

NAPHTHALENE DERIVATIVES : A NEW RANGE OF ANTIMICROBIALS WITH HIGH THERAPEUTIC VALUE

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ABSTRACT

The discovery, development and identification of biologically active compounds has gain lot of importance in the recent years, even though there is considerable number of adverse effects, the medicinal chemists have always tried to design drug substance possessing maximum therapeutic application and minimum toxicity. Combinatorial synthesis has brought lot of evolution in the recent trends of drug synthesis. Naphthalene has been identified as new range of potent antimicrobials effective against wide range of human pathogens. They occupy a central place among medicinally important compounds due to their diverse and interesting antibiotic properties with minimum toxicity.

Keywords: Naphthalene, antimicrobial activity.

INTRODUCTION

Naphthalene as antimicrobial agent

Several naphthalene containing drugs are available, such as nafcillin, naftifine, tolnaftate, terbinafine, etc. which play vital role in the control of microbial infection. Several other synthetic derivatives have also been reported which possess significant and satisfactory antimicrobial property. β -naphthol commonly used as dye possess a very good antimicrobial property¹

Chemistry of naphthalene:

1. Naphthalenes

Naphthalene is the simplest and the most important member of this class of arenas, in which two benzene rings are fused in ortho positions.

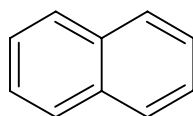


Fig-1:Naphthalene

Physicochemical properties

Naphthalene is a colorless solid which forms shining flaked-crystal, its melting point is 82.2°C. It has familiar odor of moth balls. It is very volatile and sublimes slowly at room temperature. Naphthalene is insoluble in water, moderately soluble in alcohol, highly soluble in ether and benzene. It burns with a smoky flame.

Naphthalene gives the usual aromatic electrophonic substitution reaction as shown in Fig 2.

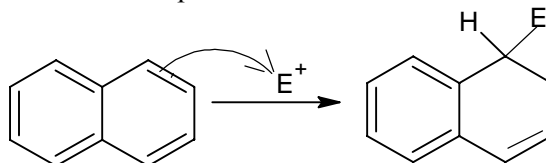


Fig.-2: Aromatic substitution reaction of naphthalene

2-Naphthol

The mono hydroxy derivatives of naphthalene are called naphthol

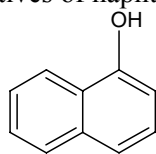


Fig.-3a: 1-naphthol

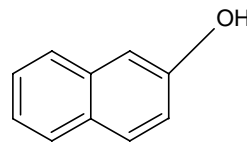


Fig.-3b: 2-naphthol

Preparation

Both 1 and 2 naphthols are prepared from the corresponding naphthalene sulphonic acids by fusion with sodium hydroxide at 300°C followed by acidification.

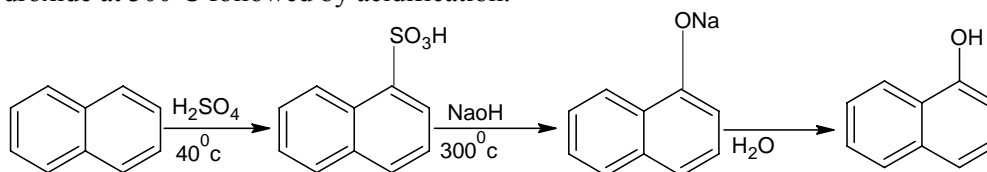


Fig.-4: Preparation of 1 and 2-naphthol from naphthalene sulphonic acid

Physicochemical properties

They are colorless solid compounds having a melting point of 123-124°C, they are insoluble in water, benzene and highly soluble in alcohol and ether. Naphthol gives all the chemical reactions characteristic of phenols².

Review of research on naphthalene

Mkpenie et al.,³ have tested azo-2 naphthol and 2-naphthol against five representative human pathogenic microorganisms i.e. *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Streptococcus faecalis*. Both azo-2 naphthol and 2-naphthol were found equally effective against all the organisms tested.

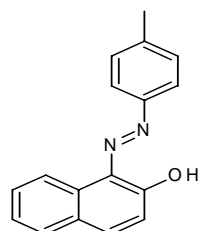


Fig.-5: 1-(4-methylphenylazo), 2-naphthol

The 2-naphthol and azo 2-naphthol were screened for the presence of antibacterial constituents against *Staphylococcus aureus* and *Escherichia coli* by Faizul et al.,⁴ they found naphthol ring as an active principal component. A series of 2-benzylidene amino naphthothiazoles were designed and synthesized incorporating the lipophilic naphthalene ring to render them more capable of penetrating various biomembranes. Schiff bases were synthesized by the reaction of naphtho [1, 2-d] thiazol-2-amine with various substituted aromatic aldehydes. 2-(2'-Hydroxy) benzylidene aminonaphtho thiazole was converted to its Co (II), Ni (II) and Cu (II) metal complexes upon treatment with metal salts in ethanol. All the compounds were evaluated for their antibacterial activities by paper disc diffusion method with Gram positive *Staphylococcus aureus* and *Staphylococcus epidermidis* and Gram negative *Escherichia coli* and *Pseudomonas aeruginosa*. The minimum inhibitory concentrations of all the Schiff bases and metal complexes were determined by agar streak dilution⁴.

Yildiz et al.,⁵ synthesized 2-hydroxy-1-naphthalene with 6,7-dihydro-13H dibenzo [e,n][1,4]dioxin-2,11 diamine of the ligands and screened in vitro for their antimicrobial potential against *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Micrococcus luteus*, *Proteus vulgaris*, *Pseudomonas aeruginosa*,

Mycobacterium segments, *Bacillus cereus*, *Liseria monocytogenes*, *Candida albicans*, *Kluyeromycesfrugilis*, *Rhodotorularubra*, *debrayomyceshanseni*, *Hanseniaspora guilliermondi* ⁵. Zeynep et al., ⁶ studied the antimicrobial activity of certain chemically synthesized compounds. The compound containing naphthalene moiety ⁶

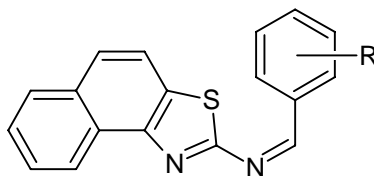


Fig.-6: Benzylidene aminonaphtho thiazole

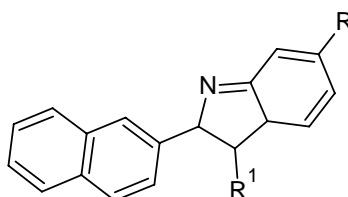


Fig.-7: 2-hydroxy-1-naphthalene with 6,7-dihydro-13H dibenzo [e,n][1,4]doximin-2,11 diamine

The compound 2-hydroxy-1-naphthalene with 6,7-dihydro-13H dibenzo [e,n] [1,4] doximin-2,11 diamine were studied on the Gram-negative bacteria like *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853), the Gram-positive bacteria like *S. aureus* (ATCC 25923), MRSA (clinical isolate), *Enterococcus faecalis* (ATCC 29212) and fungi like *Candida krusei* (ATCC 6258) and *Candida albicans* (ATCC 10231). The compound was found to have potent antibacterial and antifungal activity. Nagaraja et al., ⁸ synthesis of naphthofurans derivative coupled with both quinoline and azetidine nucleus. This compound exhibited significant antimicrobial activities ⁸.

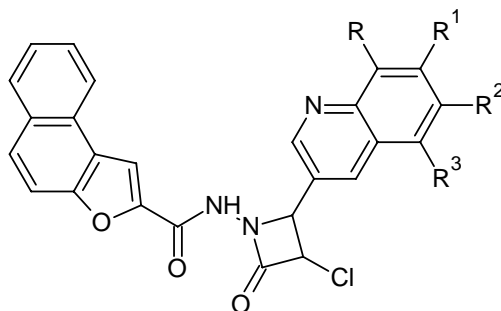


Fig.- 8: N-[3-Chloro-2-(2-chloroquinolin-3-yl)-4-oxoazetidin-1-yl] naphtho [2, 1-b] furan-2-Carboxamide

Nagaraja et al., ⁹ synthesized 2-Aryl-2,3-dihydronaphtho[2,1-b]furo[3,2-b]pyridin-4(1H)-ones were synthesized from 2-hydroxy-1-naphthonitrile 2 and characterized on the basis of chemical, analytical and spectral data. The compounds screened for antibacterial and antifungal activity⁹ were found effective against human pathogenic Gram positive and Gram negative bacteria and fungi.

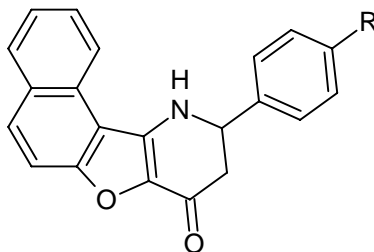


Fig.-9: 2-Aryl-2,3-dihydronaphtho[2,1-b]furo[3,2-b]pyridin-4(1H)-ones

R=H,Cl,Br,CH₃,OCH₃,NO₂

Sharma et al.,¹⁰ prepared some naphthalene derivatives by incorporating azetidiny and thiazolidiny moieties at its a- or b-positions such as a-(3-chloro-2-oxo-4-substituted)aryl-1-azetidiny naphthalenes 6–10, a-((substituted)aryl-4-oxo-1,3-thiazolidin-3-yl) naphthalenes 11–15, b-(3-chloro-2-oxo-4-substituted aryl-1-azetidiny) naphthalenes 21–25, and b-(substitutedaryl-4-oxo-1,3-thiazolidin-3-yl) naphthalenes 26–30. These compounds have also been screened for acute toxicity and anti-inflammatory and analgesic activities. Compounds which showed better anti-inflammatory and analgesic activities were also examined for their ulcerogenic liability and underwent a cyclooxygenase assay¹⁰.

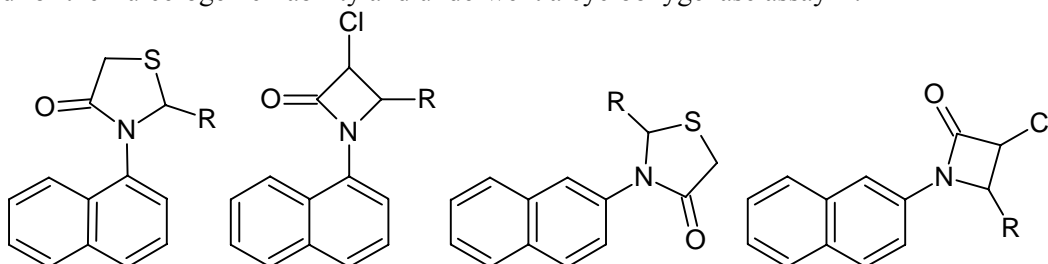


Fig.-10: Synthesis of naphthalene derivatives by incorporating azetidiny and thiazolidiny moieties

Zeynep et al.,⁶ prepared several 2-(5,5,8,8-tetramethyl-5,6,7,8 tetrahydronaphthalen-2-yl)-1H-benzimidazole-5-carboxamide analogues and evaluated for their antibacterial and antifungal activities against *S. aureus*, Methicillin-resistant *S. aureus* (MRSA), *C. albicans* and *C. krusei*⁶.

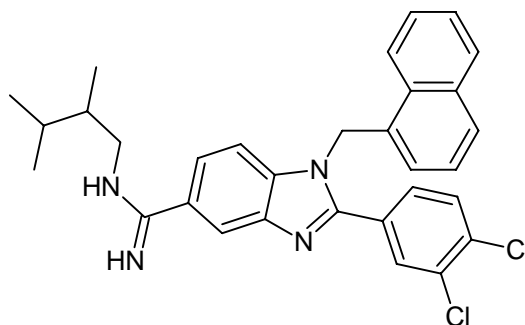


Fig.-11: 2-(5,5,8,8-tetramethyl-5,6,7,8 tetrahydronaphthalen-2-yl)-1H-benzimidazole-5-carboxamide

Goksu et al.,¹² reported that 5-bromo-6methoxynaphthalene-2-carboxylic acid and 5,6 dimethoxynaphthalene-2-carboxylic acid were having antibacterial activity against some pathogenic bacteria under in-vitro conditions¹².

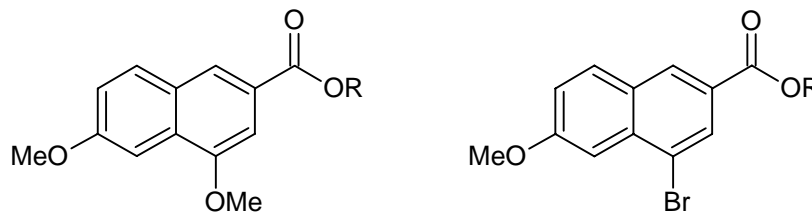


Fig.-12:(5,6 dimethoxynaphthalene-2-carboxylic acid) (5-bromo-6methoxynaphthalene-2-carboxylic acid)

Kyu Ryu et al., prepared¹³ a series of 2-arylamino-5-hydroxy-naphthalene-1,4-diones, 3-arylamino-5-methoxy-naphthalene-1,4-diones, and 2-arylamino-3chloro-5-hydroxy-naphthalene-1,4-diones and tested for their *in-vitro* antifungal activity against the *Candida* and *Aspergillus niger*¹³.

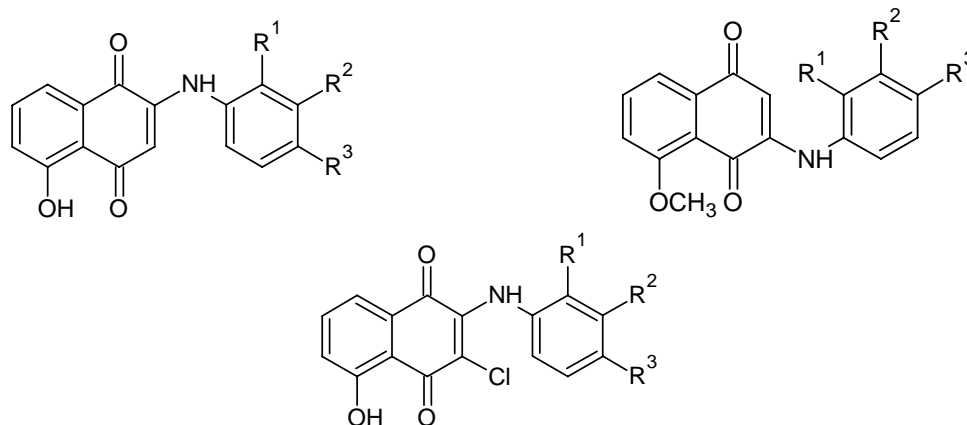


Fig.-13: A series of 2-arylamino-5-hydroxy-naphthalene-1,4-diones, 3-arylamino-5-methoxy-naphthalene-1,4-diones, and 2-arylamino-3-chloro-5-hydroxy-naphthalene-1,4-diones. R₁, R₂, R₃=H, F

Huang et al.,¹⁴ evaluated the antimicrobial potential of 18 synthetic naphthalene derivatives and tested for their anti-inflammatory activity. They prepared naphthalene derivative prepared according to the Mannich reaction¹².

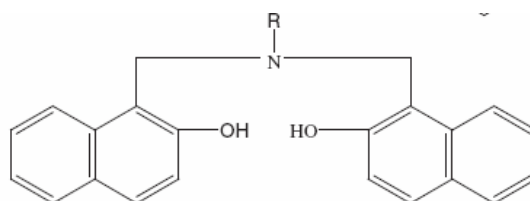


Fig.-14: Synthetic naphthalene derivative

Ahemed et al.,¹⁵ substituted several new 1 H-benzo chromene derivatives with 2-naphthols and found them to possess enhanced biological activity against bacterial, fungal and viral pathogens of human¹⁵. Azarifar et al.,¹⁶ the syntheses of twenty-four 3, dinaphthalene -1-yl substituted 2-pyrazolines containing certain groups as substituent's both on the naphthalene and pyrazoline rings. The compounds were tested in vitro for antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Shigella dysentery* and *Salmonella typhi* at a temperature of 37 °C ($\pm 1^\circ\text{C}$). It was observed that 81% of the total samples tested showed antimicrobial activity against all the organisms tested¹⁶.

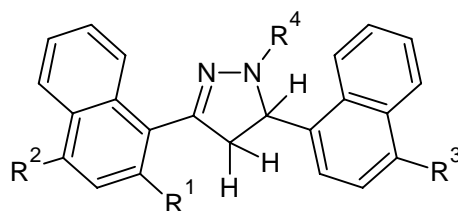


Fig.-15: 3, dinaphthalene -1-yl substituted 2-pyrazolines

Gulay et al.,¹⁷ synthesized new 5(1-/2-naphthoxy)methyl-1,3,4-oxadiazole-2(3H)-thione, 2-amino-5-(1-2-naphthoxy)methyl-1,3,4-oxadiazole, (1-naphthoxy methyl) -1,3,4-oxadiazole-2(3H)-1,3,4-oxadiazole-2(3H)-one derivatives from 1 or 2-naphthol. The antimicrobial properties of the compound were investigated against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*, *Candida albicans*, *C. krusi* and *C. parapsilosis*¹⁷. The derivatives were found effective against wide range of pathogenic bacteria and fungi.

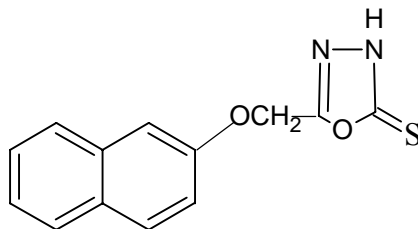


Fig.-16: 5-(1/2-naphthylloxymethyl)-1,3,4-oxadiazole-2(3H)-thione

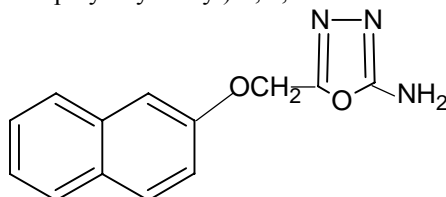


Fig.-17: 2-amino-5-(1/2-naphthylloxymethyl)-1,3,4-oxadiazole

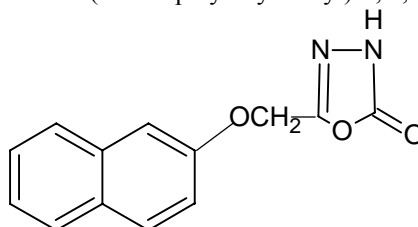


Fig.-18: (1/2-naphthylloxymethyl)-1,3,4-oxadiazole-2(3H)-one

Palaska et al.,¹⁸ synthesized sixteen 1-(2-naphthylloxyacetyl)-4-substituted-3-thiosemicarbazide, 2-(2-naphthylloxymethyl)-substitutedamino-1,3,4-oxadiazole, 2-(2-naphthylloxymethyl)-5-substitutedamino-1,3,4-thiadiazole and 5-(2-naphthylloxymethyl)-4-substituted-1,2,4-triazole-3-thione derivatives. They reported these derivatives as effective oral anti-inflammatory agents with reduced side-effects¹⁸.

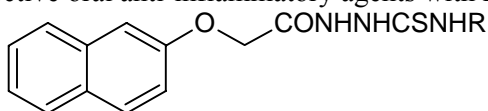


Fig.-19: 1-(2-naphthylloxyacetyl)-5-substituted-3-thiosemicarbazide

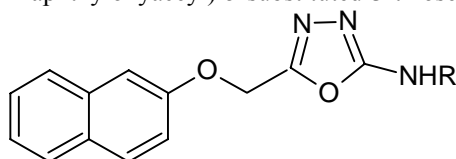


Fig.-20: 2-(2-naphthylloxymethyl)-5-substitutedamido-1,3,4-oxadiazole

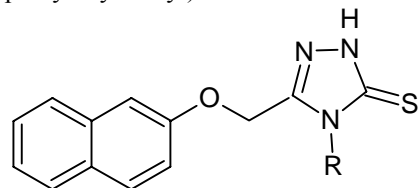


Fig.-21: 2-(2-naphthylloxymethyl)-5-substitutedamido-1,3,4-thiadiazole

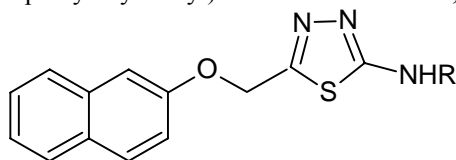


Fig.-22: 5-(2-naphthyloxymethyl)-5-substitutedamido-1,2,4-triazole-3-thiones
R=CH₃, C₂H₅, CH₂-CH=CH₂, C₆H₅

Bansal et al.,¹⁹ synthesized 1-acetyl-5-substitutedaryl-3-(β-aminonaphthyl)-2-pyrazolines and β - (substituted aminoethyl) amido naphthalenes compounds by reaction of β-acetylamino-naphthalene with different aromatic aldehydes followed by cyclisation with hydrazine hydrate and with different primary or secondary amines (Mannich's reaction), respectively. The structures of new compounds were confirmed by 1H-NMR and IR spectral data. Anti-inflammatory and ulcerogenic activities *in vivo* were evaluated and compared with the standard drugs¹⁹.

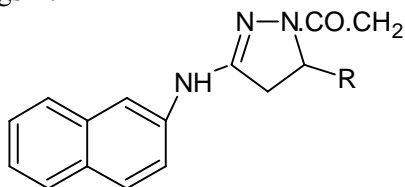


Fig.-23: 1-acetyl-5-substitutedaryl-3-(β-aminonaphthyl)-2-pyrazolines

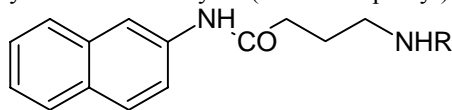


Fig.-24: β-(substituted aminoethyl) amidonaphthalenes

Strom et al.,²⁰ have reviewed the important structural features affecting the antimicrobial activity of 15-residue derivatives of lactoferricins. His investigations were based on an alanine-scan of a 15 residue bovine lactoferricin derivative that revealed the absolute necessity of two tryptophan residues for antimicrobial activity. They prepared a synthetic 15-residue derivative of bovine lactoferricin (LFB) containing naphthalene derivative and concluded that 2-naphthalene peptide more active than 1-naphthalene isomers; 2, the naphthalene moiety in 2-Nal is pointing more away from the β-carbon atom than in 1-Nal, giving 2-Nal a more elongated shape; 2-Nal thereby has a longer side chain than 1-Nal, and was able to penetrate deeper into the cell membrane of bacteria, thus offering an explanation as to why the 2-Nal peptides display a higher antimicrobial activity than the 1-Nal peptides¹⁸.

Oliveira et. al.²¹ synthesized 3-Hydrazino-naphthoquinones as analogs of lapachol. Several 1, 4-naphthoquinone derivatives having a hydrazino side chain were synthesized from 3-diazo-naphthalene-1,2,4-trione and tested as potential antimicrobial agents. These naphthoquinone derivatives 2-[N²-(1-acetyl-2-oxo-propylidene) -hydrazino] -3-hydroxy [1,4] naphthoquinone, ethyl 2-[(3-hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-hydrazono]-3-oxo-butyrate, *t*-butyl 2-[(3-hydroxy -1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-hydrazono]-3-oxobutyrate, 3-hydroxy-2-[(di -O-isopropylidene-malonate)-hydrazino]-1, 4 naphtho-quinone, and diethyl 2- [(3-hydroxy -1,4- dioxo-1,4- dihydro - naphthalene -2-yl)-hydrazono]-malonate showed greater antibacterial activity at the level of the preliminary susceptibility testing in disk²¹.

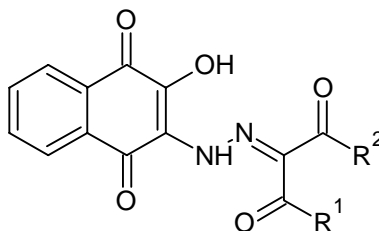


Fig.-25: Naphthoquinone derivatives

Ambrogi et al.,²² prepared new halogenated 1, 4-naphthoquinones together with other known 1, 4-naphthoquinones and screened these derivatives for their antibacterial activity by turbidimetric method and for antifungal activity by diffusion method on agar medium.

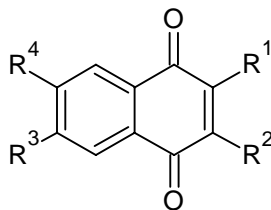


Fig.-26: 1, 4-naphthoquinones

Husain et al.,²³ showed the hypoglycemic activity of some thiosemicarbazides and naphthoxyacetic acid derivatives²³.

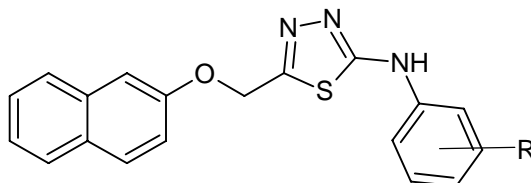


Fig.-27: 2-(aryl-amino-5-(2-naphthoxy)methyl)-1, 3, 4-thiazoles

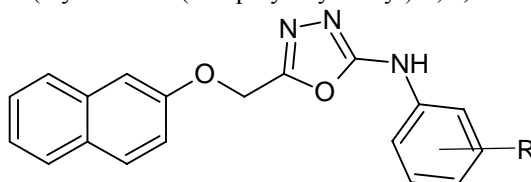


Fig.-28:2-aryl-amino-5-(2-naphthoxy)methyl-1, 3, 4-oxadiazoles

Marketed drugs containing naphthalene and azetidin-2-one¹

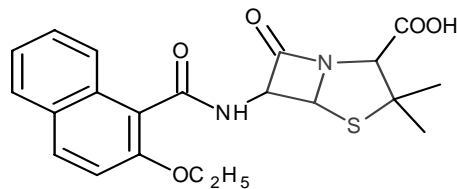


Fig.-29:Nafcillin

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