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THUMBAY
Growth Through Innovation

Synthetic utility of Schiff bases in Medicinal Chemistry

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Prelude

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The various ways by which new drugs had their origin are

- **RANDOM SCREENING FOR POTENTIAL DRUGS**
- **MODIFICATION OF LEAD COMPOUNDS**
- **MECHANISM BASED DRUG DESIGN**
- **MIXED APPROACH**

The present discussion gives an idea about modification of Lead Molecule.

Contents

- Schiff base - Introduction
- Synthesis of Schiff base
- Biological activities of various Schiff bases
- Medicinally important heterocycles derived from Schiff base
- Biological significance

Schiff Bases

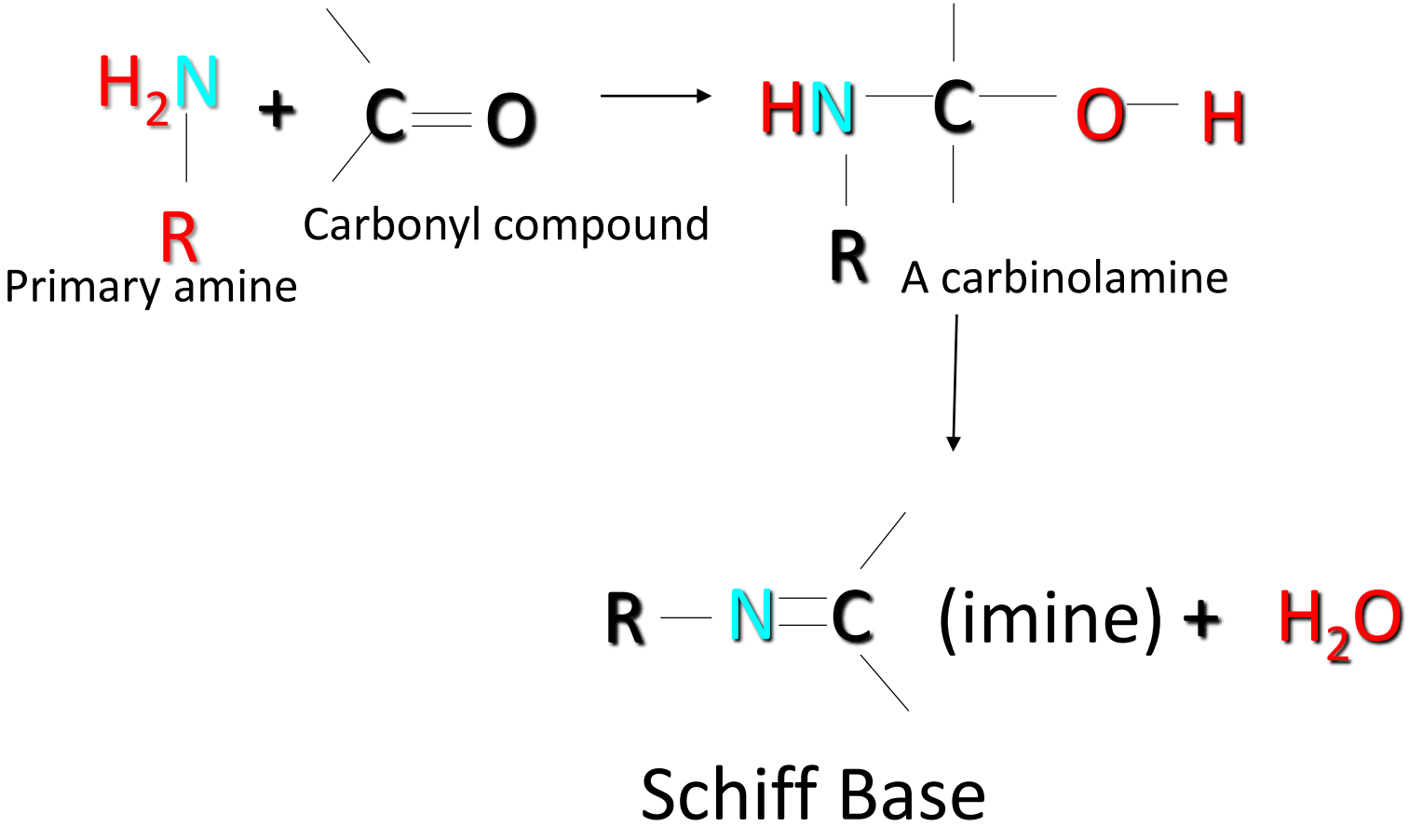
Schiff bases –named after Hugo Schiff

Formed by condensation of primary amine with aldehyde

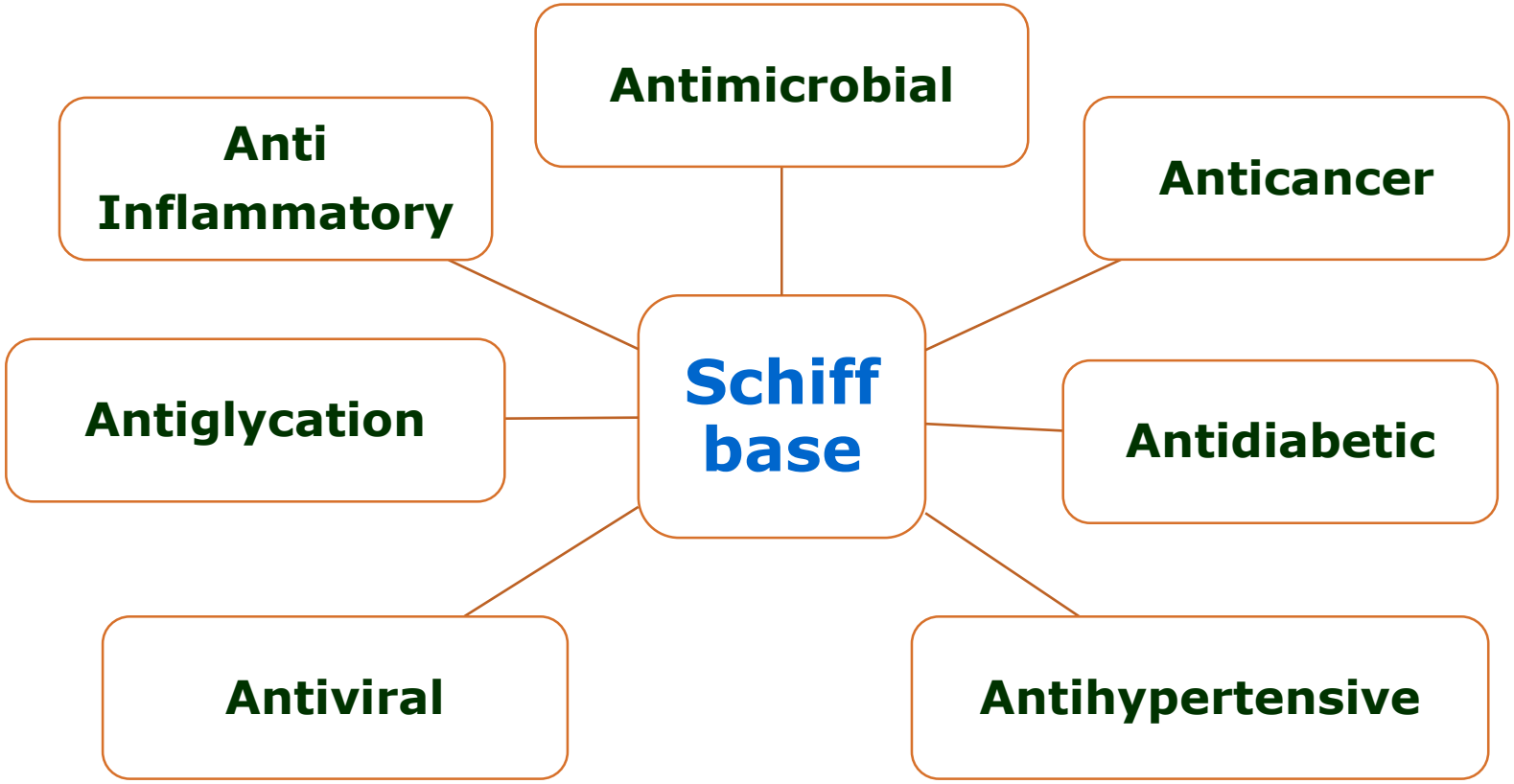
Also called azomethine (–C=N–)

Functional group-carbon-double bond with nitrogen connected to aryl or alkyl and not hydrogen

Imine (Schiff's Base) Formation

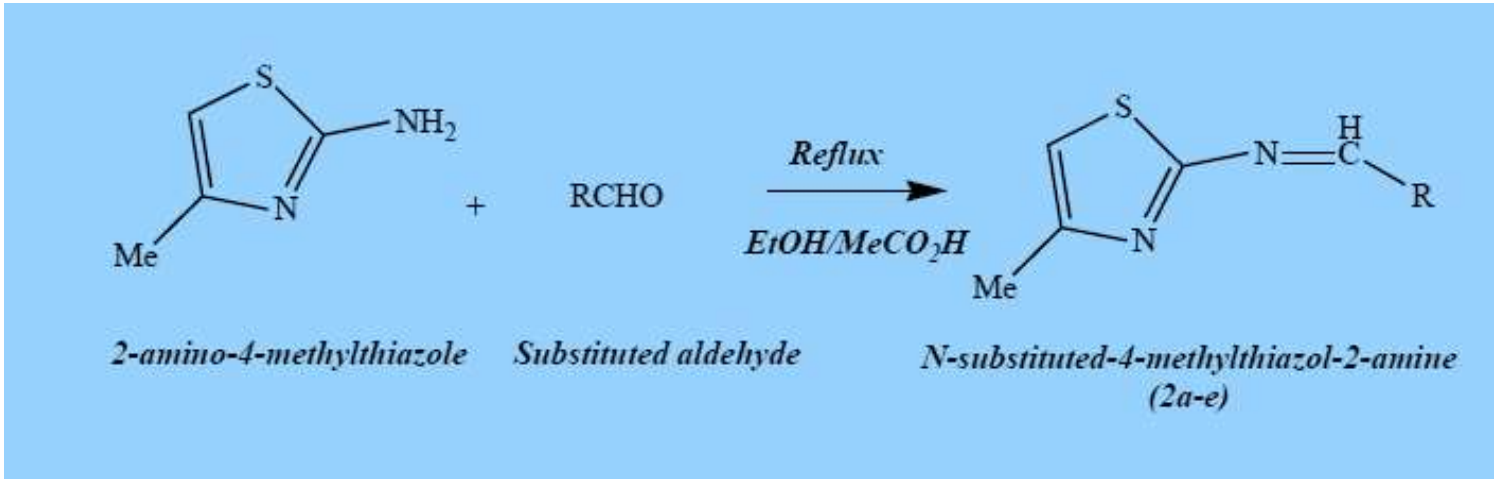


Schiff Bases: A Versatile Pharmacophore



Schiff bases-antimicrobial activity

M. Rudrapal *et al* synthesised Schiff bases of 2-aminothiazole and evaluated their antibacterial activity



Their results indicated that compounds having either aromatic substituted phenyl rings or aromatic heterocycles possess more activity.

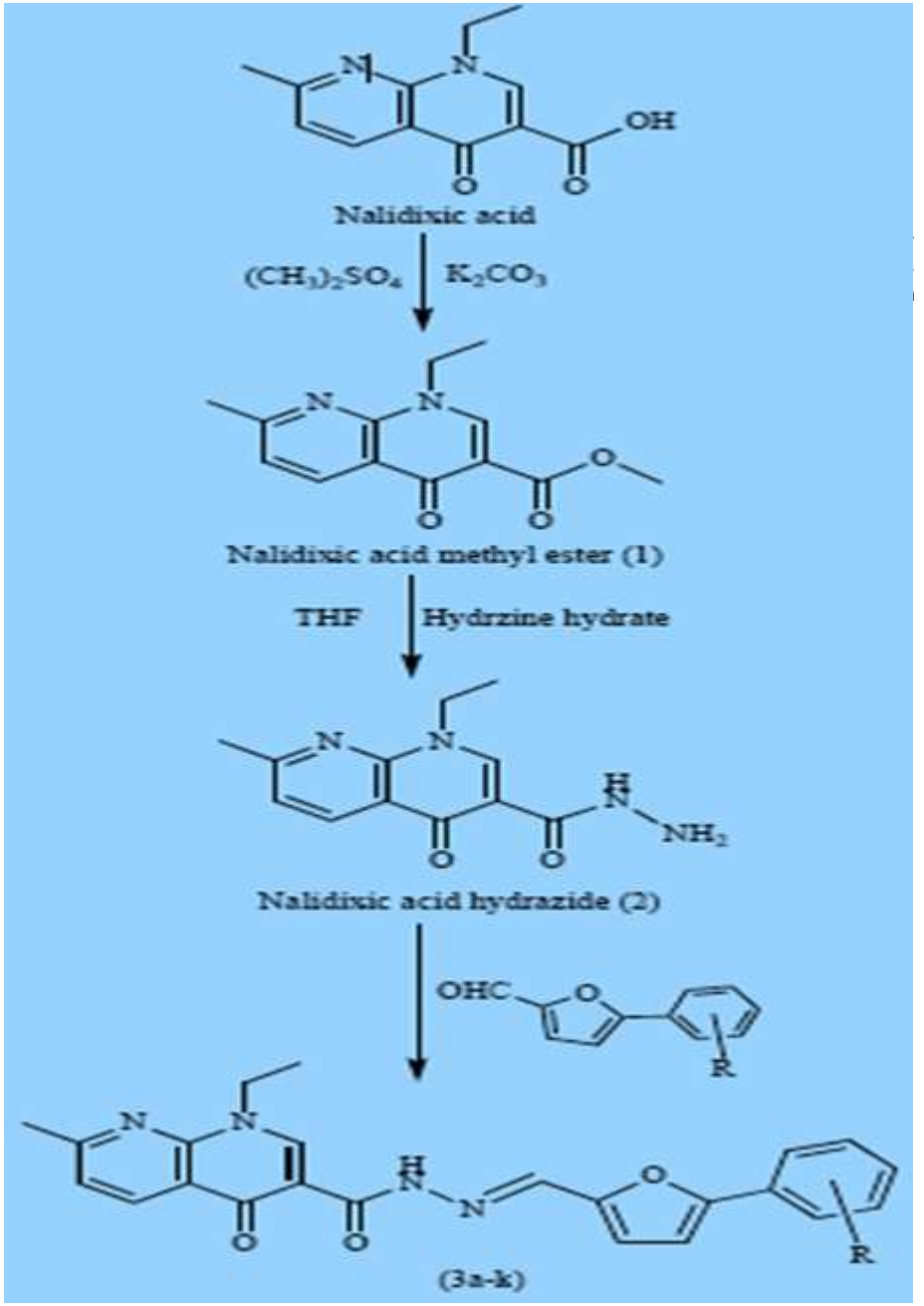
Rudrapal, M.; De, B,; Devanna, N. Synthesis and antimicrobial activity of some novel Schiff's bases of 4-methyl-2-thiazolamine. Antiinfect. Agents, 2012, 10, 72-74

Schiff bases of nalidixic acid hydrazide

Asif Husain *et al* synthesized 11 Schiff bases of nalidixic acid hydrazide.

Evaluated their antibacterial activity against four gram +ve *S.aureus*, *B. cereus*, *E. faecalis* and *S. epidermidis* and four gram -ve bacterial strains, *E. coli*, *S. typhi*, *S. dysenteriae* and *P. aeruginosa.*

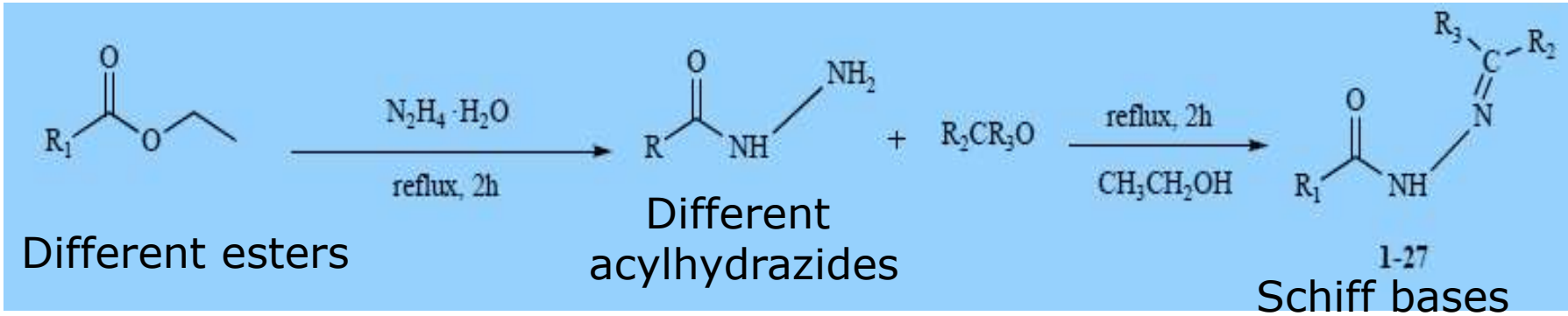
Results indicated that the substitution of aromatic ring at C-5 of furfuryl heterocyclic ring shows exciting antibacterial and anthelmintic actions.



Asif, H.; Munendra, M. V.; Versha, P.; Aftab, A.; Shah, A. K. Nalidixic acid Schiff Bases: Synthesis and biological evaluation. Lett. Drug Des. Discov. 2017, 14, 1-9

Schiff base-antioxidant activity

- Khalid Mohammed Khan reported the synthesis of acylhydrazide Schiff bases (1-27) from acylhydrazides which were synthesized from different esters.
- Compounds 1-27 have shown a varying degree of DPPH radical scavenging activity.



Khalid, M.K.; Muhammad, T.; Farzana, N.; Salman, S.; Sajjad, A.; Fazal, R.; Shahnaz, P.; Iqbal, C.M. Acylhydrazide Schiff bases: DPPH radical and superoxide anion scavengers. Med. Chem. 2012, 8, 705-710

Schiff bases-antioxidant activity

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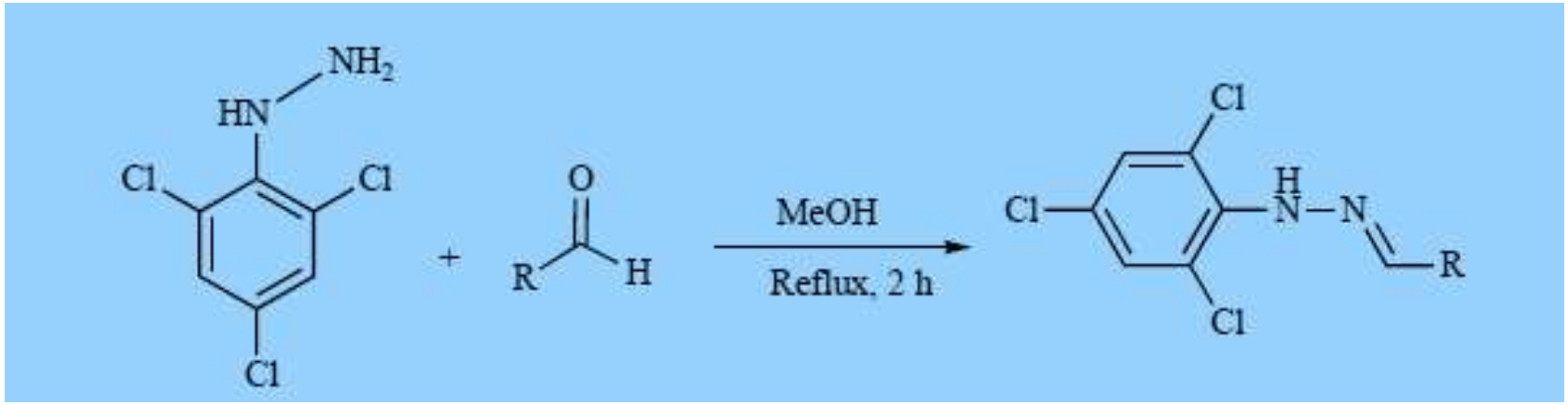
- Khalid Mohammed Khan et al reported antioxidant activity of 30 Schiff bases from 2,4,6-trichlorophenyl hydrazine by *in vitro* superoxide anion radical scavenger activity.



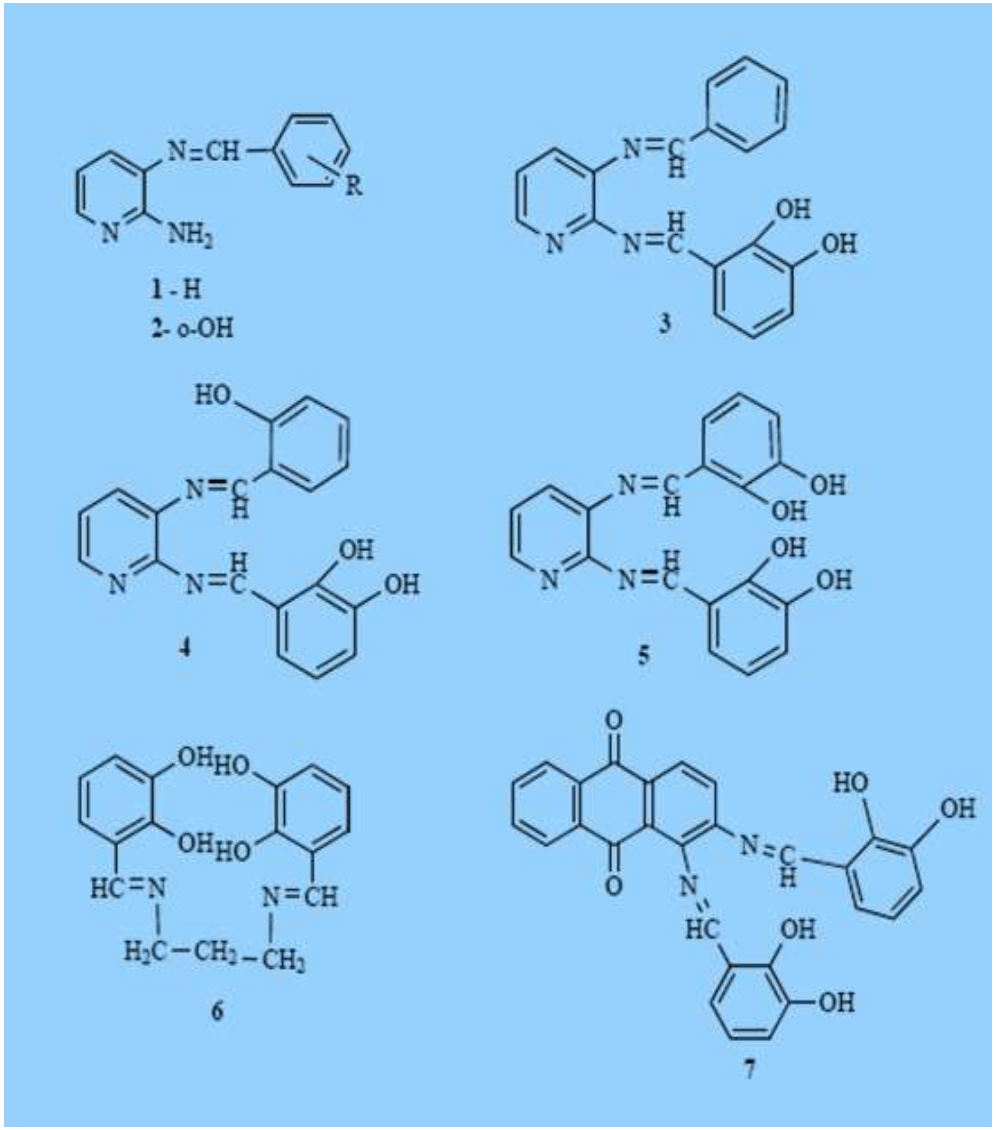
2,4,6-trichlorophenyl hydrazine

Schiff bases

Khalid, M.K.; Zarbad, S.; Viqar, U.A.; Momin, K.; Muhammad, T.; Fazal, R.; Sajjad, A.; Nida, A.; Shahnaz, P.; Iqbal C.M.; Wolfgang, V. Med. Chem. 2012, 8, 452-461

Schiff bases-antiglycation activity

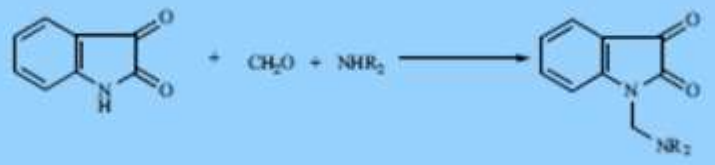
- Antiglycation property of mono, and bis Schiff bases were reported by Sabina et al.
- Mono condensed Schiff bases showed least activity
- Bis condensed schiff bases were more active.



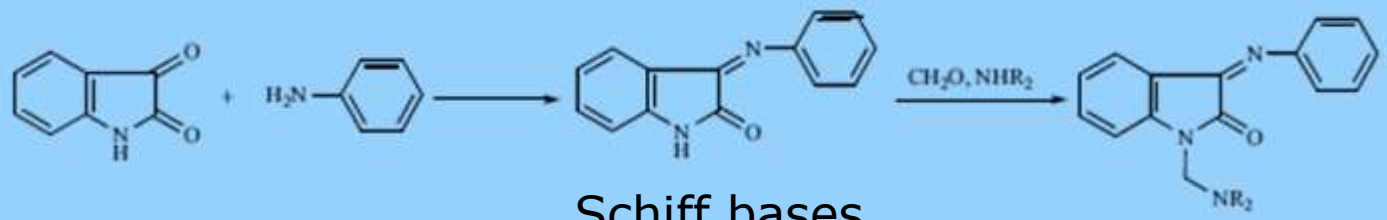
Sabina, J.L.; Minu, G.B.; Shabneez, M.; Mohamad, F.M.; Anwar, H.S. In vitro anti-glycation and anti-oxidant properties of synthesized Schiff bases. Med.Chem. 2012, 8, 409-414

Schiff bases-anticancer activity

Gang Chen et al synthesized Isatin Schiff bases which show some protection activity on the PC12 cells apoptosis induced by H_2O_2

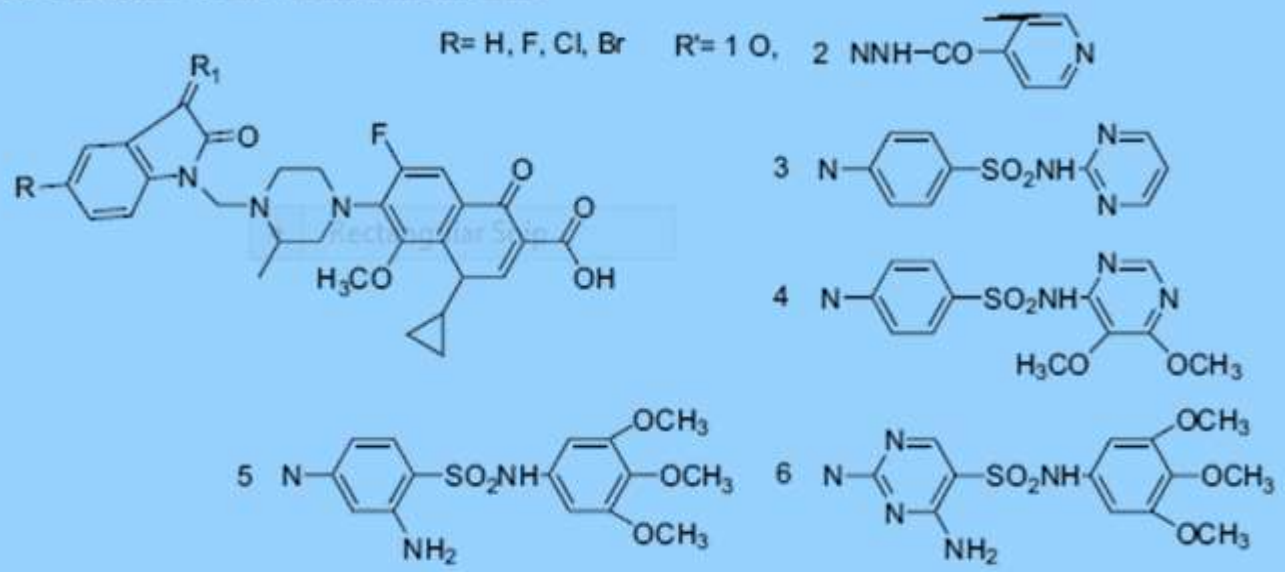


Scheme (1). The synthesis of isatin Mannich bases.



Schiff bases

Scheme (2). The synthesis of isatin Mannich and Schiff bases.

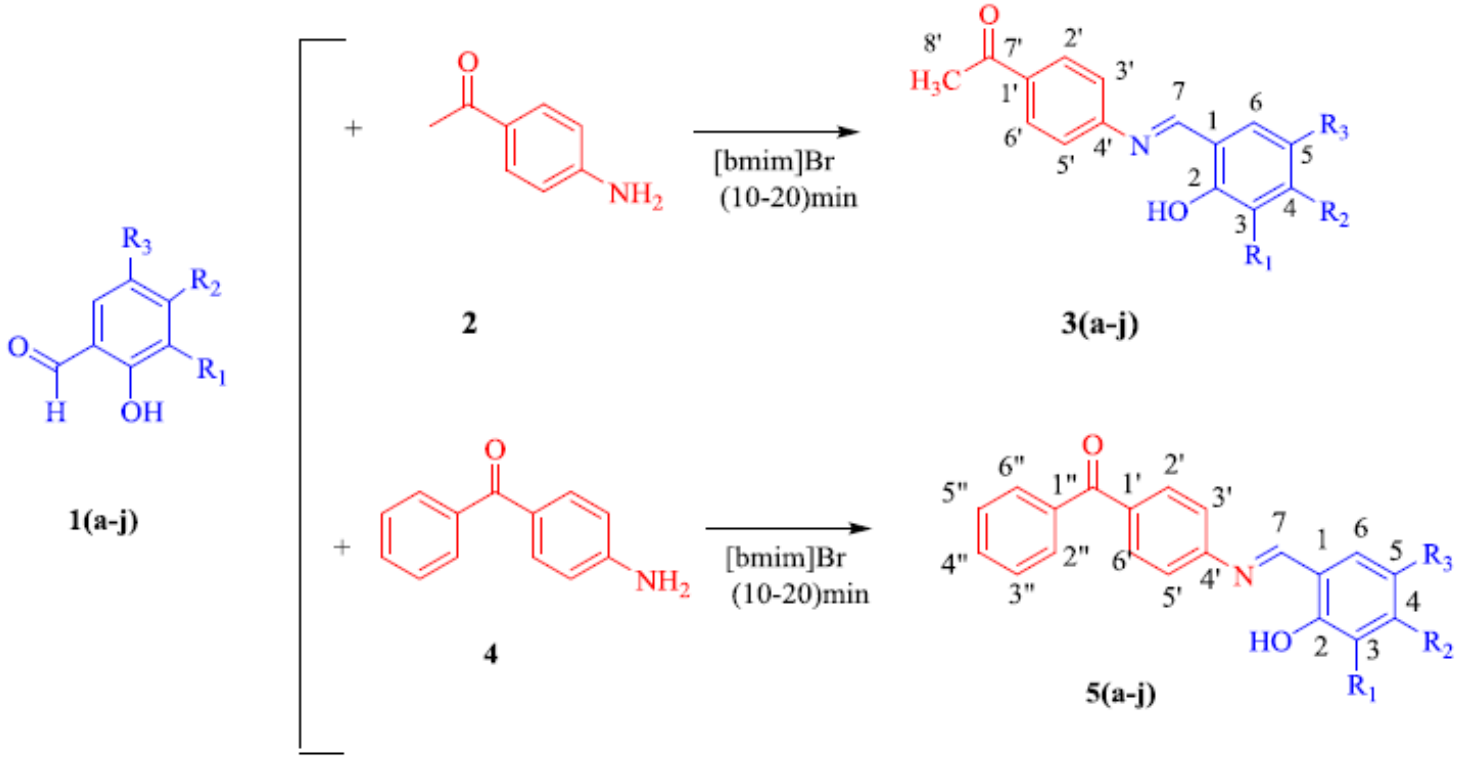


The structure of the isatin gatifloxacin Mannich bases.

Gang, C.; Yang, N.; Wei, Z.; Yanqiu, Z.; Yu, Z.; Xiaojiang, H.; Ye, W.; Shuzhen, M. Synthesis, neuro-protection and anti-cancer activities of simple isatin Mannich and Schiff bases. Lett. Drug Des. Discov. 2016, 13, 395-400

Schiff bases-choline esterase inhibitor activity

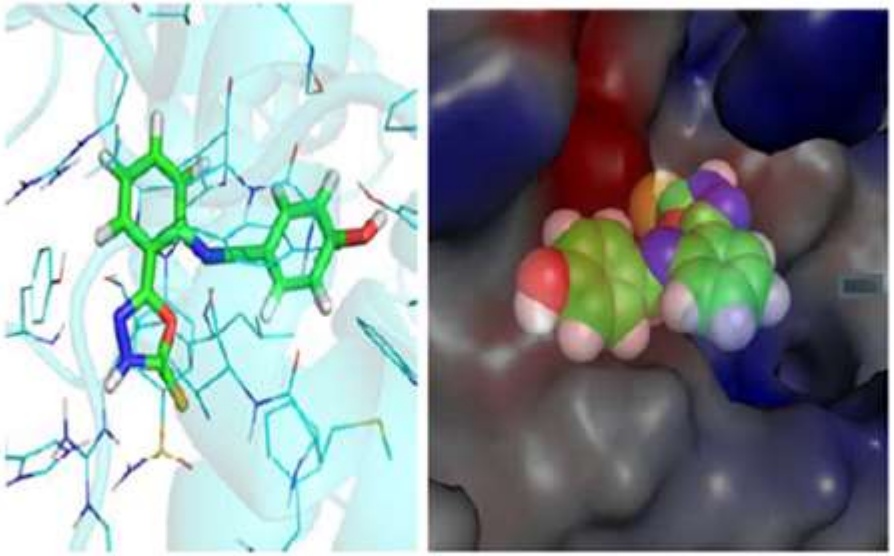
Basma M. Abd Razik et al reported benzaldehyde Schiff bases exhibited acetyl choline esterase inhibitory activity.



Basma, M.A.; Hasnah, O.; Mohammed, O.E.; Alireza, B.; Abdussalam, S.; Yalda, K.; Vikneswaran, M. Efficient synthesis and discovery of Schiff bases as potent cholinesterase inhibitors. Med. Chem. 2016, 12, 527-536

Schiff bases-antiinflammatory activity

Schiff bases of Oxadiazole derivatives emerged as potent COX 2 inhibitors

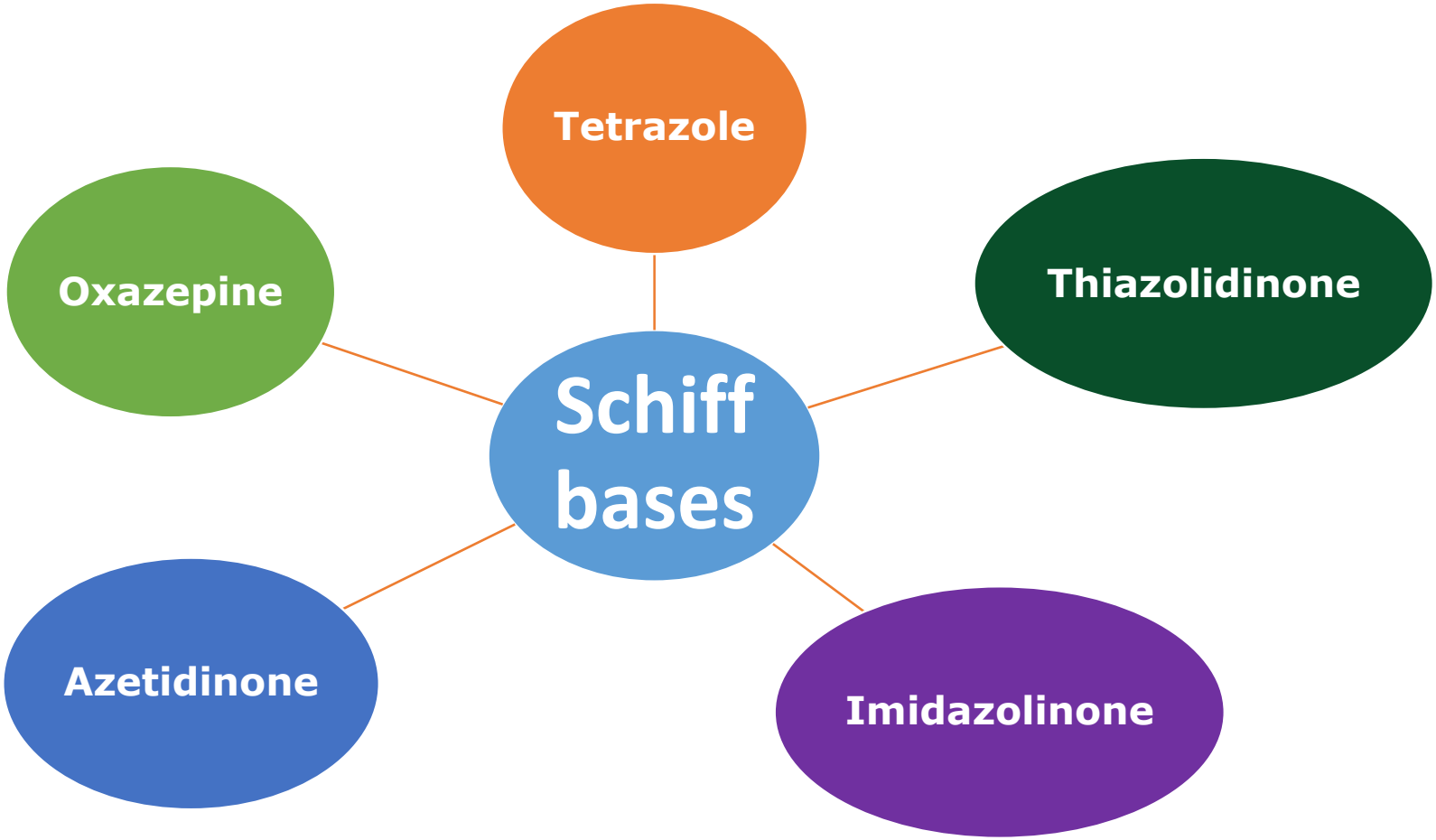


A close-up view of the docked ligand (compound 4i) in Cyclooxygenase-2 enzyme (PDB code 1CX2). a) Binding interactions of 4i (in sticks) with the neighboring protein residues (in lines) b) The fit of the compounds 4i in the active site. Color coding: Ligand carbon in green, protein carbon in cyan, nitrogen in blue, oxygen in red, sulfur in light brown, hydrogen in white.

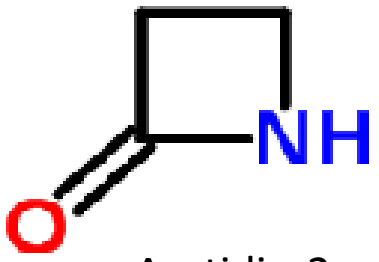
Biswa, M.S.; Subas, C.D.; Ravi K.; Jnyanaranjan, P.; Pathik, S.B. Design, green synthesis, and anti-Inflammatory activity of Schiff base of 1,3,4-oxadiazole analogues. Lett. Drug Des. Discov. 2014, 11, 82-89

Medicinally important heterocycles derived from Schiff bases

Various biologically active heterocycles synthesized from Schiff base



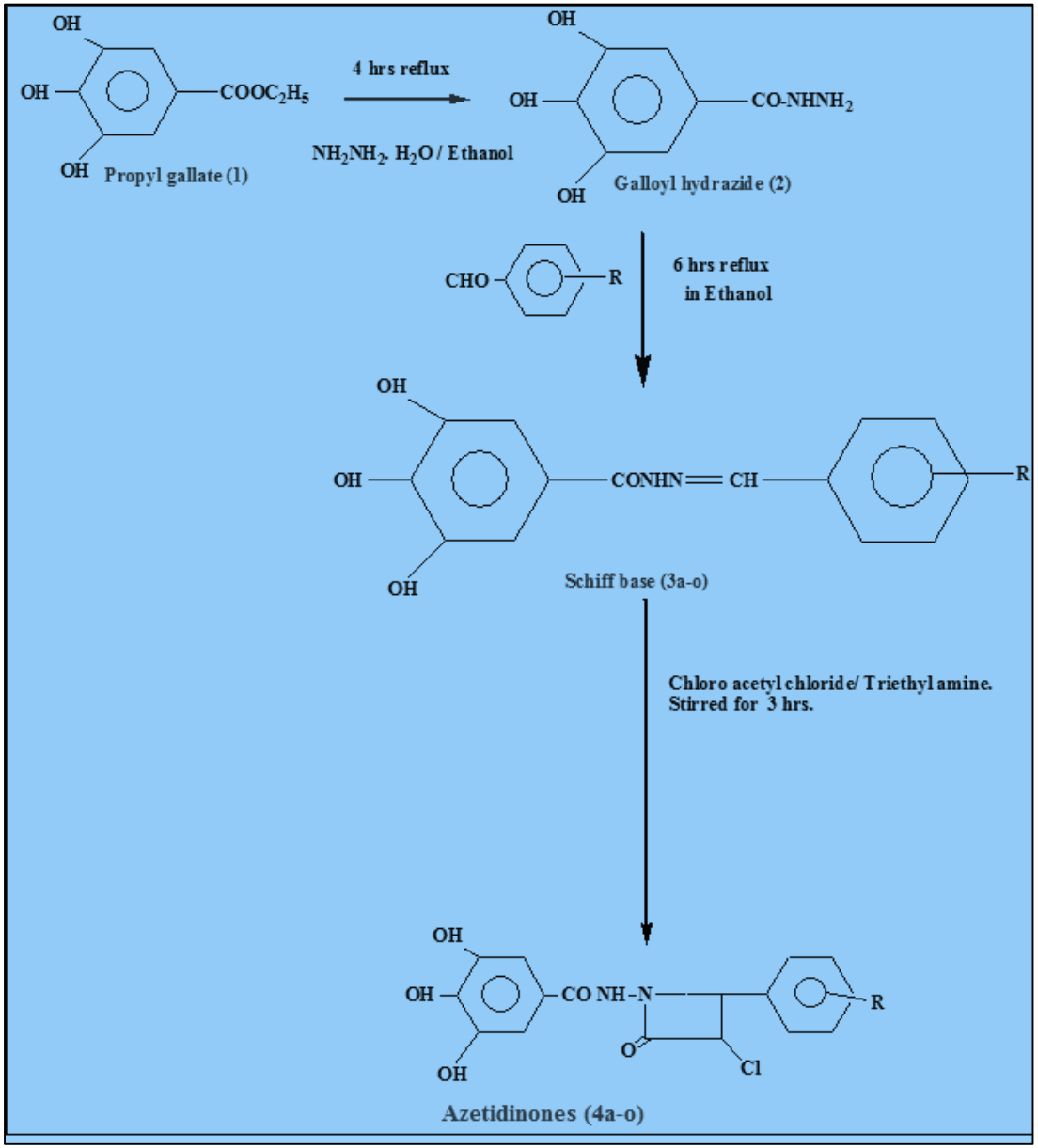
Azetidinones



Azetidin-2-one

- Also called β-lactum
- Present in antibiotics like penicillin, cephalosporins, carbapenams and monobactums
- Synthesied from schiff bases

Synthesis of azetidinone from Schiff base



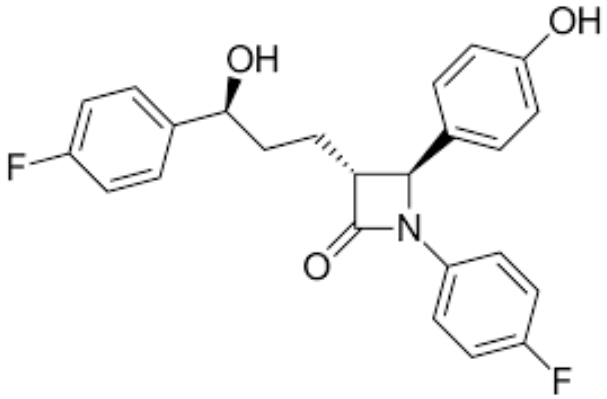
Bhavnesh, N.; Desai, K.R. Novel approach for the rapid and efficient synthesis of heterocyclic Schiff bases and azetidinones. Ind. J. Chem. 2006, 267-271.

Biological activity of azetidinones

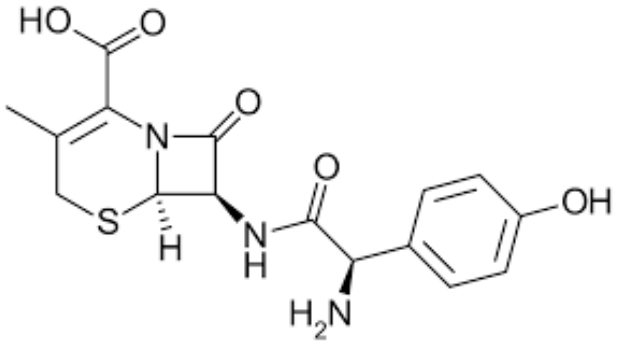
The 2-azetidinone derivatives have been reported to possess a wide range of biological activities like

- Antibacterial
- Antifungal
- Anti-inflammatory
- Analgesic
- Anticonvulsant
- Anticancer and
- Antitubercular

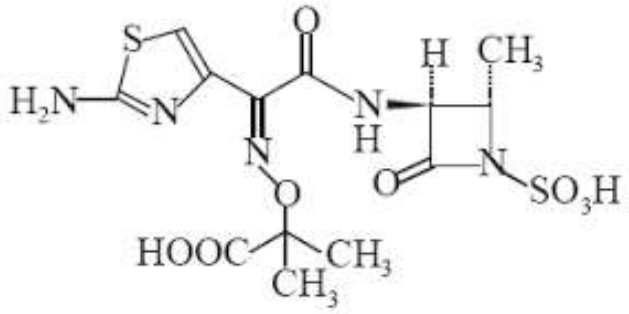
Drugs containing azetidinone



Ezetimibe- reduce intestinal absorption of cholesterol

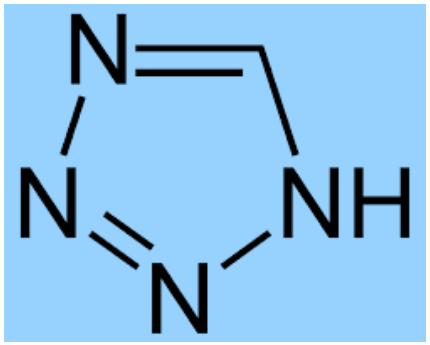


Cefadroxil-antibiotic



Aztreonam-antibiotic

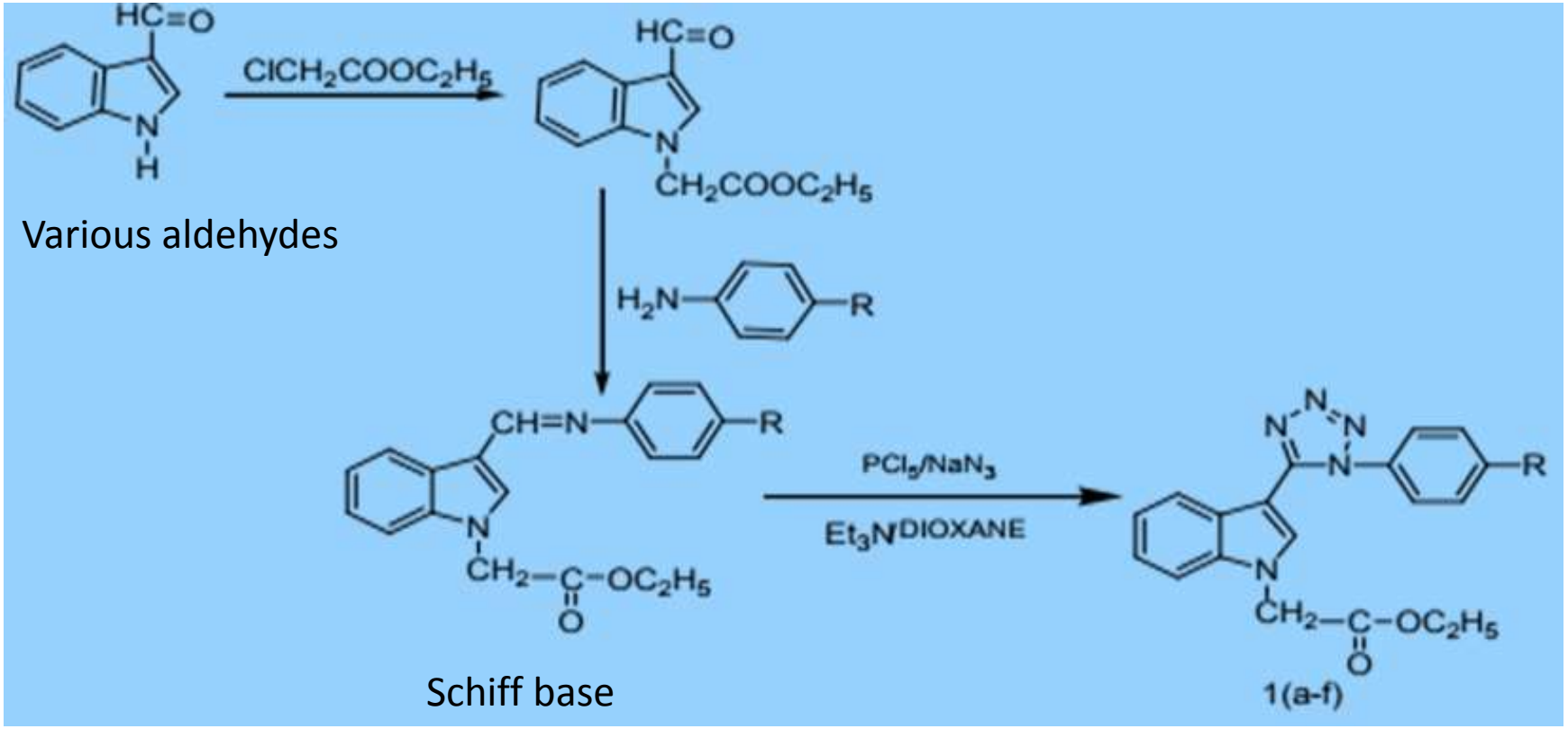
Tetrazole



- **Tetrazoles** are a class of synthetic organic heterocyclic compound, consisting of a 5-member ring of four nitrogen atoms and one carbon atom.

- The simplest is tetrazole itself, CH_2N_4.

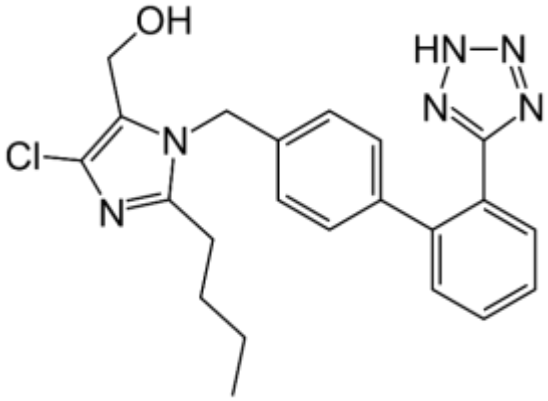
Synthesis of tetrazole from Schiff base



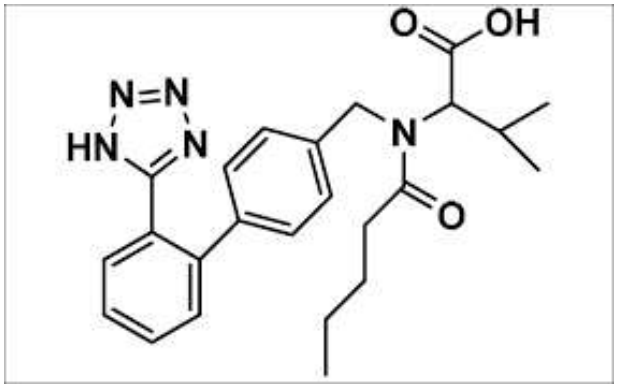
Khitam, T.; Al-Sultani, A. Synthesis, identification and evaluation the biological activity for some new heterocyclic compounds derived from Schiff bases. J. Pharm. Bio. Sci. 2017, 12, 39-47

Drugs with tetrazole

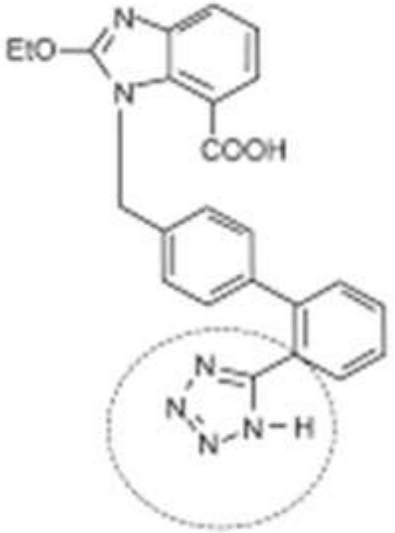
Angiotensin receptor blockers



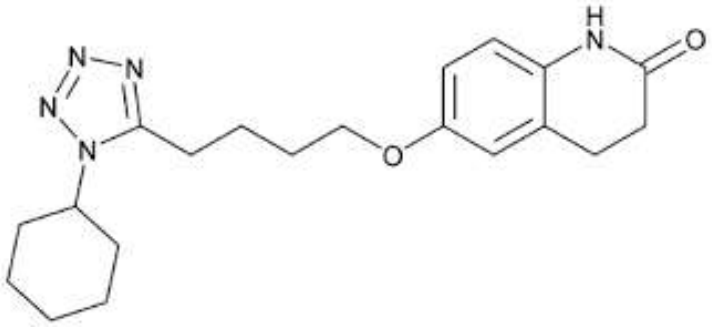
Lorsatan



Valsartan

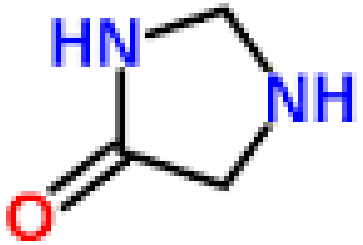


Candesartan



Cilostazol -antiplatelet drug and a vasodilator

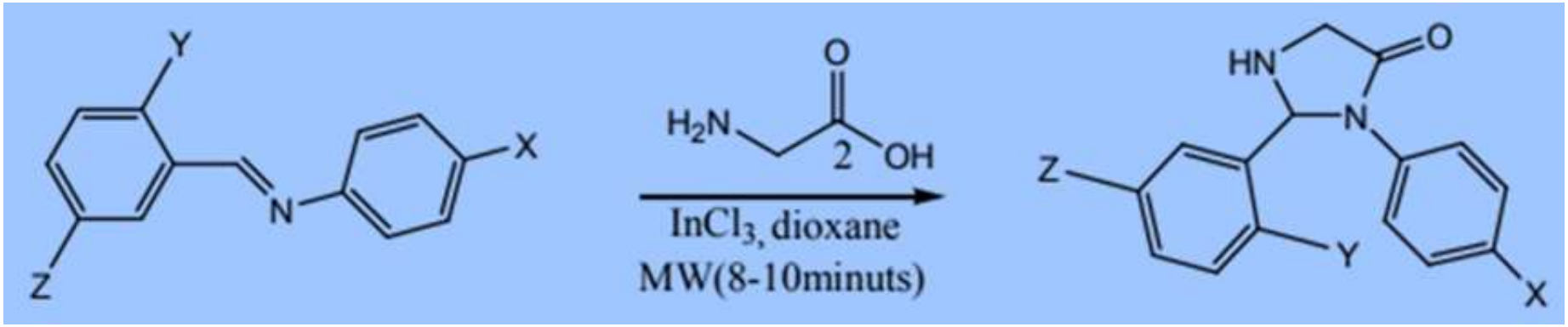
Imidazolidinone



The 4-imidazolidinones are cyclic amides

- Antifungal
- Antibacterial
- Anticancer
- Anti-inflammatory and
- Calcium-channel-blocker

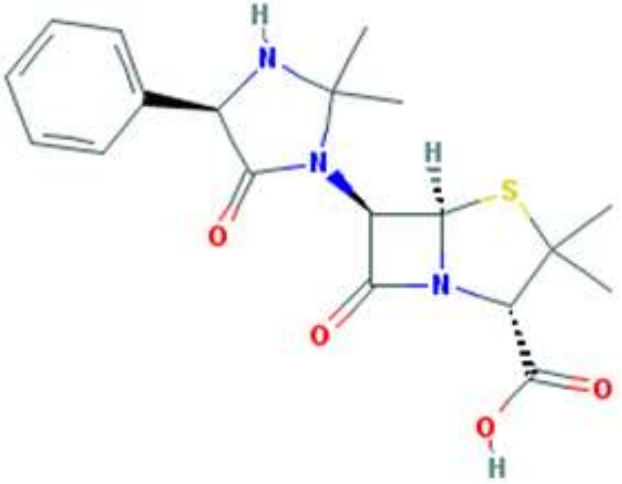
Synthesis of imidazolidinones from Schiff base



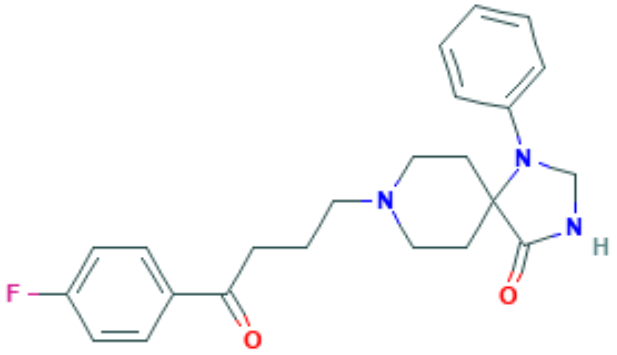
Schiff base

Amit, V.; Shailendra, K.S.,, "4-imidazolidinone – A Biologically Active scaffold," Eur. J. Med. Chem. 2008, 43, 897-905.

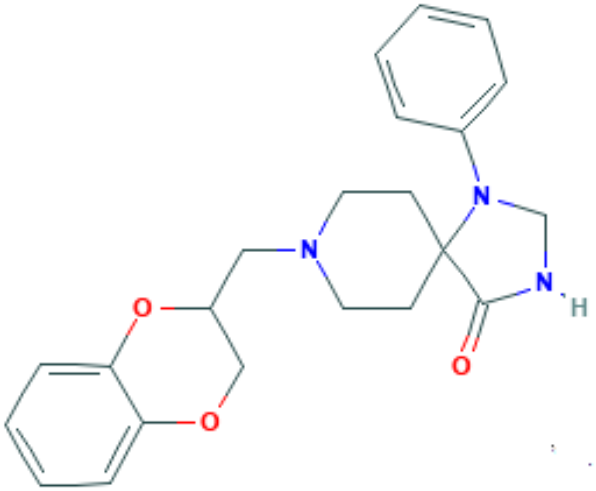
Drugs containing imidazolinones



Hetacillin- beta-lactam antibiotic



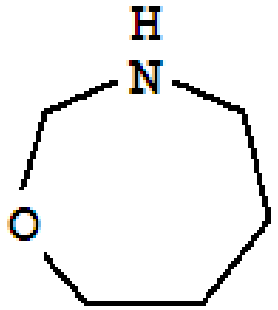
Spiperone-antipsychotic



Spiroxatrine-dopamine antagonist

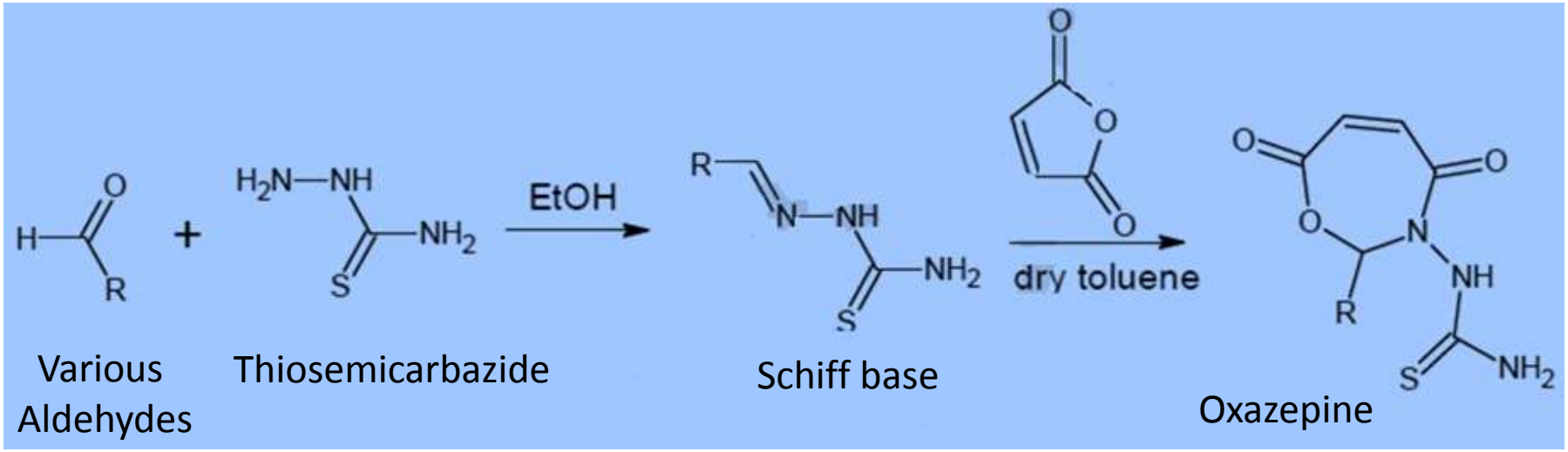
Oxazepine

- Hypnotic
- Muscle relaxant
- Anti inflammatory
- Antiepileptic
- Antibacterial and
- Antifungal



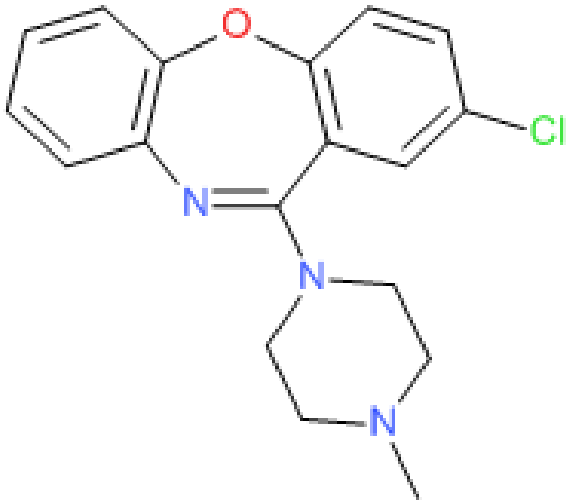
1,3-Oxazepine

Synthesis of oxazepine from Schiff base

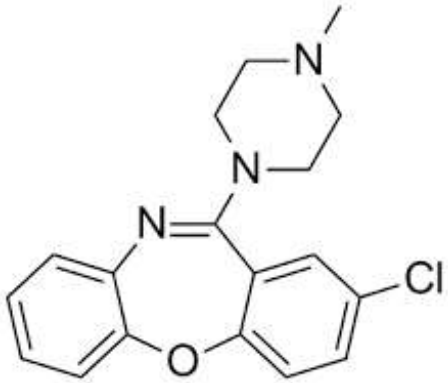


Hamak, K.F.; Eissa, H.H. Synthesis, characterization, biological evaluation and anti corrosion activity of some oxazepine derivatives from Schiff bases. Org. Chem. Curr. Res. 2013, 2, 2-7

Drugs containing oxazepine



Loxapine
Symptoms of schizophrenia



Amoxapine
Tricyclic antidepressant

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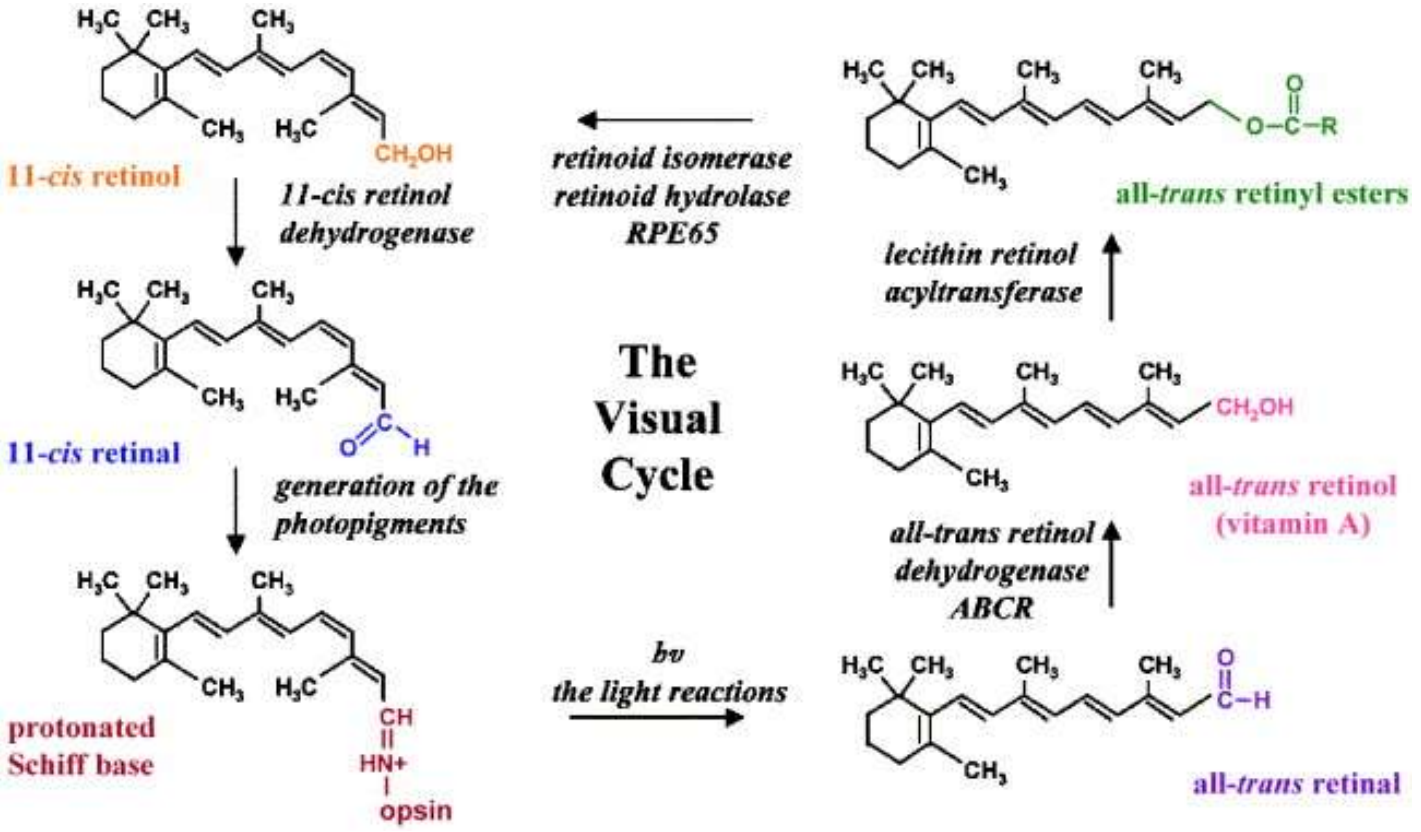
Biological Significance of Schiff Bases

Biological Significance

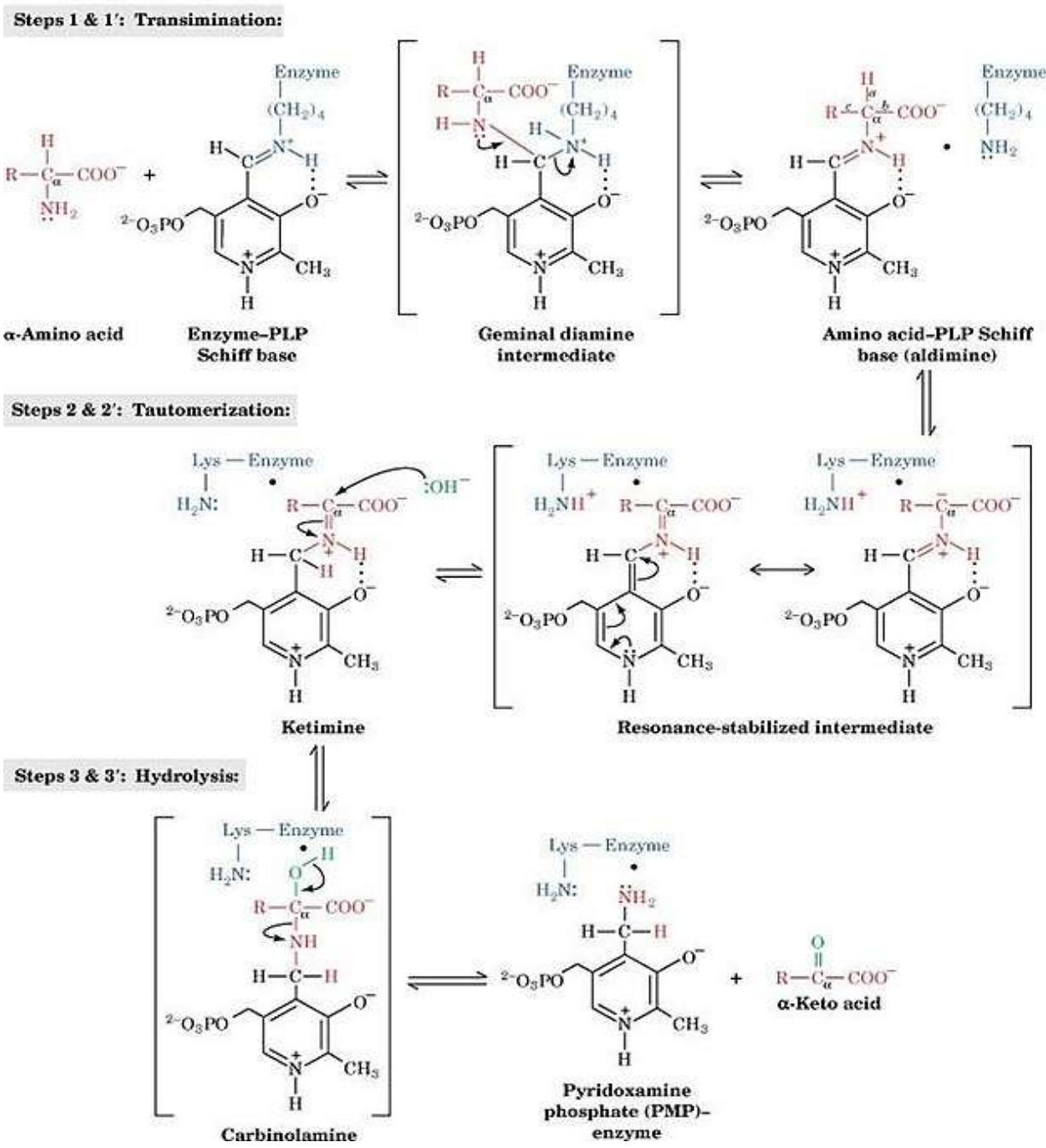
Aldehyde group of 11-cis-retinal and amino group of the protein (opsin).



Debra, A.T.; Andreas, G. Vitamin A metabolism in the retinal pigment epithelium: genes, mutations, and diseases. Prog. Retin. Eye Res. 2003, 22, 683-703.

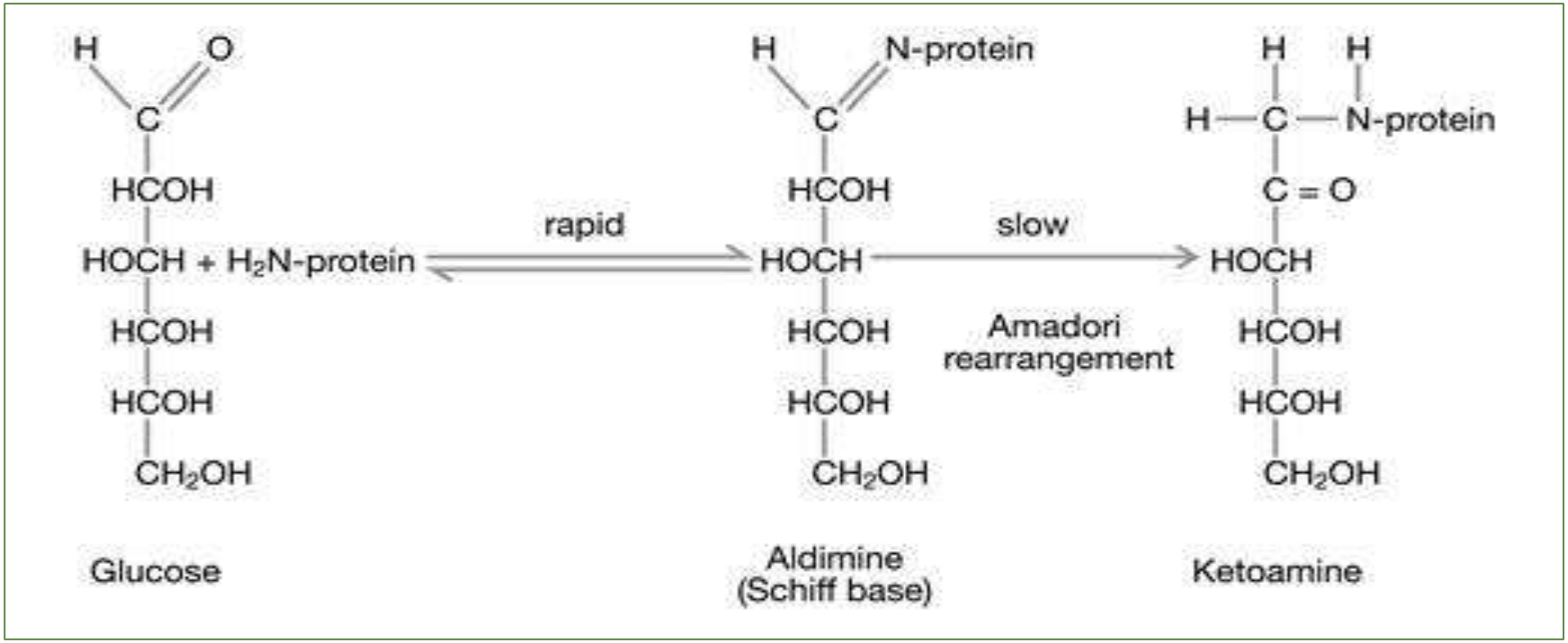
Biological Significance

Schiff base plays an important role in transamination.



Biological Significance

Glycation is the result of the covalent bonding of a sugar molecule, such as glucose or fructose, to a protein or lipid molecule, without the controlling action of an enzyme



McPherson, J.D.; Shilton, B.H.; Walton, D.J. Role of fructose in glycation and cross-linking of proteins. *Biochemistry*. 1988, **27,** 1901–1907.

Related Publications

Malaysian Journal of Science **28** (2): 197– 203 (2009)

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Synthesis and Biological Evaluation of Some Novel Nicotinic Acid Derivatives

N. Ramalakshmi[1*], L. Aruloly[1] S. Arunkumar[2], K. Ilango[2], and A. Puratchikody[3]

[1]Department of Pharmaceutical Chemistry, C. L .Baid Metha College of Pharmacy, Thoraipakkam, Chennai - 600 096, Tamilnadu, India.
[2]Department of Pharmaceutical Chemistry, S. R. M. College of Pharmacy, S. R. M. university, Kattangulathur – 603 203, Tamilnadu, India.
[3]Department of Pharmaceutical Engineering and Technology, Anna university, Trichirapalli – 620 024, Tamilnadu, India. *ramalakshminatarajan@yahoo.co.in (corresponding author)
Received in 7th July 2008, accepted in revised form 9th June 2009.

ABSTRACT In the present study, six compounds of thiazolidinone derivatives of nicotinic acid were synthesized by reacting Schiff bases with thioglycolic acid and zinc chloride in ethanol. The Schiff bases were synthesized by treating various aromatic aldehydes with nicotinic acid hydrazide. Reaction between nicotinic acid and phosphorous pentachloride gives nicotinoyl chloride. Further nicotinoyl chloride is converted to nicotinic acid hydrazide by the action of hydrazine hydrate. Structure of these products has been established by IR, ^{1}HNMR and Mass spectral data. The *in vitro* antibacterial and antifungal activities of the compounds were evaluated by paper disc diffusion method. The Minimum Inhibitory Concentration (MIC) of the compounds was also determined by agar steak dilution method. Significant antimicrobial activities were observed for some compounds of the series. Compounds were also screened for their anti-inflammatory and analgesic activity. Some of them showed comparable activity as that of the standard drug used.

(Keywords: Thiazolidinone, antimicrobial, analgesic, anti-inflammatory)

Related Publications

Tropical Journal of Pharmaceutical Research April 2011; 10 (2): 219-229

Available online at http://www.tjpr.org

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Research Article

Synthesis, Antimicrobial and Antitubercular Activities of Some Novel Trihydroxy Benzamido Azetidin-2-one Derivatives

K Ilango* and S Arunkumar

Department of Pharmaceutical Chemistry, College of Pharmacy, SRM University, Kattankulthur - 603203, Tamilnadu, India

Abstract

Purpose: *To synthesize and characterize novel trihydroxy benzamido azetidin-2-one derivatives and screen them for antimicrobial and antitubercular activities.*
Methods: *A series of novel 4-aryl-3-chloro-N-(3,4,5-trihydroxy benzamido)-2-azetidinones,* ***3a-o,*** *were synthesized by reacting various Schiff bases of galloyl hydrazide,* ***2a-o,*** *with chloroacetyl chloride in the presence of dioxan and triethylamine. Schiff bases of galloyl hydrazide,* ***2a-o,*** *were synthesized from galloyl hydrazide. The newly synthesized compounds were characterized by infrared spectroscopy (IR), mass spectroscopy (MS) and proton nuclear magnetic spectroscopy (^{1}H NMR) and elemental analysis; they were also screened for in vitro antibacterial, antifungal and antitubercular activities. Ciprofloxacin and ketoconazole were used as reference standards for antibacterial and antifungal activities, respectively, while isoniazid was used as reference standard for antitubercular activity.*
Results: *Compounds* ***3f, 3g*** *and* ***3o*** *with chlorophenyl group and compound* ***3k*** *with 4-dimethyl amino phenyl group exhibited good antimicrobial activity. Also, compounds* ***3f, 3g, 3k*** *and* ***3o*** *showed antitubercular activity with minimum inhibitory concentration (MIC) values equivalent to the standard drug (isoniazid). MIC values of* ***3f, 3g, 3k*** *and* ***3o*** *were 0.76, 0.57.0.62 and 0.83 µg/ml, respectively, while the MIC of isoniazid was 0.56.*
Conclusion: *We report the successful synthesis, spectral characterization, as well as in vitro antimicrobial and antitubercular evaluation of a series of novel trihydroxy benzamido azetidin-2-one derivatives. The work shows the emergence of new antimicrobial and antitubercular compounds.*

Keywords*: Azetidinone, Schiff bases, Synthesis, Antimicrobial activity, Antitubercular activity.*

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SYNTHESIS AND ANTITUBERCULAR ACTIVITY OF NOVEL 2-ARYL N-(3,4,5-TRIHYDROXY BENZAMIDO)-4-THIAZOLIDINONE DERIVATIVES

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ABSTRACT

A series of novel 2-Aryl -N-(3,4,5-trihydroxy benzamido)-4-thiazolidinone derivatives (3a-f) were synthesized by reacting various Schiff bases of galloyl hydrazide 2(a-f) with thioglycollic acid in presence of dioxan. The newly synthesized compounds were characterized by IR, MS, ^{1}H NMR spectrum and elemental analysis. The compounds were evaluated for antitubercular activity against *Mycobacterium tuberculosis* H37Rv by Microplate Alamar Blue Assay (MABA) method. The experimental results revealed that compound 3f exhibited promising antitubercular activity.

Key words: Gallic acid; Thiazolidinone; Antitubercular.

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