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Synthesis and Biological Activities of Some Novel Oxazepines

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Abstract: ***Novel derivatives of 1, 3-dioxoisoindolin were synthesized by the reaction between imine derivatives and Pthalic anhydride. Oxazepines are an important class of biologically active compounds and their synthesis has been receiving much attention in the field of medicinal and pharmaceutical chemistry. Compound 7b, 7f and 7h has shown activity similar or more to pencillin G, a well known antibiotic drug.***

Keywords: oxazepines, biological activity, imines derivatives, phthalic anhydride, o-aminophenol, pencillina

1. Introduction

Heterocyclic molecules are well known to play a critical role in health care and pharmaceutical drug design.Currently a number of heterocyclic compounds are available commercially as antibacterial drugs and great efforts have been put to the identification of novel antibacterial targets for novel antibacterial drug discovery[1].Schiff bases can be derived from o-aminophenol. These are the compounds containing characteristic -C=N- group. The development and synthesis of novel Schiff bases derivatives as potential chemotherapeutics still attracts the attention of organic and medicinal chemist. Besides their potential use as biologically active agents[2].Nitrogen-containing heterocycles possess diverse chemotherapeutic activities[3]. Various compounds such as alkaloids, essential amino acids, vitamins, hemoglobin, hormones, large number of synthetic drugs and dyes contain heterocyclic ring systems. There are a large number of synthetic heterocyclic compounds, like pyrrole, pyrrolidine, furan, thiophene, piperidine, pyridineand thiazole having important application and many are important intermediates insynthesis [4].

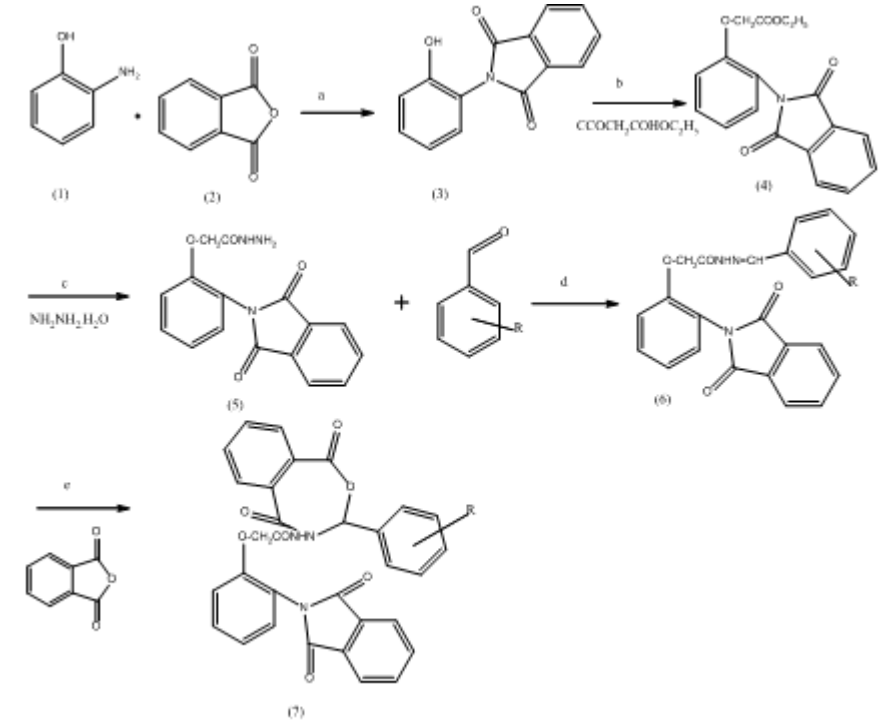
2. Results and Discussions

Generally many drugs are obtained from plants and animals, but most drugs used in modern medicine are products of advances in synthetic organic chemistry and biotechnology. The strategies adopted for the synthesis of the intermediates and target compounds are depicted in Fig. (1) [2- (1, 3-dioxoisoindolin-2-yl) phenoxy] acetamide (**7a-h)** were synthesized by the reaction between Pthalic anhydride and imino derivatives (**6a-h)** which were derived from acetohydrazide derivatives (**5)** and substituted benzaldehyde in the presence of ethanol. These were prepared by reaction between ethylacetoacetate derivatives (**4)** and hydrazine in presence of ethanol. Isoindoline-1, 3- dione derivative (**3)** was obtained by making reaction between pthalic anhydride (2) ando-aminophenol (1).The structure of the synthesized compounds **7a-h** are confirmed by IR^{1}H NMR, ^{13}C NMR and are further supported by correct elemental microanalysis given in the experimental section. Synthetic pathway for the preparation of acetamide compounds (**7a-h)** is depicted in Fig (1)

Scheme1

The IR spectrum of **7** showed band at 1680 cm^{-1}, 1786.8 cm^{-1} indicating the presence of ketone and amide functional group. The complete NMR data are presented in the experimental section.

The mass spectra displayed the correct molecular ions (M+) in accordance with the suggested structure. **Biological evolution**-To medicinal chemists, the true utility of heterocyclic structures is the ability to synthesize one library based on one core scaffold and to screen it against a variety of different receptors, yielding several active compounds. Almost unlimited combinations of fused heterocyclic structures can be designed, resulting in novel polycyclic frameworks with the most diverse physical, chemical and biological properties. The Antibacterial activities of our compounds were assessed against two gram (+); Staphylococcus aureus 96 and Streptococcus mutans and two gram (-) bacteria; E.coli and Klebsiella pneumonia. All detection was carried out by minimum inhibitory concentration (MIC). Agar spot method of Wiegand et al. with modification was used to determine the MIC of the chemicals. Briefly 100 µL of bacteria cultures were spread on to Mueller Hinton Agar (MHA) plates. Then serial dilutions of chemicals were made in a concentration range from 15.62 - 2000µg / mL inappropriate solutions (water or dimethylsulfoxide DMSO). 5µL of chemical suspensions were spotted on air dried MHA plates. The inoculated plates were incubated at 36^{0} C for 24 h. Penicillin (100µL) was used as control. The lowest concentration at which there was no visible zone of inhibition was taken as the MIC and the inhibition zone produced by each compound was measured in mm. Each test was run in triplicate.



Reagents and conditions : (a) glacial acetic acid , reflux 4 hrs (b) acetone , anhydrous K_2CO_3 Reflux 6 hrs (c) ethanol , reflux 8 hrs (d) ethanol , reflux , 5 hrs (d) MW irradiation , 25 min. , 400 w

Fig.1 R= 2-Chloro, 2-Chloro-5-Nitro, 4-Bromo, mesitaldehyde, 2-Nitro, 4-Flouro, 2- Methoxy, furfuraldehyde

Table 1: Minimum Inhibitory Concentration of the Compounds Zone of Inhibition (mm)

Compound	*Sample (R)*	*SA 96*	*SM*	*E.Coli*	*KP*
7a	2-Chloro	5	5	2	nil
7b	2-Chloro 5-Nitro	7	5	3	2
7c	4-Bromo	4	4	nil	3
7d	Meistaldehyde	5	5	3	2
7e	2-Nitro	6	5	2	nil
7f	4-Fluoro	6	7	2	nil
7g	2-Methoxy	5	4	3	2
7h	Furfuraldehyde	8	7	6	2
Pencillin G		7	8	9	7

gram (+) bacteria; Staphylococcus aureus 96 (SA96) and Streptococcus mutans (SM), gram (-) bacteria; E.coli and Klebsiella pneumonia (KP)

3. Conclusion

A short process for the preparation of oxazepine derivatives **7a-h** has been developed. Two synthetic routes have been established for the preparation of compounds

7a-hi:e conventional and microwave. The overall yields of these compounds are very good.

All the compounds were evaluated for their antibacterial activities. The compounds are found to have good activity against gram-positive bacteria than gram negative bacteria.

The compound **7b** has shown equal activity with pencillin in gram positive bacteria **SA96**. Compound **7f**has shown very good activity in gram positive bacteria **SM**. Compound 7**h** possesses high activity with gram positive **SA96**, very good activity with **SM** and also with gram negative bacteria **E.Coli**.

4. Experimental

General information

All the chemicals used in the present investigation were purchased from Sigma-Aldrich Chemicals company, Inc. USA and used without further purification. TLC was performed on aluminum sheet of silica gel 60F254, E-Merk, Germany using iodine as visualizing agent. Melting point was determined in open capillary tubes on Mel-Temp apparatus and is uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-300F, 300 MHz NMR instrument using TMS as the internal standard (Chemical shitft in$^\delta$, ppm); and IRspectra in KBr pellets on a Perkin –Elmer 882 spectrophotometer model (V max in cm^{-1}). The purity of the compounds were established by TLC and by elemental analysis (C, H, N). Elemental analysis was recorded on a Carlo Erba 1108 elemental Analyzer, Central Drug Research Institute, Lucknow, India.

General procedure

4.2.1-Preparation of 2- (2-hydroxyphenyl) isoindoline-1, 3-dione (3):A mixture of o-aminophenol (0.2mol), Pthalic anhydride (0.3mol) and toluene / glacial acetic acid (10ml) were refluxed for 4 hrs. excess solvent was removed by distillation and the residual mixture was poured over crushed ice. The resultant product was recrystallized from H_2O in good yield [5]

4.2.2-Preparation of ethyl 2-[2- (1, 3-dioxoisoindolin -2-yl) phenoxy] acetate (4): A mixture of 3 (0.1mol), ethylacetoacetate (0.1mol) and anhydrous K_2CO_3 (0.15mol) in dry acetone was refluxed on a water bath for 24 hrs.. The reaction mixture was cooled and filtered. From filtrate excess acetone was removed by distillation. Then the

reaction mixture was poured into ice cold H_2O and stirred well. The resultant product was recrystallized from ethanol[6].

4.2.3-Preparation of 2-[2- (1, 3-dioxoisoindolin-2-yl) phenoxy]acetohydrazide (5):
A mixture of 4 (0.05mol) and hydrazine hydrated (0.2mol) in ethanol (10ml) was refluxed for 4 hrs. Excess of ethanol was removed by distillation. It was collected by filtration and recrystallized from ethanol[7].

4.2.4-Preparation of N' benzlidene-2[2- (1, 3-dioxoisoindolin-2yl) phenoxy]acetohydrazide (6):A mixture of 5and appropriate aromatic aldehyde in equal amount was refluxed in ETOH for 3 hrs. The excess of solvent was removed under reduced pressure, the ppt formed after cooling was collected by filtration and recrystallized from ETOH to get the desired product[8].

4.2.5-Preparation of N-[1, 5-dioxo-3-phenybenzo[1, 3]oxazepine-4-yl]-2- (2- (1, 3-dioxoisoindolin-2-yl) phenoxy) acetamide (7): A mixture of 6 (0.1mol) and Phthalic anhydride (0.1mol) were ground with a mortar, mixed, dried and subjected to the MWir radiation for some min. After completion of the reaction mixture was cooled to room temperature and the solid obtained was recrystallized twice from absolute EtOH [9].

4.3.1-N- (3- (2-Chlorophenyl) -1, 5-dioxobenzo[1, 3]oxazepin-4-yl) -2- (2- (1, 3 dioxoisoindolin-2-yl) phenoxy) acetamide (7a): This compound was obtained in 72% yield; m.p.206 - 210^{0}C; IR (KBr): 3382-3469 (NH), 3024-3166 (ArH), 1597-1786 (C=O), 1050-1350 (C-O), 1020-1360 (CN), 1450-1600 (C=C); ^{1}H-NMR (DMSO-d6, 300MHz):5.01 (s, 2H, -OCH_2), 6.80 (m, 16H, ArH), 11.49 (s, 1H, NH), 7.69 (s, 1H, O-CH-N); ^{13}C NMR ($CDCl_3$, 100MHz) δ = 172.5, 167.5, 167.1, 140.3, 132.2, 131.1, 128.2, 123.7, 123.5, 119.7, 66.6; EI-MS: m/z 580 Anal. Calcd for $C_{31}H_{20}N_3O_7Cl$: C 63.97, H 3.43, N 7.22 Found: C 64.11, H 3.30, N 7.26

4.3.2- N- (3- (2-Chloro -5-Nitrophenyl) -1, 5-dioxobenzo[1, 3]oxazepin-4-yl) -2- (2- (1, 3-dioxoisoindolin-2-yl) phenoxy) acetamide (7b): This compound was obtained in 75% yield; m.p. 210 - 214^{0}C; IR (KBr): 3380-3461 (NH), 3020-3160 (ArH), 1594-1780 (C=O), 1056-1352 (C-O), 1025-1362 (CN), 1448-1602 (C=C); ^{1}H-NMR (DMSO-d6, 300MHz,):5.09 (s, 2H, -OCH_2), 6.85 (m, 16H, ArH), 11.51 (s, 1H, NH), 7.70 (s, 1H, O-CH-N); ^{13}C NMR ($CDCl_3$, 100MHz) δ =172.1, 167.4, 166.9, 140.5, 131.9, 131.8, 128.0, 123.4, 123.2, 119.5, 66.2; EI-MS: m/z626 Anal. Calcd for $C_{31}H_{19}N_4O_9Cl$: C 59.37, H 3.03, N 8.93 Found: C 59.40, H 3.07, N 8.96

4.3.3-N- (3- (4-bromophenyl) -1, 5-dioxobenzo[1, 3]oxazepin-4-yl) -2- (2- (1, 3-dioxoisoindolin-2-yl) phenoxy) acetamide (7c): This compound was obtained in 68% yield; m.p.203 - 208^{0}C; IR (KBr): 3386-3466 (NH), 3026-3164 (ArH), 1590-1784 (C=O), 1054-1358 (C-O), 1028-1358 (CN), 1455-1598 (C=C); ^{1}H-NMR (DMSO-d6, 300MHz):5.05 (s, 2H, -OCH_2), 6.84 (m, 16H, ArH), 11.47 (s, 1H, NH), 7.64 (s, 1H, O-CH-N); ^{13}C NMR ($CDCl_3$, 100MHz) δ = 172.3, 167.0, 166.5, 140.4, 131.6, 131.4, 128.6, 123.6, 123.4, 119.0, 66.4; EI-MS: m/z625 Anal. Calcd for $C_{31}H_{20}N_3O_7Br$: C 59.43, H 3.19, N 6.71 Found: C 59.47, H 3.22, N 6.74

4.3.4-2- (2- (1, 3-dioxoisoindolin-2-yl) phenoxy) -N- (3-mesityl-1, 5dioxobenzo[1, 3]oxazepin-4-yl) acetamide (7d): This compound was obtained in 74% yield; m.p.215 - 218^{0}C; IR (KBr): 3387-3454 (NH), 3018-3169 (ArH), 1580-1789 (C=O), 1046-1346 (C-O), 1018-1366 (CN), 1458-1610 (C=C); ^{1}H-NMR (DMSO-d6, 300MHz):5.11 (s, 2H, -OCH_2), 6.78 (m, 16H, ArH), 11.45 (s, 1H, NH), 7.60 (s, 1H, O-CH-N); ^{13}C NMR ($CDCl_3$, 100MHz) δ = 172.0, 167.1, 166.7, 140.2, 131.4, 131.5, 128.9, 123.6, 123.2, 119.2, 66.1; EI-MS: m/z589 Anal. Calcd for $C_{34}H_{27}N_3O_7$: C 69.26, H 4.58, N 7.13 Found: C 69.30, H 4.62, N 7.18

4.3.5-2- (2- (1, 3-dioxoisoindolin-2-yl) phenoxy) -N- (3- (2-nitrophenyl) -1, 5-dioxobenzo[1, 3]oxazepin-4-yl) acetamide (7e): This compound was obtained in 70% yield; m.p.209 - 212^{0}C; IR (KBr): 3376-3472 (NH), 3016-3160 (ArH), 1588-1789 (C=O), 1059-1352 (C-O), 1022-1354 (CN), 1442-1606 (C=C); ^{1}H-NMR (DMSO-d6, 300MHz):5.08 (s, 2H, -OCH_2), 6.83 (m, 16H, ArH), 11.50 (s, 1H, NH), 7.62 (s, 1H, O-CH-N); ^{13}C NMR ($CDCl_3$, 100MHz) δ = 172.4, 167.0, 166.9, 140.0, 132.4, 131.6, 128.1, 123.0, 123.0, 119.4, 66.5; EI-MS: m/z592 Anal. Calcd for $C_{31}H_{20}N_4O_9$: C 62.83, H 3.37, N 9.45 Found: C 62.88, H 3.42, N 9.49

4.3.6- 2- (2- (1, 3-dioxoisoindolin-2-yl) phenoxy) -N- (3- (4-fluorophenyl) -1, 5 dioxobenzo[1, 3]oxazepin-4-yl) acetamide (7f): This compound was obtained in 64% yield; m.p.203 - 206^{0}C; IR (KBr): 3376-3465 (NH), 3024-3170 (ArH), 1590-1778 (C=O), 1048-1354 (C-O), 1022-1370 (CN), 1444-1601 (C=C); ^{1}H-NMR (DMSO-d6, 300MHz):5.06 (s, 2H, -OCH_2), 6.87 (m, 16H, ArH), 11.48 (s, 1H, NH), 7.59 (s, 1H, O-CH-N); ^{13}C NMR ($CDCl_3$, 100MHz) δ = 172.7, 167.6, 167.4, 140.7, 132.0, 131.2, 128.5, 123.5, 123.1, 119.6, 66.0; EI-MS: m/z564 Anal. Calcd for $C_{31}H_{20}N_3O_7F$: C 65.84, H 3.53, N 7.43 Found: C 65.88, H 3.55, N 7.48

4.3.7- 2- (2- (1, 3-dioxoisoindolin-2-yl) phenoxy) -N- (3- (2-methoxyphenyl) -1, 5 dioxobenzo[1, 3]oxazepin-4-yl) acetamide (7g): This compound was obtained in 78% yield; m.p.212 - 216^{0}C; IR (KBr):3381-3470 (NH), 3022-3162 (ArH), 1590-1780 (C=O), 1051-1353 (C-O), 1023-1359 (CN), 1453-1603 (C=C); ^{1}H-NMR (DMSO-d6, 300MHz): 5.02 (s, 2H, -OCH_2),
6.76 (m, 16H, ArH), 11.54 (s, 1H, NH), 7.66 (s, 1H, O-CH-N); ^{13}C NMR ($CDCl_3$, 100MHz) δ = 171.9, 167.3, 167.2, 140.1, 132.1, 131.0, 128.3, 123.3, 123.3, 119.3, 66.7; EI-MS: m/z577Anal. Calcd for $C_{32}H_{23}N_3O_8$: C 66.55, H 3.98, N 7.27 Found: C 66.59, H 3.99, N 7.29

4.3.8-2- (2- (1, 3-dioxoisoindolin-2-yl) phenoxy) -N- (3- (furan-2-yl) -1, 5-dioxobenzo[1, 3]oxazepin-4-yl) acetamide (7h): This compound was obtained in 72% yield; m.p.219 - 220^{0}C; IR (KBr): 3376-3467 (NH), 3027-3169 (ArH), 1599-1785 (C=O), 1055-1354 (C-O), 1010-1350 (CN), 1446-1607 (C=C); ^{1}HNMR (DMSO-d6, 300MHz):5.14 (s, 2H, -OCH_2), 6.90 (m, 16H, ArH), 11.46 (s, 1H, NH), 7.51 (s, 1H, O-CH-N); ^{13}C NMR ($CDCl_3$,

100MHz) $^{\delta}$ =172.6, 167.3, 166.8, 140.6, 132.3, 131.7, 128.7, 123.8, 122.9, 119.1, 66.3, EI-MS: m/z537 Anal. Calcd for $C_{29}H_{19}N_3O_8$: C 64.80, H 3.53, N 7.82 Found: C 64.84, H 3.57, N 7.87

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