Medicinal significance of furan derivatives: A Review

Rumpa Banerjee, Kumar HKS, Mrityunjay Banerjee*

Department of Medicinal Chemistry, Institute of Pharmacy and Technology, Salipur, Cuttack, Odisha-754202, India

ABSTRACT

Furan is a planer five-member heterocyclic ring with 4C and 1O atom and in ring O is present in 1st positions. The furan ring is a constituent of several important natural products, including furanoflavonoid, furanolactones, furanocoumarins and many natural terpenoids. Being a non polar aromatic compound and presence of the ether oxygen which adds polarity as well as the potential for hydrogen bonding, it improves pharmacokinetic characteristics of lead molecules and thus used as a remedy to optimize solubility and bioavailability parameters of proposed poorly soluble lead molecules. Furan derivatives have occupied a unique place in the field of medicinal chemistry. The incorporation of the furan nucleus is an important synthetic strategy in drug discovery. The high therapeutic properties of the furan related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Drugs have broadened scope in remedying various dispositions in clinical medicines. Numerous methods for the synthesis of furans and also their various structure reactions offer enormous scope in the field of medicinal chemistry. This articles aims to review the work reported, their chemistry and biological activities of furans during past years.

Keywords: Anti anxiolytic; anti bacterial; anti cholinergic; anti fungal; anti glaucoma; anti histamine; anti neoplastic; anti viral.

INTRODUCTION

Medicinal chemistry is the discipline which determines the influence of chemical structure on biological activity and the practice of medicinal chemistry involves the organic synthesis of new compound based largely on the modification of structure and identifying their biological activity. Medicinal chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level. Every drug has specific target in the body. These targets or receptors are believed to be associated with disease and disorder. The newly discovered compounds interact with these receptors to show their potentiality to treat the disease or disorder. The high therapeutic properties of the furan related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents which can act on various targets or receptors in the body like they act as MAO inhibitors, kappa opioid receptor agonist, sigma receptor agonist, GABA receptor agonist, COX-2 inhibitor, Beta blockers, mu opioid receptor agonist, muscarinic receptor agonist, α-adrenergic blockers, calcium channel blockers etc. Furan drugs have broadened scope in remedying various dispositions in clinical medicines. Medicinal properties of Furan include anticancer, antidepressant, anti-anxiety, analgesic, anti-inflammatory, muscle relaxant, antihypertensive, antiarrhythmic, antimicrobial like antibacterial or antifungal or antiviral, antiaging agents, anti-ulcer, antithistaminic, anticholinergic, anti-parkinsonism, anti-diuretic, and inhibition of sickle cell formation. Infectious microbial disease causes worldwide problem, because microbes have resisted prophylaxis or therapy longer than any other form of life. In recent decades, problems of multidrug-resistant microorganisms have reached an alarming level in many countries around the world. Resistance of antimicrobial agents such as β-lactam antibiotics, macrolides, quinolones and vancomycin etc. and different species of bacteria causes increased important global problem (Shingalapur RV et al., 2009).

Structure and pharmacological activities

Furans are well known heterocyclic compounds which are common and have important feature of a variety of medicinal agents. Furan is a 5-membered planar ring, which is soluble in most organic solvents. It is the most reactive compound of the 5-membered heterocyclic compounds. It is a nonpolar compound. The electrophilic substitution reactions of furan take place preferably in 2-position. On account of its high reactivity very mild reagents are required as compared to other compounds. Compounds containing the furan ring are generally excellent solvents. Some are miscible with both water and with hexane. Presence of the ether oxygen adds polarity as well as potential for hydrogen bond-
ing. Compound containing the furan or tetra hydrofuran ring are biologically active and are present in a number of pharmaceutical products. Furfurylamine is an intermediate in the diuretic, furosemide. Tetrahydrofurfurylamine may also have pharmaceutical applications. 5-(Dimethyl amine methyl) furfuryl alcohol is an intermediate in the preparation of ranitidine, which is used for treating ulcers. 2-Acetylfuran, prepared from acetic anhydride and furan is an intermediate in the synthesis of cefuroxime, a penicillin derivative. 2-Furoic acid is prepared by the oxidation of furfural. Both furoic acid and furoyl chloride are used as pharmaceutical intermediates. 2-Tetrahydrofuroic acid also finds applications.

On the basis of various literature surveys furan derivatives shows various pharmacological activities

- Antidepressant activity.
- Antianxiolytic activity.
- Anti inflammatory activity and analgesic activity.
- Muscle relaxant drugs.
- Antihypertensive drugs.
- Antiarrhythmic drugs.
- Antimicrobial activity.
- Antiglaucoma activity.
- Steroidal activity.
- Anti-ulcer activity.
- Antidiuretic activity.
- Anorectic activity.
- Inhibition of sickle cell formation.
- Antiageing activity.
- Antiparkinsonism activity
- Antihistaminic and anticholinergic activity
- Antineoplastic activity
- Insecticide activity.

Antidepressant activity

*Geiparvarin* is a coumarin derivative found in the leaves of the Australian Willow (*Geijera parviflora*) (Lahey FN and Macleod JK, 1967). It is a monoamine oxidase inhibitor (Carotti A et al., 2002) and has antitumor properties (Baraldi PG et al., 1989; Valenti P et al., 1997; Viola G et al., 2004).

Siramesine (Lu 28-179) is a sigma receptor agonist, selective for the α2 subtype (Soby KK et al., 2002). In animal studies, siramesine has been shown to produce anxiolytic (Sanchez C et al., 1997) and antidepressant (Sanchez C and Papp M, 2000) effects.

\[
1' - \{4 - [1 - \{4 - \text{flurophenyl}\} - 1H - \text{indol} - 3 - yl] \text{butyl}\} - 3H - \text{spiro} - \{2 - \text{benzofuran} - 1, 4' - \text{piperidine}\}
\]

Antianxiolytic activity

*Vilazodone* (De Paulis T, 2007) (marketed as Viibryd) is by Clinical Data for the treatment of major depressive disorder. By 2009 two phase III clinical antidepressant developed trials with positive results had been completed. Vilazodone was approved by the FDA for use in the United States to treat major depressive disorder in 10mg, 20mg, and 40mg doses on January the 21st, 2011.

\[
5 - \{4 - [5 - \text{cyano} - 1H - \text{indol} - 3 - yl] \text{butyl}\} \text{piperazin} - 1 - yl \text{benzofuran} - 2 - \text{carboxamide}
\]

NS-2664 is an anxiolytic drug (Mirza NR and Nielsen E, 2006).

\[
5 - \text{furan} - 3 - yl - 1 - (3 - \text{imidazol} - 1 - \text{yl} - \text{phenyl}) - 1H - \text{benzoimidazole}
\]

*BHFF* is a compound used as a positive allosteric modulator at the GABAB receptor. It has anxiolytic effects in animal studies, and good oral bioavailability (Malherbe P et al., 2008).

\[
5, 7 - \text{bis} - (1, 1 - \text{dimethylethyl}) - 3 - \text{hydroxyl} - 3 - \{\text{tri fluoro methyl}\} - 2 - (3H) \text{benzofuranone}
\]
Analgesic and anti-inflammatory activity

2-Ethoxy methyl Salvinorin B is a semi-synthetic analogue of the natural product salvinorin A and has increased affinity and intrinsic activity at the κ-opioid receptor (Munro TA et al., 2008).

![Chemical structure of 2-Ethoxy methyl Salvinorin B](image1)

(2S, 4aR, 6aR, 7R, 9S, 10aS, 10bR) - 9 - (ethoxy methoxy) - 2 - (3 - furanyl) dodecahydro -6a, 10b - dimethyl - 4, 10 - dioxo - 2H - naphtha [2, 1 - c] pyran - 7 - carboxylic acid methyl ester

Firocoxib is a non-steroidal anti-inflammatory drug of the COX-2 inhibitor (coxib) class.

![Chemical structure of Firocoxib](image2)

3- (Cyclopropyl methoxy) 5, 5 - dimethyl - 4 - (4 - methyl sulfonyl phenyl) furan -2- one

Rofecoxib is a nonsteroidal anti-inflammatory drug (NSAID) used to treat osteoarthritis, acute pain conditions, and dysmenorrhoea and has now been withdrawn over safety concerns about increased risk of heart attack and stroke (Padi S and Kulkarni S, 2004). Rofecoxib is a selective COX-2 inhibitor.

![Chemical structure of Rofecoxib](image3)

4- (4- methylsulfonylphenyl) -3- phenyl -5H- furan -2- one

MIRFENTANIL is a fentanyl derivative with strong selectivity for the μ opioid receptor (France CP et al., 1991; Carr DJ et al., 1996).

![Chemical structure of MIRFENTANIL](image4)

N-[1- (2-phenylethyl) piperidin-4-yl]-N-pyrazin-2-yl-2-furamide

RO4-1539 (Furethyl nor levorphanol) is an opioid analgesic drug from the morphinan series. It acts as a potent μ-opioid agonist (Hellerbach J et al., 1966).

Muscle relaxant activity

Dantrolene is a muscle relaxant that acts by abolishing excitation-contraction coupling in muscle cells, probably by action on the ryanodine receptor and decreasing intracellular calcium concentration (Krause T et al., 2004).

![Chemical structure of Dantrolene](image5)

1- [[5- (4-nitrophenyl) -2- furyl] methylidene amino] imidazolidine -2, 4- dione

Antihypertensive activity

Ancarolol is an antihypertensive agent and acts as a beta blocker.

![Chemical structure of Ancarolol](image6)

N-[2- [3- (tert-butyl amino) -2- hydroxy-propoxy] phenyl furan -2- carboxamide

Prazosin is a sympatholytic drug used to treat high blood pressure (hypertension) (Shen and Howar, 2008). It belongs to the class of alpha-adrenergic blockers.

![Chemical structure of Prazosin](image7)

2- [4- (2-furoyl) piperazin-1-yl] -6,7- dimethoxy quinazolin -4- amine

Terasin (Tripathy KD, 2009a) is a selective alpha 1 antagonist used for treatment of symptoms of an enlarged prostate (BPH). It also acts to lower the blood pressure.

![Chemical structure of Terasin](image8)

6, 7- dimethoxy -2- [4- (tetrahydrofuran -2-yl carbonyl) piperazin -1- yl] quinazolin -4- amine
Antiarrhythmic activity

Azimilid (Braunwald E et al., 2001) is a class III antiarrhythmic drug (used to control abnormal heart rhythms).

\[
\text{Azimilid} \rightarrow \text{class III antiarrhythmic drug}
\]

Amiodarone is a class III antiarrhythmic agent. It is used in the treatment of angina pectoris (P Cote et al., 1979; Singh BN and Vaughan Williams EM, 1970). The injection should not be given to neonates, because the benzyl alcohol it contains may cause the fatal "gasping syndrome".

\[
\text{Amiodarone} \rightarrow \text{class III antiarrhythmic agent}
\]

Dronedarone (Dale KM and White CM, 2007) is a drug used mainly for the indication of atrial fibrillation and atrial flutter.

\[
\text{Dronedarone} \rightarrow \text{drug used for atrial fibrillation and atrial flutter}
\]

Lanatoside C (Trease GE and Evans WC, 2005) is a cardiac glycoside, which can be used by the intravenous route. Its main indications are rapid response atrial fibrillation and paroxysmic supraventricular tachycardia.

\[
\text{Lanatoside C} \rightarrow \text{cardiac glycoside}
\]

Antimicrobial activity

Ceftiofur is an antibiotic of the cephalosporin type (third generation) (Donaldson SC et al., 2006).

\[
\text{Ceftiofur} \rightarrow \text{antibiotic of the cephalosporin type}
\]

Nalfurafine is a κ-opioid receptor agonist marketed as a treatment for uremic pruritus in people undergoing hemodialysis. As of January 2010, it is also being investigated for the treatment of pruritus in patients with chronic liver disease (Kevin KC et al., 2011).

\[
\text{Nalfurafine} \rightarrow \text{κ-opioid receptor agonist}
\]

Roseophilin is an antibiotic isolated from Streptomyces griscovirides (Furstner A, 2003).

\[
\text{Roseophilin} \rightarrow \text{antibiotic isolated from Streptomyces griscovirides}
\]

©JK Welfare & Pharmascope Foundation | International Journal of Research in Phytochemistry & Pharmacology
Santonin is a drug which was widely used in the past as an anthelminthic. Large doses, however, produce toxic effects, aphasia, muscular tremors and epileptiform convulsions, and the disturbances of vision may go on to total blindness (Modern Drug 1995).

\[
\text{(3S, 3aS, 5aS, 9bS) -3, 5a, 9r - trimethyl - 3a, 5, 9b - tetra hydro naphtha [1, 2 -b] furan-2, 8 (3H, 4H) - di-one}
\]

Diloxanide furoate is an anti/protozoal drug used in the treatment of Entamoeba histolytica (Fernandes H et al., 2009) and some other protozoal infections.

4-[(dichloroacetyl) (methyl amino) phenyl furan-2-carboxylate

Fumoxicillin is an antibiotic. This antibacterial agent is a prodrug of amoxicillin which increases bioavailability (Daniel Lednicer 1990).

\[
\text{(2S, 5R, 6R) -6- [[(R)- [(2- Furanyl methylene) amino] (4-hydroxyphenyl) acetyl] amino] -3,3- dimethyl -7-oxo -4- thia -1- azabicyclo [3.2.0] heptanes -2- carboxylic acid}
\]

Furazolidone is an antibacterial. It is used to treat diarrhoea and enteritis caused by bacteria or protozoan infections (H. Parham and B Aibaghi Esfahani, 2008). It is also used for Giardiasis.

\[
\text{3- within (5-nitro -2- furyl) methylene] amino} -1,3- oxazolidin -2- one
\]

Nifuratel (R N Gruneberg and A Leakey, 1976) is a drug used in gynecology. It is a local antiprotozoal and antifungal agent that may also be given orally.

\[
\text{5-[(methylthio) methyl] -3- [[(1E)- (5-nitro-2-furyl) methylene] amino} -1,3- oxazolidin -2- one
\]

Nifuroxide is an oral nitrofuran antibiotic, patented since 1966 and used to treat colitis and diarrhea in humans and non-humans (USPTO).

\[
\text{4- Hydroxy -N'}- [(5- nitrofuran -2-yl] methylene] benzhydrazide}
\]

Nifurquinazol (NF-1088) is an antibacterial agent of the nitrofuran class (Chapman and Hall 1996). It was never marketed.

\[
\text{2,2'- [[(2- (5- nitrofuran -2- yl] quinazolin -4- yl] imino) diethanol}
\]

Nifurtoinol is a nitrofuran-derivative antibiotic used in the treatment of urinary tract infections. It is also known as “hydroxymethylNitrofurantoin” (Stricker BH et al., 1988).

\[
\text{3- (hydroxyl methyl) -1- [[(1E)- (5- nitro -2-furyl) methylene] amino} -imidazolidine -2,4- dione}
\]

Nitrofurantoin (KD Tripathy 2009 b) is an antibiotic. It is usually used in treating urinary tract infection.

\[
\text{(E) -1- [[5- nitro -2- furyl] methylidene amino] imidazolidine -2, 4- dione}
\]

Nifurtimox is a 5-nitrofuran and is used to treat diseases caused by trypanosomes including Chagas disease (Coura JR and De Castro SL, 2002) and sleeping sickness. It is given by mouth and not by injection. Nifurtimox is in a Phase II clinical trial for the treatment of pediatric neuroblastoma and medulloblastoma.

\[
\text{(RS) -3- methyl -N'}- [(1E)- (5- nitro -2-furyl) methylene] thiomorpholin -4- amine 1,1- dioxide}
\]

Nitrofurazone (KD Tripathy 2009 c) is a bactericidal compound is used as an antibiotic.
5-nitro-2-furaldehyde semicarbazone

**Antigliaucoma activity**

**Pilocarpine** (KD Tripathy 2009 d) is a parasympathomimetic alkaloid obtained from the leaves of the genus *Pilocarpus*. It is a non-selective muscarinic receptor agonist. Pilocarpine has been used in the treatment of chronic open-angle glaucoma and acute angle-closure glaucoma for over 100 years. Pilocarpine is often used as an antidote for scopoline, atropine, and hyoscyamine poisoning.

\[(3S, 4R)-3\text{-ethyl}-4\text{-[(1-methyl-1H-imidazol-5-yl)methyl] dihydrofuran-2(3H)-one}\]

**Steroidal activity**

**Fluticasone furoate** is a synthetic corticosteroid derived from fluticasone, used for the treatment of allergic rhinitis. It can be administered by a nasal spray (Bruni FM et al., 2009).

\[(6\alpha,11\beta,16\alpha,17\alpha)-6,9\text{-difluoro-17-\{[(fluoromethyl]thio]carbonyl\}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl2-furanocarboxylate}\]

**Mometasone furoate** is a glucocorticoid steroid used topically to reduce inflammation of the skin or in the airways. It is used in the treatment of inflammatory skin disorders (Tan RA and Corren J, 2008).

\[(11\beta,16\alpha)-9,21\text{-dichloro-11-hydroxy-16-methyl-3,20-dioxopregna-1,4-dien-17-yl 2-furoate}\]

**Antiiulcer activity**

**Lupitidine** is an H₂ receptor antagonist described as an antiulcer agent (Lam BL, Pridgen LN, 1982).

\[(2S)-1\text{-7-ethyl-1H-furo[2,3-g]indazol-1-yl} \text{propan-2-amine}\]

©JK Welfare & Pharmascope Foundation | International Journal of Research in Phytochemistry & Pharmacology
Diuretic activity

Furosemide is a loop diuretic used in the treatment of hypertension, congestive heart failure and edema. It is also sometimes used in the management of severe hypercalcemia in combination with adequate rehydration (Rossi S 2004).

4- chloro -2- (furan -2- yl methyl amino) -5-sulfamoyl benzoic acid

Inhibition of formation of sickle cell

Hydroxymethyl furfural inhibits the formation of sickled cells in the blood (Abdulmalik et al., 2005).

5- (hydroxymethyl) -2- furaldehyde

Antiageing activity

Kinetin is a kind of cytokinin, a class of plant hormone that promotes cell division. Since 1994, kinetin has been thoroughly tested for its powerful anti-aging effects in human skin cells.

N6- furfuryl adenine

Antiparkinsonian activity

ZM-241,385 is useful for the treatment of Alzheimer’s disease (Dalligna OP et al., 2004) and Parkinson’s disease (Golembiowska K et al., 2004).

2- (7- amino -2- (furan -2- yl) - [1, 2, 4] triazolo [1, 5-a] [1, 3, 5] triazin -5- yl amino) ethyl) phenol

Preladenant(SCH-420,814) acts as a potent and selective antagonist at the adenosine A2A receptor. It is being researched as a potential treatment for Parkinson’s disease (Hodgson RA et al., 2009).

CONCLUSION

The reviewed furan moiety has shown a wide spectrum of biological activities. The various substituted furan are having significant antimicrobial activity. Significant antiviral and anti asthmatic activity is displayed by some effective substituted furan derivative which presently leading drug in the market in entire. Some modified furans are found to be effective as anti-
hypertensive, antiulcer, whereas some of the derivatives of furan are found to show the anti-asthmatic, anti-viral action. Recently it was proven that some of the important marketed furan nucleosides containing drug having different biological or pharmacological activity were discussed in above text. The furan nucleoside based pharmaceutical are rapidly becoming very important class of therapeutic agents and are likely to replace many existing organic based pharmaceuticals in the very near future. The furan based pharmaceuticals will be produced on a large scale by modern drug discovery company by different research development processes and will become available commercially for therapeutic use. With the key benefits including favorable time to market and high rate of success in clinical trial compared with traditional pharmaceuticals due to diverse biological action with less toxicity, so in future therapeutic furan drug will play a pivotal role in the treatment of different diseases. The biological profiles of this new generation of furan represent much progress with regard to the older compounds.

REFERENCES


Gołembiowska K, Dziubina A. Striatal adenosine A(2A) receptor blockade increases extracellular dopamine release following l-DOPA administration in intact and


KD Tripathy, Essentials of medical pharmacy, Jaypee Brothers Medical Publishers (P) Limited, New Delhi. 6th Ed. 2009: (a)134; (b)735; (c) 862; (d) 97-98; (e) 630.

Krause T, Gerbershagen MU, Fiege M, Weisshorn R, KD Tripathy, Essentials of medical pharmacy, Jaypee Brothers Medical Publishers (P) Limited, New Delhi. 6th Ed. 2009: (a)134; (b)735; (c) 862; (d) 97-98; (e) 630.


Pichichero ME. Cephalosporins can be prescribed safely for penicillin-allergic patients. The Journal of family practice. 2006; 55 (2): 106–12


Smith BM, Thomsen WJ, Grottick AJ. The potential use of selective 5-HT2C agonists in treating obesity. Ex-


