ARTICLE

Synthesis of novel oxazolidinedione derivatives by using different methods

Shriram S Purohit*, Devendra Kumar

All Res. J. Chem., **2014**, 5, 1-11

All your results are good results!

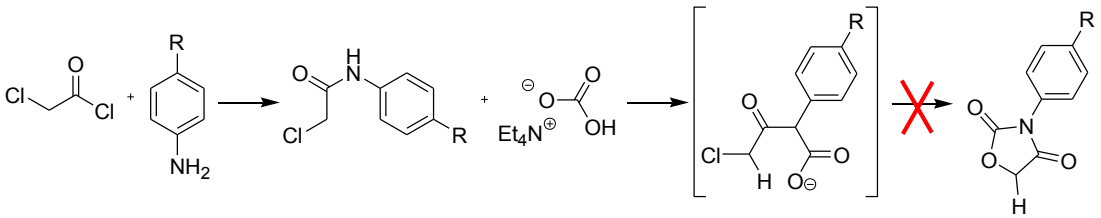
Issue 1, Vol 5, 2014, 1-11

Synthesis of novel oxazolidinedione derivatives by using different methods.

Shriram S Purohit*, Devendra Kumar

Department of Pharmaceutical Chemistry, S.E.T.'s College of Pharmacy S.R.Nagar, Dharwad-580002, Karnataka, India

Graphical Abstract



Abstract:This research article is about the synthesis of Oxazolidine-2,4-diones using tetraethyl ammonium hydrogen carbonate (T.E.A.H.C.). Synthesis by using TEAHC did not give proper results due to the requirement of extremely anhydrous conditions of all reactants, solvents and the reaction environment. Though all solvents and reactants used were rigorously dried, the results were not repetitive as mentioned in the previous literatures, specifically *in-vacuo* conditions. We also used oxalyl chloride to synthesize oxazolidine-4,5-diones but even in extremely dry conditions of all reactants and the solvents, the prominent peaks were not observed in the final products.

Keywords: *TEAHC, oxazolidinedione, oxalyl chloride.*

Introduction

Oxazole possesses different biological activities. Some of the medicinally important derivatives containing oxazole are Trimethadione and Linezolid which possess antiepileptic[1]and antibacterial[2] properties. Apart from this, oxazolidinone, oxazole benzyl esters, phenyl oxazolidine and spiroxazolidine possess different biological activities like anti-bacterial,[3] anti-tuberculosis,[4]cardiac activity[5] and muscarinic agonist.[6]Oxazolidine-2,4-diones are compounds having the structure shown in figure **5(I)**. A lot of oxazolidine-2,4-dione derivatives are known in which R, R' and R" represent hydrogen, alkyl, aryl or heterocyclic substituents.[7]Oxazolidine-2,4-diones are similar in general properties to the hydantoins[8] and may be prepared by analogous methods. Indeed 2-imino-4-oxazolidinediones (pseudohydantoins) **(II)** are sometimes formed instead of the isomeric hydantoins and hydrolysis of the imino group which then gives the corresponding oxazolidine-2,4-dione. Replacement of the sulfur atom of 5,5-dimethyl-2- thio-4-oxazolidion[9]**(III)** by oxygen gave 5,5-dimethyloxazolidine-2,4-dione and led to recognition of the oxazolidinedione ring system **(I)** in 1878.[10,11]Many 2,4-oxaaolidinediones were originally regarded as the isomeric tartronimides**(IV)**,[12]but with the possible exception of triphenylmalonimide (**V** : R = C_6H_5), there appear to be no authentic examples of the axetidine 2,4-dione ring system **(IV & V)**.[7]Oxazolidine-2,4-diones are a class of biologically active compounds.[13] They are employed as anti-convulsants, particularly in the symptomatic treatment of absence seizures.[8] 3,5,5-trimethyloxazolidine-2,4-dione (Trimethadione) is the most active, but even 5-ethyl-3,5-dimethyloxazolidine-2,4-dione

(Paramethadione) and 3-allyl-5-methyloxazolidine-2,4-dione (Malidone) display interesting therapeutic properties.[14]

Dissociation of the imide-hydrogen atom of oxazolidine-2,4-diones permits quantitative estimation of the compounds by titration with 0.1***N*** sodium hydroxide and use of a suitable indicator, e.g., phenolphthalein.[15,16,17] N-Alkylation reduces the stability of the ring system to such an extent that ring fission occurs rapidly with consumption of one equivalent of alkali, and this is utilized in the quantitative estimation of 3,5,5-trimethy-1,2 -oxazolidinedione.[17]

Oxazolidine-2,4-diones possessing an imide-hydrogen atom are stable towards boiling water or diluted mineral acids and are recovered from their O-alkyl and 2(or 4)-imino derivatives and from 2-alkylthio-4-oxazolones, by acid hydrolysis.[18]

Acetone, potassium cyanide, and potassium thiocyanate in the presence of concentrated hydrochloric acid lead to 5,5-dimethyl-2-thio-4-oxazolidone (Figure **1**).[18]

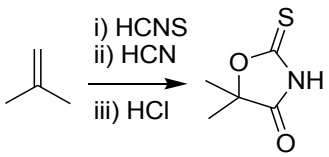


Figure 1: Synthesis of 5,5-dimethyl-2-thio-4-oxazolidone

Esters of *α*-hydroxy acids condense with guanidine (50% solution in ethanol) to yield 2-imino-4-oxazolidones, which are isomeric with hydantoins and are frequently termed pseudohydantoins; the imino compounds are readily hydrolyzed to oxazolidine-2,4-diones (e.g., R = H, CH_3, C_6H_5) (Figure **2**).[18]

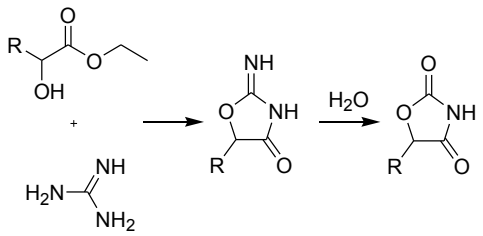


Figure 2: Isomerization of 2-imino-4-oxazolidones to oxazolidine-2,4-dione.

Oxazolidine-2,4-diones[112] are formed from dialuric acids **(I)** by the action of aqueous sodium hydroxide either at room temperature or at 100°C for 20-30 min. and in many cases (especially when R = aryl) the products **(II)** crystallize from the acidified solutions (Figure **3**).[18]

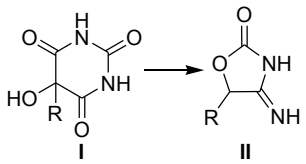


Figure 3: Synthesis of oxazolidine-2,4-dione from dialuric acid.

5-Bromobarbituric acids, when treated with aqueous alkali, give bromoureides as intermediates in this conversion, and the condensation of esters of α-halogen acids with urea (or substituted urea) lead to 2-imino-4-oxazolidones, presumably via the chloroureides (Figure **4**).[18]

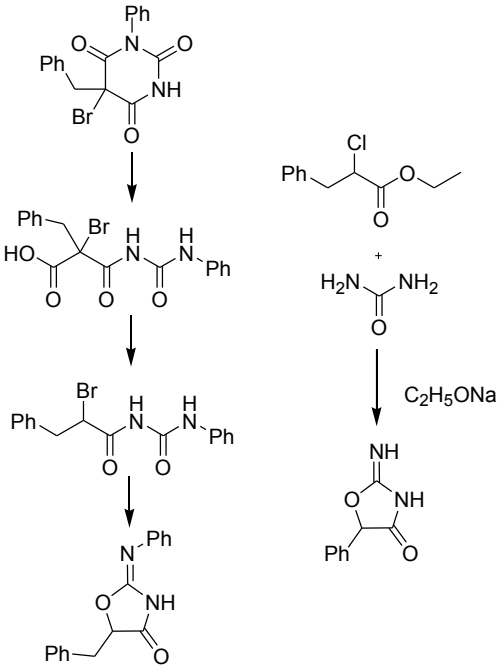


Figure 4: Synthesis of 2-imino-4-oxazolidones.

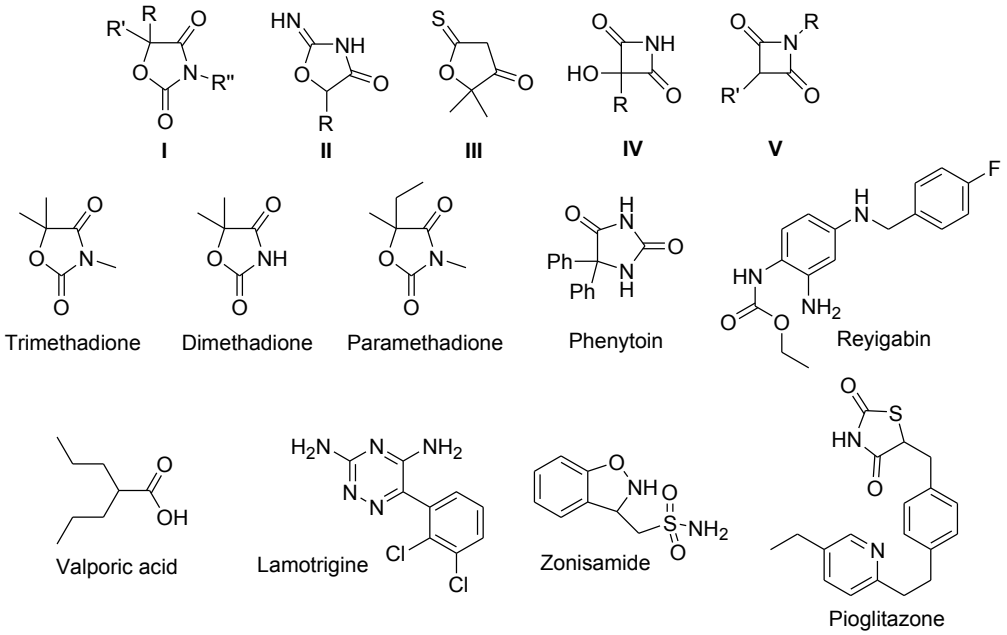


Figure 5: Structures of different drugs.

Methods

Compounds **1(a-d)** were synthesized by treating different *p*-substituted anilines with chloro acetyl chloride. When the above reaction was carried out at 0°C, it gave very good and highly pure white crystalline products. All the reactions of anilides and TEAHC (Tetraethylammonium hydrogen carbonate) were carried out in extremely dry conditions. The products 1(e-h) are crystalline in nature. Different p-acetamido benzene sulfonamides 2(d,e) were synthesized by using N-(4-sulfamoylphenyl)acetamide (2b) and 4-aminobenzoyl chloride (2c), 2d as a condensation product between 2b and 2c compounds and 2e by treating 2b with chloro acetyl chloride, which resulted as 2d,whereas 2e was obtained by treating 2b with chloro acetyl chloride. When 4-(acetylamino) benzene sulfonyl chloride 2a was reacted with glycine, 2f was obtained.

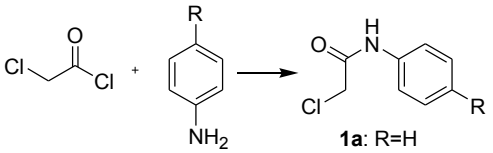
Different *N*-phenylbenzamides were prepared by treating *p*-nitroaniline with *p*-substituted benzoylchloride, which resulted in **3b**. These nitro derivatives were reduced by using concentrated HCl and granulated tin. As the reduced product obtained by extraction was very much crude, we distilled off the aqueous part and extracted from it **3c**. **3d** was prepared by reacting **3c** with chloroacetyl chloride.

In another type of reaction, oxalyl chloride derivatives were prepared by treating different anilides**1(a-d)** with oxalyl chloride in aprotic solvents, leading to compounds **4(a-d)**. During synthesis of oxazolidine-2,4-dione using diethyl carbonate, we prepared different α-hydroxyanilides by using lactic acid chloride which were subjected to react with *p*-substituted anilines to get **5(a-e)**. Ethyl-*L*-lactate was also used with diethyl carbonate to synthesize oxazolidine-2,4-dione.

1.Synthesis of oxazolidine-2,4-dione using TEAHC.

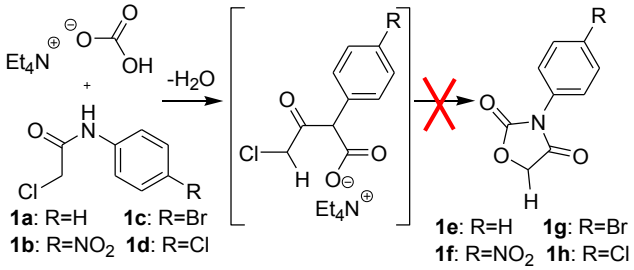
A. Synthesis of substituted oxazolidine-2,4-dione using different anilides.

Step-I Synthesis of substituted anilides.



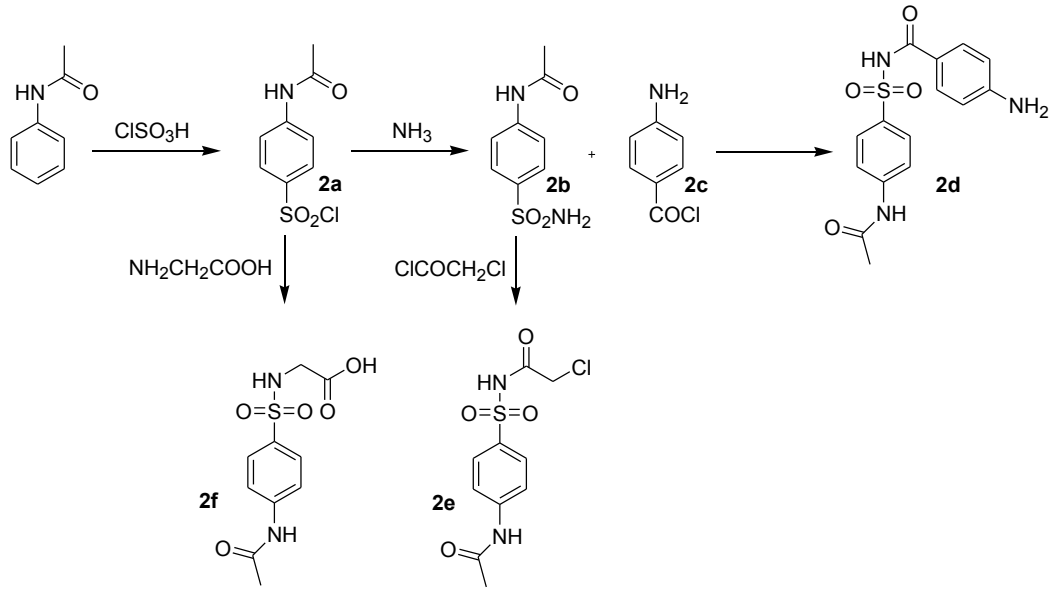
1a: R=H
1b: R=NO_2
1c: R=Br
1d: R=Cl

Step-II Synthesis of 3- substituted oxazolidine-2,4-dione.

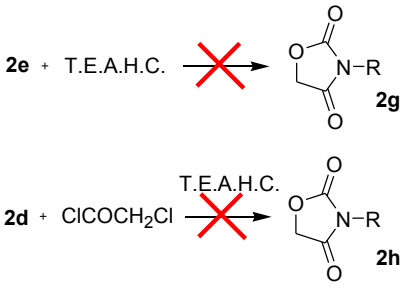


B. Synthesis of substituted oxazolidine-2,4-dione using different p-acetamidobenzene sulfonamide.

Step-I Synthesis of different p-acetamidobenzenesulfonamide.

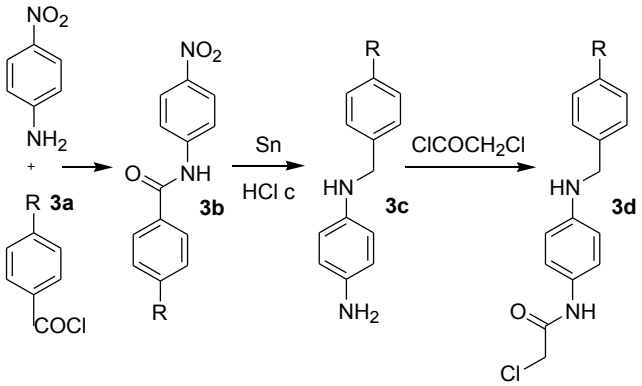


Step-II Synthesis of 3- substituted oxazolidine-2,4-dione.

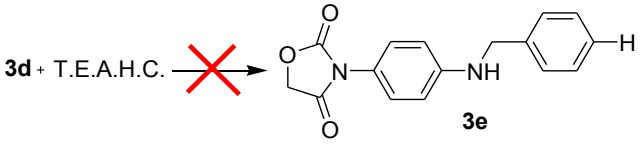


C. Synthesis of substituted oxazolidine-2-4-dione using different *N*-phenylbenzamides.

Step-I Synthesis of different *N*-phenylbenzamides.

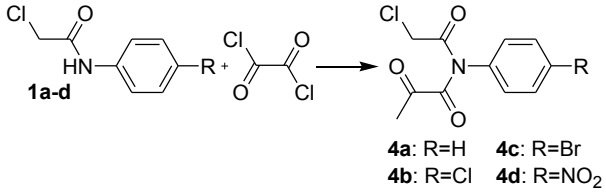


Step-II Synthesis of 3- substituted oxazolidine-2,4-dione.

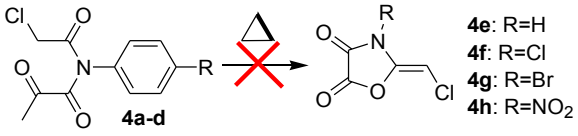


2. Synthesis of 2,3-disubstitutedoxazolidine-4,5-dione using oxalylchloride and anilides.

Step-I Synthesis of different oxalylchloride derivative of anilides 1(a-d).

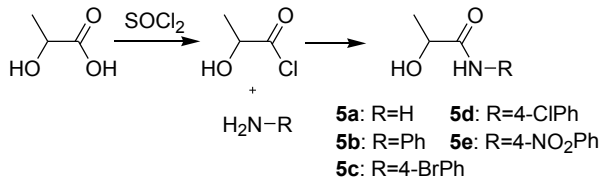


Step-II Synthesis of different oxazolidine-4,5-dione.

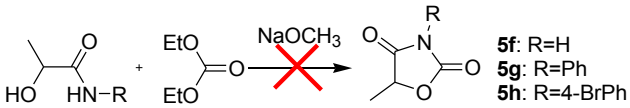


3. Synthesis of oxazolidine-2,4-dione using diethylcarbonate.

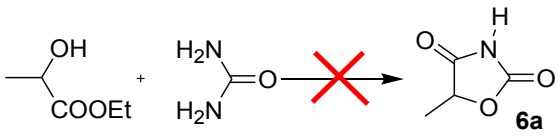
Step-I Synthesis of different 2-hydroxyanilides.



Step-II Synthesis of different oxazolidine-2,4-dione.



4. Synthesis of oxazolidine-2,4-dione using ethyl-*L*-lactate.



Results & Discussion

We tried to synthesize oxazolidine-2,4-dione and oxazolidine-4,5-dione derivatives by using 4 different schemes. i.e. **(1)** Synthesis of Oxazolidine-2,4-dione using TEAHC. **(2)** Synthesis of 2,3-disubstituted-oxazolidine-4,5-dione using oxalyl chloride &anilides. **(3)** Synthesis of Oxazolidine-2,4-dione using diethylcarbonate. **(4)** Synthesis of Oxazolidine-2,4-dione using ethyl-*L*-lactate.

Synthesis of oxazolidine-2,4-dione by using TEAHC **1(e-h), 2(g,h), 3e** did not give proper results. According to procedure,[20]TEAHC should react with anilides and lead to oxazolidinedione since all the anilides**1(a-d)** synthesized used as reactants, showed proper physical and spectral properties. During the reaction, all reactants and solvents were rigorously dried and the reaction was carried out under vacuum (using Schlenk flask), but all these measures did not work.

We also used Oxalyl chloride to synthesize oxazolidine-4,5-diones but even under dry conditions of all reactants and solvents, the primary amine peak was observed in the IR spectra which are not present even in our reactant. In this case, intermediates **4(a-d)** which were isolated showed some appreciating physical results, but their spectral results constantly showed a primary amine peak.

It was also observed that, when diethylcarbonate and *α*-hydroxyanilides **5(a-e)** were used or ethyl-*L*-lactate to synthesize oxazolidine-2,4-diones**5(f-h)** and **6a**, these reactions are equilibrium type reactions, and even in the presence of an excess amount of one reactant, the equilibrium slightly shifted towards forward and a complex mixture of products are obtained with very low yield.

Conclusion

By using all 4 procedures, no positive results were observed in laboratory conditions. By our work, we concluded that either the synthesis of oxazolidine-2,4-dione and oxazolidine-4,5-dione required an inert atmosphere or other more efficient inorganic or organic catalyst to complete these reactions.

Experimental

Chemicals

Chemicals used in the synthesis of the compounds described were purchased from Sigma Aldrich, Spectro-chem Pvt. Ltd, and S.D. Fine Chem. Ltd. They were TEAHC, Oxalyl chloride, Diethylcarbonate, and Ethyl-*L*-lactate.

Instruments

Melting points were determined in SHITAL-Digital programmable melting point apparatus and are uncorrected;

IR spectra were recorded on Bruker spectrophotometer by using KBr pellets. The ^{1}H and $^{13}CNMR$ was recorded on BrukerAvance III NMR 400 MHz instruments using DMSO as solvent and TMS as internal standard, with chemical shifts expressed as δ values (ppm). Mass spectra (MS) were taken in JEOLGCMATE II GC‑Mass spectrometer using electron impact ionization (EI) technique. Microanalyses of the compounds were performed on LecoTru Spec CHNS Analyzer to estimate C, H and N elements.

Chemical Synthesis

Synthesis of Oxazolidine-2,4-diones using T.E.A.H.C.

(A) Synthesis of substituted Oxazolidine-2,4-dione using different anilides.

(I) Synthesis of substitute anilides.[19,20]**1(a-d)** (Scheme1, A, I)

Aniline (20 mmol) was dissolved in 30 ml of dichloromethane and cooled up to 0°C, then chloroacetylchloride (10 mmol) was added drop wise and the solution was stirred for 2h at room temperature. Solution obtained was washed with 15 ml water then 15mlammoniumchloride (saturated) solution and again 15 ml water. After drying over magnesium sulphate and evaporation of the solvent, crystalline product was obtained.

2-chloro- N-phenylacetamide(**1a**): MP: 136-39 ^{0}C, yield = 90%. IR (KBr cm^{-1}) 1780.10 (C=O), 3437.19 (NH-str), 3060.00 (C-H; aromatic), 1625.15 & 1495.88 (C=C; aromatic). Anal. Calcd. For C_8H_8ClNO: C (56.65%) H (4.75%) Cl (20.90%) N (8.26%) O (9.43%). Found: C (56.05%) H (4.20%) Cl (20.25%) N (7.95%) O (8.93%).

2-chloro-N-(4-nitrophenyl)acetamide(**1b**): MP: 200-03 ^{o}C, yield = 85.75%. IR (KBr cm^{-1}) 1670.07 (C=O), 3263.03 (NH-str), 3079.51 (C-H; aromatic), 1612.67 & 1486.96 (C=C; aromatic). Anal. Calcd. For $C_{15}H_{12}NO$: C (44.77%) H (3.29%) Cl (16.52%) N (13.05%) O (22.37%). Found: C (44.20%) H (2.90%) Cl (16.20%) N (12.94%) O (21.87%).

N-(4-bromophenyl)-2-chloroacetamide(**1c**): MP: 180-83 ^{o}C, yield = 78.36%. IR (KBr cm^{-1}) 1669.87 (C=O), 3263.11 (NH-str), 3072.26 (C-H; aromatic), 1610.45 & 1484.86 (C=C; aromatic). Anal. Calcd. For $C_8H_7NOClBr$: C (38.67%) H (2.84%) Br (32.15%) Cl (14.27%) N (5.64%) O (6.44%). Found: C (38.21%) H (2.24%) Br (31.94%) Cl (13.89%) N (5.01%) O (6.21%).

2-chloro- N-(4-chlorophenyl) acetamide(**1d**):MP: p 140-45 ^{o}C, yield = 86.23%. IR (KBr cm^{-1}) 1669.85 (C=O), 3264.08 (NH-str), 3080.31 (C-H; aromatic), 1613.44 & 1488.57 (C=C; aromatic). Anal. Calcd. For $C_8H_7NOClBr$: C (47.09%) H (3.46%) Cl (34.75%) N (6.86%) O (7.84%). Found: C (46.41%) H (3.04%) Cl (34.21%) N (5.86%) O (7.24%).

(II) Synthesis of 3-substituted Oxazolidine-2,4-dione.[20]**1(e-h)** (Scheme 1, A, II).

During synthesis of 2,4-Oxazolidinedione all reagents and solvents used were extremely anhydrous. Anilides**1(a-d)** (1 mmol) was dissolved in 15 ml of acetonitrile and TEAHC (1.5 mmol) was added and the reaction was performed in a vacuum using Schlenk flask (the Schlenk flask containing all reactants was sealed with rubber septa at one end and other end was connected with vacuum pump. For 45 minute vacuum pump was operated and then this end (connected with vacuum pump) was also closed). The solution was stirred at 50 °C (120h) and the reaction was monitored by TLC. The solvent was removed in reduced pressure. Precipitate obtained was recrystallized by a suitable solvent.

3-phenyl-1,3-oxazolidine-2,4-dione(**1e**): MP: 77-80^{0}C, yield = 30.52%. IR (KBrcm^{-1}) 1663.45 (C=O), 3379.12 & 3306.18 (NH; str.doublet), 3099.58 (C-H; aromatic), 1605.26 & 1495.05 (C=C; aromatic.). $^{1}HNMR$ (*d*DMSO, 400 MHz),δ10.7 (1H, s, *J*=109.8), 7.7 (2H, t, *J*=99.9, C2 & C6 aromatic), 7.3 (2H, q, *J*=109.7, C3&C5 aromatic), 7.1(1H, q, *J*=119.8, C4 aromatic), 3.3 (21H, m, *J*=126.5). $^{13}CNMR$ (DMSO, 100 MHz) δ: 21.06, 38.67, 38.95, 39.23, 39.51, 39.78. 40.06. 40.34, 120.25, 124.46, 128.67, 137.65, 156.96, 162.10; MSm/z: found 226.351 (M^{+}), 227.361(8.26%) O (9.43%). Found: C (56.05%) H (4.20%) (M+1); calcd. 177.156. .Anal. Calcd. For $C_9H_7NO_3$: C

(61.02%) H (3.98%) N (7.91%) O (27.09%). Found: C (57.05%) H (4.47%) Cl (21.01%) N (8.04%) O (8.93%).

3-(4-nitrophenyl)-1,3-oxazolidine-2,4-dione(**1f**): MP: 160-65^{0}C, yield = 28.88%. IR (KBr cm^{-1}) 1663.45 & 1605.26 (C=O), 3379.12 & 3360.18 (NH; str. doublet), 2919.31 (C-H; aromatic), 1551.75 & 1495.05 (C=C; aromatic). Anal. Calcd. For $C_9H_6N_2O_5$: C (48.66%) H (2.72%) N (12.61%) O (36.01%). Found: C (44.77%) H (2.98%) Cl (16.52%) N (12.59%) O (22.07%).

3-(4-bromophenyl)-1,3-oxazolidine-2,4-dione(**1g**): MP: 160-64^{0}C, yield = 32.00%. IR (KBr cm^{-1}) 1657.52 (C=O), 3255.13 & 3186.26 (NH; str. doublet), 3068.86 (C-H; aromatic), 1602.27 & 1472.14 (C=C; aromatic). Anal. Calcd. For $C_9H_7NO_3Br$: C (42.22%) H (2.36%) Br (31.21%) N (5.47%) O (18.75%). Found: C (39.01%) H (2.54%) Br (31.01%) Cl (13.45%) N (4.79%) O (6.87%).

3-(4-chlorophenyl)-1,3-oxazolidine-2,4-dione(**1h**): MP: 177-82^{0}C, yield 30.12%. IR (KBr cm^{-1}) 1659.43 (C=O), 3415.06 & 3308.47 (NH; str.doublet), 2913.90 (C-H; aromatic), 1595.13 & 1484.36 (C=C; aromatic). Anal. Calcd. For $C_9H_7NO_3Cl$: C (51.08%) H (2.86%) Cl (16.75%) N (6.62%) O (22.68%). Found: C (37.97%) H (2.24%) Br (31.94%) Cl (13.89%) N (5.01%) O (5.21%)

(B) Synthesis of 3-substituted Oxazolidine-2,4-dione using different *p*-acetamidobenzene sulfonamides.

(I) Synthesis of different *p*-acetamidobenzenesulfonamides[21, 22] **2(b-f)** (Scheme 1, B, I)

4-(acetylamino)benzenesulfonyl chloride (**2a**)*, N-(4-sulfamoylphenyl) acetamide*(**2b**)*,4-aminobenzoyl chloride* (**2c**).

Compound **2a,2b** and **2c** were prepared by following the general procedure mentioned in the literature.[23,24]

N, N-{[4-(acetylamino)phenyl]sulfonyl}-4-aminobenzamide (**2d**):Compound **2b**(0.009 mol) and 4-aminobenzoyl chloride **(2c)** (1.6 mol) were dissolved in acetone and triethylamine was added (equivalent to HCl liberated). Solution was stirred with heating (45-50^{0}C) for 1h. After cooling, a precipitate was obtained, which was filtered and dried. MP: 220-25^{0}C, yield = 50.5%. IR (KBr cm^{-1}) 1684.12 (C=O), 3306.90 (NH-str), 3053.39 (C-H; aromatic), 1588.10 & 1371.04 (C=C; aromatic), 1318.38 (S=O- asymmatric str.), 1170.02 (S=O- symmatricstr.). Anal. Calcd. For $C_{15}H_{15}N_3O_4S$: C (54.04%) H (4.54%) N (12.60%) O (19.20%) S (9.62%). Found: C (54.71%) H (4.45%) N (12.50%) O (19.21%) S (9.78%).

N-{[4-(acetylamino)phenyl]sulfonyl}-2-chloroacetamide (**2e**): Compound **2b** (0.008 mol) was dissolved in methanol and cooled to ^{0}C, then chloroacetylchloride (1.008 mol) was added along with triethylamine (equivalent to HCl liberated). The mixture was stirred at room temperature until a clear solution was formed. Solvent was evaporated to obtain the desired product. MP: 217-19^{0}C, yield =40.54%. IR (KBr cm^{-1}) 1656.73(C=O), 3367.52 (NH-str), 3213.45 (C-H; aromatic), 1595.22 & 1393.87 (C=C; aromatic), 1325.11 (S=O- asymmetric str.), 1154.79 (S=O- symmetric str.). Anal. Calcd. For $C_{10}H_{11}N_2O_4SCl$: C (41.31%) H (3.81%) Cl (12.19%) N (9.64%) O (22.01%) S (11.03%). Found: C (41.21%) H (3.23%) Cl (12.54%) N (9.78%) O (22.71%) S (11.43%).

({[4-(acetylamino)phenyl]sulfonyl} amino) acetic acid (**2f**): Equimolar amount of 4-(acetylamino) benzenesulfonylchloride (**2a**) and glycine were dissolved in water to make a clear solution and heated gently for 1h. Solution was then cooled down and extracted with (salting out) dichloromethane. MP: 250-55^{0}C, yield = 45.00%. IR (KBr cm^{-1}) 1761.86 (C=O), 1675.09 (C=O, carboxalic), 3268.48 (NH-str), 3097.94 (C-H; aromatic), 1611.54 & 1495.92 (C=C; aromatic), 1345.80 (S=O- asymmetric str.), 1194.02 (S=O- symmetric str.). Anal. Calcd. For $C_{10}H_{12}N_2O_5S$: C (41.86%) H (3.90%) N (10.85%) O (30.98%) S (12.42%). Found: C (41.86%) H (3.90%) N (10.85%) O (30.98%) S (12.42%).

(II) Synthesis of 3-substituted Oxazolidine-2,4-dione[20] (**2g, 2h**) (Scheme 1, B, II)

0.0068 mol of **2e**were dissolved in acetonitrile and 0.0103 molTEAHC was added. Solution was stirred at 50^{0}C (105h) and the reaction was monitored by TLC. Equimolar amount (0.006 mol) of **2d** and chloroacetylchloride were added at 0° and chloroform was used as solvent**.** After 1h of stirring, the solvent was evaporated and the product was dried.

Then, the dried product (0.001 mol) was dissolved in acetonitrile and treated with TEAHC (0.0015 mol). The reaction was monitored with TLC (120h). On completion of reaction, the solvent was evaporated.

(C) Synthesis of 3-substituted Oxazolidine-2,4-dione using *N*-phenylbenzamides.

(I) Synthesis of different ***N***-phenylbenzamides[25, 26] **3**(**b-d**) (Scheme 1, C, I)

p-Nitroaniline (0.018 mol) was added drop wise to benzoylchloride (0.019 mol) at 0^0C and stirred at room temperature for 2h. White precipitate was obtained which was filtered and washed with dichloromethane (**3b**). Dried product (**3b**) (1 g) was treated with granulated tin (2 g) and conc. HCl (10 ml) and refluxed on water bath for 4h. Mixture was cooled and 40% NaOH was added until a clear solution was obtained and extracted with diethylethyl ether (**3c**). Dried product (**3c**) (0.01 mol) was dissolved in chloroform and cooled to 0^0C. Chloroacetylchloride (0.02 mol) was added drop wise and triethylamine was added (Equivalent to HCl liberated). Solution was stirred with heating (45-60^0C) for 5h. Resultant solution was washed with water and dried (**3d**).

N-(4-nitrophenyl)benzamide (**3b**):MP: 190-95^0C, yield = 70.71%. IR (KBr cm^{-1}) 1656.96 (C=O), 3334.98 (NH-str), 2922.56 (C-H; aromatic), 1602.63& 1403.22 (C=C; aromatic). Anal. Calcd. For $C_{13}H_{10}N_2O_3$: C (64.46%) H (4.16%) N (11.56%) O (19.82%). Found: C (64.86%) H (4.16%) N (11.52%) O (19.21%).

N-(4-aminophenyl)benzamide (**3c**): MP: 127-31^0C, yield = 30.23%. IR (KBr cm^{-1}) 1656.81 (C=O), 3367.31 & 3294.09 (NH-str, doublet), 3216.95 (NH-str, singlet), 2926.48 (C-H; aromatic), 1595.81 & 1392.45 (C=C; aromatic). Anal. Calcd. For $C_{13}H_{12}N_2O$: C (73.56%) H (5.70%) N (13.20%) O (7.54%). Found: C (73.56%) H (5.70%) N (13.20%) O (7.54%).

N-{4-[(chloroacetyl) amino] phenyl} benzamide(**3d**): MP: 238-42^0C, yield = 20.00%. IR (KBr cm^{-1}) 1656.43 (C=O), 3308.47 (NH-str), 2913.90 (C-H; aromatic), 1595.12 & 1484.36 (C=C; aromatic). Anal. Calcd. For $C_{15}H_{14}N_3O_2Cl$: C (62.40%) H (4.54%) Cl(12.28%) N (9.70%) O (11.08%). Found: C (62.40%) H (4.54%) Cl (12.28%) N (9.70%) O (11.08%).

Synthesis of 2, 3-disubstituded Oxazolidine-4,5-diones using oxalylchloride and anilides.

(I) Synthesis of oxalyl chloride derivative of anilides[27]**4**(**a-d**) (Scheme 2, I)

Anilides**1**(**a-d**)(1 mol) were dissolved in 20 ml of CCl_4 and oxaloylchloride (1 mol) was added. Reaction mixture was refluxed for 24h. After completion of reaction the solution was concentrated and dichloromethane was added. To this solution charcoal was added and filtered. On addition of hexane to the filtrate, a precipitate was obtained.

[(chloroacetyl)(phenyl)amino] (oxo)acetyl chloride (**4a**): MP: 107-09^0C, yield = 30.12%. IR (KBr cm^{-1}) 1766.81 & 1684.88 (C=O), 3302.39 (NH-str), 3091.21 (C-H; aromatic), 1599.48 & 1496.91 (C=C; aromatic). Anal. Calcd. (C=C; aromatic). Anal. Calcd. For $C_{10}H_7NO_3Cl_2$: C (46.18%) H (2.71%) Cl (27.26%) N (5.39%) O (18.46%). Found: C (46.18%) H (2.52%) Cl (27.53%) N (5.22%) O (18.26%).

[(chloroacetyl)(4-chlorophenyl)amino](oxo) acetyl chloride (**4b**):MP: 190-95^0C, yield = 25.32%. IR (KBr cm^{-1}) 1754.25 & 1675.83 (C=O), 3316.74 & 3247.22 (NH-str, doublet), 2931.88 (C-H; aromatic), 1606.30 & 1489.59 (C=C; aromatic). Anal. Calcd. For $C_{10}H_6NO_3Cl_3$: C (40.78%) H (2.05%) Cl (36.11%) N (4.76%) O (16.30%). Found: C (40.78%) H (2.05%) Cl (36.11%) N (4.76%) O (16.30%).

[(4-bromophenyl)(chloroacetyl)amino] (oxo) acetyl chloride (**4c**): MP: 178-82^0C, yield = 25.30%. IR (KBr cm^{-1}) 1754.87 & 1674.69 (C=O), 3312.81 & 3258.22 (NH-str), 3081.55 (C-H; aromatic), 1612.07 & 1490.46 (C=C; aromatic). Anal. Calcd. For $C_{10}H_6NO_3Cl_2Br$: C (35.43%) H (1.78%) Br (23.57%) Cl (20.92%) N (4.13%) O (14.16%). Found: C (35.43%) H (1.78%) Br (23.57%) Cl (20.92%) N (4.13%) O (14.16%).

[(chloroacetyl)(4-nitrophenyl)amino](oxo) acetyl chloride(**4d**): MP: 230-35^0C, yield = 28.60%. IR (KBr cm^{-1}) 1767.03 & 1683.02 (C=O), 3303.26 (NH-str), 3097.60 (C-H; aromatic), 1603.78 & 1495.83 (C=C; aromatic).

Anal. Calcd. For $C_{10}H_6N_2O_5Cl_2$: C (39.37%) H (1.98%) Cl (23.24%) N (9.18%) O (26.22%). Found: C (39.37%) H (1.98%) Cl (23.24%) N (9.18%) O (26.22%).

(II) Synthesis of 2, 3-disubsstitudeOxazolidine-4,5-dione[27]**4**(**e-g**) (Scheme 2, II)

4(**a-c**) was heated up to just below their melting point for 5 min. to get **4**(**e-g**).

(2Z)-2-(chloromethylidene)-3-phenyl-1,3-oxazolidine-4,5-dione(**4e**):MP: 162-63^{0}C, yield = 30.00%. IR (KBr cm^{-1}) 1766.38 & 1685.04 (C=O), 3303.14 (NH; str.), 3095.51 (C-H; aromatic), 1600.75 & 1497.16 (C=C; aromatic). Anal. Calcd. For $C_{10}H_6NO_3Cl$: C (53.71%) H (2.70%) Cl (15.85%) N (6.26%) O (21.46%). Found: C (53.23%) H (2.62%) Cl (15.31%) N (6.52%) O (21.61%).

(2Z)-2-(chloromethylidene)-3-(4-chlorophenyl)-1,3-oxazolidine-4,5-dione(**4f**): MP: 200-05^{0}C, yield = 28.80%. IR (KBr cm^{-1}) 1669.21 & 1616.05 (C=O), 3266.71 & 3198.68 (NH; str. doublet), 3083.32 (C-H; aromatic), 1550.56 & 1490.18 (C=C; aromatic). Anal. Calcd. For $C_{10}H_5NO_3Cl_2$: C (46.54%) H (1.95%) Cl (27.48%) N (5.43%) O (18.60%). Found: C (46.54%) H (1.95%) Cl (27.48%) N (5.43%) O (18.60%).

(2Z)-3-(4-bromophenyl)-2-(chloromethylidene)-1,3-oxazolidine-4,5-dione (**4g**): MP: 180-85^{0}C, yield = 30.22%. IR (KBr cm^{-1}) 1670.55 (C=O) 3263.09 & 3192.35 (NH; str. doublet), 3075.14 (C-H; aromatic), 1610.54 & 1484.81 (C=C;aromatic). Anal. Calcd. For $C_{10}H_5NO_3ClBr$: C (39.70%) H (1.67%) Br (26.41%) Cl (11.72%) N (4.63%) O (15.87%). Found: C (39.12%) H (1.68.01%) Br (26.12%) Cl (11.12%) N (4.12%) O (15.21%).

Synthesis of 2,4-Oxazolidinedione using diethyl carbonate

(I) Synthesis of different 2-hydroxyanilides[28]**5**(**a-e**) (Scheme 3, I)

Lactic acid (4 ml) was treated with thioneylchloride (20 ml) and heated (60-70°C) for 30 min. Then, to this solution chloroform (15 ml) was added and equimolar amount of 4-substituted aniline (NH_3in **5a**) dissolved in chloroform (20 ml) was added. Precipitate obtained was filtered and washed with chloroform.

2-hydroxypropanamide (**5a**):MP: 86-90^{0}C, yield = 80.10%. IR (KBr cm^{-1}) 1755.34 (C=O), 3319.44 & 3243.58 (NH-str, doublet), 3490.00 (OH; str.). Anal. Calcd. For $C_3H_7NO_2$: C (40.44%) H (7.92%) N (15.72%) O (35.92%). Found: C (40.44%) H (7.92%) N (15.72%) O (35.92%).

2-hydroxy- N-phenyl-propanamide(**5b**): MP: 225-30^{0}C, yield = 75.00%. IR (KBr cm^{-1}) 3437.19 (OH-str.), 1780.10 (C=O), 3430.00 (NH-str), 3060.00 (C-H; aromatic), 1625.15 & 1495.88 (C=C; aromatic). Anal. Calcd. For $C_9H_{11}NO_2$: C (65.44%) H (6.71%) N (8.48%) O (19.37%). Found: C (65.44%) H (6.71%) N (8.48%) O (19.37%).

N-(4-bromophenyl)-2-hydroxy-propanamide (**5c**): MP: 0-55^{0}C, yield = 78.36%. IR (KBr cm^{-1}) 3400.00 (OH-str.), 1669.87 (C=O), 3263.11 (NH-str), 3072.26 (C-H; aromatic), 1610.45 & 1484.86 (C=C; aromatic). Anal. Calcd. For $C_9H_{10}NO_2Br$: C (44.29%) H (4.13%) Br (32.74%) N (5.74%) O (13.11%). Found: C (44.29%) H (4.13%) Br (32.74%) N (5.74%) O (13.11%).

N-(4-chlorophenyl)-2-hydroxy-propanamide (**5d**):MP: 270-76^{0}C, yield = 70.75%. IR (KBr cm^{-1}) 3433.29(OH-str.), 1669.85 (C=O), 3264.08 (NH-str), 3080.31 (C-H; aromatic), 1613.44 & 1488.57 (C=C; aromatic). Anal. Calcd. For $C_9H_{10}NO_2Cl$: C (54.15%) H (5.05%) Cl (17.76%) N (7.02%) O (16.03%). Found: C (54.15%) H (5.05%) Cl (17.76%) N (7.02%) O (16.03%).

2-hydroxy- N-(4-nitrophenyl) propanamide (**5e**): MP: 257-60^{0}C, yield = 70.00%. IR (KBr cm^{-1}) 3400.00 (OH-str.), 1670.07 (C=O), 3263.03 (NH-str), 3003.19 (C-H; aromatic), 1612.67 & 1488.96 (C=C; aromatic). Anal. Calcd. For $C_9H_{10}N_2O_4$: C (51.43%) H (4.80%) N (13.33%) O (30.45%). Found: C (51.43%) H (4.80%) N (13.33%) O (30.45%).

(II) Synthesis of different Oxazolidine-2,4-dione[29]**5**(**f-h**) (Scheme 3, II)

Sodium (1.05 g) was dissolved in dry methyl alcohol (8-10 mol) in a three-necked flask. After the solution had cooled to 35°C, the 2-hydroxy amide **5(a-c)** (1 mol) was added in solution in diethyl carbonate (1.16 mol) and when necessary, sufficient methyl alcohol (3-8mol) to bring about

the complete solution of the amide. The resulting reaction mixture was then heated to the refluxing temperature (56-70°C) until the reaction was completed (monitored by TLC). At the end of the reaction period, the alcohol was distilled off, the cooled residue was dissolved in water, and the solution was extracted with ether to remove traces of uncreated starting material. By acidification of the aqueous layer, the oxazolidinedione was separated. If the oxazolidinedione solidified the product it was filtered off and dried. In the preparations involving low melting or water soluble derivatives, the acidified aqueous solution was extracted with isopropyl ether.

1,3-oxazolidine-2,4-dione(**5f**): MP: 110-16 ^{0}C, yield = 20.20%. IR (KBr cm^{-1}) 1661.61 & 1625.76 (C=O), 2925.29 (C-H; str). ^{1}HNMR (*d*DMSO, 400 MHz),δ 1.2 (2H, d, CH_2), 7.5 (1H, s, NH), 7.2 (1H, s, CH), 7 (1H, s, CH). Anal. Calcd. For $C_4H_5NO_3$: C (35.65%) H (2.99%) N (13.86%) O (47.49%). Found: C (51.43%) H (4.80%) N (13.33%) O (30.45%).

3-phenyl-1,3-oxazolidine-2,4-dione (**5g**): MP: 125-30^{0}C, yield = 25.00%. IR (KBr cm^{-1}1766.38 & 1685.04 (C=O), 3303.14 (NH; str), 2922.73 (C-H; aromatic), 1600.75 & 1497.16 (C=C; aromatic). Anal. Calcd. For $C_{10}H_9NO_3$: C (61.02%) H (3.98%) N (7.91%) O (27.09%). Found: C (52.43%) H (3.80%) N (14.33%) O (31.45%).

3-(4-bromophenyl)-1,3-oxazolidine-2,4-dione(**5h**): MP: 150-52^{0}C, yield = 22.30%. IR (KBr cm^{-1}) 1579.34 (C=O), 2927.01 (C-H; aromatic), 1420.11 (C=C; aromatic). ^{1}HNMR (*d*-DMSO, 400 MHz),δ 8(1H, s, *J*=159, CH), 3.2 (6H, m, *J*=23.3, aromatic &oxazole), 2.5(3H, m, *J*=23.5, CH_3). Anal. Calcd. For $C_{10}H_8NO_3Br$: C (42.22%) H (2.36%) Br (31.21%) N (5.47%) O (18.75%). Found: C (32.22%) H (2.24%) Br (24.01%) N (4.01%) O (17.01%).

Synthesis of 2,4-Oxazolidinedione using ethyl-L-lactate[30](**6a**) (Scheme 4).

Ethyl-*L*-lactate (3 mol), urea (1 mol), $NaOCH_3$ (0.5 mol), methanol (1 ml), ethanol (10 ml) was refluxed for 12h. On completion of reaction the mixture was concentrated, acidified with dil. HCl and extracted with diethylether.

1,3-oxazolidine-2,4-dione(**6a**): MP: 195-200 ^{0}C, yield = 21.00%. IR (KBrcm^{-1}) 1738.34 & 1666.36 (C=O), 3171.83 (C-H;str.). ^{1}HNMR (*d*-DMSO, 400 MHz),δ 7.2 (2H, s, *J*=199, CH_2), 1.2 (1H, m, *J*=198.8, CH). Anal. Calcd. For $C_4H_5NO_3$: C (35.65%) H (2.99%) N (13.86%) O (47.49%). Found: C (31.29%) H (2.28%) Br (25.12%) N (3.01%) O (15.12%).

Acknowledgements

We thank Dr. (Prof.) V.H. Kulkarni, Principal & Sri. H.V. Dambal, President, S.E.T's College of Pharmacy, Dharwad, India, for providing the necessary facilities. Our sincere thanks to Dr. S. D. Joshi, Professor & Head, Department of Pharmaceutical Chemistry, S. E. T's College of Pharmacy, Dharwad, India, for his kind support.

References

1. Abraham, D. J.Anticonvulsants. In *Burger's medicinal chemistry and drug discovery*, 6th ed; Virginia, Wiley-interscience, A john wiley and sons, inc, publication. vol 6, pp. 263-328.

2. Yves, L. J. *Bioorganic & Medicinal Chemistry*, **2007,** 15, 2479-2513.

3. Weon, B. I.; Choi, S.H.; Park, J. Y.; Choi, S.H.; Finn, J.; Yoon, S.H. *Euro. J. Med. Chem.,* **2011**, 46, 1027-1039.

4. Abraham, D. J. Antianxiety agents. In *Burger's medicinal chemistry and drug discovery*, 6th ed; Wiley-interscience, A john wiley and sons,inc., publication,. vol 6, pp. 563-628.

5. Moraski, G. C.; Chang, M.; Estrada, A. V.; Franzblau, S. G.; Mollmann, U.; Miller, M. J. *Euro. J. Med. Chem.,* **2010**, 45, 1703-1716.

6. Gudaprthi, V.; Bharathi, K.; Omprakash, G. *Asian J. Chem.,***2011**, 23,765-769.

7. Tsukamoto, S. I.; Ichihara, M.; Wanibuchi, F.; Usuda, S.; Hidaka, K. *J. Med. Chem*., **1993**, 36,2292-2299.

8. Clark-Lewis, J. W. *Chem. Revs.,* **1958**, 58, 63-99.

9. Urech, F. *Chem. Revs.,* **1873**, 6, 1113-1117.

10. Urech, F. *Chem. Revs.,* **1878**, 11, 4679.

11. Urech, F. *Chem. Revs.,* **1880**, 13,485-486.

12. Chemische, F.E.; Sohne. German patent 107,720 (October 23, 1899); Friedlander 6, 563-4. (book T-I,1).

13. Casadeia, M. A.; Stefania, C.; Achille, I. *Tetrahedron,* **1995**, 51(20), 5891-900.

14. Mercier, J. *Anticonvulsant drugs in International encyclopedia of pharmacology and therapeutics.* Mercier J., editor. Pergamon UK limited; **1989**. pp. 1261-1263. Press: Oxford 1973. vol 1. pp. 213-215.

15. Kamal, A.; Rajesh, V.C.R.N.C.S.; Azeeza, S.; Swapna, P.; Khan, M. N.A.*Eur. J. Med. Chem*., **2011**, 46,893-900.

16. Ware, E. *Chem. Rev*., **1950**, 46,403–70.

17. Davies, J. S. H.; Hook, W. H.; Long, F. *J Chem. Soc.,***1950**, 36-41.

18. Clark-Lewis, J. W. *Chem. Rev.,* **1958**, 58, 63-99.

19. Murugesana, S.; Gangulya, S.; Magab, G. *Der PharmaciaLettre*, **2011**, 3,317-332.

20. Cesa, S.; Mucciante, V.; Rossi, L. *Tetrahedron,***1999**, 55,193-200.

21. Brian, S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. Investigation and characterization of organic compound. In *Vogel's textbook of practical organic chemistry*. 5th ed. London: Longman scientific and technical, Longman group UK limited; **1989**. pp. 1284-1286.

22. Brian, S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R.; Aromatic sulfonicacid and their derivative. In *Vogel's textbook of practical organic chemistry*. 5th ed. London: Longman scientific and technical, Longman group UK limited; **1989**. pp. 883-886.

23. Brian, S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R.; Aromatic compound. In *Vogel's textbook of practical organic chemistry*. 5th ed. London: Longman scientific and technical, Longman group UK limited; **1989**. pp. 883-884.

24. Brian, S.; Hannaford, A.J.; Smith, P. W. G.; Tatchell, A. R. Aromatic compound. In *Vogel's textbook of practical organic chemistry*.5th ed. London: Longman scientific and technical, Longman group UK limited; **1989**. pp. 1261-1262.

25. Brian, S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. Miscellaneous aromatic nitrogen compound. In *Vogel's textbook of practical organic chemistry*.5th ed. London: Longman scientific and technical, Longman group UK limited; **1989**.pp.955-957.

26. Brian, S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. Aromatic compound. In *Vogel's textbook of practical organic chemistry*.5th ed. London: Longman scientific and technical, Longman group UK limited; **1989**. pp. 892-894.

27. Spezia, A. J.; Smit, L. R. *J. Org. Chem*., **1963**, 28, 1805–1811.

28. Brian, S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. Investigation and characterization of organic compound. In *Vogel's textbook of practical organic chemistry*. 5th ed. London: Longman scientific and technical, Longman group.

29. Wallingford, V. H.; Thorpe, M. A.; Stoughton, R. W. *J. Am. Chem. Soc.,***1945**, 67, 522-523.

30. Sohda, T.; Mizuno, K.; Tawada, H.; Sugiyama, Y.; Fujita, T. *et al*., *Chem. Pharm. Bull*., **1982**, 30, 3563-3573.