-benzo[b]pyrrolo[3,4-f][1,2,4] triazolo[4,3-d][1,4]thiazepine-10,12(9aH,11H)-dione(1.3)

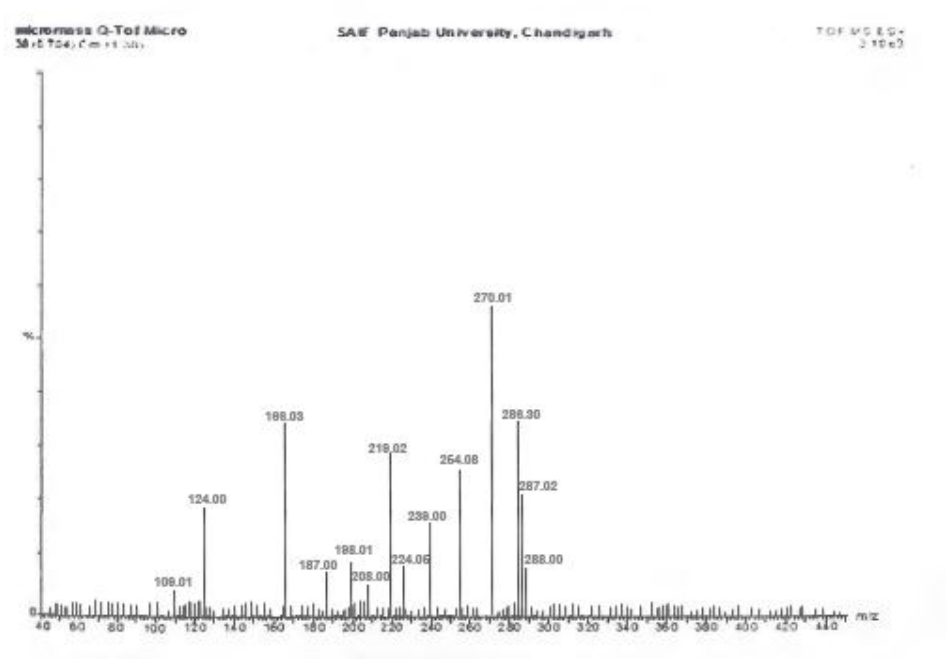


Figure 2:Mass spectra of (*E*)-3-Methyl-1H-benzo[b]pyrrolo[3,4-f][1,2,4] triazolo[4,3-d][1,4]thiazepine-10,12(9aH,11H)-dione(1.3)

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