Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 4, Issue 2, 2012

Review Article

A SYSTEMIC REVIEW OF SCHIFF BASES AS AN ANALGESIC, ANTI-INFLAMMATORY

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Received: 23 February 2012, Revised and Accepted: 29 March 2012

ABSTRACT

Schiff bases are aldehyde - or ketone - like compounds in which the carbonyl group is replaced by an imine or azomethine group. They are widely used for industrial purposes and also exhibit a broad range of biological activities. The reaction is acid catalysed, however only aldehydes and ketones which do not aldolize easily in acidic media, can be condensed with amines in presence of strong acid catalyst (e.g. BF_3-etherate, anhydrous $ZnCl_2$ or $POCl_3$). Aromatic aldehydes and aliphatic or aromatic ketone gives stable azomethines. The basic mechanism is a two step addition elimination mechanism. In the first step, the nitrogen base adds to the carbonyl compound to give a carbinolamine intermediate, followed by elimination of water to form the carbon-nitrogen double bond. Rate of condensation passes through a maximum with changing acidity, falling off on either side of an optimum pH. Generally the optimum pH range is 3-5. Schiff bases are biologically active compounds and have been reported to possess various important pharmacological properties like antifungal, anticancer, anticonvulsant and diuretic activities. Schiff bases are derived from heterocycles has been reported to posses cytotoxic properties. This short review compiles examples of the most promising analgesic, anti-inflammatory Schiff bases. An overview of synthetic methodologies used for the preparation of Schiff bases is also described.

Keywords: Schiff bases, Analgesic activity, Anti-inflammatory activity, Azomethine group.

INTRODUCTION

Schiff bases, named after Hugo Schiff[1], are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions. Structurally, a Schiff base (also known as imine or azomethine) (Fig. 1) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C=O) has been replaced by an imine or azomethine group. Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis, and as polymer stabilizers. Schiff bases have also been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties. Imine or azomethine groups are present in various natural, natural-derived, and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities. In this review we present the general approaches to the synthesis of Schiff bases. We also highlight the most significant examples of compounds belonging to this class, which exhibit analgesic, anti- inflammatory, and non ulcerogenic activities to have been reported in the literature. The relationship between Schiff bases and other pharmacological activities, such as antiproliferative activities, are not included in this review.

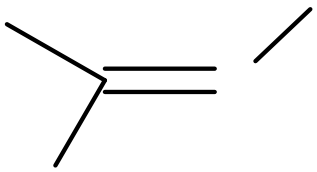


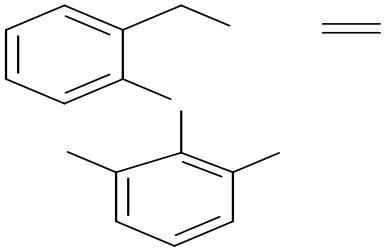
Fig. 1: General structure of a Schiff base

BIOLOGICAL ACTIVITIES OF SCHIFF BASES

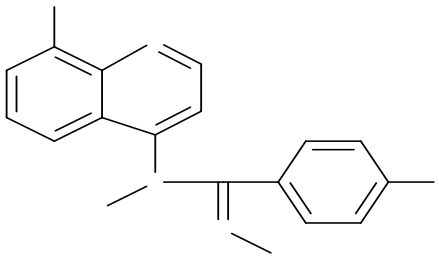
Analgesic, Anti-inflammatory activity

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain and inflammation, particularly for different types of arthritis.[2] Among the most popular NSAIDs worth mentioning is diclofenac sodium, which is approved in more than 120 countries across the globe since its introduction, 28 years ago, and is ranked 30th among the top 200 drugs with respect to new prescriptions. The pharmacological activity of NSAIDs is related to the suppression of prostaglandin biosynthesis from arachidonic acid by inhibiting the enzyme prostaglandin endoperoxidase, popularly known as cyclo-oxygenase (COX). It was discovered that COX exists in two isoforms, COX-1 and COX-2, which are regulated and expressed differently. COX-1 provides cytoprotection in the gastrointestinal tract (GIT), whereas inducible COX-2 selectively mediates inflammatory signals. Since most of the currently available NSAIDs in the market show greater selectivity for COX-1 than COX-2, chronic use of NSAIDs, including diclofenac, may elicit appreciable GI irritation, bleeding and ulceration. The incidences of clinically significant GI side effects due to long term use of NSAIDs are very high (30%) and cause some patients to abandon NSAID therapy. GI damage from NSAID is generally attributed to two factors.Local irritation by the direct contact of carboxylic acid (–COOH) moiety of NSAID with GI mucosal cells (topical effect) and decreased tissue prostaglandin production in tissues which undermines the physiological role of cytoprotective prostaglandins in maintaining GI health and homoeostasis. Synthetic approaches based upon chemical modification of NSAIDs have been taken with the aim of improving safety profile and in turn therapeutic window of this NSAID. Several studies have described the derivatization of the carboxylate function of representative NSAID with less acidic azoles, viz. 1,3,4-oxadiazole, Triazole, etc. which resulted in an increased anti-inflammatory activity with reduced ulcerogenicity. Furthermore, it has been reported in the literature that certain compounds bearing 1, 3, 4-oxadiazole nucleus possess significant anti-inflammatory activity. In our attempt to discover new, safer and potent agents for treatment of inflammatory diseases, we have replaced the carboxylic acid group of diclofenac acid with less acidic heterocycle, 1,3,4-oxadiazole, in order to accentuate potency and reduce GI toxicities associated with the parent diclofenac due to its free –COOH group. The compounds designed so were found to possess much significant analgesic-anti-inflammatory profile with significant reduction in potential for ulcerogenic toxicities.

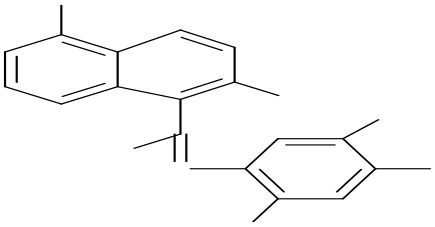
Zhou *et al* (2010) reported the synthesis of 17 novel Schiff's bases, N, N'-(Z-allylidene-1, 3-diyl) bisamino acid methyl esters which exihibit moderate analgesic activity against tail-flick mouse model. Thus the present Schiff's bases are able to treat chronic pain from inflammation. 2i,j exhibited even higher anti-inflammatory activities.[2]



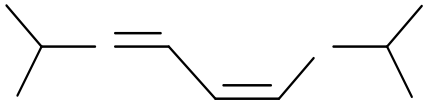
(2a)



(2b)



(2c)

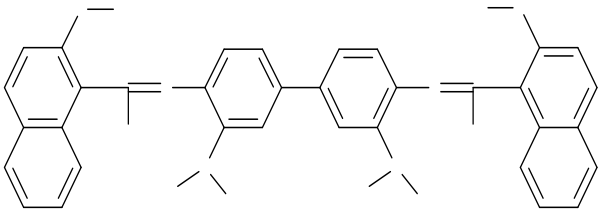


(3)

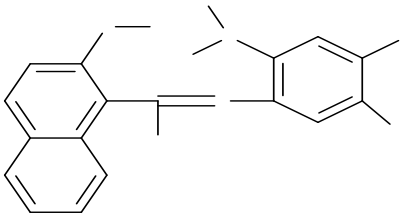
3i	$-CH(CH_3)CH_2CH_3$
3j	$-CH_2CH(CH_3)_2$

Fig. 2

Sondhi *et al* (2006) reorted the synthesis of N-(acridin-9-yl)-4 (benzo[d]imidazol/oxazol-2-yl) benzamides Schiff bases which exhibit analgesic and anti-inflammatory activity. Compounds 3a and 3b(c) showed good anti-inflammatory activity and good analgesic activity.[3]



(3a)

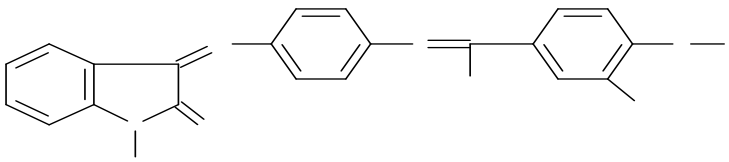


3b(c)

	R_1	R_2
3b(c)	H(Cl)	Cl(H)

Fig. 3

Chinnasamy *et al* (2010) reported the synthesis of series of novel Schiff bases of Isatin.These compounds were screened for the analgesic activity by tail-immersion method. 3-(4-(4-Hydroxy-3-methoxylbenzylideneamino)phenylimino) indoline-2-one exhibited better analgesic activity when compared to standard pentazocine.In this compounds containing electron-donating groups exhibit better analgesic activity than the electron-withdrawing groups.4i exhibited better analgesic activity.[4]



(4i)

Fig. 4

Bhandari *et al* (2008) reported the synthesis of series of novel Schiff bases having potential analgesic, anti-inflammatory activity without GI toxicities, toxicity associated with all traditional NSAIDs having new chemical entities. In this series compounds 5b, 5c, 5e, and 5g exhibited very significant anti- inflammatory activity compared to standard drug diclofenac.[5]

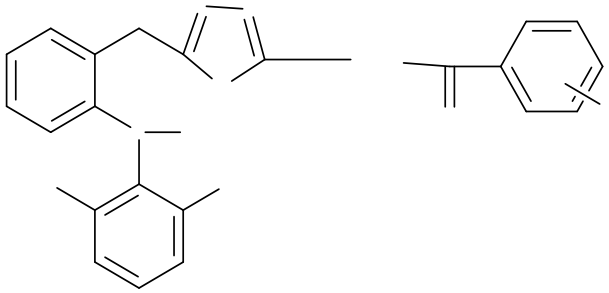
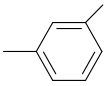
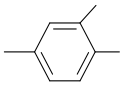
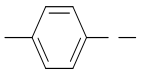
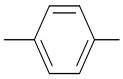
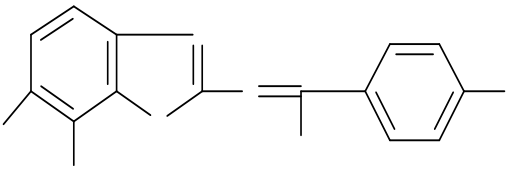


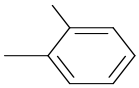
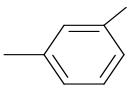
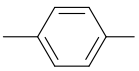
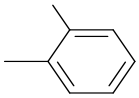
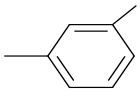
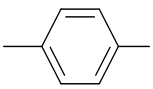
Fig. 5

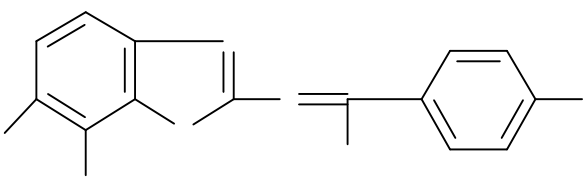
Compound	R
5b	
5c	
5e	
5g	

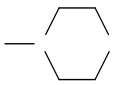
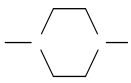
Sathe *et al* (2011) reported the synthesis of series of novel fluorobenzothiazole Schiff bases with fluorine at 6th position. Ibuprofen was used as standard reference anti-inflammatory drug. Fluorobenzothiazole Schiff base derivatives have potent anti-inflammatory activity with good therapeutic values and minium toxic levels.[6]



(6a-f)

Compounds	R
6a	
6b	
6c	
6d	
6e	
6f	

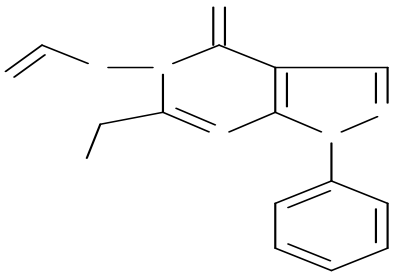


6g	
6h	
6i	-N(C_6H_5)$_2$

(6g-i)

Fig. 6

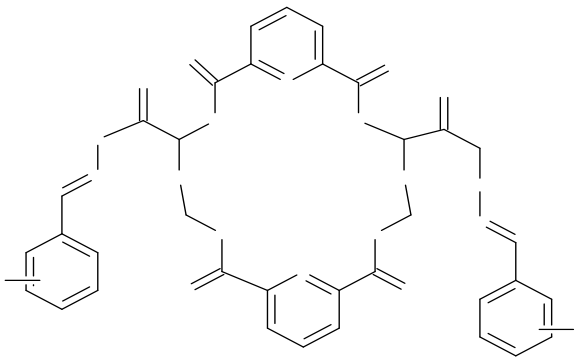
Hussein *et al* (2011) reported the synthesis of series of novel Schiff bases bearing Pyrazolo[3, 4-D]Pyrimidine-4-ones. Some of the newly synthesized compounds7a, 7b, 7c, 7d and 7e showed good anti-inflammatory activities and more safe on liver enzymes in rats. The presence of Br atom, a good withdrawing group in compound 7e makes it more anti-inflammatory potency than compounds 7a, 7b, 7c and 7d.[7]



Compound	Ar	R
7a	α-naphthyloxy	C_6H_4OH-2
7b	β- naphthyloxy	C_6H_5
7c	β- naphthyloxy	$C_6H_4OCH_3$-4
7d	α-naphthyloxy	$C_6H_4N(CH_3)_2$-4
7e	α-naphthyloxy	$C_6H_{4\text{-}Br\text{-}2}$

Fig. 7

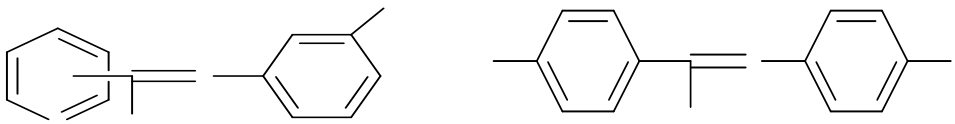
Ali *et al* (2011) reported the synthesis of series of novel macrocyclic Schiff bases containing amino acid and pyridine moiety having good anti-inflammatory and analgesic activities. Macrocyclic bisimides and macrocyclic bis-hydrazones 8d, 8e, 8f, 8i, 8j showed good analgesic and anti-inflammatory activity comparable to diclofenac potassium and valdecoxib as reference drugs.[8]



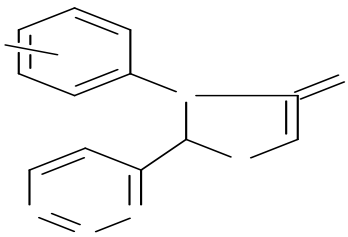
Compound	X
8d	2,6-Cl_2
8e	3,4-Cl_2
8f	2-Cl-6-F
8i	4-OCH_3
8j	3,4,5-$(OCH_3)_3$

Fig. 8

Vazzana *et al* (2004) reported the synthesis of series of novel Schiff base derivatives of 2,3-diaryl-1,3-thiazolidin-4-one having anti-inflammatory activity against the rat hind paw edema induced by carrageenan. The *N*-(2/3/4-pyridinylmethylene)-3-trifluoromethylbenzenamines **A-C** shows the potent anti-inflammatory activity. The Schiff bases **D-G** and the thiazolidinone derivatives **H-N** were screened for Anti-inflammatory activity.[9]



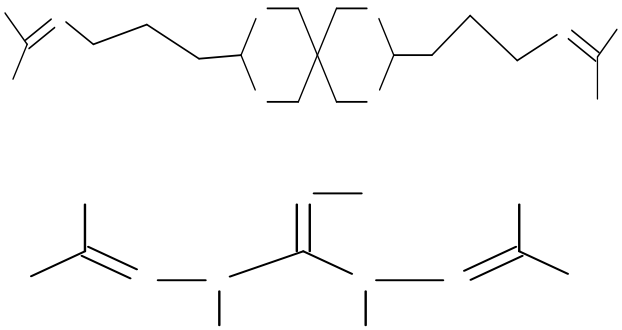
(A-C) (D-G)

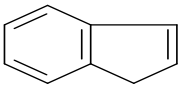


(H-N)

Fig. 9

Sondhi *et al* (2006) reported the synthesis of series of novel *bis* Schiff bases of hydrazone and guanidine derivatives are heterocyclic molecules possess analgesic and anti-inflammatory activity. Among all compounds10a and 10b exhibited potent anti-inflammatory and analgesic activity.[10]



Compound	R	R1
10a		H

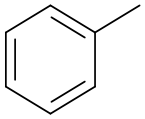
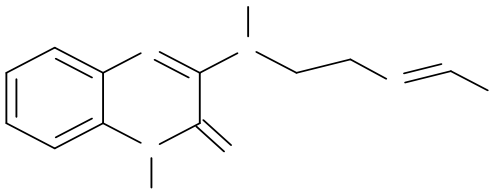
Compound	R	R1
10b		CH_3

Fig. 10

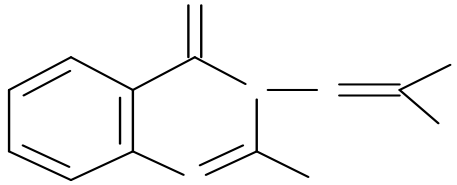
Ghadage *et al* (2011) reported the synthesis of series of novel Schiff bases of quinoxaline-2(1H)-one as potent anti-inflammatory agents. Among all compounds (11a) showed maximum anti-inflammatory activity, while compound (11b) showed slight anti-inflammatory activity at both dose when compared with standard drug. [11]



Compound	Ar
11a	CH_3O-C_6H_4CHO
11b	C_6H_5-CH_2CH=CHCHO

Fig. 11

Alagarsamy *et al* (2003) reported the synthesis of series of novel Schiff bases of 2-benzylamino-3-substituted quinazolin-4(3*H*)-ones having analgesic and anti-inflammatory activities. Among all synthesized compounds, compound 12c is equipotent with diclofenac sodium. The compounds 12a, 12b and 12c showed more potent anti-inflammatory activity than diclofenac sodium. C-2 and N-3 disubstituted quinazolines exhibit analgesic and anti-inflammatory activities.[12]



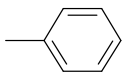
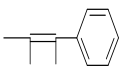
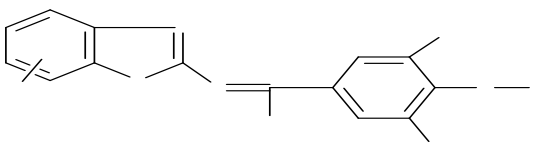
Compound	R1	R2
12a	CH_3	CH_2CH_3
12b	H	
12c	H	

Fig. 12

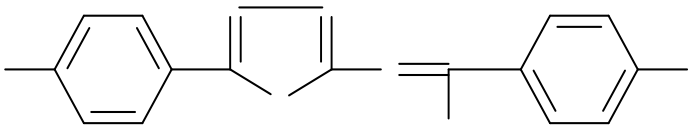
Geronikaki *et al* (2003) reported the synthesis of series of novel LO. Compound 2d exerts significant anti-inflammatory and not a high LO inhibitory activity.Thiazolyl/thiazolinyl/benzothiazolyl Schiff bases having anti-inflammatory activity against asthma, rheumatoid arthritis and psoriasis. Thiazolyl and benzothiazolyl groups are of importance in biological systems as anti-inflammatory, analgesic agents and inhibitors on lipoxygenase activities. vanilloids, possess high anti-inflammatory activity. Only two compounds 13a and 13d are inhibiting in vitro soybean LO.[13]



	R_1	R_2	R_3
13a	H	H	H
13d	I	OCH_3	H

Fig. 13

Pandey *et al* (2011) reported the synthesis of series of novel Schiff bases of 2-amino-5-aryl-1, 3, 4-thiadiazole derivatives possess analgesic activity against swiss albino mice, anti-inflammatory activity against Wister albino rats. Using pentazocine and indomehacin as standard drug. Among all compounds 14a, 14b, 14c and 14e shows potent analgesic activity and 14b, 14c, 14f, and 14j shows anti-inflammatory activity.[14]



Compound	R	R'
14a	OCH_3	OH
14b	OH	OH
14c	Cl	OH
14e	N(CH3)2	OH
14f	OCH_3	NO_2
14j	$N(CH_3)_2$	NO_2

Fig. 14

Jayashekhar *et al* (1997) reported the synthesis of series of novel Schiff bases of mesalazine. Among the Schiff bases compound 15 exhibited the maximum anti-inflammatory activity comparable with that of aspirin. Mesalazine is a 5-aminosalicylic acid is used to treat acute exacerbations of the inflammatory bowel disease and ulcerative colitis. The anti-inflammatory action of 5-ASA in GUT is due to its powerful inhibition of synthesis of leukotrienes.[15]

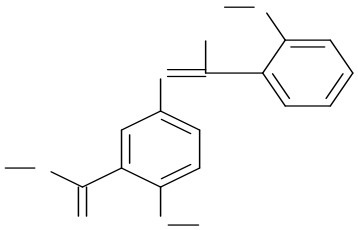
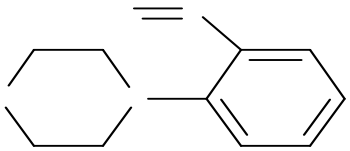


Fig. 15

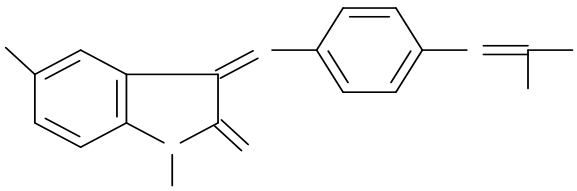
Panneerselvam *et al* (2009) reported the synthesis of novel Schiff bases of 4-(2 Aminophenyl)-Morpholines.N-benzylidine-2-morpholoino benzenamine (16a) and N-(3-nitro benzylidine)-2-morpholino benzenamine (16b) exhibited significant analgesic and anti-inflammatory activities. Substitution of 4-phenyl morpholine to quinazoline moiety results in potent analgesic and anti-inflammatory activities.[16]



Compound	R
16a	C_6H_5
16b	$mNO_2C_6H_4$

Fig. 16

Nirmal *et al* (2010) reported the synthesis of novel Schiff bases analogues of 3-(4-amino) Phenylimino) 5-fluoroindolin-2-one. Among the Schiff bases compound N_3 exhibited significant analgesic activity. Among the title compounds studied 17a, 17b, and 17c exhibited significant anti- inflammatory activity comparable to reference standard diclofenac sodium. The test compounds showed only mild ulcerogenic side effect when compared to aspirin.[17]



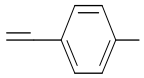
Compound	R	R1
17a	CH_3	CH_2CH_3
17b	CH_2CH_3	CH_2CH_3
17c		

Fig. 17

CONCLUSION

This short review compiles examples of the most promising analgesic, anti- inflammatory Schiff bases. An overview of synthetic methodologies used for the preparation of Schiff bases is also described.

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