Mini Review
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Hydroxytriazenes- a promising class of anti-inflammatory compounds

Abstract

Hydroxytriazenes are much studied series of compounds for their application as spectrophotometric and complexometric reagents for almost entire first transition series. A number of voluminous reviews have been published by our group during last couple of years.1–10 However, in recent years we have focused on the interesting biological activities of this series of compounds with diverse modification in their structures. We have synthesized a number of hydroxytriazenes and characterized using various physicochemical techniques. The hydroxytriazenes have been synthesized by coupling alkyl or aryl hydroxylamine with aryl diazonium chlorides. Very interesting bio-activities have been found in this class of compounds varying from anti-bacterial, anti-fungal, anti-oxidant, analgesic, wound healing, anti-diabetic and even cytotoxic activities. The present review focuses on anti-inflammatory activity found in the series of hydroxytriazenes prepared by the group. The recent publication by our research group clearly indicates moderate to excellent anti-inflammatory activity in these compounds which needs further research on this area. They can be excellent future anti-inflammatory drugs if explored further. The present review brings forward recent papers published by our group or elsewhere along with method of their synthesis which is extremely simple, involves only few steps with minimum synthetic set up and gives excellent yields in aqueous medium. It is almost a green synthetic method for a series of drug precursor molecules.

Keywords: hydroxytriazenes, anti-inflammatory activity

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Introduction

Hydroxytriazenes behave like bidentate ligands which have alpha hydroxyl group relative to azo group. The synthesis includes reduction of an alkyl or aryl nitro compound in neutral medium to get hydroxylamine and diazotization of an aromatic amine to get diazonium chloride. When these two that is hydroxylamine and respective diazonium salt are coupled we get hydroxytriazene as a product. A general scheme reported by Elkins and Hunter and further modified by Sogani & Bhattacharya[11] for synthesis of hydroxytriazenes is as shown in Scheme 1. The present review discribe anti-infammatory activities of hydroxytrizenes reported by our research group till 2016.

A. **Agarwal Shilpa et al.**[12] have reported synthesis of six new (compound code Compound-I to Compound-VI) N [(4-aminophenyl) sulfonyl] acetamide based hydroxytriazenes. Further, their theoretical prediction for probable activities using PASS (Prediction of Activity Spectra for Substance) shows that hydroxytriazenes may have a number of activities but specifically anti-inflammatory, antiradical and anti-diabetic activities have been experimentally validated which proves that theoretical predictions (88% to 97.10%) agrees with the experimental results (89% to 98.31%). The object of the paper is to establish Computer Aided Drug Design (CADD) model using our compounds.

B. **Patidar Ashok Kumar et al.**[13] have synthesized a series of hydroxytriazenes (compound code 4a-4h) and characterized using their spectral and physical analysis. All synthesized compounds were screened for probable activities using PASS (prediction of activity spectra for substances) and Pa value as reported 95.2% to 80.9% indicating their excellent probability to have anti-inflammatory activity. Synthesized compounds show good agreement of anti-inflammatory activities as predicted by PASS.

C. **Chauhan LS et al.**[14] have reported the anti-inflammatory activity of some substituted hydroxytriazenes on carrageenan-induced hind paw edema and cotton pellet granuloma models in albino rats (Wister strain). It is reported that the hind paw edema was produced by sub planter injection of carrageenan and the paw volume was measured plethysmograph after 0.5, 1, 2, 3 & 5h. As reported in sub-acute model, cotton pellet granuloma was produced by implanting 50±1mg. sterile cotton in axilla under ether anesthesia. The animals were administered hydroxytriazenes (HD-1, HD-2, HD-3) dissolved in DMSO at dose (5mg/kg) and diclofenac sodium (5mg/kg), as standard drug. All hydroxytriazenes showed maximum inhibition of edema up to 1h. After 1h the parent compound HD-1 did not show any significant activity, but the other hydroxytriazenes HD-2 and HD-3 showed significant activity up to 5h. In sub-acute models, the hydroxytriazenes HD-2 and HD-3 exhibited significant activity by reducing the granuloma weights by 69.62% and 56.86% respectively hydroxytriazenes (HD-2 and HD-3) show significant anti-inflammatory effect on both acute and sub-acute inflammation.

D. **Chauhan Lalit Singh et al.**[15] have studied the anti-inflammatory activity of hydroxytriazenes (HD) on carrageenan-induced hind paw edema and cotton pellet granuloma models in albino rats (Wister strain). The hind paw edema was produced by sub planter injection of carrageenan and the paw volume was measured plethysmoggraph after 0.5, 1, 2, 3 & 5h. Cotton pellet granuloma was produced by implantation of 50±1mg sterile cotton pellets in axilla region under ether anesthesia. The animals

were given orally hydroxytriazenes (10mg/kg), dissolved in 10% DMSO and diclofenac sodium (10mg/kg), as standard drug. All hydroxytriazene compounds showed maximum inhibition of edema at 1 hour. After 1h, the parent compound HD-1 did not show any significant activity, but the other hydroxytriazene compounds HD-2, HD-3 and HD-4 show significant activity up to 5 hour. The granuloma pouch model, the hydroxytriazenes; HD-2, HD-3 and HD-4 exhibited a 70.56%, 57.51% and 57.12% reduction in granuloma weights respectively. It was found that hydroxytriazenes (HD-2, HD-3 and HD- 4) possess significant anti-inflammatory effect on both acute and sub-acute inflammation (Table 1).

Table 1 The compounds which have been reported for anti-inflammatory activity in review are summaries in tabular form with code no of each compound

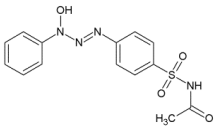
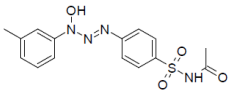
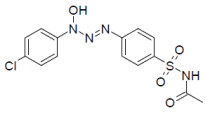
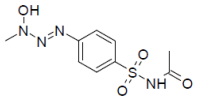
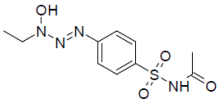
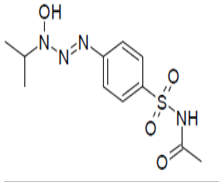
S. No.	Codes	Name of Compound	Structure	Anti-Inflammatory Activity (% Inhibition)	Reference
1	Compound-I	3-hydroxy-3-phenyl-1-(4-acetylsulfonyl)phenyl triazene		89.82	Agarwal Shilpa et al. [12]
2	Compound-II	3-hydroxy-3-(3-methylphenyl)-1-(4-acetylsulfonyl)phenyl triazene		96.19	
3	Compound-III	3-hydroxy-3-(4-chlorophenyl)-1-(4-acetylsulfonyl)phenyl triazene		90.61	
4	Compound-IV	3-hydroxy-3-methyl-1-(4-acetylsulfonyl)phenyl triazene		97.03	
5	Compound-V	3-hydroxy-3-ethyl-1-(4-acetylsulfonyl)phenyl triazene		96.19	
6	Compound-VI	3-hydroxy-3-(1-methylethyl)-1-(4-acetylsulfonyl)phenyl triazene		98.31	

Table Continued..

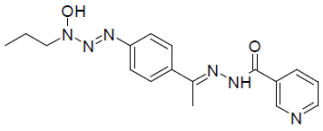
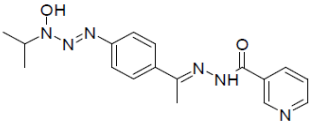
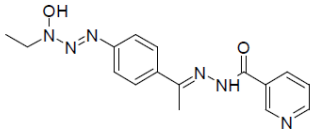
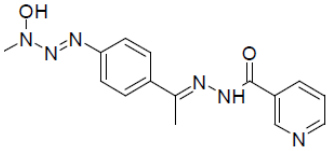
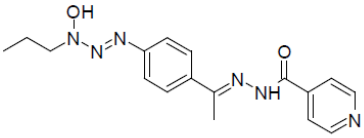
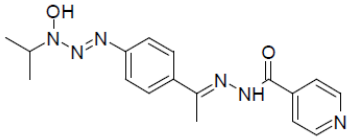
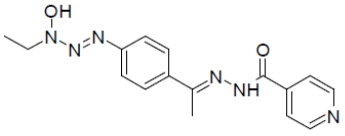
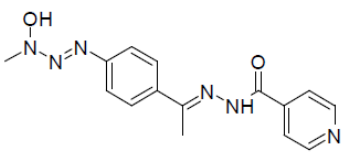
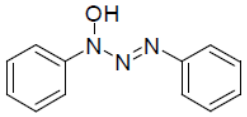
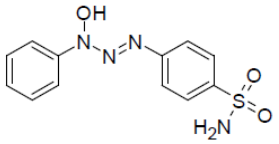
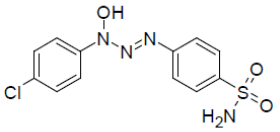
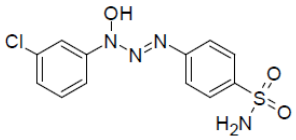
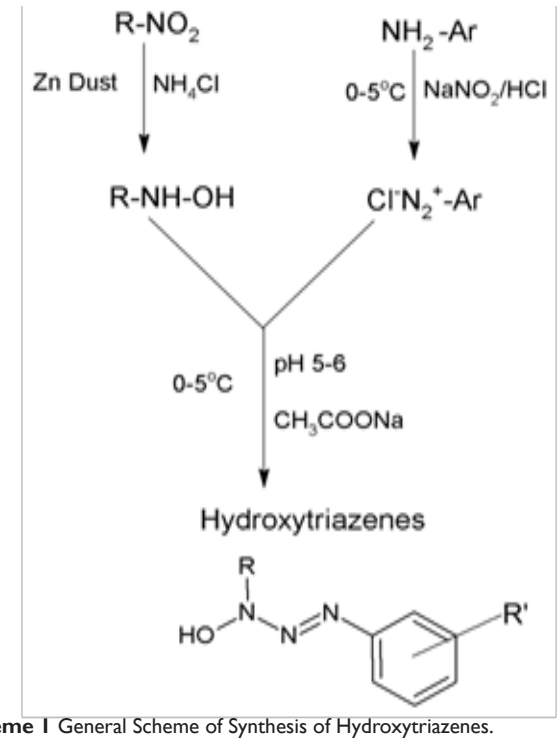
S. No.	Codes	Name of Compound	Structure	Anti-Inflammatory Activity (% Inhibition)	Reference
7	4a	3-hydroxy-3-n-propyl-1-[N'-(1-phenylethylidene) pyridine-3-carbohydrazide]triazene		84.90	
8	4b	3-hydroxy-3-isopropyl-1-[N'-(1-phenylethylidene) pyridine-3-carbohydrazide]triazene		82.07	
9	4c	3-hydroxy-3-ethyl-1-[N'-(1-phenylethylidene) pyridine-3-carbohydrazide]triazene		77.83	
10	4d	3-hydroxy-3-methyl-1-[N'-(1-phenylethylidene) pyridine-3-carbohydrazide]triazene		75.64	
11	4e	3-hydroxy-3-n-propyl-1-[N'-(1-phenylethylidene) pyridine-4-carbohydrazide]triazene		81.13	Patidar Ashok et al. [13]
12	4f	3-hydroxy-3-isopropyl-1-[N'-(1-phenylethylidene) pyridine-4-carbohydrazide]triazene		79.24	
13	4g	3-hydroxy-3-ethyl-1-[N'-(1-phenylethylidene) pyridine-4-carbohydrazide]triazene		78.30	
14	4h	3-hydroxy-3-methyl-1-[N'-(1-phenylethylidene) pyridine-4-carbohydrazide]triazene		73.58	

Table Continued..

S. No.	Codes	Name of Compound	Structure	Anti-Inflammatory Activity (% Inhibition)	Reference
15	HD-1	3-hydroxy-1,3-diphenyltriazene		4.68	
16	HD-2	3-hydroxy-3-phenyl-1-(4-sulfonamido) phenyltriazene		71.13	
17	HD-3	3-hydroxy-3-p-chlorophenyl-1-(4-sulfonamido) phenyltriazene		58.33	
18	HD-4	3-hydroxy-3-m-chlorophenyl-1-(4-sulfonamido) phenyltriazene		57.95	Chauhan LS et al. [14,15]



Scheme 1 General Scheme of Synthesis of Hydroxytriazenes.

Discussion

The inflammation is a protective response to cell injuries in animals which is manifested by clinical signs such as erythema, edema, hyperalgesia, pain and loss of function at microscopic level. In above reviews carrageenan induced acute inflammation model has been used and the results have been compared with standard drug Diclofenac sodium. The drug is categorized as a NSAID (Non-steroid anti-inflammatory drug) which acts at the periphery and not at CNS (Central Nervous System). Acting at the site of tissue injury these drugs block the synthesis of ecosanoids which finally blocks the cycloxygenase (COX) pathway. Thus, probable mechanism of action of carrageenan induced edema is bi-phasic; the first phase is attributed to release of histamine-HT, Kinins in the first hour, while the second phase is the release of prostaglandin like substance in 3-4 hours. Further the hydroxytriazenes exhibit structure dependent anti-inflammatory properties.

Conclusion

The mini review thus highlights the drug candidature of hydroxytriazenes and good possibility of finding some excellent drugs from these compounds.

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Conflict of interest

The author declares no conflict of interest.

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