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Synthesis of benzoazepino incorporated analogues of 1, 5-benzodiazepine of medicinal interest

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ABSTRACT

Exceedingly facile single step expedient protocols based on the versatility and reactivity of corresponding: (dimethylaminomethylene) ketone (6) and chalcone (7) derivatives, have been developed to provide an easy incorporation of the benzoazepine based privileged templates, on to the (1,5)-benzodiazepine nucleus (2) linked on to its 2-position through a p-phenoxyl bridge.

Keywords: Chalcone, (Dimethylaminomethylene) Ketone, Benzodiazepines, Anti-HIV activity.

1. INTRODUCTION

The use of 'privileged heterocyclic scaffolds' [1] in the development of potential therapeutic agents is a rapidly emerging subject in medicinal chemistry [2]. Benzodiazepines and their analogues are among the heterocyclic scaffolds which belong to this class [3]. Heterocyclic systems containing benzodiazepine skeleton have attracted the attention of chemists owing to this nuclei having been identified in the literature as the most promising pharmacophores in drugs design and synthesis [4]. Literature is replete with the chemistry of azepines as their derivatives have been endowed with broad spectrum of biological properties [5-7] including the anti-HIV activity.

It has been observed that incorporation of certain bioactive pharmacophores in the existing drug molecules sometimes exert a profound influence on the biological profile of the molecules. Based on these observations, it was anticipated that incorporation of the bioactive azepine moiety into the molecular framework of [1,5]-benzodiazepine could produce interesting series of compounds with enhanced biological activities. Scheme 1 depicts the study based on this assumption and presents the synthesis of benzoazepine incorporated analogues of [1,5]-benzodiazepines, from the corresponding active synthans - the dimethylamino methylene ketone 6 and the chalcone 7 respectively.

2. EXPERIMENTAL

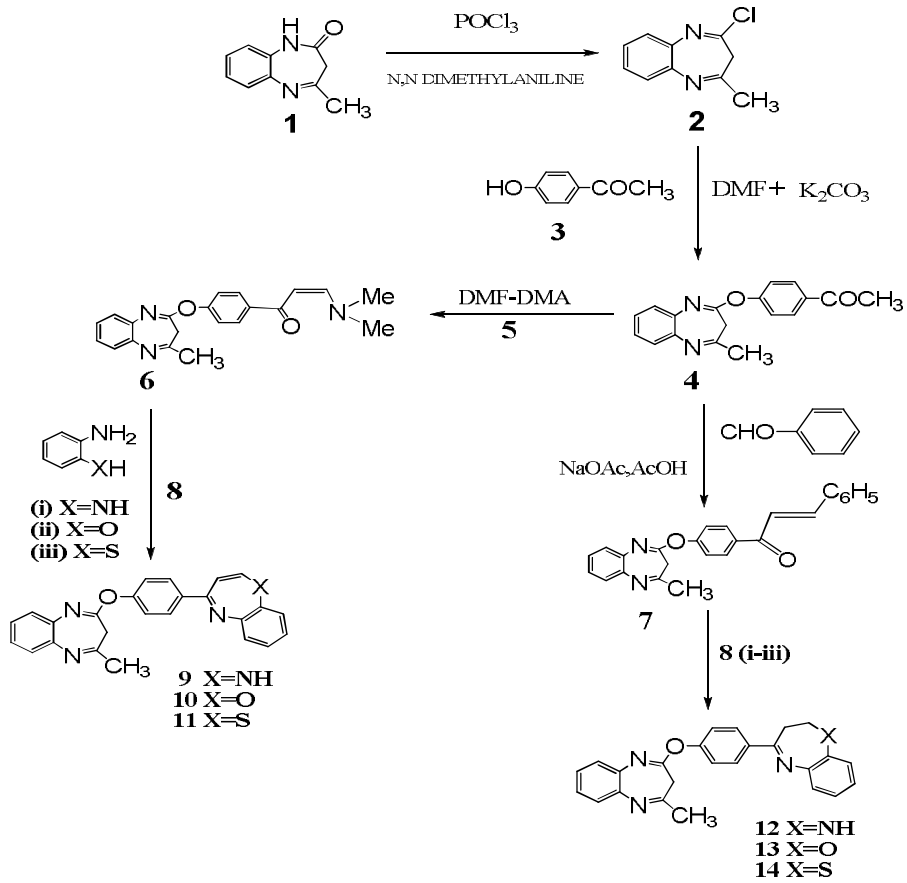
Melting points were determined in an open capillary and are uncorrected. The IR sprectra were recorded on Schimadzu FTIR-8400S. 1HNMR spectra were recorded in CDCl3 on Bruker DRX-400 MHz spectrometer using TMS as internal reference and values are expressesd in δ ppm. Mass spectra were taken on a Joel SX-102 (EI) 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).

2.1. Preparation of 2-chloro- 4-methyl-3H-benzo [1, 5]-benzodiazepine (2)

The mixture of 1 [8-10] (8.70 g., 0.05 mol), N,N-dimethylaniline (2.38 mL 0.02 mol), POCl3 (4.5 mL 0.05 mol) and benzene (100 ml) was refluxed for 7 hrs and then allowed to cool overnight. The cold 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 NaHCO3 solution. It was then extracted three times with dichloromethane to give 2 (8.52 g., yield: 72%); m.p: 142-145 °C; IR (KBr) cm-1 : 3010[C-H str. ArH],1580[C=C str. ArH], 1550[C=N str.], 650[C-Cl str.]; 1HNMR (CDCl3) δ ppm 7.30-7.40[m, 4H, ArH], 2.51 [s,2H,CH_2],1.90[s,3H,CH_3]; MS: m/z: 192.65(M^+,30%),194.04(M+2,10%); Anal.Calcd. /found for $C_{10}H_9ClN_2$: C, 62.35/62.66; H, 4.71/4.73; N,14.54/14.62.

2.2. Preparation of 1-(4-(4-methy-3H-benzo[b][1,5]-diazepin-2-yloxy)phenyl)ethanone (4)

A mixture of 2 (0.192 g., 0.001 mol) and p-hydroxyacetophenone (1.632 g., 0.012 mol) and anhydrous potassium carbonate (0.28 g., 0.002 mol) in DMF (5 mL) was irradiated under microwave, at 190°C for 15 min. The mixture was poured into ice-water, and the pH was adjusted to 7 by adding 5% HCl and the mixture was extracted three times with EtOAc. On removal of the solvent



Scheme-1

in vacuo, the obtained crude product 4 was purified by PTLC on a silica column (eluent: petroleum ether/EtOAc) (0.20 g., yield: 61%); m.p: 198-200°C; IR (KBr) cm^{-1} : 3030 [C-H str. ArH], 1575 [C=C str. ArH], 1545 [C=N str.], 1720[C=O], 1110[C-O str.]; ^{1}HNMR ($CDCl_3$) δ ppm: 7.32-7.42 [m,4H,ArH], 7.77[d,2H,ArH phenoxyl], 7.06[d,2H,ArH phenoxyl], 2.50[s,3H,CH_3], 2.57[s,2H,CH_2], 1.93[s,3H,CH_3]; MS: m/z: 292.33(M^+ 26.0%); Anal. Calcd. /found for $C_{18}H_{16}N_2O_2$: C, 73.95/73.72; H, 5.52/5.54; N,9.58/9.53

2.3. Preparation of (Z)-3-(dimethylamino)-1-(4-(4-methyl-3H-benzo[b] [1, 5] diazepine-2-yloxy) phenyl) prop-2-en-1-one (6)

Compound 4 (2.21 g., 0.0076 mol), N,N-dimethylformamide dimethyl acetal (15 mL), was heated under reflux for 1 h. and concentrated. The residue was triturated with hexane, filtered and washed with hexane to give 6 (1.96 g., yield:66%); m.p:210-212°C; IR (KBr)cm^1:3088[C-Hstr.], 3420[N-Hstr.],1705[C=O], 2929[C-Hstr.], 1290[C-Nstr.], 1610[C=Cstr.ArH], 1532[C=Nstr.], 1090[C-Ostr.], ^{1}HNMR(CDCl3)δppm7.31-7.44[m,4H,ArH], 6.61[s,1H,CH], 8.05[d, 2H, ArH phenoxyl], 7.14[d, 2H, ArH phenoxyl], 3.04[S, 6H, $N(CH_3)_2$], 5.99[d,1H,CH], 2.57[s,2H,CH_2], 1705[C=O], 1.93[s, 3H, CH_3]; MS: m/z:347.41(M^+ 26.0%); Anal. Calcd./found for $C_{21}H_{21}N_3O_2$: C, 72.60/72.49; H,6.09/6.12;N,12.10/12.04.

2.4. Preparation of (Z) 2-methyl-(4-(4-phenybuta-1,-3-dien-2-yl) phenoxyl)-3H benzo[b] [1, 5] diazepine (7)

A mixture of 4 (2.92 g., 0.01 mol), benzaldehyde (1.06 g., 0.01 mol) and fused sodium acetate (0.82 g., 0.015 mol) in glacial acetic acid (5.0mL) was refluxed for 5 h. The reaction mixture was cooled and poured into water. The resulting solid was filtered, washed with water and recrystallized from aqueous ethanol to furnish 7 (2.73 g., yield: 65%) ; m.p: 216-218 °C; IR (KBr) cm-1 : 2999 [C-H str.], [C-H str. ArH],1205 [C-N str.],1499[C=C str.ArH], 1690[C=O], 1569 [C=N str.],1090 [C-O str.]; 1HNMR (CDCl3)δppm:7.29-7.41[m,4H,ArH], 7.59[d,H,CH], 8.06[d,H,CH], 8.05[d,2H,ArH phenoxyl], 7.14[d,2H,ArH phenoxyl], 7.33-7.60[s,5H,ArH], 2.55[s,2H,CH_2], 1.90[s,3H,CH_3]; MS:m/z:380.44(M^+ 31.2%); Anal.Calcd. /found for $C_{25}H_{20}N_2O_2$: C,78.71/78.52; H,5.12/5.14; N,7.32/7.56.

2.5. Preparation of 4-(4-(4-methyl-3H-benzo[b] [1,4]- diazepin-2-yloxy) phenyl)-1H-benzo[b][1,5] diazepine (9)

-en-1-one (6) (4.16g.,0.012 mol) and ethanol (20 mL) was refluxed for 5 h. The solvent was distilled under reduced pressure and the residue was quenched on crushed ice. It was extracted with chloroform, washed with water and dried over anhydrous sodium sulphate to give 9 (0.40., yield 68%); m.p:171-175 ^{0}C. ; IR (KBr) cm-1 : 3035 [C-H str. ArH], 1590 [C=C str. ArH], 1570 [C=N str.], 1160 [C-O str.] 3310 [N-H str.]; 1HNMR(CDCl3) δppm: 7.54-7.59[m,4H,ArH], 7.06[d,2H,ArH phenoxyl], 7.72 [d,2H,ArH phenoxyl], 5.04[d,1H, CH], 4.57 [d,1H,CH], 4.01[s,1H,NH], 2.54 [s,2H,CH_2], 1.92[s,3H,CH_3], 6.86-7.08 [m,4H,ArH]; MS: m/z: 392.45(M^+25.1%); Anal.Calcd./found for $C_{25}H_{20}N_4O$, C,76.79/76.62; H,5.35/5.32; N,13.90/14.20 .

2.6. Preparation of 4-(4-(4-methyl-3H-benzo[b][1,4]- diazepin-2-yloxy) phenyl) benzo[b][1,5] oxazepine (10)

Compound 10 was prepared by the same method as for 9 by using a mixture of aminophenol(1.09g.,0.01mol),(Z)3(dimethylamino)1(4(4methyl3Hbenzo[b][1,4]diazepine-2-yloxy)phenyl)prop-2-en-1-one (6) (4.16g.,0.012 mol) and ethanol (20 mL) to give 10 (0.42g.,yield 70%); m.p:179-181ºC. ; IR (KBr) cm-1 : 3040 [C-H str. ArH], 1600 [C=C str. ArH], 1720 [C=N str.], 1120 [C-O str.]; 1HNMR (400MHz, CDCl3) δ ppm: 7.34-7.47[m,4H, ArH], 7.69[d, 2H, ArH phenoxyl],7.02[d,2H, ArH phenoxyl], 5.18[d, 1H, CH],8.30[d,1H,CH],2.56[s,2H,CH_2],1.93[s,3H,CH_3],6.95-7.16 [m, 4H, ArH]; MS: m/z: 393.44(M^+26.9%); Anal.Calcd./found for $C_{25}H_{19}N_3O_2$: C,76.72/77.51; H 5.46/5.48; N, 13.85/14.20.

2.7. Preparation of 4-(4-(4-methyl-3H-benzo[b][1,4]- diazepin-2-yloxy) phenyl) benzo[b][1,5] thiazepine (11)

Compound 11 was prepared by the same method as for 9 by using a mixture of o-aminothiophenol (1.25 g., 0.01mol), (Z)-3-(dimethylamino)-1-(4-(4-methyl-3H-benzo[b][1,4]diazepin-2-yloxy)phenyl)prop-2-en-1-one (6) to give 11 (4.16g.,0.012 mol) and ethanol (20 mL) (0.47., yield 74%); m.p:177-179ºC. ; IR (KBr) cm-1 :3015 [C-H str. ArH], 810[C-S str.] 1590 [C=C str. ArH], 1550 [C=N str.] 1090 [C-O str.]; 1HNMR (CDCl3)δppm:7.38-7.49[m,4H,ArH], 7.74[d,2H,ArH phenoxyl], 7.07[d,2H,ArH phenoxyl], 7.85[d,1H,CH], 6.10[d,1H,CH], 2.57[s,2H,CH_2], 1.95[s,3H,CH_3],7.17-7.30[m, 4H, ArH]; MS: m/z: 409.50(M^+25.1%); Anal.Calcd./found for

A mixture of o-phenylenediamine (1.08 g., 0.01mol), (Z)-3-(dimethylamino)-1-(4-(4-methyl-3H-benzo[b][1,4]diazepin-2-yloxy)phenyl)prop-2

$C_{25}H_{19}N_3OS$: C,79.10/79.27; H,5.01/5.03; N,10.09/10.21.; S,7.61/7.79.

2.8. Preparation of 2-(4-(2, 3-dihydro-1H-benzo[b][1,4]- diazepin-4-yl) phenyl) benzo[b][1,5] diazepine (12)

A mixture of o-phenylenediamine (1.08 g., 0.01mol), (Z)-2-(methyl-4-(4-(4-phenylbuta1,-3dien-2-yl) phenoxy)-3H-benzo[b][1,5]diazepin (7) (4.56g.,0.012 mol) and ethanol (20 mL) was refluxed for 5 h. The solvent was distilled under reduced pressure and the residue was quenched on crushed ice. It was extracted with chloroform, washed with water and dried over anhydrous sodium sulphate to give 12 (0.39., yield 74%); m.p:-180-182ºC. ; IR (KBr) cm-1 : 3310 [C-H str. ArH], 1550 [C=C str. ArH], 1500 [C=N str.], 1190[C-O str.] 3300 [N-H str.] 1HNMR(CDCl3)δppm:7.30-7.40[m,4H,ArH],7.04[d,2H,ArH phenoxyl],7.85[d,2H,ArH phenoxyl], 3.29 [t,2H,CH] ,3.01[t,2H,CH] ,2.58[s,2H,CH_2], 1.91 [s,3H,CH_3] 4.0[s,1H,NH], .89-7.23 [m,4H, ArH]; MS: m/z: 394.47(M^+29.3%); Anal.Calcd./found for $C_{25}H_{22}N_4O$: C,75.12/75.40; H, 5.62/5.59; N, 14.20/14.13

2.9. Preparation of 4-(4-(4-methyl-3H-benzo[b][1,4]- diazepin-2-yloxy) phenyl-2,3dihydro benzo[b][1,5]oxaiazepine (13)

Compound 13 was prepared by the same method as for 12, by using mixture of o-aminophenol (1.09 g., 0.01mol), (Z)-2-(methyl-4-(4-(4-phenylbuta1,-3dien-2-yl) phenoxy)-3H-benzo[b][1,5]diazepine (4.56g.,0.012 mol) and ethanol (20 mL) to give 12 (0.36., yield 69%); m.p:-196-198ºC. ; IR (KBr) cm-1 : 3050[C-Hstr.],2920[CHstr.ArH],1650[C=Cstr.],1610[C=Cstr.ArH],1530[C=Nstr.],1090[COstr.];1HNMR(CDCl3)δppm:7.36-7.44[m,4H,ArH], 7.05[d,2H,ArH phenoxyl], 7.83[d,2H,ArH phenoxyl], 3.48[t,2H,CH], 4.02[t,2H,CH], 2.55[s,2H,CH_2], 1.95[s,3H,CH_3], 6.68-7.34[m,4H,ArH]; MS: m/z: 395.47(M^+32.4%); Anal.Calcd./found for $C_{25}H_{21}N_3O_2$: C,76.93/76.74; H, 5.35/5.37; N, 10.63/10.59.

2.10. Preparation of 4-(4-(4-methyl-3H-benzo[b][1,4]- diazepin-2-yloxy) phenyl-2,3-dihydro benzo[b][1,5]thiazepine (14)

Compound 14 was prepared by the same method as for 12, by using mixture of o-aminothiophenol (1.25 g., 0.01mol), (Z)-3-(dimethylamino)-1-(4-(4-methyl-3H-benzo[b][1,5]diazepine (7) (4.56g.,0.012 mol) and ethanol (20 mL) to give 14. (0.43., yield 76%);

m.p:-160-163ºC. ; IR (KBr) cm-1 : 3020 [C-H str. ArH], 1580 [C=C str. ArH], 1600[C=Nstr.], 792[CSstr.], 1100[COstr.]; 1HNMR(CDCl3) δppm: 7.38-7.42 [m,4H,ArH], 7.66[d, 2H, ArH phenoxyl], 7.03[d, 2H, ArH phenoxyl], 6.10[d,2H,CH], 7.85[d,2H,CH], 2.55[s,2H,CH_2], 1.96[s,3H,CH_3],7.17-7.32[m,4HArH]; MS: m/z: 413.52 (M^+29.1%); Anal. Calcd./found for $C_{25}H_{21}N_3OS$: C,72.97/72.61; H,5.14/5.16; N,9.18/9.08; S,7.66/7.75

3. RESULTS AND DISCUSSION

Ubiquity of azepine nucleus in chemical literature is undoubtedly a consequence of multifarious biological response which they elicit in combating a variety of body ailments. Recent demonstrations that their derivatives can be used as privileged templates in the development of potential agents for the treatment of AIDS8 has stimulated further interest in this nucleus from yet another perspective. As a part of our endeavor to synthesize novel heterocyclic scaffolds of anticipated biological activity from easily accessible starting materials, we report, herein the preliminary results of our study on the synthesis of benzodiaazepine incorporated [1,5]-benzodiazepine analogues 9-14, linked to its 2-position through a p-phenoxyl bridge. A perusal of literature9 on the potential of 2-(dimethylaminomethylene) ketones and chalcones in synthesis, has demonstrated that these were readily available by the base catalyzed condensation of the carbonyl species containing an active methylene group with (i) DMF-DMA (ii) C6H5CHO respectively. Application of this strategy on 4 formed the intermediates 6 and 7 respectively in moderate to good yield. The versatility of these novel precursors in the formation of benzoazepine nucleus was examined by allowing these to react with o-phenylenediamine, o-aminophenol, o-aminothiophenol 8(i-iii) to give the corresponding 1,5-benzodiazepine,benzoxazepine, and benzothiazepine incorporated analogues of 1,5-benzodiazepines 9-14 respectively, in acceptable yields. Compound 2 was in turn realized in two steps using a reported in procedure[10] which involved the reaction of acetoacetate ester with o-phenylene diamine, followed by treatment with POCl3 in presence of DMA which afforded the corresponding 2-chloro 1,5 benzodiazepine derivative 2. Its reaction with p-hydroxyacetophenone yielded 4 in good yield. All the synthesized compounds gave satisfactory elemental analysis, IR,1HNMR and MS spectral data consistent to the structures assigned to the molecules.

4. CONCLUSION

In conclusion, two elegant protocols have been developed to provide an easy access to the novel benzoazepine incorporated analogues of [1,5]- benzodiazepines linked to its 2-position through a p-phenoxyl bridge, in high yield and purity, using the potential of corresponding 2-(dimethylaminomethylene) ketones (6) and chalcone (7) respectively.

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