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 e 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, antymyobacterial, anti-HIV activity, genotoxic, herbicidal, analgesic, anti-inflammatory, muscle relaxants, anticaner, antimalarial, anti fungal and insecticidal agent [7].

Aryl Urea Derivatives
Urea and its derivatives have been investigated for their biological activities including antiatheroscerotic, 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 1828, 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 anticaner, 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 phosphene, 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 CO2 reacting with ammonium, ethylene oxide or ethanol. Some researchers have also synthesized urea derivatives through amines reacting with CO2 in the presence of catalysts, such as 1,8-diazabicyclo[5.4.0]undec-7-ene, CsOH, Cs2CO3, Au/poly, [Bmin] OH2O or KOH/PEG1000, using ionic liquids, N-methylpyrrolidone or CO2 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-3-nonsubstituted/chloro-3methyl-2(3H) –benzoazolones 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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Anticonvulsant activity

Ramesh et al. synthesized, five Arylurea derivatives using microwave irradiation 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].

| 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| -OCH₃| 0 | O   |
| 6         | -Cl| -H | 0 | S   |
| 7         | -Cl| -H | 1 | S   |

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].

| Compound | X/R   |
|----------|-------|
| 8        | p-OCH₃|
| 9        | p-Cl  |

Antiproliferative activity

Jung et al. synthesized aminoisoquinolinylureas by nitration of 1-chloroisouquinoline using a mixture of nitric and sulphuric acids gave 1-chloro-5-nitroisouquinoline which is then treated with 7 N ammonia solution in methanol led to nucleophilic displacement and formation of 1-amino-5-nitroisouquinoline 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 IC₅₀ value of 0.41 μM [19].
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 | ![Structure](image1.png) |
| 18   | N-(2-Nitrophenyl)-N’-(1-phenylethyl)urea | ![Structure](image2.png) |
| 19   | N-(3-Nitrophenyl)-N’-(3-nitrophenyl)urea | ![Structure](image3.png) |
| 20   | N-(4-Chlorophenyl)-N’-(2’-nitrophenyl)urea | ![Structure](image4.png) |
| 21   | N-(3-Nitrophenyl)-N’-(3’-nitrophenyl)urea | ![Structure](image5.png) |

Antiulceric activity

Vijaya et al. tested unsymmetrically substituted urea derivative Compound 23 for the anti ulcerogenic 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 | ![Structure](image6.png) |

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 isothiocyanate. 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 | ![Structure](image7.png) |

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-chlorbenzylamine derivatives 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 | ![Structure](image8.png) |

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
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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].

### 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 rhodain as standard. Two of the scaffolds, the urea scaffold and the aryl thiourea scaffold, exhibited activity against Trypanosoma cruzi in vivo and both enzymes in vitro. The Compound 27 showed activity at 3.1 µM IC₅₀ against cruzain and a 3 µM IC₅₀ against rhodain. Infected cells treated with D16 survived 22 days in culture compared with 6 days for their untreated counterparts.

Two compounds Compounds 28 and 29 were active against both proteases below 10 µM which were tested in a cell culture assay of Trypanosoma 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 parasitosis of cells but on treatment with Compound 28 or 29 the cells survived up to 10 days [24].

### 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 and HT-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 (IC₅₀ 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].

### 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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