An Efficient Synthesis of 1,5-Benzodiazepine Derivatives Catalyzed by Potassium Aluminium Sulfate Dodecahydrate & Evaluation of Their Antioxidant Activity

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ABSTRACT: 1,5- Benzodiazepines and its derivatives constitute an important class of heterocyclic compounds which have proven its medicinal identity as anticancer, antioxidant, cardiovascular agents, viral infection, anticonvulsant, analgesic, sedative, antidepressive, and hypnotic agents. Keeping this in mind, the current research work is to synthesize 2,3-Dihydro-1H-1,5-Benzodiazepines by the condensation of various substituted chalcones and o-phenylenediamine in the presence of double salt, potassium aluminium sulfate dodecahydrate. The structure of the synthesized molecules was confirmed on the basis of physical data and extensive spectral studies. All the compounds have been screened for antioxidant activity using DPPH radical scavenging method. All the compounds showed good free radical scavenging activity (IC50 value between 62- 15 mcg/ml) when compared with the standard ascorbic acid. The results indicated that 2,3-Dihydro-1H-1,5-Benzodiazepines could be the potential candidates eliciting antioxidant activity, and further studies can be conducted using molecular modeling tools for designing 1,5-benzodiazepines having better activity. © 2011 IGJPS. All rights reserved.

KEYWORDS: 1,5-Benzodiazepines; Double Salt; Potassium Aluminium Sulfate Dodecahydrate; Antioxidant; DPPH.

INTRODUCTION

Heterocyclic compounds containing five or six membered ring with one or more nitrogen atoms are always of great importance in the pharmaceutical sector because of having bioisosteric factor\cite{1} and 1,5-benzodiazepines, in specific, offers a wide range of array of biological and therapeutic functions along with its use as precursor for the synthesis of some fused rings benzodiazepine derivatives, such as triazolo-, oxadiazolo-, oxazino-, furano-benzodiazepine etc\cite{2-6}.

Previously in our lab, we had catalytically synthesized 3-(4-1H-Indol-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepin-2-yl)-2H-Chromen-2-one, using potassium aluminium sulfate dodecahydrate, Double Salt(KAl(SO4)\textsubscript{2}. 12 H2O), a non-toxic and inexpensive catalyst. Double salt had reported to be used widely for many reactions, but our team members had strategically developed its utilization in the synthesis of 1,5-benzodiazepines and surprisingly, it eased the synthesis. Literature reported use of 1,5-
benzodiazepines as potential antioxidants[7]. Keeping these facts in mind, we had synthesized few analogues of 1,5-benzodiazepine with the help of Double Salt and evaluate them for their radical scavenging activity.

**MATERIALS & METHODS**

*Synthesis of Potassium Aluminium Sulfate Dodecahydrate:*
Add 25ml of 3M KOH in a 250 ml Beaker containing Aluminium Pieces. Proceed the reaction in fuming hood and filter it while hot to remove undissolved carbon particles. Cool the reaction mixture and acidify it with continuous stirring using 3M H2SO4. Concentrate the mixture and allow it to stand for overnight to crystallize Potassium aluminium sulfate dodecahydrate, a catalyst(Double Salt)[4].

*Synthesis of Indole -3-aldehyde (RV-1) *
Synthesis of RV-1 was done as per the standard procedure[4].

![Figure 1 Synthesis of 1,5-Benzodiazepine Derivatives using Potassium Aluminium Sulphate Dodecahydrate](image-url)
Figure 2 Synthesis of RVB-05 using Potassium Aluminium Sulphate Dodecahydrate

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<tr>
<td>RVB-08</td>
<td>H</td>
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Table 1 Various derivatives of 1,5-Benzodiazepine

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<tr>
<td></td>
<td>RVB-011</td>
<td>H</td>
<td>-OCH₃</td>
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Synthesis of 7,8- substituted-3-acetyl-2H-chromen-2-one (RVC-01-011)
Took 0.05 mole of Salicylaldehyde derivatives & 0.05 mole of ethylacetoacetate in a conical flask. Mixture was subjected to cool in an ice bath, followed by addition on 1 ml of piperidine with continuous stirring. The reaction mixture was kept at freezing pt. temp for 3 hrs, followed by addition of cold ethanol to break the lumps, filter the product and wash the product using cold ethanol. Dried it in the vacuum condition.

Synthesis of 3-(3-substituted-acryloyl)-2H-Chromen-2-one (RVCH-01-011)
Equimolar concentration of RV-1/RV-2 & 3-acetyl-2H-chromen-2-one derivatives(RVC-01-011) was added in 50 ml ethanol with continuous stirring at 32 °C for 30 min, followed by addition of 10% KOH. The reaction mixture was continued to stir for next 4 Hrs. The container was kept overnight at room temperature, following by pouring of the reaction mixture into ice cold water, acidified using dilute HCL. The product was filtered out and dried in vacuum conditions.

Synthesis of 3-(4-substituted)-2,3-dihydro-1H-benzo[b][1,5]diazepin-2-yl)-2H-7,8-substituted-chromen-2-one (RVB-01-011)
0.05 moles of RVCH-01-011 & 0.06 moles of 0-phenylenediamine were added in 40 ml of ethanol containing 500 mg of double salt with continuous stirring for 2 hrs, followed by dilution with water. Extract the benzodiazepine analogue using ethylacetate successively for 3 times. Decant it and passed it through sodium sulfate. Kept it under dessicator for drying.

RESULTS & DISCUSSION

Hybridization of coumarins with 1,5-benzodiazepine is the insight of the current research work. Accordingly, a series of 2,3-dihydro-1H-benzo[b][1,5]diazepin-2-yl)-2H-Chromen-2-ones were prepared and their structures were characterized by using the physical and spectral data.

3-(4-1H-Indol-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepin-2-yl)-2H-Chromen-2-one (RVB-01)[4]: C₂₆H₁₉N₃O₂; Mol. Wt. 405.45g/mol; Calcd. Log P: 3.98±1.10; UV(nm) : 275.4 ; LC-ESI-MS : 404.8 [M+Na]+, 426.7 (M-1+Na)+; FT-IR(KBr ,cm⁻¹): 3329.25 (NH), 3055.35,2922.25(Ar-H), 1716.70 (C=O), 1602.90 (C=C), 1226(C-O-C); 1H-NMR (ppm): 3.3(s, 1H, 3ο- CH), 3.9 (s, 1H, Diazepin-NH), 1.225, 2.2161(d, 2H, 2ο- CH), 6.7-8.5 (m, 14H, Ar-H), 10.7(s, 1H, indolyl-NH).
3-(4-(thiophen-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepin-2-yl)-2H-chromen-2-one (RVB-03): C_{22}H_{16}N_{2}O_{2}S; Mol wt. 372.44 g/mol; Calcd. Log P: 3.73 ± 1.11; UV(nm): 279.70; FT-IR(KBr, cm⁻¹): 3360(N-H), 3064.99 & 2926.11(Ar-H), 1710.92(C=O), 1602.90(C=C), 613.38(C-S), 1226.77(C-O-C).

3-(4-(1H-indol-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepin-2-yl)-8-methoxy-2H-chromen-2-one (RVB-04): C_{27}H_{21}N_{3}O_{3}; Mol. Wt. 435.47 g/mol; Calcd. Log P: 3.60 ± 1.11; UV(nm): 281.30; FT-IR(KBr, cm⁻¹): 3379.40 (N-H), 3047.63 & 2922.25 (Ar-H), 1703.20(C=O), 1637.62 & 1577.82(C=C), 1234.48(C-O-C); \textsuperscript{1}H-NMR(ppm): 9.9267(s, 1H, indolyl-NH), 6.5-8.7(m, 13H, Ar-H), 3.75(3H, methoxy-CH₃), 4.1(1H, aromatic NH), 1.32, 1.98(2H, methylene), 2.3(1H, methine).

2-[4-(1H-indol-3-yl)-2,3-dihydro-1H-1,5-benzodiazepin-2-yl]phenol (RVB-05): C_{32}H_{19}N_{2}O; Mol. Wt. 353.42 g/mol; Calcd. Log P: 2.44 ± 1.10; UV(nm): 217.0 & 280.60; FT-IR(KBr, cm⁻¹): 3396.76( N-H), 3240.52(O-H), 3049.56, 2960.83 & 2920.32(Ar-H), 1695.49(C=O), 1631.83 & 1577.82(C=C str), 1238.34(C-O-C); \textsuperscript{1}H-NMR(ppm): 9.9(s, 1H, indolyl-NH), 6-8.5(m, 13H, Ar-H), 3.3(s,1H, methylene), 2.0, 2.3(2H, methine), 4.0(1H, aromatic NH), 5.5(1H, OH).

3-(4-(1H-indol-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepin-2-yl)-7-(diethylamino)-2H-chromen-2-one (RVB-08): C_{30}H_{28}N_{4}O_{2}; Mol. Wt. 476.57 g/mol; Calcd. Log P: 5.70 ± 1.16; UV(nm): 263.10; FT-IR(KBr, cm⁻¹): 3400.15(N-H), 3010 & 2950.46(Ar-H), 1705.20(C=O), 1608.40(C=C str.), 1240.29(C-O-C).

3-(4-(thiophen-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepin-2-yl)-2H-chromen-2-one (RVB-010): C_{26}H_{25}N_{3}O_{2}S; Mol. Wt. 443.56 g/mol; Calcd. Log P: 5.45 ± 1.16; UV(nm): 300.00; FT-IR(KBr, cm⁻¹): 3377.47(N-H), 3095.85, 2964.69 & 2922.25(Ar-H), 1703.20(C=O), 646.17(C-S), 1612.54(C=C str), 1240.27(C-O-C); \textsuperscript{1}H-NMR(ppm): 9.99(s, 1H, indolyl-NH), 6-8.5(m, 13H, Ar-H), 4.0(1H, Ar-H), 3.7(3H, methoxy-CH), 3.1(1H, methine), 1.2, 1.9(2H, methylene).

7-(diethylamino)-3-(4-thiophen-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepin-2-yl)-2H-chromen-2-one (RVB-011): C_{23}H_{16}N_{2}O_{3}S; Mol. Wt. 402.46 g/mol; Calcd. Log P: 3.67 ± 1.12; UV(nm): 299.30, 205; FT-IR(KBr, cm⁻¹): 3346.61(N-H), 3095.85, 2924.18 & 2841.24(Ar-H), 1703.2(C=O), 636.53(C-S), 1614.47(C=C str), 1033.88(C-C-H), 1246.06(C-O-C); \textsuperscript{1}H-NMR(ppm): 1.22 & 2.4(2H, methylene), 3.8(3H, methoxy- CH₃), 3.3(1H, methine), 4.04(1H, aromatic C-NH), 6.28-8.0(11H, Ar-H).
All the 1,5-benzodiazepine analogs were evaluated for their radical scavenging potential with the help of DPPH radical scavenging protocol. Seven concentrations were taken into consideration i.e. 1000, 500, 250, 125, 62.5, 31.25 and 15.625 µg/ml.

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<th>µg/ml</th>
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Table 2 Results of the Antioxidant Screening of 1,5-Benzodiazepine Analogues.

Results revealed that all the molecules have strong antioxidant activity even at concentration of 15.625 µg/ml and it is dose dependent. Test molecules except RVB-04 have IC50 value below 30 µg/ml which is good indication and could be attributed by 1,5-benzodiazepine scaffold. It has been observed by the analysis of these results that methoxy group on the chromen-2-one and thiophenyl ring at 4th position of 1,5-benzodiazepine i.e. RVB-011 reduced the free radicals much better than the rest of derivatization. Further tailoring the structure of RVB-011 can augment the drug discovery in the anti-clastogenic segment.

ACKNOWLEDGEMENT

The authors are grateful to the management of Manipal University for providing necessary facility for the fulfillment of this work. R K Singla is receiving Young Scientists Fellowship from Department of Science & Technology(Ministry of Science & Technology), Government of India(SR/FT/LS-149/2011).

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