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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.

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[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[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)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].

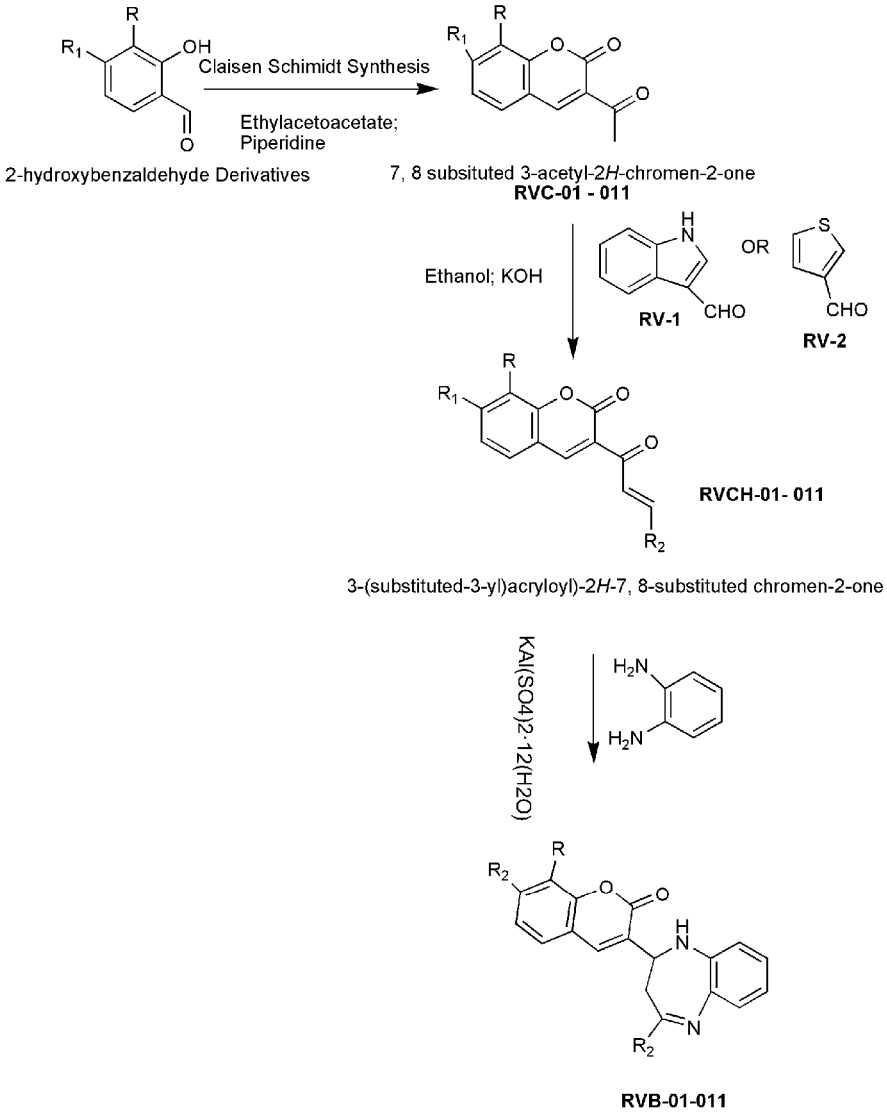


Figure 1 Synthesis of 1,5-Benzodiazepine Derivatives using Potassium Aluminium Sulphate Dodecahydrate

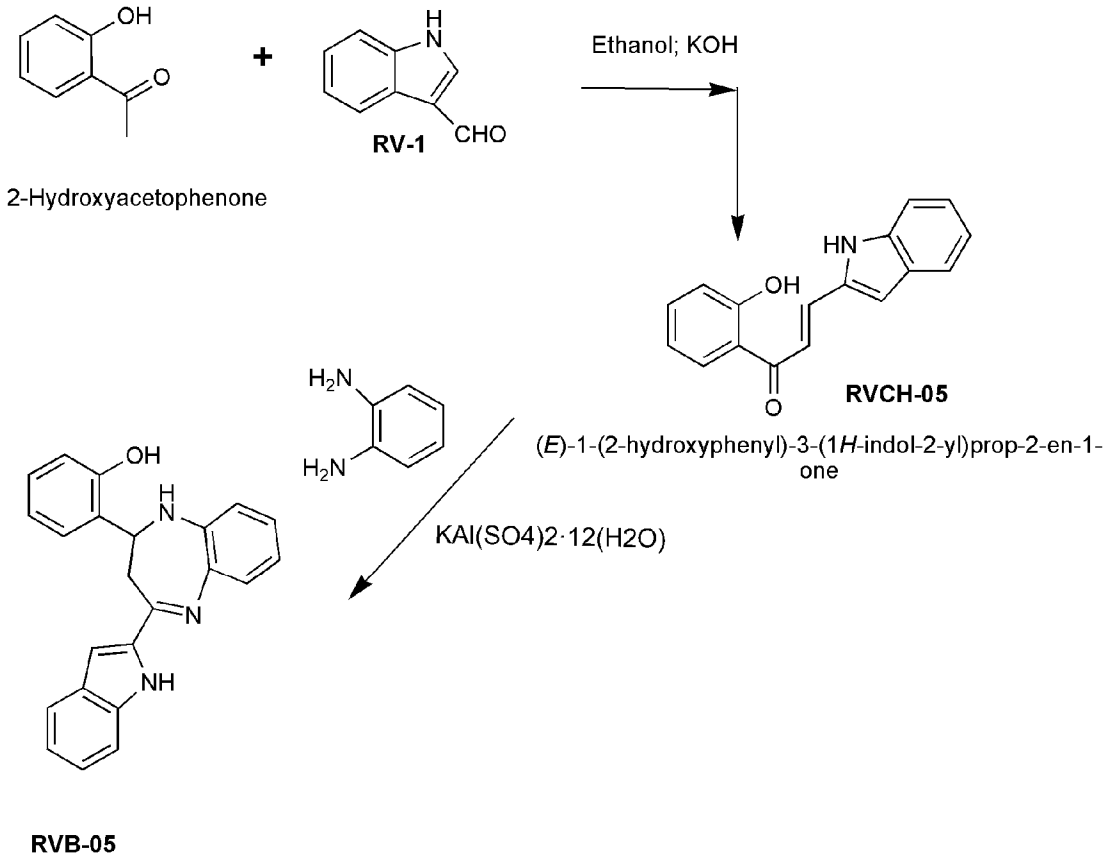
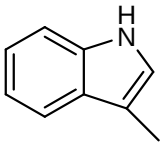
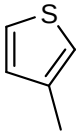
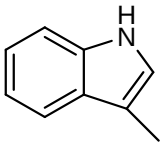
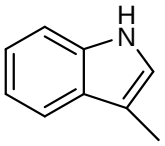


Figure 2 Synthesis of RVB-05 using Potassium Aluminium Sulphate Dodecahydrate

Compd. Code	R	R1	R2
RVB-01	H	H	
RVB-03	H	H	
RVB-04	-OCH_3	H	
RVB-08	H	-$N(C_2H_5)_2$	

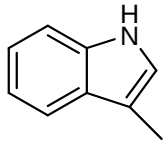
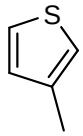
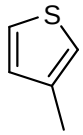
RVB-09	H	$-OCH_3$	
RVB-010	H	$-N(C_2H_5)_2$	
RVB-011	H	$-OCH_3$	

Table 1 Various derivatives of 1,5-Benzodiazepine

*Synthesis of 7,8- subsitituted-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 ^oC 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]: $C_{26}H_{19}N_3O_2$; Mol. Wt. 405.45g/mol; Calcd. Log P: 3.98±1.10; UV(nm) : 275.4 ; LC-ESI-MS : 404.8 m/z$(M)^+$, 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, 3^o - CH), 3.9 (s, 1H, Diazepin-NH), 1,225, 2.2161(d, 2H, 2^o- 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):** $C_{22}H_{16}N_2O_2S$; 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):** $C_{27}H_{21}N_3O_3$; 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); ^{1}H-NMR(ppm): 9.9267(s, 1H, indolyl-NH), 6.5-8.7(m, 13H, Ar-H), 3.75(3H, methoxy-CH_3), 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):** $C_{23}H_{19}N_3O$; 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); ^{1}H-NMR(ppm): 9.9(s, 1H, indolyl- NH), 6.6-8.7(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):** $C_{30}H_{28}N_4O_2$; 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-(1H-indol-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepin-2-yl)-7-methoxy-2H-chromen-2-one **(RVB-09):** $C_{27}H_{21}N_3O_3$; Mol. Wt. 435.474 g/mol; Calcd. Log P: 3.92 ± 1.11; 3400.62(N-H), 2922 & 2854.74(Ar-H), 1703.20(C=O), 1608.69(C=C str.), 1238.34(C-O-C); ^{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-CH3), 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-010):** $C_{26}H_{25}N_3O_2S$; 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); ^{1}H-NMR(ppm): 6.02 – 8.55(m, 11H, Ar-H), 1.1299(6H, 1^o-CH_3), 3.3816(4H, 2^o- CH_2), 4.04(1H, aromatic C-NH), 1.9, 2.4(2H, methylene), 3.44(1H, methine).

*7-methoxy-3-[4-(thiophen-3-yl)-2,3-dihydro-1H-1,5-benzodiazepin-2-yl]-2H-chromen-2-one***(RVB-011):** $C_{23}H_{18}N_2O_3S$; 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); ^{1}H-NMR(ppm): 1.22 & 2.4(2H, methylene), 3.8(3H, methoxy- CH_3), 3.3(1H, methine), 4.04(1H, aromatic C-NH), 6.2816-8.0(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.

Code of the Compound	% Inhibition							IC50 µg/ml
	1mg/ml	500 µg/ml	250 µg/ml	125 µg/ml	62.5 µg/ml	31.25 µg/ml	15.625 µg/ml	
RVB-01	97.492	96.385	96.017	95.279	87.976	55.739	35.674	15-30
RVB-03	95.648	94.762	94.200	93.508	81.337	53.600	34.568	15-30
RVB-04	99.041	99.001	98.820	82.148	57.952	34.715	21.880	30-60
RVB-05	96.680	96.680	96.238	95.574	84.804	54.411	43.641	15-30
RVB-08	99.705	99.115	99.557	98.525	97.197	76.025	46.592	15-25
RVB-09	97.123	96.902	94.984	94.467	73.222	55.592	33.166	15-30
RVB-010	90.484	90.336	89.377	88.222	75.214	55.149	33.461	15-30
RVB-011	98.664	96.771	96.656	96.467	95.279	87.017	57.878	<15.0

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 4^{th} 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.

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