Medicinal chemistry

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Role of Aryl Urea Containing Compounds in Medicinal Chemistry

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Abstract

Aryl urea is an entity which is being synthesized in many of its derivative form from past few years; the entity is major source of interest for many of medicinal chemist to explore its various biological activities. In present study, we review the chemistry of aryl urea and its pharmacological actions as an anticonvulsant, antimicrobial, antiviral and anti inflammatory agent by studying its various synthesized derivatives. This review can be helpful to develop various more new compounds possessing aryl urea moiety that could be better in terms of efficacy and lesser toxicity.

Keywords: Aryl urea derivative; Anticonvulsant; Antimicrobial; Anticancer; Antiviral activity

Introduction

Medicinal chemistry according to Burger "tries to be based on the ever increasing hope that biochemical rationales for drug discovery may be found". In contrast he described pharmaceutical chemistry as being concerned primarily with modifications of structure having known physiologic or pharmacologic effects and with analysis of drugs, Medicinal chemistry as practiced encompasses both definitions, but the most difficult and at the same time the most rewarding challenge is the rational design of new therapeutic agents and finding the biochemical pathways through which drugs exert their beneficial effects.

The role of medicinal chemist is to design and synthesize a newly discovered medicinal or a pharmaceutical agent with increased potency and duration of action and decreasing adverse s effects. The focus on development of new synthetic drug compound as drugs has resulted in the incorporation of many other disciplines, such as biochemistry and molecular biology into medicinal chemistry. These areas include biology, computer-aided design, x-ray crystallography, metabolism and pharmacokinetics, legal and regulatory affairs, clinical franchise management, pharmaceutics and process research chemistry [1-6].

Heterocycles are part of organic chemistry and plays a lead role in the biological activities. The presence of heterocyclic is found in all kinds of organic compounds. It helps in the manufacturing of synthetic drugs, fungicides and dyes which are helpful in antibacterial, antimyobacterial, anti-HIV activity, genotoxic, herbicidal, analgesic, anti inflammatory, muscle relaxants, anticancer, antimalarial, antifungal and insecticidal agent [7].

Aryl Urea Derivatives

Urea and its derivatives have been investigated for their biological activities including antiatherosclerotic, antibiotic and hypoglycaemic effect and antitumour activities. Some of the urea derivatives are in use as hypnotics, sedatives and anticonvulsants, antibacterial and anticancer agents. Urea, which is a naturally occurring compound, was the first organic compound which has synthesized in lab by Wohler in 1928, and played important physiological and biological roles in animal kingdom. Synthesis of urea became a remarkable step in the history of synthetic organic chemistry [8]. Some of the urea derivatives are thio-urea, phenyl urea, sulphur urea etc have been found to exhibit a potent inhibiting effect on HIV-1 protease enzyme and as an anticancer, anticonvulsive and sedative-hypnotic activities. They are also served as an extensive application as agrochemicals, resin precursors and synthetic intermediates [9].

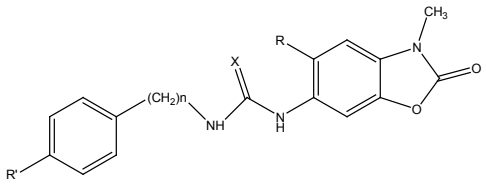
Traditional synthesis of urea derivatives involves the reaction of amines with phosgene, CO or isocyanate, which has tremendous toxicological and environmental problems. Alternative routes have also been developed, which involve amines reacting with urea, ethylene carbonate or diethyl carbonate. However, these expensive reagents originate from CO_2 reacting with ammonium, ethylene oxide or ethanol. Some researchers have also synthesized urea derivatives through amines reacting with CO_2 in the presence of catalysts, such as 1,8-diazabicyclo[5.4.0]undec-7-ene, CsOH, Cs_2CO_3, Au/poly, [Bmim] OH_2O or KOH/PEG1000, using ionic liquids, *N*-methylpyrrolidone or CO_2 as solvent [10].

Although a large number of antibiotics and chemotherapeutics are available for medical use, the antimicrobial resistance created a substantial need of new class of antibacterial agents in the last decades. Derivatives of urea, thiourea and thiosemicarbazide play a vital role in the field of medicinal chemistry by regulating various pharmacological activities. Literature survey reveals that urea and thiourea derivatives showed a broad spectrum of biological Activities as anti-HIV, antiviral, HDL- elevating antibacterial, analgesic properties [11-14].

Different Activity of Urea Derivatives

Antimicrobial activity

Gulkok et al. synthesized few compounds of urea and thio urea derivatives by the reaction of 6-amino-5-nonsubstituted/chloro-3-methyl-2(3*H*) –benzoxazolones with appropriate isocynates and thio –isocynates and were evaluated for their anti-microbial and antifungal activity. Out of which five urea compounds (1 to 5) and two thiourea derivatives (6 and 7) exhibited good activity against *Escheria coli* with Minimum Inhibitory Concentration of 32 µg [15].



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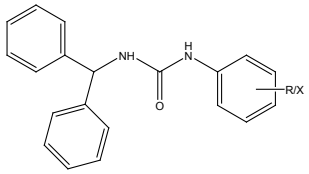
Compounds	R	R'	N	X
1	-H	-H	0	O
2	-H	-Cl	0	O
3	-H	-H	2	O
4	-Cl	-H	0	O
5	-Cl	-OCH_3	0	O
6	-Cl	-H	0	S
7	-Cl	-H	1	S

Anticonvulsant activity

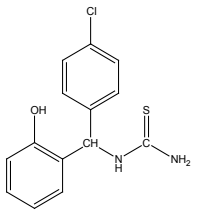
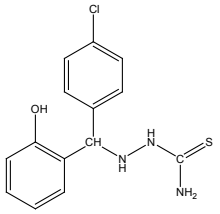
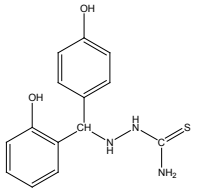
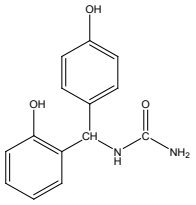
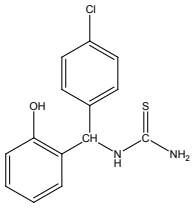
Ramesh et al. synthesized, five Arylurea derivatives using microwave irridation which were evaluated for their anticonvulsant activity by induced Pentylene tetrazole Convulsion (PTZ) in mice. Diazepam was used as Standard Drug. Compounds 8 (1-(4- methoxyphenyl)-3-(diphenylmethyl)urea) and 9 (1-(4-chlorophenyl)-3-(diphenylmethyl) urea) were found to possess potent anticonvulsant activity [16].



Compound	X/R
8	p-OCH_3
9	p-Cl

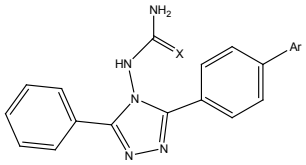
Antibacterial activity

Umadevi et al. synthesized few compounds by condensing urea, Thio urea and thiosemicarbazide with phenol and substituted aromatic aldehyde and these compounds was further evaluated for antibacterial activity *in vivo* against *Bacillus subtilis, Salmonella aureus, Salmonella typhi* and *Shigella dysentry*. Ampicillin was taken as standard drug. Compounds 10 to 14 shows significant antibacterial activity [17].

S No	Compounds	Structure
10	1-(4-chlorophenyl) (2-hydroxyphenylmethyl) thiourea	
11	2-(2-hydroxyphenyl) (4-hydroxyphenyl) (methyl) hydrazinecarbothioamide	
12	2-(2-hydroxyphenyl) (4- hydroxyphenyl) (methyl) hydrazinecarbothioamide	
13	1-(2-hydroxyphenyl) (4-hydroxyphenyl) methyl) urea	
14	1-4Chloro phenyl 2 hydroxy phenyl methyl urea	

Anti-inflammatory activity

Cherala et al. synthesized a series of 1- [3-(4-substitutedphenyl)-5-phenyl-4H-1,2,4-triazol-4-yl]urea and 1-[3-(4- substitutedphenyl)-5-phenyl-4H-1,2,4-triazol-4-yl]thiourea derivatives and these compounds were further evaluated for antiinflammatory activity by using Carragenean-induced paw edema rat model. Diclofenac sodium gum acacia in normal saline was used as standard drug. All the compounds {15(a-h)} showed a significant anti-inflammatory activity *in vivo*. The maximum activity was observed at 3rd and 4th hour showed potent anti-inflammatory activity [18].

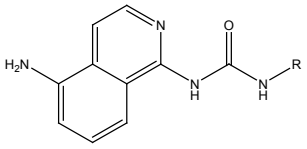


15(a-h)

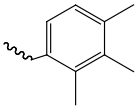
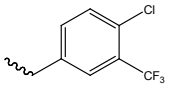
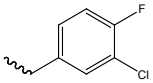
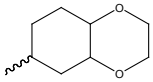
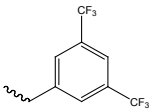
Compound	X	Ar
15a	O	-C_6H_5
15b	O	-C_6H_4(p-Cl)
15c	O	-C_6H_4(p-OCH_3)
15d	O	-Furfuryl
15e	S	-C_6H_5
15f	S	-C_6H_4(p-Cl)
15g	S	-C_6H_4(p-OCH_3)
15h	S	-Furfuryl

Antiproliferative activity

Jung et al. synthesized aminoisoquinolinylureas by nitration of 1-chloroisoquinoline using a mixture of nitric and sulpuric acids gave 1-chloro-5-nitroisoquinoline which is then treated with 7 N ammonia solution in methanol led to nucleophilic displacement and formation of 1-amino-5-nitroisoquinoline which is then reacted with the appropriatearyl isocyanate derivatives gives the corresponding diarylurea derivatives. Reduction of the nitro group with palladium over carbon in hydrogen atmosphere produced aminoisoquinolinylureas. These compounds were further screened for *in vitro* antiproliferative activity against line A375P human melanoma cell. Sorafenib was taken as a reference standard. Compounds {16(a-e)} showed superior potency against A375P to Sorafenib whereas compound 16(e) shows highest potency possessing 3,5-bis(trifluoromethyl)phenyl terminal ring with IC_{50} value of 0.41 μM [19].

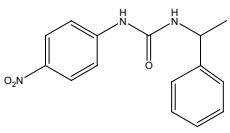
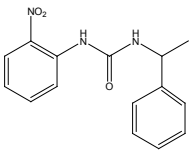
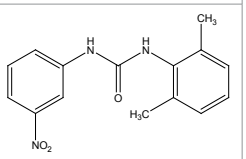
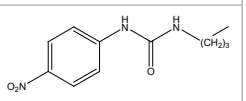
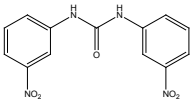
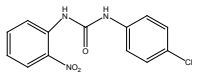


16(a-e)

Compound	R
16a	
16b	
16c	
16d	
16e	

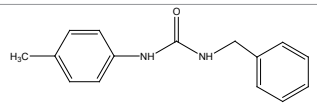
Antidepressant activity

Parveen et al. synthesized fourteen *N*-nitrophenyl-*N*'-(alkyl/aryl)urea and symmetrical 1,3-disubstituted urea derivatives All the synthesized compounds were subjected for antidepressant activity *in vivo*, using Tail Suspension test using Phenelzine was taken as standard drug. Among them, compound 17 demonstrated higher antidepressant activity (89.83%), whereas compounds 18-22 showed activity values between 36 to 59% which were also larger than the standard drug [8].

S No	Compounds	Structure
17	*N*-(4-Nitrophenyl)-*N*'-(1'-phenylethyl)urea	
18	*N*-(2-Nitrophenyl)-*N*'-(1'-phenylethyl)urea	
19	*N*-(3-Nitrophenyl)-*N*'-(3'-nitrophenyl)urea	
20	*N*-(4-Chlorophenyl)-*N*'-(2'-nitrophenyl)urea	
21	*N*-(3-Nitrophenyl)-*N*'-(3'-nitrophenyl)urea	
22	*N*-(4-Chlorophenyl)-*N*'-(2'-nitrophenyl)urea	

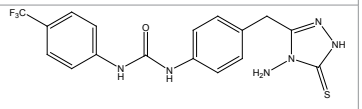
Antiulcernic activity

Vijaya et al. tested unsymmetrically substituted urea derivative Compound 23 for the antiulcer genic activity of alcohol and aspirin induced ulcer models on rats by taking ranitidine as standard drug. Ulcer index was calculated by histopathological studies. The test compound at a concentration of 50 and 100 mg/kg exhibited a protective effect on ulcer-induced models in a dose dependent manner, and was comparable with the standard drug ranitidine [20].

S No	Compounds	Structures
23	1-benzyl-3-(4-methylphenyl)urea	

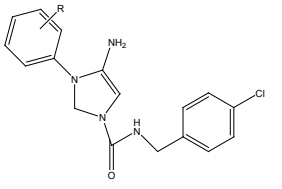
Antiacetylcholinesterase activity

Mohsen et al. synthesized few urea and thiourea derivatives bearing 1,2,4-triazole ring by reacting 4-(amino-phenyl) acetic acid with corresponding isothiocynate. All these synthesized compounds were further evaluated for their ability to inhibit acetylcholinesterase using a modification of Ellamans spectrometer method which is based on the reaction of released Thiocholine to give a coloured product with a chromogenic reagent, 5,5-dithio-bis-(2-nitrobenzoic acid). Donepezil was taken as standard drug. Among all of the compound only Compound 24, showed noteworthy anti-AChE activity based on the activity halogen atom on the phenyl ring have made good contribution to anti cholinesterase activity [21].

S No	Compounds	Structures
24	1-(4-(2-(1-(prop-1-en-2-yl) hydrazinyl)2(methylamino) ethyl)phenyl)-3-methyl urea	

Antiviral activity

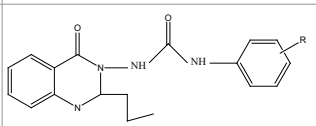
Rajtar et al. Synthesized four compounds of 1-(1-arylimidazolidine-2-ylidene)-3arylalkylurea derivatives by the reaction of ethyl N-(1-arylimidazolidine-2-ylidene)carbamic acid ester with 4-chlorbenzylaminederivatives of 1-(1-arylimidazolidine-2-ylidene)-3-arylalkylurea were obtained and these compounds were evaluated for *in vitro* antiviral activity. Ribavirin was taken as reference compound against Coxsackie virus B3 (CVB3) using the cytopathic effect (CPE). Only compound 25 slightly influenced the CVB3 replication by reducing the virus replication level by 0.77 log, which resulted in reducing the titre by 12.8% [22].

S No	Compounds	Structures
25	1-(1-arylimidazolidine-2-ylidene)-3-(4-chlorbenzyl)urea derivative	 where R=H, 2,3-diC_{H3},2-C_{H3},4-C_{H3}

CNS activity

Kashaw et al. synthesized a series of Compounds 26(a-i) by using a solution of 2- propyl-benzoxazin-4-one, substituted phenyl semicarbazides in glacial acetic acid and then refluxed for 4 h and it

was then poured into crushed ice and left overnight. The solid which was separated out was filtered, washed with cold distilled water, dried and recrystallized from hot ethanol. These compounds were further evaluated for CNS depressant and sedative-hypnotic activity. All the compounds showed significant CNS activity [23].

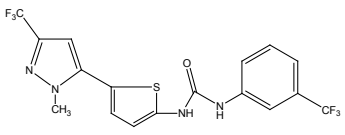
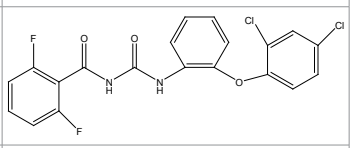
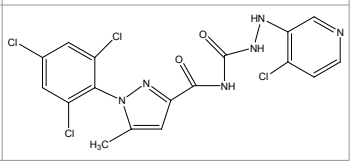
S No	Compound	Structure
26	1-(4-substituted-phenyl)-3-(4-oxo-2-propyl-4H- quinazolin-3-yl)-urea	

Compound	R
26(a)	-H
26(b)	-F
26(c)	-Br
26(d)	-I
26(e)	*m*-CH_3
26(f)	*p*-CH_3
26(g)	-CH2-CH_3
26(h)	-OCH_3
26(i)	-OCH_2-CH_3

Antitrypanosomal activity

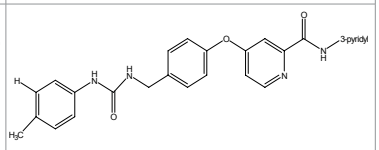
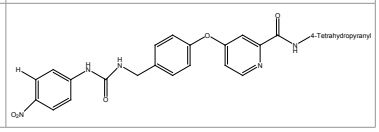
Xiaohui et al. identified nine compounds with varied scaffolds by using DOCK 4.0.1, were found to be significantly active at concentrations below 10 μM against cruzain and rhodesain as standard. Two of the scaffolds, the urea scaffold and the aroyl thiourea scaffold, exhibited activity against *Trypanosoma cruzi in vivo* and both enzymes *in vitro*. The Compound 27 showed activity at 3.1 μM IC_{50} against cruzain and a 3 μM IC_{50} against rhodesain. Infected cells treated with D16 survived 22 days in culture compared with 6 days for their untreated counterparts.

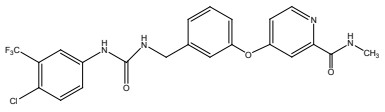
Two compounds Compound 28 and 29 were active against both proteases below 10 μM which were tested in a cell culture assay of *Trypnosoma cruzi* infection of mammalian cells. No toxicity was observed against the mammalian cells. For both compounds, inhibition of parasite replication was observed. Mammalian cells infected with parasites died at 6 days from parasitolysis of cells but on treatment with Compound 28 or 29 the cells survived upto 10 days [24].

S No	Compounds	Structures
27	5P(1-methyl-3-tri£uoromethylpyrazol-5-yl)-thiophene 3P-tri£uoromethylphenyl urea	
28	Urea derivatives	
29	Urea derivatives	

Antitumor activity

Shen et al. synthesized a series of some new benzyl urea derivatives which were screened for their inhibitory activities on MX-1, HepG2, Ketr3 andHT-29 cell lines. Compounds 30 and 31 showed greater inhibitory activity against HT-29 and MX-1, respectively when compared to sorafenib as standard. Compound 30 having a *N*-3-pyridyl moiety, not only exhibited significant inhibitory activity against HT-29 cell line (IC_{50} 3.82 μmol.L^{-1}), but also possessed an improved solubility at pH 7.2. In this way, compound 30 could serve as a valuable lead for further structural modifications to develop new agents against colon cancer [25].

S No	Compounds	Structures
30	1-(4-(2-(Pyridin-3-ylcarbamoyl)pyridine-4-yloxy) benzyl)-3-(4-methylphenyl) urea	
31	1-(4-(2-(Tetra hydropyran-4-ylcarbamoyl)pyridin-4-yloxy) benzyl)-3-(4-nitrophenyl)urea	



Sorefenib

Future aspects of aryl ureas

The present review study showed that aryl urea derivatives signify an important class of compounds possessing a wide spectrum of biological activities. The aryl ureas are one of the simplest of all chemicals which are used in clinics. The ureides have ensured to exhibit significant antibacterial activity. Some of the important pharmacologically activities ascribed to ureides are anti-tumour, anticancer, antidiabetic and hyperglycemic. They are all new compounds and interesting to determine their physiological properties. Various recent new drugs developments in aryl urea derivatives show better effect and less toxicity. This has been noticed so far, that modifications on aryl urea moiety displayed interesting biological activities. It will be exciting to observe that these modifications can be utilized as potent therapeutic agents in future.

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