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Research Article

Short Notes on Diaryl Ureas Derivatives

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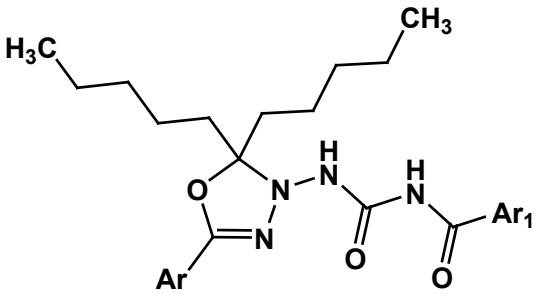
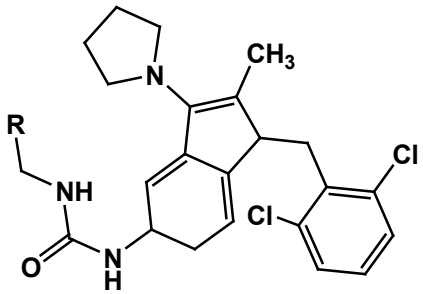
Ureas are a very important class of compounds due to their extensive application as agrochemicals, dyes for cellulose fibers, antioxidants in gasoline, hair dyes, additives in hydrocarbon fuels, detergents, and polymers, corrosion inhibitors and as synthetic intermediates.[1] Disubstituted ureas not only possess industrial application, their biological potency is also widely exploited. Substituted ureas have been of recent interest due to potent biological activities like HIV protease inhibitors,[2,3] FKBP12 inhibitors[4,5] and semicarbazides as CCK-B receptor antagonists[6] and endothelin antagonist.[7] A series of ureas 1 as MAO (Mono Amino Oxidase) inhibitors and evaluated their MAO-inhibiting activity by kynuramine fluorimetric assay method and concluded that the urea functionality can be used as pharmacophoric group in development of new leads.[8] α-Thrombin, is involved in many physiological functions such as coagulation, platelet aggregation, lymphocyte mitosis, monocyte chemotaxis, and endothelial cell proliferation. Many of these cellular effects are mediated by activating the cell-surface receptor PAR-1, which is also known as thrombin receptor.[9,10] Studies with high-affinity peptidic and peptide-mimetic agonists have demonstrated that PAR-1 is the major receptor responsible for mediating platelet aggregation, cell proliferation, inflammatory responses and neurodegeneration.[11] α-Thrombin, by means of PAR-1 activation, might be also mechanistically involved in regulating hepatic fibrogenesis. Moreover, many studies support the notion that PAR-1 plays a pivotal role in angiogenesis.[12] This means that this receptor is an attractive drug-discovery target for the possible treatment of various disorders such as thrombosis, restenosis, atherosclerosis, inflammation, cancer metastasis and stroke.[13] Several approaches are used for the synthesis of molecules which can act as PAR-1 antagonists. Caliendo et al. have synthesized molecular libraries 2 which contain urea functionality and tested their PAR-1 antagonist activity.[14] Some of the tested compounds exhibited better PAR-1 antagonist activity than standard drug RWJ54003.



1 Ar=Ar_1=phenyl, substituted phenyl



2 R=phenyl, substituted phenyl

Gastrin and cholecystokinin (CCK) belong to the polypeptide hormone family and are found in both the central nervous system (CNS) and gastrointestinal tissue. Gastrin is a stimulant of gastric acid secretion. The receptors for gastrin and CCK have been classified into two subtypes: CCK-A and CCK-B/gastrin. Efforts to find potent and selective CCK-B/gastrin inhibitor would lead to drug molecule which would be useful in treatment of hypersecretion of gastric acid.[15] The initial efforts of the first nonpeptide CCK receptor antagonist, Asperlicin. Chemical modification of Asperlicin, using various pharmacophores, produced potent selective CCK-A receptor antagonists 3 and many of them contain urea functionality. Later on it was found that urea functionality is essential to show CCK-B/gastrin receptor antagonist activity.[16] The integrin VLA-4 (very late antigen 4; a4bl; CD49d/CD29) is a non-covalently bound hetero dimeric glycoprotein receptor expressed on the cell surface of most leukocytes. It binds to vascular cell adhesion molecule-1(VCAM-1), expressed on

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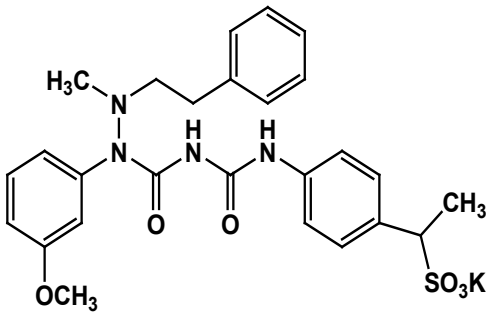
cytokme-stimulated endothelial cells and the alternatively spliced connecting segment-1 domain of fibronectin. It also plays an important role in the activation, proliferation and differentiation process of the immune cells within the parenchyma. Anti-VLA-4 antibodies and small molecular VLA-4 antagonists 4 have been reported to inhibit leukocyte infiltration into extravascular tissue and prevent tissue damage in inflammatory animal models of asthma, multiple sclerosis (MS), rheumatoid arthritis and inflammatory bowel disease (IBD).[17,18] Molecular libraries of small molecules 5 which may act as potent VLA-4 antagonists and all the compounds contain urea functionality.[19]



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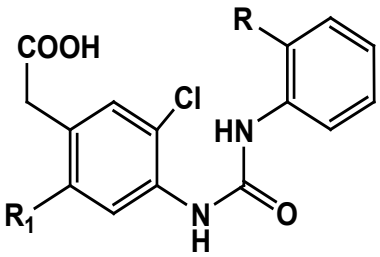

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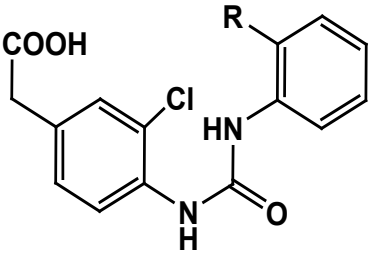

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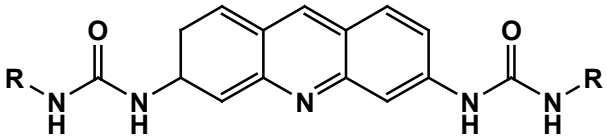
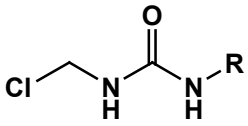
Several novel diarylureas 6 which contain acridine moiety are also evaluated for cytotoxic activity against various types of cell lines along with DNA-binding activities.[20]



6 R=phenyl, substituted phenyl

Aryl chloroethylureas 7–9 extensively as one of the class agents which are expected to act as anti-microtubules or redox modulating agents.[21,22] Due to this property, they are evaluated for anticancer activity against cancer which affects gastro intestinal tract and colon.[23]



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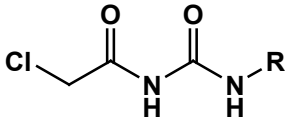

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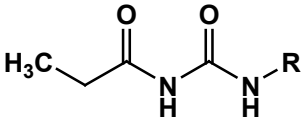

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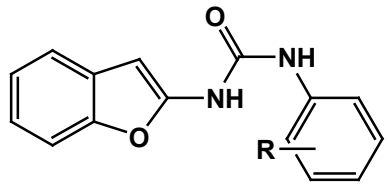
R=phenyl, substituted phenyl

Apart from these, compounds containing urea and semicarbazide functionality are found to possess broad spectrum of biological and pharmacological activities like antimalarial, antibacterial, antifungal, anti-inflammatory and anthelmintic activities.[24-27] In spite of biological significance of urea functionality, there are few reports on synthesis and biological evaluation of compounds which contain both benzofuran and urea moiety. This stimulated us to synthesize novel molecules, which contain both benzoflxran and urea functionality, and to evaluate their biological and pharmacological profile.

Even though numerous methods are available for the synthesis of ureas,[28-30] ureas are most commonly synthesized by reaction of an amine with phosgene.[31] This approach is particularly efficient for symmetrical ureas. However, in the case of nonsymmetrical ureas, the synthetic efficiency is limited by the formation of symmetrical urea side products. Another method of choice for urea formation is the coupling of an alkyl or aryl carbamate with an amine.[32] In this case, the reaction is reversible and may not reach completion.[17] The need for development of novel methods further increased with the discovery of biological significance of ureas. As a result, during the last years there has been considerable interest towards the development of new efficient, selective and environmentally friendly protocols for their preparation of diarylureas, which are able to supplant the classical synthesis based on phosgene or isocyanates[33,34] (mainly prepared in turn from phosgene itself).[35] The direct metal-catalyzed conversion of amines and CO to ureas provides an alternative method to phosgene and its derivatives. Many methods based on catalytic carbonylation for preparation of ureas have been investigated over many years.[36-38] In recent years, several approaches are designed for the synthesis of mono and disubstituted ureas. Some of the methods are

- By the reaction of unsubstituted urea with alkylamines or their hydrochloride salts[39]
- By aminolysis of isonitriles or cyanamides[40]
- By conversion of nitrourea into disubstituted urea by the action of amines[41]
- From the reaction of alkali metal cyanates with amines[42]
- By reductive alkylation by which substituent may be introduced into urea[43]
- By using Curtius rearrangement in carbohydrazide or carbonyl chloride is used.[44]



3a-3l

10a R=H

10b R=2-C1

10c R=4-C1

10d R=2-CH_3

10e R=3-CH_3

10f R=4-CH_3

10g R=4-C_2H_5

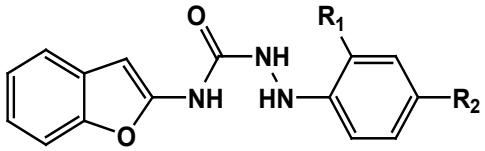
10h R=2-OCH_3

10i R=4-OCH_3

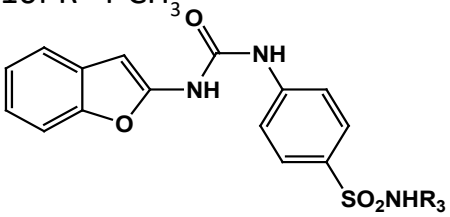
10j R=4-F

10k R=3-CI-4-F

101 R=2-Phenyl



11a-b 11aR_1=H **11b**R_1=NO_2



12aR_3 = H

12bR_3=2-Diazene

12c R_3= 5-CH_3-Isoxazolyl

12dR_3=2,3-OCH_3-4-Pyridyl

Some selected compounds were evaluated for anti-inflammatory, analgesic, antipyretic, anti-bacterial, anti-fungal and anthelmintic activities.

Conflict of Interest: None

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