Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2015, 7(8):246-251
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Novel oxoketene dithioacetal based protocols to the synthesis of a series of 3-amino acids and sulpha drugs embellished analogues of the privileged 1, 4 benzodiazepines for their possible use as CCK_A antagonists

Sumitra Nain[*1], Swapnil Sharma[1], Dharma Kishore[2] and Sarvesh Paliwal[1]

[1]*Department of Pharmacy, Banasthali University, Banasthali, Rajasthan, India*
[2]*Department of Chemistry, Banasthali University, Banasthali, Rajasthan, India*

ABSTRACT

Expedient protocols based on the versalility of oxoketenedithio acetals in synthesis ,has been developed to the preparation of the library of many amino acids and sulpha drugs embellished analogues of the privileged 1,4 benzodiazepines for their possible use as CCK_A antagonists .The process to its preparation proceeded with the reaction of 3-oxoketene dithio acetal analogues of 1,4 benzodiazepin-2- one with amino acids and sulpha drugs followed by treatment of the resulting species with alkali to deliver 3(a-d) ,4(a-b), 5(e-f) and (6 c-d) respectively ,in acceptable yields.

Keywords: 5-Phenyl -1,4 benzodiazepin-2- one, oxoketene dithio acetals , CCK_A antagonists

---

INTRODUCTION

Development of compound libraries of small bicyclic and tricyclic ring systems capable of sustaining the requirement of anticipated biological activities by them,has been a major focus of research in the area of chemical biology and medicinal chemistry[1] .In view of this the development of exquisite protocols and efficient practical methodogies to access small molecules of medicinal importance have been of special interest in synthesis .Eversince, a study conducted by Waldmann et.al[2]. on the quantitative analysis of physiologically active natural product scaffolds showed that ones with two or three rings in their molecules were most often found in physiologically active natural products, it has triggered the interest of many chemists to utilize the potential of small molecules, in the design and development of molecular probes for biological evaluations.

The ubiquity of the bicyclic 1,4 benzodiazepine nucleus in medicinal chemistry has been due to this nucleus having been recognized to belong to the class of “privileged medicinal structures” by virtue of its ability to provide ligands to a number of functionally and structurally discrete biological receptors[3]. Its importance in the literature as an “evergreen heterocyclic material” in drug design and development has undoubtedly been a consequence of the multifarious biological response which it elicits in combating a variety of body ailments[4]. Its use has ,not been merely confined to the management of stress related conditions or in the treatment of mental disorders as psychopharmacological agents or as neoplastic agents(discovered ever since the anti-cancer antibiotics bearing the pyrrolo-[1,4] –benzodiazepine framework were isolated from the actinomyces species)[5]but their additional novel applications have been continuously emerging .Recent demonstrations that their derivatives can be used as potential agents in the control and treatment of AIDS[6] (TIBO, Pirenzepine and FDA approved anti-HIV agent -Nevirapine to

name a few) and also as potential CCK_A antagonists has stimulated further interest in this nucleus from yet another perspective[7].This has precisely been the reason for the enormous development of libraries of biologically important materials from this class of compounds[8].

The importance of the amino acids, peptides and sulfa drugs in the area of medical field can never be overstated[9-10]. Ever since, to the discovery of anti-HIV activity in FDA approved "delavirdine" embellished with a sulfonamide group in its molecular framework,the interest on the various facets of the chemistry of this motif in imparting biological activity has increased exponentially thereafter[11].

Encouraged by the medicinal potential of 1,4 benzodiazepines, amino acid and sulfa drug motifs, we report in this communications the preliminary results of our study which have emanated on attaching the amino acid and sulfa drug moieties on to the 3-position of 1,4 benzodiazepine nucleus, by exploiting the potential of corresponding oxoketene dithioacetal derivatives in this venture,This study was conceived on this premise that their presence in tandem in the same molecular framework should contribute significantly to the anticipated biological activity in the resulting materials[12].

MATERIALS AND METHODS

The chemicals required in this study were obtained from commercial sources and used without any further purification. All the melting points were taken in open capillaries and are uncorrected. The reactions were monitored by TLC using toluene/ethyl acetate/formic acid (5:4:1). as the solvent system on silica gel G plates. . IR spectra of the samples were recorded on Schimadzu FTIR-8400 infrared spectrometer on KBr, ^{1}HNMR on Bruker AC 300F in $CDCl_3$+DMSO-d_6 using TMS as internal standard (with chemical shifts expressed in δ, ppm) and the mass spectra on Jeol-JMS-D-300 mass spectrometer.

The starting materials 7-chloro-5-phenyl-1,3-dihydro 2H-[1,4]—benzodiazepin-2-one (**1**) and 7-nitro -1,5- diphenyl-1,3-dihydro-2H-[1,4] benzodiazepin-2-one (**2**) were prepared based on the procedure reported in literature[13] .

General method for the preparation of 7-chloro-5-phenyl-1,3–dihydro-2H-[1,4-benzodiazepin-2-one-3yl] carbonyl amino acids 3(a-d)

7-Chloro-5-phenyl-1,3-dihydro-2H[1,4]-benzodiazepin-2-one (**1**) (8.1 g, 0.03 mole) was added to a stirred solution of carbon disulphide (3g, 0.04 mole) in DMF (10 ml) at 0-5^{o}C and kept for 30 min..The mixture was allowed to stand for further 30 min at room temp.,after adding potassium t-butoxide (6.72 g, 0.06 mol) in DMF (20.0 ml) and benzene (15 ml) .To the resulting suspension methyl iodide (5 g, 0.08 mol) was slowly added and the mixture was refluxed for 3 h..The completion of the reaction was checked by TLC using toluene/ethylacetate/formic acid (5:4:1) as solvent system.The solvent from the reaction mixture was removed under reduced pressure and the residue has taken in chloroform (50 ml) washed with water and dried over anhydrous sodium sulphate.Removal of solvent yielded the crude dithioacetal (9.6 g,85.71%),To a portion of this (0.37 g, 0.001 mole) taken in DMF (20 ml) and amino acids or sulphonamide corresponding to 0.001 mole was added and the reaction mixture was irradiated in a microwave at 160 ^{o}C for 8 min..The completion of reaction was checked by TLC using toluene/ethylacetate/formic acid (5:4:1) as solvent system.Solvent from the reaction mixture was removed under reduced pressure and remaining part was poured on crushed ice.It was extracted with benzene ,which was washed with water and dried over anhydrous sodium sulphate .The crude product was taken in anhydrous THF (20 ml) ,potassium t-butoxide corresponding to 0.03 mol was added and the suspension was stirred at room temp for 8 h.The mixture was poured on crushed ice and extracted with benzene,and washed with water ,dried over anhydrous sodium sulphate to give **3(a-d)** and **4(a-b).**

Same procedure was used in the preparation of 7-nitro -1,5- diphenyl-1,3-dihydro-2H-[1,4] benzodiazepin-2-on-3yl]-carbonyl amino acids **5(e-h)**and **6(c-d)** from 7-nitro -1,5- diphenyl-1,3-dihydro-2H-[1,4] benzodiazepin-2-one (**2**).

(3a, R=CH_3): $C_{19}H_{16}ClN_3O_4$; brown powder; (0.29 g, 76.31%), m.p. 251-253 ^{0}C IR (cm-):3135, 3025, 1695, 1647, 1633, 1620, 1537, 1487, 1411, 1376, 1280, 1231, 1170, 1119, 1055, 834, 795, 780, 712; 1H-NMR (DMSO): 7.92 (2H, d, J = 7.2 Hz), 7.59-7.54 (2H, m), 7.48-7.43 (2H, m), 7.40-7.35 (2H, m), 5.13 (1H, s), 4.68 (1H, d, J = 2.7 Hz), 1.35 (3H, s); ESI-MS: m/z 386.08 $(M+H)^{+\cdot}$ Cal(%) For $C_{19}H_{16}ClN_3O_4$: C;59.15 H;4.18; Cl;9.19; N;10.89.Found; C;59.27 H;4.16; Cl;9.13; N;10.79.

(3b,R=CH_2CH_3): $C_{25}H_{20}ClN_3O_4$; yellow solid (0.37 g, 80.43%), m.p. 257-259 ^{0}C IR(cm-):3093, 3029, 1665, 1634, 1605, 1522, 1470, 1433, 1380, 1367, 1288, 1255, 1165, 1128, 1065, 985, 968, 787, 710, 625, 511; 1H-NMR (DMSO): 7.93 (2H, d, J = 7.2 Hz), 7.59-7.54 (2H, m), 7.48-7.43 (1H, t, J = 7.2 Hz), 7.34-7.04 (8H, m), 5.04 (1H, s), 4.91-4.87 (1H, m), 3.14-3.11 (1H, m), 2.97-2.95 (1H, m); ESI-MS: m/z 462.11 $(M+H)^+$. Cal(%) For $C_{25}H_{20}ClN_3O_4$: C;65.01; H;4.36; Cl;7.68; N;9.10.Found; C;65.00; H;4.34; Cl;7.63; N;9.09.

(3c,R=$CH(CH_3)_2$):$C_{21}H_{20}ClN_3O_4$;Yellow colour powder (0.32 g, 80%), m.p.255-257 ^{0}C IR(cm-):3195, 2996, 1670, 1610, 1560, 1509, 1447, 1411, 1339, 1257, 1178, 1167, 1082, 1067, 988, 970, 820, 798, 732, 630, 579, 530; 1H-NMR (DMSO): 7.70 (2H, d, J = 7.2 Hz), 7.59-7.54 (2H, m), 7.48-7.44 (2H, m), 7.40-7.28 (2H, m), 5.13 (1H, s), 4.48-4.46 (2H, m), 1.46 (6H, s); ESI-MS: m/z 414.04 $(M+H)^+$. For $C_{21}H_{20}ClN_3O_4$: C;60.95; H;4.87; Cl;8.57; N;10.15.Found; C;60.93; H;4.84; Cl;8.52; N;10.13.

(3d,R=Pyrrolyl): $C_{21}H_{18}ClN_3O_4$; Yellow, brown powder: (0.35 g, 87.5%), m.p. 253-255^{0}C; IR(cm-):3193, 2974, 2935, 1629, 1596, 1507, 1467, 1423, 1386, 1365, 1277, 1246, 1155, 1110, 1017, 803, 782, 615, 681, 510; 1H-NMR (DMSO): 7.92 (2H, d, J = 7.2 Hz), 7.59-7.54 (2H, m), 7.48-7.43 (2H, m), 7.40-7.35 (2H, m), 5.06 (1H, s), 4.77 (1H, d, J = 2.7 Hz), 3.83-3.74 (2H, m), 2.17-1.97 (4H, m); ESI-MS: m/z 411.99 $(M+H)^+$. For $C_{21}H_{18}ClN_3O_4$: C;61.24; H;4.41; N;10.20; Found; : C;61.27; H;4.43; N;10.19.

(4a,R=CH_3): $C_{24}H_{19}ClN_4O_5S$; yellow powder; (0.35 g, 70.00%), m.p.234-236^{0}C; IR(cm-):3120, 2970, 2925, 1630, 1590, 1515, 1466, 1381, 1290, 1247, 1174, 1112, 1050, 1033, 929, 809, 770, 621; 1H-NMR (DMSO): 8.05-7.88 (6H, m), 7.60-7.54 (2H, m), 7.48-7.43 (3H, m), 7.30-7.25 (1H, m), 5.13 (1H, s), 2.06 (3H, s); ESI-MS: m/z 511.43 $(M+H)^+$. For $C_{24}H_{19}ClN_4O_5S$: ;56.42;H;3.75;Cl;6.94;N;10.97,S;6.28.Found;C;56.41;H;3.77;Cl;6.96;N;10.94,S;6.26.

(4b,R=Pyridyl): $C_{27}H_{20}ClN_5O_4S$; brown solid (0.46 g, 86.76%), m.p. 240-242^{0}C ; IR(cm-):3121, 3030, 1672, 1659, 1651, 1525, 1500, 1450, 1414, 1305, 1280, 1195, 1139, 1070, 830, 800, 780, 734, 645, 520; 1H-NMR (DMSO): 8.49 (1H, d, J = 6.6 Hz), 7.98-7.92 (6H, m), 7.69-7.64 (2H, m), 7.48-7.43 (4H, m), 7.40-7.35 (1H, m), 6.51-6.50 (2H, m), 5.13 (1H, s); ESI-MS: m/z 546.25 $(M+H)^+$. For $C_{27}H_{20}ClN_5O_4S$: C;59.39 H;3.69; Cl;6.49; N;12.83; S;5.87 Found; : C;59.35 H;3.67; Cl;6.47; N;12.85;S;5.88.

(5e,R=CH_3): $C_{24}H_{18}N_4O_6$; brown powder; (0.38g , 84.44%), m.p. 234-236 ^{0}C IR(cm-):3095, 2935, 2910, 2880, 1636, 1620, 1605, 1520, 1467, 1419, 1375, 1358, 1260, 1221, 1165, 1105, 1025, 810, 767, 755; ^{1}H-NMR (CD_3OD): 8.70 (1H, d, J = 1.8Hz), 8.44 (1H, d, J = 7.8 Hz), 7.92 (3H, d, J = 7.2 Hz), 7.60-7.58 (2H, m), 7.49-7.29 (6H, m), 5.10 (1H, s), 4.10-3.98 (2H, m); ESI-MS: m/z 459.84 $(M+H)^+$. Cal(%) For $C_{24}H_{18}N_4O_6$: C;62.88;H;3.96; N;12.22; Found; C;62.83;H;3.94; N;12.21.

(5f,R=CH_2CH_3): $C_{31}H_{24}N_4O_6$; yellow solid (0.48 g, 88.88%), m.p. 238-240 ^{0}C ,IR(cm-):3005, 2957, 2910, 1630, 1595, 1512, 1466, 1370, 1288, 1232, 1175, 1122, 1066, 795, 745, 730, 709, 678, 615, 460; 1H-NMR (DMSO): 8.70 (1H, d, J = 2.7 Hz), 8.43 (1H, d, J = 7.2 Hz), 7.92 (3H, d, J = 7.5 Hz), 7.61-7.58 (2H, m), 7.49-7.39 (5H, m), 7.24-6.99 (6H, m), 5.04 (1H, s), 4.90 (1H, d, J = 2.4 Hz), 3.14-3.12 (1H, m), 2.97-2.95 (1H, m); ESI-MS: m/z 549.76 $(M+H)^+$. For $C_{31}H_{24}N_4O_6$: C;67.88; H;4.41; Cl;7.68; N;10.21 Found; C;67.84; H;4.40; Cl;7.63; N;10.20.

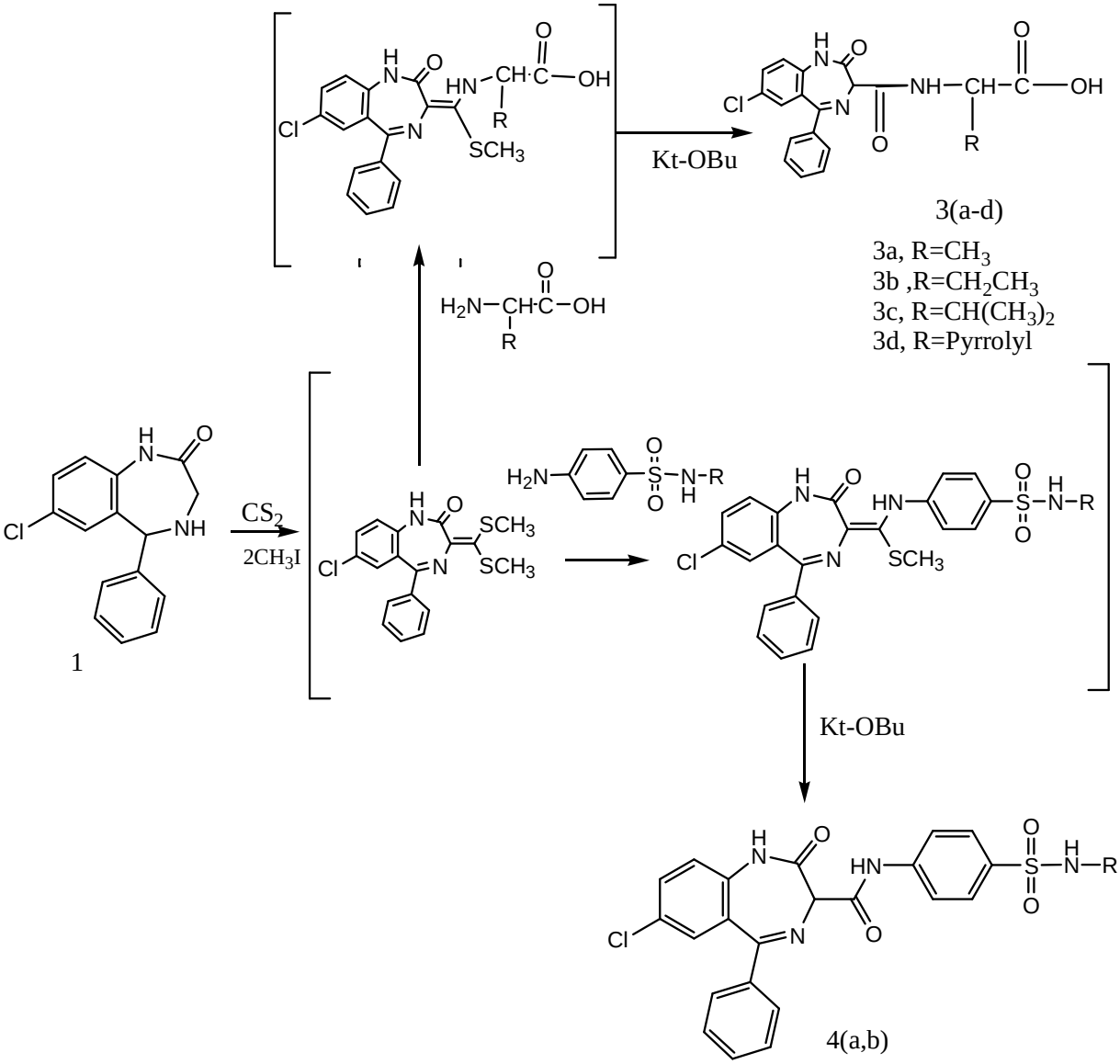
(5g,R=$CH(CH_3)_2$): $C_{27}H_{24}N_4O_6$; IR(cm-): Deep yellow colour powder (0.38 g, 77.55%), m.p.235-237 ^{0}C ,3110, 3057, 1630, 1618, 1595, 1520, 1487, 1417, 1390, 1344, 1278, 1230, 1167, 1123, 1038, 823, 780, 765, 711, 643, 505; 1H-NMR (DMSO): 8.69 (1H, d, J = 2.4 Hz), 8.42 (1H, d, J = 7.2 Hz), 7.93 (3H, d, J = 7.2 Hz), 7.61-7.58 (2H, m), 7.49-7.31 (6H, m), 5.13 (1H, s), 4.49-4.46 (2H, m), 1.45 (6H, s); ESI-MS: m/z 501.35 $(M+H)^+$. For $C_{27}H_{24}N_4O_6$: C;64.79; H;4.83; N;11.19.. Found; C;64.83; H;4.92; N;11.21.

(5h,R=Pyrrolyl): $C_{27}H_{22}N_4O_6$; brown powder; (0.36 g, 73.46%), m.p. 233-235^{0}C; IR(cm-):3085, 1670, 1598, 1560, 1447, 1395, 1367, 1330, 1228, 1169, 1085, 1065, 996, 799, 624, 582, 539; 1H-NMR (DMSO): 8.66 (1H, d, J = 7.8 Hz), 8.41 (1H, d, J = 7.5 Hz), 8.16 (2H, d, J = 7.8 Hz), 7.58-7.55 (2H, m), 7.48-7.43 (2H, m), 7.39-7.29 (5H, m), 5.06 (1H, s), 4.77 (1H, d, J = 2.7 Hz), 3.83-3.75 (2H, m), 2.17-1.91 (4H, m); ESI-MS: m/z 499.75 $(M+H)^+$. For $C_{27}H_{22}N_4O_6$: C;65.05; H;4.45; N;11.24.Found; C;65.03; H;4.42; N;11.26.

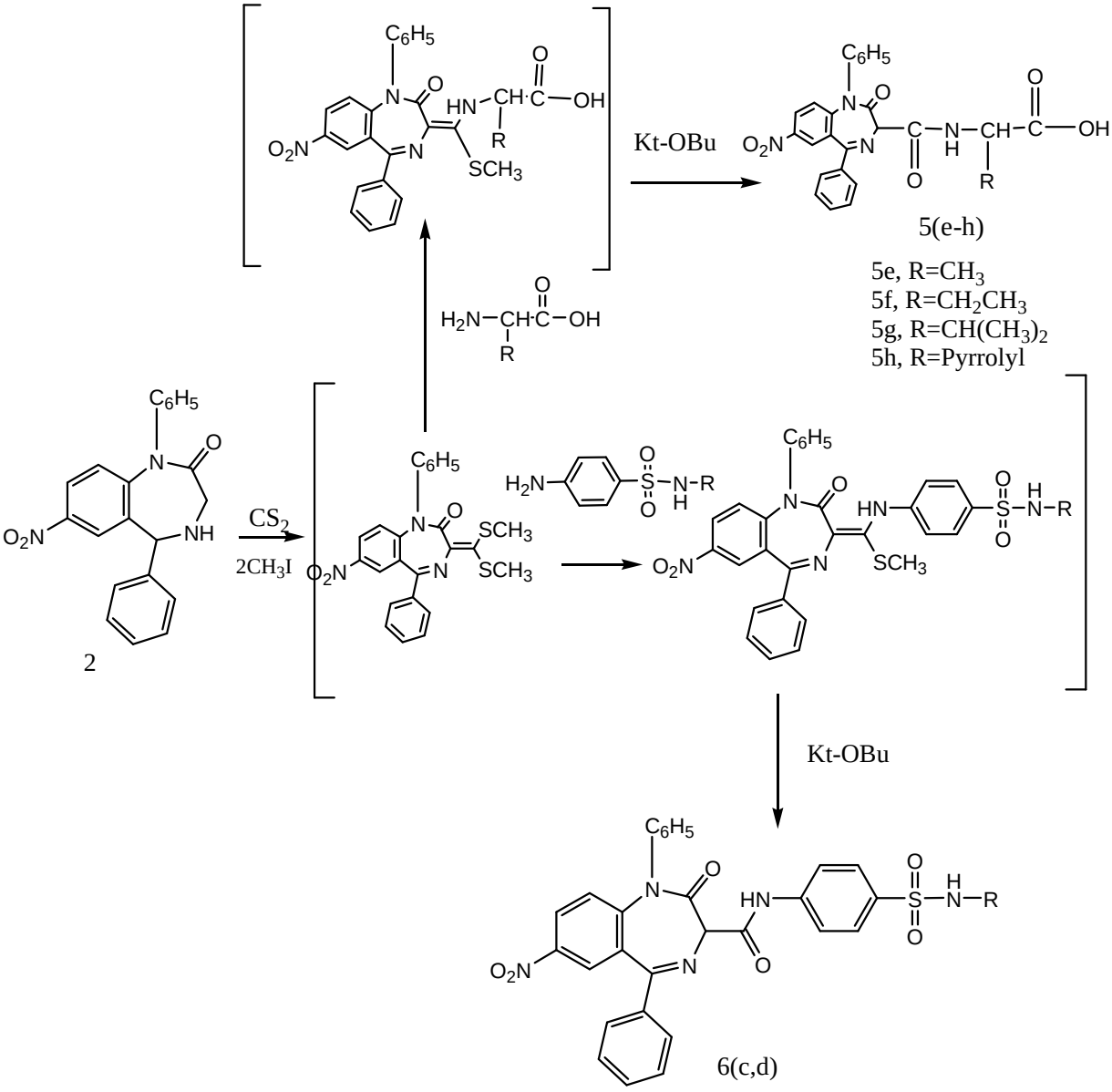
(6c,R=CH_3): $C_{24}H_{19}ClN_4O_5S$; brown powder; (0.51 g, 86.44%), m.p. 252-254^{0}C; IR(cm-):3167, 2970, 2918, 1620, 1600, 1510, 1465, 1380, 1280, 1238, 1181, 1176, 1107, 1021, 960, 945, 810, 780, 762, 605; 1H-NMR (DMSO): 8.72 (1H, d, J = 6.6 Hz), 8.53 (1H, d, J = 7.2 Hz), 8.49 (2H, d, J = 6.6 Hz), 7.98-7.91 (7H, m), 7.59-7.54 (2H, m),

7.48-7.29 (4H, m), 5.13 (1H, s), 2.04 (3H, s); ESI-MS: m/z 598.55 $(M+H)^+$. For $C_{24}H_{19}ClN_4O_5S$: C;60.29; H;3.88; N;11.72; S;5.37. Found; C;60.26; H;3.78; N;11.74;;S;5.32.

(6d,R=Pyridyl): $C_{33}H_{24}N_6O_6S$; brown solid (0.59 g, 95.16%), m.p. 258-260^{0}C ;IR(cm-):3122, 2980, 2920, 1680, 1610, 1575, 1506, 1430, 1398, 1345, 1340, 1231, 1185, 1095, 1070, 998, 812, 801, 745, 715, 625, 590, 530, 510; 1H-NMR (DMSO): 8.49 (1H, d, J = 2.7 Hz), 7.98-7.91 (8H, m), 7.60-7.53 (4H, m), 7.48-7.43 (4H, m), 7.40-7.35 (2H, m), 6.57 (2H, m), 5.14 (1H, s); ESI-MS: m/z 633.82 $(M+H)^+$. For $C_{33}H_{24}N_6O_6S$: C;62.65; H;3.82; N;13.88; S;5.07 Found; C;62.64; H;3.81; N;13.86; S;5.09.



Scheme 1a



Scheme 1 b

RESULTS AND DISCUSSION

In this communication ,we describe a facile one pot entry to 3-amino acids and 3-sulpha drugs embellished analogues of 7-chloro (and 7-nitro), 1,5 -diphenyl -1,3-dihydro -2H[1,4] benzodiazepin-2-ones 3(a-d), 4(a-b), 5(e-h) and 6(c-d) from corresponding 3-oxoketene dithioacetal derivatives respectively[14] .

The starting material 7-chloro (and 7-nitro substituted) 5-phenyl (and 1,5 diphenyl)-1,3 –dihydro 2H[1,4] benzodiazepin-2-ones (1,2) were prepared using the reported procedures[15].

The 3-CH_2 group of 1 and 2 has been reported to be fairly active to undergo reaction with carbon disulphide and methyl iodide in presence of a base ,to from the corresponding oxoketene dithio acetal derivatives[16]. The thiomethyl ether function of the ketene dithio acetals have been demonstrated to be highly prone to undergo nucleophillic

displacement reactions with amines.Interestingly ,the second thio methyl ether function has been reported to respond well,to bases (to undergo hydrolysis with alkali) to result products bearing an amide bond.

This methodology was applied on (1 and 2).which on reaction with CS_2 and MeI in presence of potassium-t-butoxide formed the corresponding oxoketene dithioacetal derivatives respectively[17].The synthetic routes applied to the preparation of 3(a-d), 4(a-b) and 5(e-h)and 6(a-b) from 1 and 2 has been depicted in scheme 1a and b respectively .The intermediates which resulted from the reaction of 3-oxoketene dithioacetal with amino acids and on the reaction of sulpha drugs underwent a facile hydrolysis with ethanolic solution of potassium ter. butoxide to the desired products 3(a-d),4(a-b), 5(e-h) and 6(c-d) respectively[18].

The structures of all the compounds were established on the basis of their microanalysis, IR, ^{1}HNMR, and MS data, which were found to be consistent to the structures assigned to these molecules.

This study has resulted in the development of the library of twelve active materials which are presently undergoing clinical trials for the exploration of their CCK_A antagonist activity.

CONCLUSION

In summary,the results which have emanated from this study clearly indicate that 3-oxoketene dithioacetal derivatives of 7-chloro-5-phenyl-(7-nitro-1,5 diphenyl)-1,3-dihydro-2H-1,4]diazepin-2-one provide a very convenient one pot synthetic entry to the 3-amino acid and 3-sulphonamido substituted analogues of medicinal interest.

Acknowledgement
The authors are thankful to the Vice Chancellor of the university for providing all necessary facilities to carry out this research work.

REFERENCES

[1] Liu Yan-Song and Huang Wei-Yuan, *J. Chem. Soc., Perkin Trans.1*, **1997**;981-988.
[2] Koch M.A.,Schuffenhauer and A., Waldmann,H., *Proc. Natl. Acad. Sci. U.S.A.* **2005**;*102:* 17272-17277.
[3] Sternbach Leo H, *Angewandte Chemie* **1971**;10:1:34-43.
[4] Lokensgard JR., Chao C C and Gekker G, *Molecular Neurobiology*, **1988**;18**:** 23-33.
[5] Puodziunaite B D, Janciene R, Kosychova L. and Stumbreviciute Z., *Arkivoc*,**2000**; 1(iv);512
[6] Yarchoan R, Mitsuya H. and Thomas R. V., *Science*, **1989**; 245: 412–415.
[7] Evans B E, Rittle K. E. and Bock M. G., *Journal of Medicinal Chemistry* ,**1988**;31:12:2235-2246.
[8] Yaguchi Shin-ichi,. Fukui Y , Koshimizu I., Yoshimi H. , Matsuno T, Gouda H. ,. Hirono S,. Yamazaki K and Yamori. T. , *J. National Cancer Institute*, **2006**; 98: *8*: 545-556.
[9] Sanders RD, Godlee A, Fujimori T, Goulding J, Xin G, Salek-Ardakani S, Snelgrove RJ, Ma D, Maze M. and Hussell T. *Crit Care Med.* **2013** ;41(7):1627-36.
[10] Ping Liu, Thomas J. Lanza , Jr., Marc Chioda and Carrie Jones *Med. Chem. Lett*., **2011**; 2 :(12):933–937.
[11] Agrawal A, Srivastava K,. Puri S K and Chauhan P.M.S., *Bioorg. Med. Chem. Lett*., **2005**, 15, *22*, 531-533.
[12] Chauhan SMS and Junjappa H, *Tetrahydron* ,**1979**;32:14.
[13] Lattmann et.al ,*United states patent application publication*;**2007**;1-31.
[14] Marino JP and Kostusyk JL,*Tetrahydron*,**1979**;20:27:2489.
[15] Bock MG.,Dipardo RM and Rottle K E,*J Med Chem.***1986**;29:1941-1952.
[16] Junjappa H, Ila H and Asokan CV,*Tetrahydron*,**1990**;46:16:5423.
[17] Tiwari A.and Srivastava P.,*Synthetic Communications* ,**2009**;39:16:2837-2842.
[18] Potts Kevin T. and Cipullo M.,*J.Am. Chem Society* ,**1981**;103:3584-3585.