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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NOVEL AMIDE DERIVATIVE CONTAINING OXAZOLE MOIETY

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ABSTRACT

In the present study, synthesis of some novel Oxazole contains amide analog [2a-l] have been carried out by condensing N-(4-acetylphenyl)-2-(10-oxo-10, 11-dihydrodibenzo [b, f] thiepin-2-yl) propanamide with various aromatic derivatives by using ethanol as a solvent in presence of catalyst (Cl_2, Br_2 or I_2) under reflux condition. Structures of synthesized compounds have been confirmed by spectral data (IR, ^1H NMR) and elemental analysis. The entire newly synthesized compound has been evaluated for their antibacterial activities.

KEYWORDS: Amide, Oxazole, Reflux, Spectral data, Antimicrobial activity.

INTRODUCTION

An amide is a class of organic compounds containing a nitrogen atom attached to an acyl group. Amides are considered a derivative of carboxylic acids in which hydroxyl group has been replaced by amine or ammonia. Amides can be prepared from amines, anhydrides, esters, carboxylic acid etc. Amide is an important class of antimicrobial agents which possesses antimicrobial[1,2,3], antibacterial[4], antifungal, antimycobacterial activities and photosynthesis inhibition activity.[5,6] Several derivatives of amides were found to display different activities like anti-inflammatory and analgesic activities[7,8,9], Several amides also possess brain antihypoxic activity[10], antinociceptive[11] and insecticidal activity.[12]

Oxazole are an important class of five-member aromatic heterocycles compound containing one oxygen and one nitrogen atom in their structures. Oxazole are key building block of natural products, pharmaceuticals and synthetic intermediates.[13,14,15] Oxazole have not only attracted great interest due to their appearance such as subunit of various biologically active

natural products but also because of their utilities are valuable precursor in many useful synthetic transformation.[16] Among the numerous heterocyclic moieties of biological and pharmacological interest, the oxazole ring is endowed with various activities such as hypoglycemic[17], anti-inflammatory[18] and antibacterial[19] activities. It is reported that D2-isoxazole derivatives can be used as bet adrenergic receptor antagonist.[20] The oxazole derivatives have raised considerable attention to medicinal research and a large number of investigations on their synthesis and biological activity have been reported. All these activities developed our interest to synthesize a new series of oxazole derivative having amide moiety.

1. Condensation of 2-(10-oxo-10, 11-dihydrodibnzo [*b, f*] thiepin-2-yl) propionic acid with 4-aminoacetophenone give N-(4-acetylphenyl)-2-(10-oxo-10, 11-dihydrodibenzo [*b, f*] thiepin-2-yl) propanamide **[1]** in a very good yield. This condensed product **[1]**, further on reaction with various aromatic urea derivatives gives N-{4-[4-(N-substituted anilino)-1, 3-oxazole-2-yl] phenyl}-2-(10-oxo-10, 11-dihydrodibenzo [*b, f*] thiepin-2-yl) propanamide [**2a-l]**. The structures of synthesized compound were assigned on the basis of elemental analysis, IR, ^{1}H NMR data. All new synthesized compounds were characterized and evaluated for their in vitro antibacterial activities.

2. MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. All the products have been characterized by elemental analysis, IR and ^{1}H NMR studies. IR spectra were recorded on Perkin Elmer 100 spectrophotometer in KBr disc and. ^{1}H NMR spectra were recorded on Bruker spectrometer (400 MHz) using TMS as an internal standard, chemical shift in δ ppm.

Procedure for the synthesis of N-(4-acetylphenyl)-2-(10-oxo-10, 11-dihydrodibenzo [b, f] thiepin-2-yl) propanamide [1]

Thionyl chloride (99.6 gm, 0.837 mol) was charged in 500 ml 3-nacked round bottom flask. 2-(10-oxo-10,11-dihydrodibnzo [*b,f*]thiepin-2-yl)propionic acid (25.0 gm, 0.083 mol) was added slowly by maintaining temperature below 25°C. The mixture was then heated to 75-80°C for 3 hours. After completion of reaction (monitored by TLC, System - Chloroform: Methanol: 8:2) thionyl chloride distilled out and fresh ethylene dichloride (200 ml) was added followed by dropwise addition of 4-aminoacetophenone (12.4 gm, 0.059 mole) in ethylene dichloride (25 ml) and triethylamine (8.4 gm, 0.083) below 15°C. This mixture was

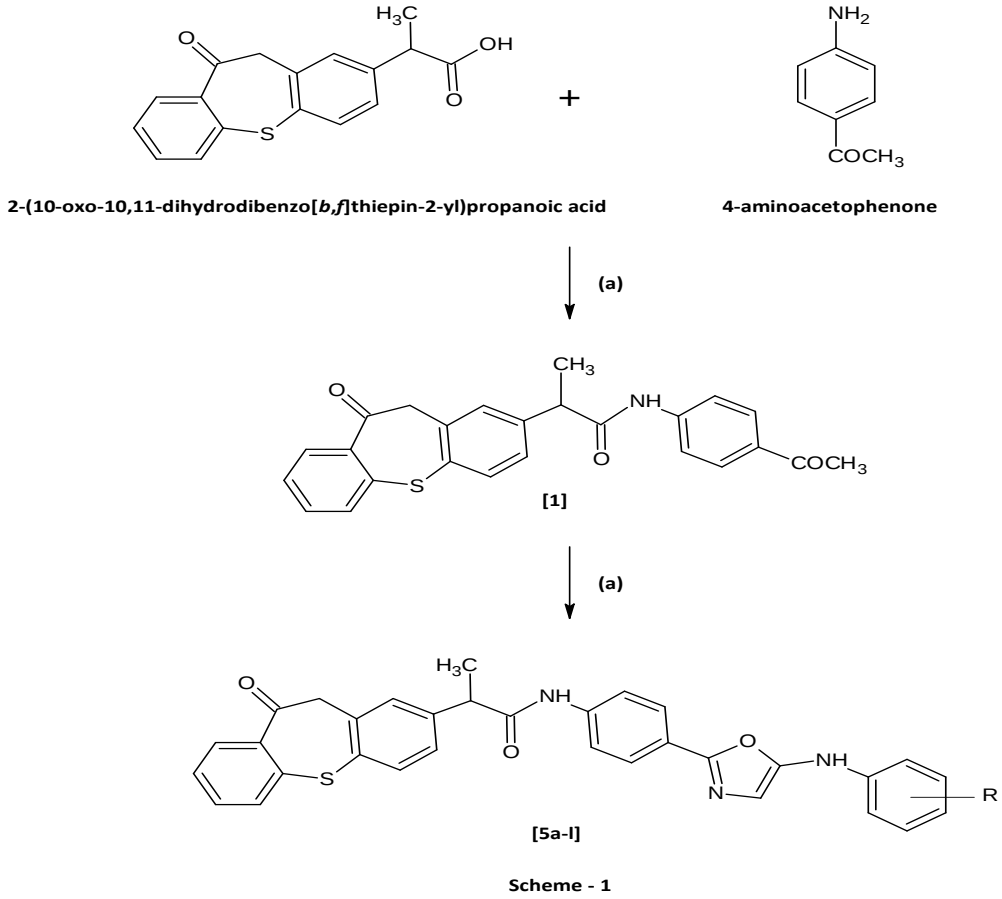
refluxed for 3-4 hrs. After completion of reaction (monitored by TLC, System -Chloroform: Methanol: 8:2), water (200 ml) was added and layer separated. Organic layer washed with 5% hydrochloric acid, 10% $NaHCO_3$ solution finally washed with water. Organic layer concentrated and finally, it was crystallized from n-Hexane to give N-(4-acetylphenyl)-2-(10-oxo-10, 11-dihydrodibenzo [*b,f*] thiepin-2-yl) propanamide as yellow solid **[1].** Yield 88%, M.P. 107°C.

Procedures for the synthesis N-**{4-[4-(3-chloroanilino)-1, 3-oxazole-2-yl] phenyl}-2-(10-oxo-10, 11-dihydrodibenzo [*b, f*] thiepin-2-yl) propanamide [2j]**

N-(4-acetylphenyl)-2-(10-oxo-10, 11-dihydrodibenzo [*b,f*] thiepin-2-yl) propanamide **[1]** (5.0 gm, 0.012 mol) was dissolved (in 30 ml) ethanol. To this, 3-chlorophenyl urea (4.11 gm, 0.024 mol) was added followed by drop wise addition of Bromine (1.92 gm, 0.012 mol). The mixture was refluxed for 8 hours. After completion of reaction, (monitored by TLC, System -Chloroform: Methanol: 8:2) water (125 ml) added and heated until solid gone into the solution then filtered and filtrate make alkaline with ammonium hydroxide, thus obtained precipitate was filtered and dried. Finally, product was recrystalised from alcohol to give N-{4-[4-(3-chloroanilino)-1, 3-oxazole-2-yl] phenyl}-2-(10-oxo-10, 11-dihydrodibenzo [*b, f*] thiepin-2-yl) propanamide **[2j]**. Yield: 0.71%., M.P. 171°C.

Similarly, reaction of Amides with various urea derivatives carried out to give related Oxazole derivative **[2a-l]**. Their data are shown in table-1.

NMR δ ppm in (DMSO-d_6) 1.45 (3H, d, CH_3), 2.52 (2H, s, CH_2), 3.95(1H, q, CH_2), 8.89(1H, s, CH), 9.97 (1H, s, NH), 10.30 (1H, s, NH), 6.94-7.80 (15H, m, Ar-H).



Scheme - 1

Reagent & Condition: (a) Thionyl chloride, Triethyl amine, Ethylene dichloride, 3-4 hrs Reflux; (b) Aromatic urea, Br_2, EtOH, Ammonium hydroxide, 10 hrs Reflux.

Table 1: Physical characterization.

Code No	R	Mole. Wt	M.P. (°C)	Yield (%)	Elemental analysis (%) Found/ Calc		
					C	H	N
2-a	-H	531.62	171-177	71	72.29/72.31	5.07/5.09	7.90/7.92
2-b	4-CH_3	545.65	188-192	69	72.64/72.62	5.34/5.32	7.70/7.73
2-c	3-CH_3	545.65	167-173	76	72.64/72.62	5.34/5.3	7.70/7.69
2-d	3-OCH_3	561.65	177-178	66	70.56/70.58	5.18/5.20	7.48/7.50
2-e	4-OCH_3	561.65	163-167	83	70.56/70.53	5.18/5.15	7.48/7.51
2-f	2-Cl	566.06	157-164	85	67.86/67.88	4.57/4.59	7.42/7.45
2-g	4-F	549.61	159-163	78	69.93/69.95	4.71/4.73	7.64/7.67
2-h	4-Cl	566.06	201-205	88	67.86/67.88	4.57/4.59	7.42/7.43
2-i	4-NO_2	576.62	118-122	75	66.65/66.67	4.49/5.53	9.71/9.72
2-j	3-Cl	566.06	119-125	72	67.86/67.89	4.57/4.60	7.42/7.45
2-k	2,6-CH_3,	559.67	151-155	69	72.96/72.95	5.59/5.57	7.50/7.48
2-l	2,4-CH_3,	559.67	143-168	70	72.96/72.98	5.59/5.56	7.50/7.52

Table 2: In vitro antimicrobial activity of newly synthesized compound [2a-l].

Antibacterial Activity		
Zone of Inhibition (mm)		
	Gram negative	Gram positive
Code. No.	*Escherichia coli*	*Staphylococcus aureus*
2-a	62.5	250
2-b	200	200
2-c	125	500
2-d	200	500
2-e	500	500
2-f	500	500
2-g	250	100
2-h	200	125
2-i	250	62.5
2-j	100	250
2-k	125	250
2-l	200	62.5
Ref-1	100	250
Ref-2	25	50

Where Ref-1=Ampicillin, Ref-2= Ciprofloxacin.

N-{2-[4-{5-(4-chlorophenyl)-4, 5-dihydro-1H-pyrazol-3-yl} sulfonyl) phenyl] ethyl} - 3-ethyl - 4-metyl-2-oxo-4, 5-dihydro-1H-pyrrole-1-carboxamide [2b]: IR (cm^{-1}) 1700(–COHN str), 1667 (C=O), 3286 (-NH), 1357 (-C-H), 1606 (C=C), 2971 ($-CH_3$), 1331(S=O), 1158 (SO_2NH), 651(C-Cl), 1513(C=N), 1229 (C-N), 709 (C-S).

N-{2-[4-{5-(3,4-dimethylphenyl)-4, 5-dihydro-1H-pyrazol-3-yl} sulfonyl) phenyl] ethyl} - 3- ethyl - 4-metyl-2-oxo-4, 5-dihydro-1H-pyrrole-1-carboxamide [2k]: IR (cm^{-1}) 1701(–COHN str), 1660 (C=O), 3286 (-NH), 1356 (-C-H), 1610 (C=C), 2970 ($-CH_3$), 1329(S=O), 1155 (SO_2NH), 1513(C=N), 1228 (C-N), 682 (C-S).

Antimicrobial activity

The antimicrobial assay method has been determined by using Kirby-Bauer method disc diffusion method, in this method, reference drug and the compound to be tested were dissolved in dimethyl sulfoxide (DMSO) and disc was prepared with whatman filter paper. Plates were prepared with maeller-Hinton agar medium for rapidly growing organism. Inoculum was prepared with sterile saline and turbidity was adjusted to 10^8 Cfu [colony forming unit] per milliliter. Common standard strain was used for screening of antibacterial activities. Serial dilutions were prepared in primary and secondary screening. The control

tube containing no antibiotic is immediately sub cultured by spreading a loopful evenly over a quarter of plate of medium for the growth of the test organisms and put for incubation at 37°C overnight. The MIC of the control organism is read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of organism is recorded as the MIC. The amount of growth from the controlled tube before incubation is compared. The results of antimicrobial activities are given.

RESULT OF DISCUSSION

The compound of scheme (2a-l) have been successfully carried out and tested for their efficiency as antibacterial in vitro against gram negative (Escherichia coli) and gram positive (Staphylococcus aureus) bacteria strains by measuring the inhibition zone in mm as recommended by National Committee for Clinical Laboratory Standard (NCCLS). The summary of antimicrobial activity shown in table- 2. It reveals comparable activity with standard drug. Most of the compound showed moderate to good antibacterial activity against the strain used.

CONCLUSION

The substituted amide Oxazole moieties are already known for different biological activities. As per the result of the screening described in table-2, it is clearly indicated that the compound of the scheme are having good antibacterial activity equipotent with the standard drugs. For the above results; one can establish that the synthesized substituted Oxazole can be rich source for the exploitation. Therefore in search of new generation of the active compound, it may be useful to explore the possibility in this area by making or introducing different functional group as substitution. This may result into better pharmacological agents.

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