AJMAS
https://journal.utripoli.edu.ly/index.php/Alqalam/index eISSN 2707-7179

Review Article

A Review on Biological and Medicinal Significance of Furan

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ARTICLE INFO

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Received*: 18-01-2023*
Accepted*: 15-02-2023*
Published*: 18-02-2023*

Keywords*. Furan, Pharmacological Activities, Heterocyclic.*

ABSTRACT

An important group of heterocyclic compounds with significant biological characteristics are furan derivatives. The creation of furan derivatives and their testing for various pharmacological properties have received a lot of attention over the past few decades. Various substances with anti-bacterial properties have a fundamental skeleton made up of furan rings. These molecules are frequently used in antiviral, antifungal, anti-inflammatory, analgesic, antidepressant, anti-anxiolytic, anti-parkinsonian, anti-glaucoma, muscle relaxant, antihypertensive, diuretic, anti-ulcer, anti-ageing, and anticancer medications. The biological activity of furans can alter noticeably due to a slight modification in the pattern of substitution. In the realm of medicinal chemistry, furan derivatives have taken on a special position. An important synthetic technique in the search for new drugs is the inclusion of the furan nucleus. The great therapeutic efficacy of furan-related medicines has promoted the medicinal chemists to create large number of novel chemotherapeutic agents. The field of medicinal chemistry encompasses a diverse array of opportunities due to the different ways that furans derivatives can be synthesized as well as their various structural reactions. This article aims to review previous work on the medicinal and biological activities during past years.

Cite this article. *Saeid H, Al-sayed H, Bader M. A Review on Biological and Medicinal Significance of Furan. Alq J Med App Sci. 2023;6(1):44-58. https://doi.org/10.5281/zenodo.7650255*

INTRODUCTION

The word furan **1**, which means bran, is derived from the Latin *furfur*. Carl Wilhelm Scheele described 2-furoic acid, the first furan derivative, in 1780. Then, as a byproduct of the manufacture of formic acid, it was discovered in 1832 by the German chemist Johann Wolfgang Dobereiner. German scientist Carl Harries discovered the structure of furfural in 1901. A class of heterocyclic aromatic chemicals known as furan is distinguished by ring structure composed of one oxygen atom and four carbon atoms. Furan, the most basic compound in the furans family, it's a colorless, volatile, and slightly poisonous liquid with a boiling point of 31.36 °C. Additional members of the furans are synthesized in large scale for usage as solvents and chemical raw materials [1, 2].

1

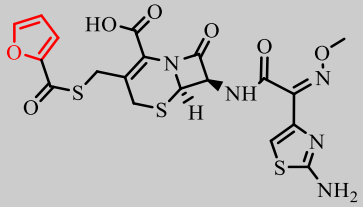
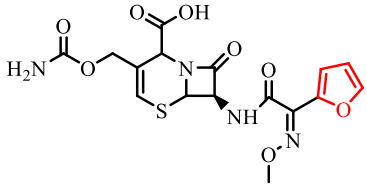
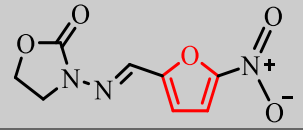
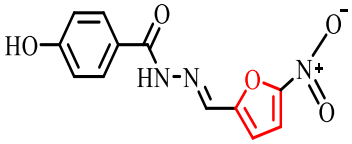
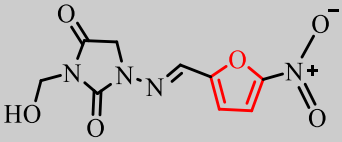
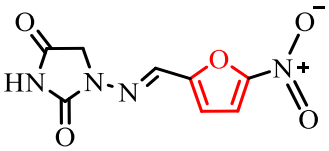
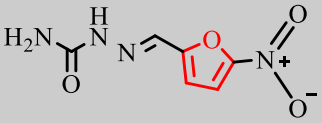
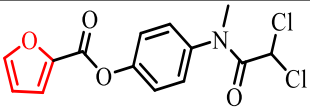
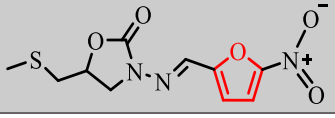
Furan is the most reactive compound of the 5-membered heterocyclic compounds. Due to its strong reactivity, extremely weak reagents are needed in comparison to other substances. In general, compounds with the furan ring make excellent solvents. Some substances are miscible with hexane and water. The ether oxygen's presence increases polarity and the possibility of hydrogen bonding.

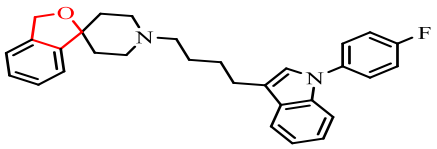
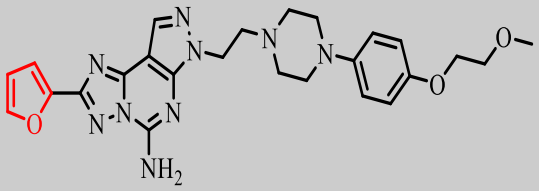
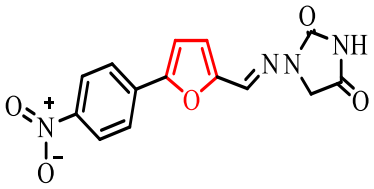
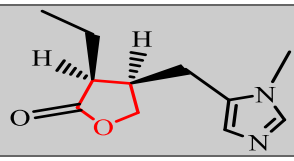
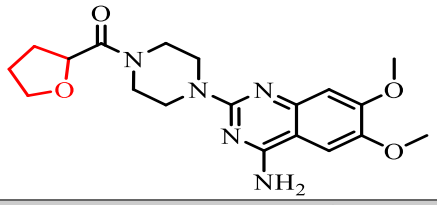
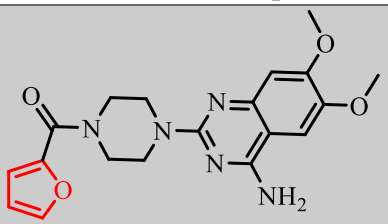
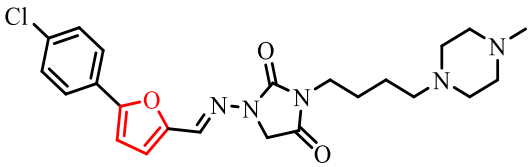
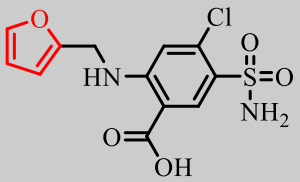
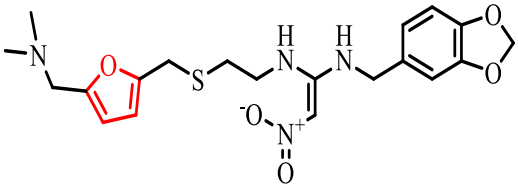
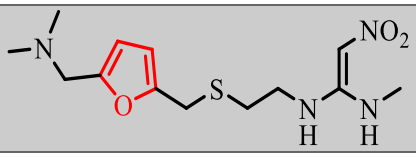
Furan pharmaceuticals provide a wider range of potential treatments for different clinical conditions. Furan has a number of therapeutic benefits, including being antimicrobial like antibacterial or antifungal or antiviral, anti-inflammatory, analgesic, antidepressant, anti-anxiolytic, anti-parkinsonian, anti-glaucoma, muscle relaxant, antihypertensive, diuretic, anti-ulcer, anti-ageing, and anticancer [3].

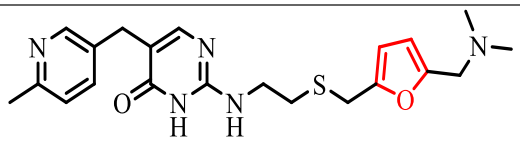
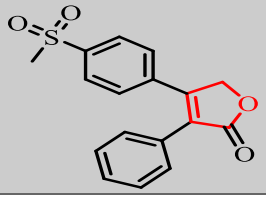
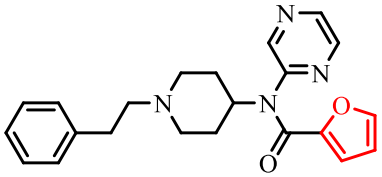
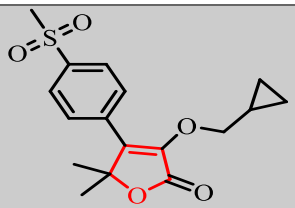
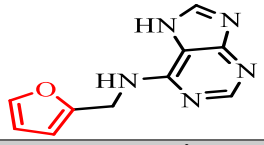
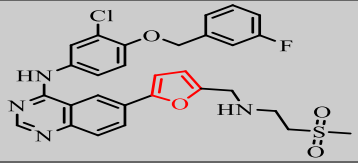
Medicinal significance of furan

There are numerous substituted furan derivatives that have received clinical approval that contain a mono and fused furan in conjunction with other heterocyclic. A list of the medications and their notable pharmacological activities can be found in **Table 1**[4].

Table 1. Clinically approved drugs containing furan ring

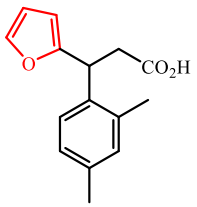
Sr.no	Name of the drug	Structure	Approved activity
1	Ceftiofur		Antibacterial activity
2	Cefuroxime		Antibacterial activity
3	Furazolidone		Antibacterial activity
4	Nifuroxazide		Antibacterial activity
5	Nifurtoinol		Antibacterial activity
6	Nitrofurantoin		Antibacterial activity
7	Nitrofurazone		Antibacterial activity
8	Diloxanide		Antiprotozoal activity
9	Nifuratel		Antiprotozoal and antifungal activity

10	**Siramesine**		**Antidepressant activity**
11	**Preladenant**		**Anti-parkinsonian activity**
12	**Dantrolene**		**Muscle relaxant activity**
13	**Pilocarpine**		**Antiglaucoma activity**
14	**Terazosin**		**Antihypertensive activity**
15	**Prazosin**		**Antihypertensive activity**
16	**Azimilid**		**Antiarrhythmic activity**
17	**Furosemide**		**Diuretic activity**
18	**Niperotidine**		**Antiulcer activity**
19	**Ranitidine**		**Antiulcer activity**

20	**Lupitidine**		**Antiulcer activity**
21	**Rofecoxib**		**Analgesic and anti-inflammatory activity**
22	**Mirfentanil**		**Analgesic and anti-inflammatory activity**
23	**Firocoxib**		**Analgesic and anti-inflammatory activity**
24	**Kinetin**		**Anti-ageing activity**
25	**Lapatinib**		**Anti-cancer activity**

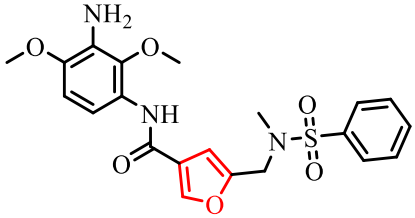
Biological significance of furan as anti-microbial agents

3-aryl-3-(furan-2-yl) propanoic acid derivatives were created and their antibacterial effectiveness was assessed. The best result demonstrated by compound **2**, which suppressed the growth of *Escherichia coli* at a concentration of MIC 64µg/ml [5].



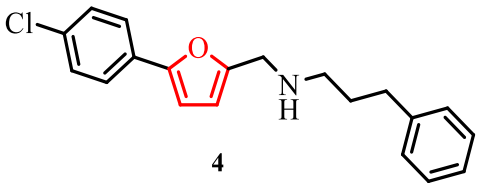
2

2,4-disubstituted furan derivative **3** exhibited better antibacterial activity especially against *Proteus vulgaris* and *Escherichia coli* [6].



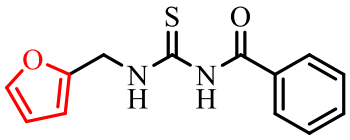
3

A novel arylfuran derivative **4** was found to possess considerable activity against both Gram-negative (*Escherichia coli*) and Gram-positive (*Staphylococcus aureus*) bacteria indicating a broad spectrum of action of this novel compounds [7].



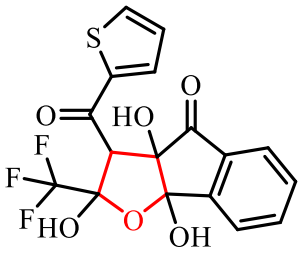
4

1-benzoyl-3-furan-2-ylmethyl-thiourea **5** exhibited antibacterial effect against, *Listeria Monocytogenes*, *Bacillus cereus* and *Staphylococcus aureus* [8].



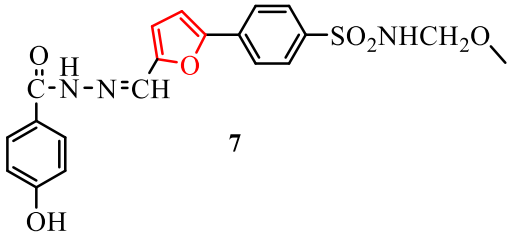
5

Compound **6** was effectively synthesized, and its antibacterial activity was assessed. This compound was found to display wide-ranging antimicrobial action against thirteen strains of bacteria, with activity more than streptomycin and tetracycline against *Pseudomonas fluorescens* [9].



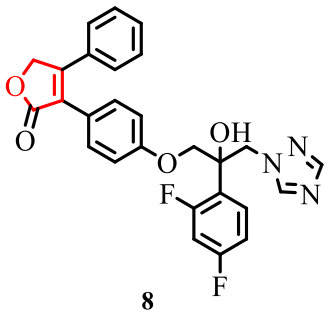
6

In another study, some furan-substituted compound were created and assessed for their antibacterial activity. In this series compound **7** was found to be equipotent against *Bacillus cereus*, *Shigella dysenteriae*, *Klebsiella pneumonia*, *Staphlococcus aureus*, *Staphylococcus epidermidis*, and *Klebsiella pneumonia* when compared with ampicillin as standard [10].



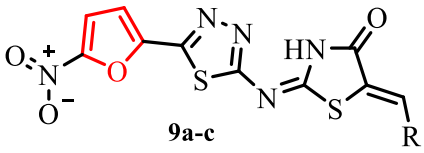
7

Patel *et al*, reported the hybrid compounds containing the pharmacophores present in furanones and fluconazole as antifungal agents. Compound 8 demonstrated extremely strong antifungal effects against *Candida albicans* (MIC_{50} value of 0.5 µg/mL), *Candida glabrata* (MIC_{50} value of 0.5 µg/mL), also a notable antifungal activity against *Candida tropicalis* (MIC_{50} value of 2 µg/mL) [11].



8

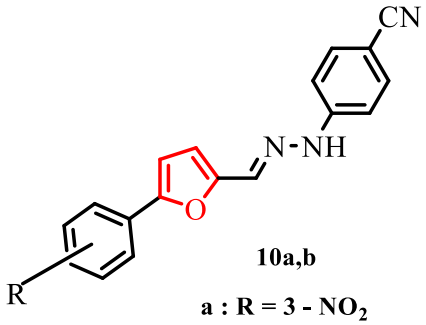
Twenty five 2-(5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-ylimino)thiazolidin-4-one derivatives are synthesized and assessed for their effectiveness against three *Helicobacter pylori* strains. Compounds **9a-c** exhibited strong antibacterial activity against *Helicobacter pylori* strains (inhibition zone > 30 mm) in 100 µg/disc and (inhibition zone > 20 mm) in 50 µg/disc [12].



9a-c

a : R= 4-methoxyphenyl
b : R= 4-hydroxyphenyl
c : R= 5-nitro-2-furyl

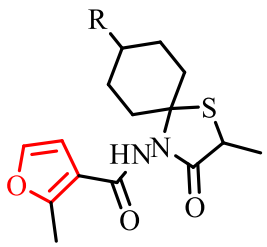
The synthesis and assessment of furan-based hydrazone compounds was reported by Altintop *et al*. According to the *in vitro* screening test, compound **10a** was the most hopeful antifungal agent against *candida albicans*, *trichoderma harzianum* and *fusarium species*, whereas compound **10b** was the most potent antifungal agent against *aspergillus ochraceus* [13].



10a,b

a : R = 3 - NO_2
b : R = 4 - Cl -2-NO_2

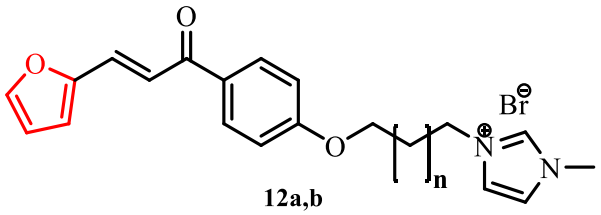
Furan-substituted spirothiazolidinones analogues **11a,b** had superior activity against influenza A/ H3N2 virus, comparing to other spirothiazolidinones carrying another aromatic moiety [14].



11a,b

a : R = C_2H_5
b : R =C_3H_7

Garcia *et al*. Reported [15] the antiprotozoal activity of furanchalcone–imidazole hybrids **12** against *Leishmania (V) panamensis* and *Trypanosoma cruzi*.

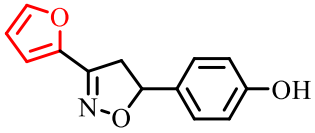


12a,b

a: n=7
b: n=10

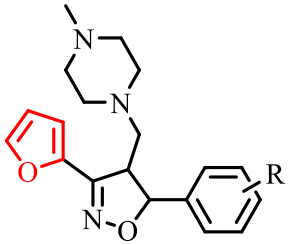
Biological significance of furan as central nervous system agents

A series of 3-(furan-2-yl)-5-(substituted phenyl)-4,5-dihydro-1,2-oxazole derivatives were synthesized as antidepressant and antianxiety agents. Out of these 4-[3-(furan-2-yl)-4,5-dihydro-1,2-oxazol-5-yl]phenol **13** emerged as the most potent antidepressant agent acting through MAO inhibition without any significant neurotoxicity. The observed MAO inhibitory action could also be responsible for its promising antianxiety effects [16].



13

Several 1-{[3-(furan-2-yl)-5-substituted phenyl-4,5-dihydro-1,2-oxazol-4 yl]methyl}-4-methyl piperazine, compounds have been synthesized. Compounds **14a,b** have demonstrated significant antidepressant effect and outstanding anti-anxiety activity, as measured by the FST and plus maze techniques, respectively [17].

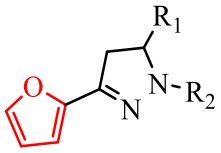


14a,b

a : R=H

b : R=4N(CH_3)$_2$

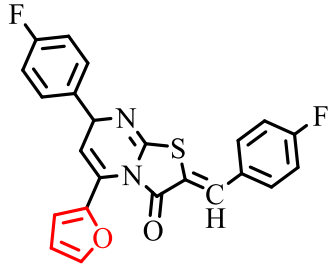
Twelve 3-(2-furyl)-pyrazoline derivatives were created. By using albino mice in Porsolt's behavioural despair (forced swimming) test, the compounds' antidepressant effects were examined. Two out of the synthetic chemicals **15a,b** have shown significant antidepressant activity, but generally, the synthesized compounds having a 2-furyl substituent at the pyrazoline ring's fifth position. **15c-g** possess remarkable anticonvulsant activity, when tested for their anticonvulsant activity by using MES and scMet tests [18].



15a-g

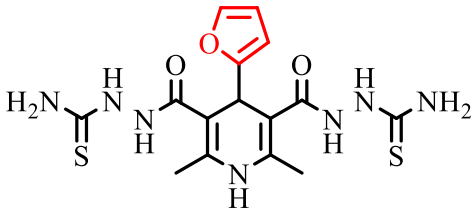
a : R_1 = 2-Furyl , R_2 = phenyl
b : R_1 = 2-Furyl , R_2 = $CSNH_2$
c: R_1 = phenyl , R_2 = $CSNHC_2H_5$
d: R_1 = 2-Furyl , R_2 = $CSNHCH_3$
e : R_1 = 2-Furyl , R_2 = $CSNHC_2H_5$
f : R_1 = 2-Furyl , R_2 = $CSNHC_3H_5$
g : R_1 = 2-Furyl , R_2 = $CSNHC_6H_5$

Additionally, the antiepileptic activity of furan derivatives was determined by MES and scPTZ model along with its neurotoxicity. Compound **16** shown improved antiepileptic activity without any neurotoxicity [19].



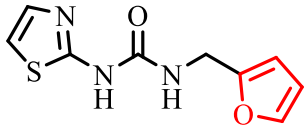
16

Another study evaluated the anticonvulsant efficacy of 1,4-dihydropyridine derivatives. Results demonstrated that compound **17** is highly active compared to the reference drug phenytoin, these attributed to the existence of furan ring in 4-position of 1,4-dihydropyridine ring [20].



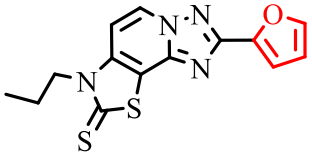
17

By exploiting the catalepsy and oxidative stress caused by haloperidol in mice, it was thought that the synthesis of 1-(substituted aryl)-3-(thiazol-2-yl)urea derivatives would lead to the discovery of new antiparkinsonian agents with an enhanced pharmacological profile. Maximum reduction in cataleptic activity was seen in furfuryl substituted derivative **18**, exhibiting 75.1% reduction in catalepsy whereas standard A2A antagonist, SCH58261 reduced 86.4% of catalepsy [21].



18

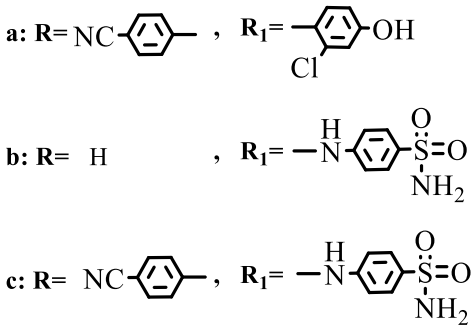
Furthermore, the antiparkinsonian and neuroprotective activity of some furan derivatives was determined using haloperidol prompted catalepsy and oxidative stress in mice. Compound **19** showed the better antiparkinsonian and antioxidant activity between them [22].



19

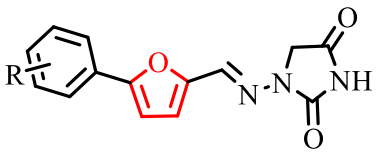
Twenty-one dantrolene analogues are synthesized with the intention of investigating structure-activity connections for the inhibition of acetylcholinesterase and human monoamine oxidases, two well-known target enzymes for medications treating Alzheimer's disease. Compounds **20a,b** exhibited strong inhibition of MAO B with IC_{50} values of 0.68 and 0.81 µM, respectively, while compound **20c** displayed good acetylcholinestrase inhibitor activity [23].

20a-c



Biological significance of furan as muscle relaxant agents

The general synthesis of dantrolene and its analogues with various substituents on its phenyl ring has been developed. Two different Ca^{2+} release modes from the sarcoplasmic reticulum (SR) of mouse skeletal muscle fibers have been used to assess the effects of synthetic analogues: the rate of Ca^{2+}-induced Ca^{2+} release (CICR) in saponin-treated skinned muscle fibers and the measurement of twitch contraction caused by physiological Ca^{2+} release (PCR) of intact skeletal muscle. Although the main compound dantrolene inhibits both twitch contraction and CICR, other structurally modified counterparts, such as **21a**, only inhibit twitch contraction, while **21b,c** showed inhibitory effect on CICR [24].

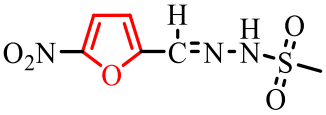


21a-c

a : R = 4-CH_3O
b : R = 2-NO_2
c : R = 2,6-$(NO_2)_2$

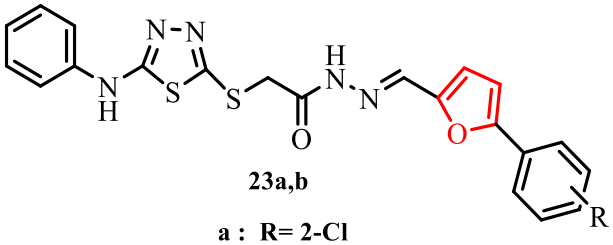
Biological significance of furan as anti-glaucoma agents

Three furan sulfonyl hydrazones derivatives were produced and estimated for their carbonic anhydrase inhibitory activity. Among them compound **22** containing withdrawing group (NO_2) has highest inhibition effect on hCA I isozyme than others [25].



22

N'-(5-arylfuran-2-yl)methylene-2-[(5-(phenylamino)-1,3,4-thiadiazol-2-yl)thio]acetohydrazide derivatives were created and assessed for their ability to inhibit human carbonic anhydrase isozymes (hCA I and hCA II). Particularly, compound **23b** was discovered to be a potential hCA I inhibitor with an IC_{50} value of 0.14 nM when compared to acetazolamide (IC_{50} = 5.8 nM), and compound **23a** was discovered to be a potential hCA II inhibitor with an IC_{50} value of 0.15 nM when compared to AAZ (IC_{50} = 6.7 nM) [26].

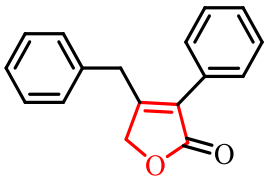


23a,b

a : R= 2-Cl
b : R= 4-Cl

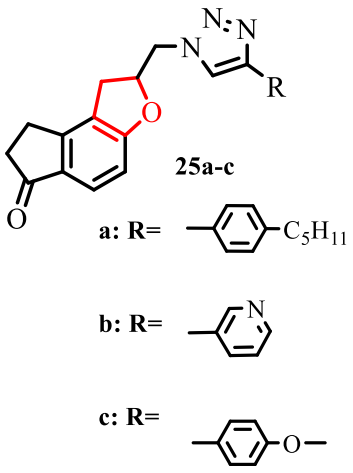
Biological significance of furan as anti-hypertensive agents

4-Benzyl-3-phenyl-5H-furan-2-one **24** was discovered after *Malbranchea filamentosa* was screened for bioactive substances which inhibit Ca^{+2}-induce vasoconstriction in rat aortic rings pre-treated with high K^{+} or norepinephrine [27].



24

A series of hybrid compounds between dihydrofuran, indanone and triazole has been prepared followed by biological evaluation as angiotensin converting enzyme (ACE) inhibitors. Among the synthesized compounds, compounds **25a-c** exhibited good ACE inhibitor activity (>70%) at 2.0 µM concentration comparable to clinical drug Lisinopril [28].



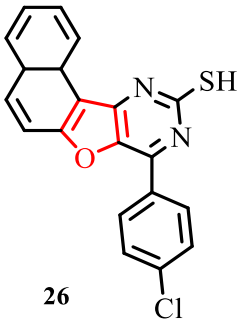
25a-c

a: R=

b: R=

c: R=

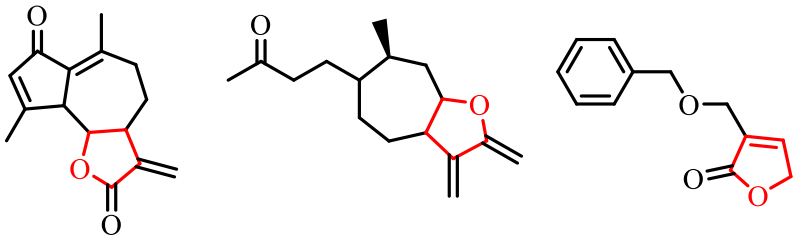
A number of 2-Macropto-4-substituted-Naphtho[2,1-b]furo[3,2-d]pyrimidines, have been screened for their diuretic activity. Compound **26** showed a considerable diuretic effect as compared with that of furosemide [29].



26

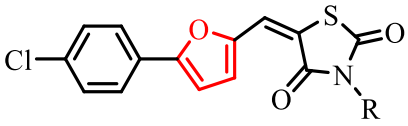
Biological significance of furan as Anti-Ulcer Agents

Recently, significant gastrointestinal cytoprotective activity of dehydroleucodine **27a**, xanthatin **27b**, and 3-benzyloxymethyl-5H-furan-2-one **27c** is efficacious in an animal model of stomach ulcer prompted by mast cell stimulation, these finding suggest that lactones could be effective in treating peptic ulcer disease in humans and may become valuable tools for designing and developing novel therapeutic agents for digestive disorders associated with inappropriate mast cell activation [30].

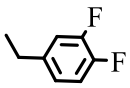


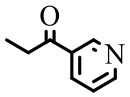
27b **27c**

A series of substituted 5-((5-(4-chlorophenyl)furan-2-yl)methylene)thiazolidine-2,4-dione derivatives were produced and screened for their *in vitro* H^+, K^+-ATPase inhibitory activity. H^+, K^+-ATPase activity of **28a,b** were comparable with those of known H^+, K^+-ATPase blocker lansoprazole which is a potential anti-ulcer drug [31].

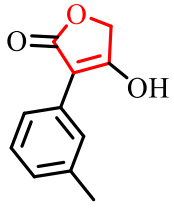


28a,b

a : R = 

b : R = 

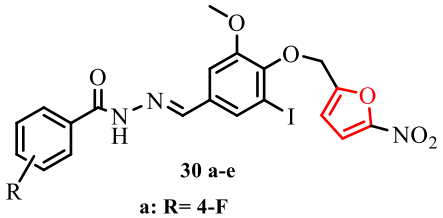
Twenty 3-arylfuran-2(5H)-ones were created and tested for their ability to block urease and kill *H. pylori*. A comparison of the urease inhibitory activity of these compounds to that of acetohydroxamic acid revealed that 3-(3-methylphenyl)furan-2(5H)-one **29** had the most anti-H. pylori activity (2.6 g/mL) [32].



29

Biological significance of furan as anti-inflammatory and analgesic agents

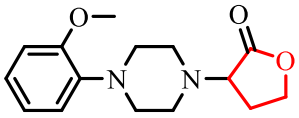
Some hydrazide-hydrazone derivative linking furan moiety were created and valued for anti-inflammatory activity using carrageenan induced inflammatory rat model. Compounds **30a-e** exhibited significant anti-inflammatory activity [33].



30 a-e

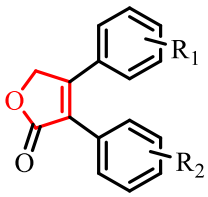
a: R= 4-F
b: R= 4-OH
c: R= 4-SO_2CH_3
d: R= 2,4-difluoro
e: R= 3,4,5-trimethoxy

A series of 3-substituted derivatives of dihydrofuran-2(3H)-one were created and their analgesic potency was evaluated utilizing the hot plate and writhing test. Derivative **31** showed strong analgesic activity higher than the reference compounds (morphine and acetyl salicylic acid) [34].



31

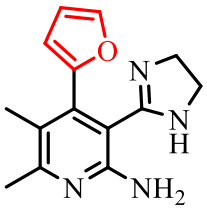
Several series of diarylfuranone derivatives **32** have been extensively developed and investigated as selective COX-2 inhibitors, most of these compounds exhibited COX-2 inhibitory potency comparable and even more than rofecoxib [35, 36]



32

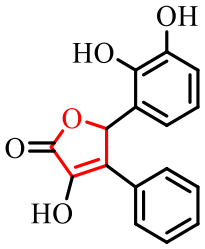
Biological significance of furan as anti-oxidant agents

Some novel pyridine and imidazole derivatives bearing a biologically active furan moiety was to synthesize and evaluate the antioxidant activity using ABTS method. The strongest antioxidant activity, comparable to ascorbic acid, was shown by compound **33** [37].



33

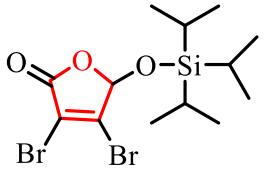
The most potent antioxidant among the substances the scientists reported was compound **34**, which had a 2,3-dihydroxyphenyl ring in the fifth position of the furan ring and had the ability to quench superoxide anions (IC_{50} value of 0.187 µM), scavenge DPPH radicals (IC_{50} value of 10.3 µM), and prevent lipid peroxidation (IC_{50} value of 0.129 µM) [11].



34

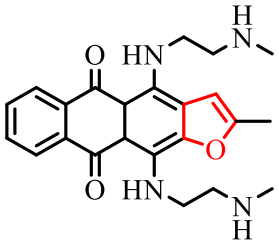
Biological significance of furan as anti-cancer agents

Silylation of 5-hydroxyl group in mucobromic acid (MBA) bearing furan-2(5H)-one core leads to develop a set of novel compounds with increased cytotoxic potency against cancer cells. Interestingly, compound **35** showed to be most active against colorectal cancer cell lines [38].



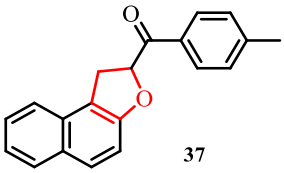
35

A number of anthrafurandione analogues of the anticancer drug ametantrone were successfully synthesized by Shchekotikhin *et al*. Compound **36** was establish to be significantly more effective than other drugs against drug-resistant cell lines with P-glycoprotein overexpression or p53 gene deletion, according to studies evaluating anti-proliferative efficacy on a section of mammalian tumor cell lines. Additionally, this derivative diminished *in vitro* topoisomerase I-mediated DNA uncoiling at low micromolar concentrations [39].



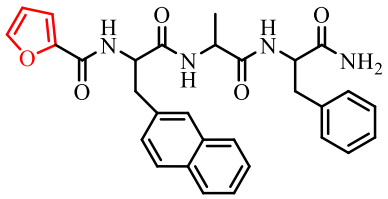
36

The anti-proliferative activity of a number of 1,2-dihydronaphtho[2,1-b]furan derivatives was assessed against human triple negative MDA-MB-468 and MCF-7 breast cancer cells line. Among twenty-one synthesized compounds. Compound **37** was found to have best anti-proliferative activities based on the results of numerous biochemical and microscopic investigation [40].



37

Using HeLa cells as a model, a number of furan-conjugated tripeptides were created and tested against human cervical cancer cells. Despite the fact that other conjugates demonstrated intriguing inhibitory activity against HeLa cells, conjugation **38** was found to be the most effective, with an IC_{50} 0.15 ± 0.05 µg/Ml. The suggested the mechanism of action of conjugate **38** on cervical cancer cells relies on the membranolytic effect and mitochondrial modification [41].



38

CONCLUSION

The reviewed furan moiety has established medicinal and biological importance from researchers and scientists. This heterocyclic moiety can be found in several commercially available medicines. From all above, various substituted furan derivatives have antimicrobial (antibacterial, antifungal, and antiviral) and central nervous system (antidepressant, anxiolytic, anticonvulsant, antiparkinsonian, in addition to their effect on Alzheimer's disease) activities. They also have muscle relaxant, anti-glaucoma, cardiovascular, anti-ulcer, anti-inflammatory, analgesic, antioxidant, and anticancer activities. It is evident from all these activities that the furan moiety is extremely valuable in medicinal chemistry.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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