"Synthesis and Antifungal Activities of Thiazolidinone Derivatives"

A MINOR RESEARCH PROJECT CARRIED OUT UNDER THE FINANCIAL ASSISTANCE OF UNIVERSITY GRANTS COMMISSION,WRO,PUNE.

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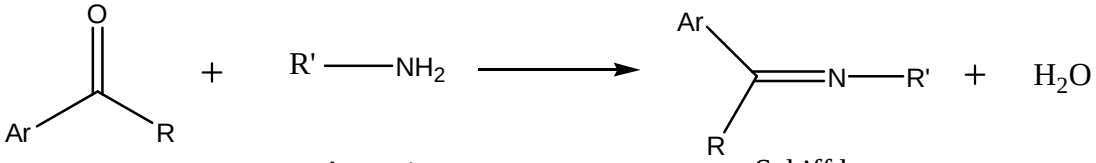
Executive Summary of the Project

INTRODUCTION AND ORIGIN OF THE RESEARCH PROBLEM:

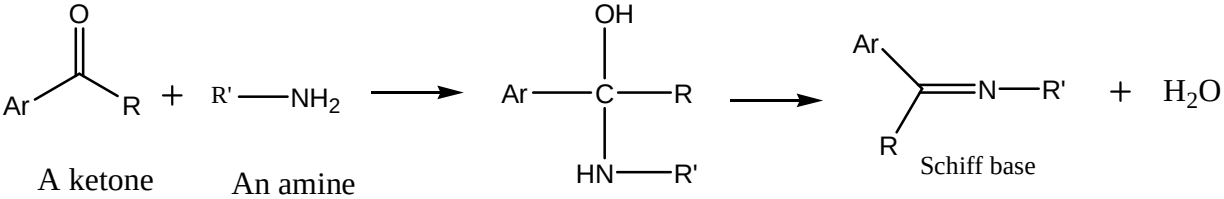
Introduction:

A compound formed by the reaction between an aromatic amine and an aldehyde or ketone is known as Schiff base. Schiff bases were first discovered by Hugo Schiff[1] and hence they are referred as Schiff bases. In general a Schiff base can be prepared as follows.



A ketone An amine Schiff base

A number of reviews of the Schiff bases have been published[2].The kinetics of formation of Schiff bases in aqueous solution have been extensively studied[3-4]. It has been formed that the reaction is of second order. This reaction proceeds by a two-step mechanism involving a carbinolamine intermediate.

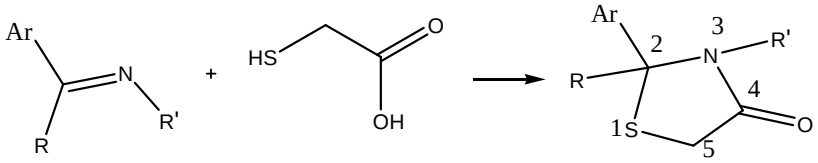


A ketone An amine Schiff base

Some Schiff bases have been noted to exhibit photochromism and thermochromism and most of these are electrochemistry[5], Fluorescence[6] and luminescence[7], properties of some Schiff bases have also been studied.

Schiff bases have been investigated by FTIR [8] and ^{1}H NMR[9] spectra.

Many types of reaction like hydrolysis, reduction oxidations, addition, substitution and metal complex formation have been studied with Schiff bases.



Schiff base Thioglycolic acid Thiazolidin-4-one

As per the proposed work in present minor research project, first the literature survey on the proposed topic is completed in connection to synthesis of the concern substances. During the project period I have visited various libraries and collected different research references, publication done by various researchers.

Origin of the Research Problem:

Schiff bases were first synthesized by H. Schiff[1] and they are useful as intermediates[2] in many reactions. It has varied applications in the field of synthesis[2], medicine[10], catalysis[11-12], polymers[13], druq-interrnediates[14a,b], dyes[15] and analysis[16]. Many types of reaction like complexation[17], reduction[18] and oxidations[19] have been studied with Schiff bases. The Schiff bases also plays important role in many biochemical reactions[20-21]. Schiff bases also exhibits antibacterial[22], antifungal[23], drug-bioactivity[24] and anticancer[25] activity.

Schiff bases have been further used for the synthesis of varied heterocycles such as azetidone and Thiazolidinones[26-28]. Thiazolidinone are well known for various pharmaceutical properties[29-30], antimicrobial[31], antidiabetics[32], antifungal[33], anti-TB[34], anti HIV[35], analgesic, anti-inflarnrnatory[36] and ulcerogenic activity[37]. Looking to this we propose to study Schiff bases and their heterocyclic compounds i.e thiazolidinones, which may be used for developing pharmacologically important molecules viz. 4-thiazolidinones[26-28].

OBJECTIVES OF THE STUDY

1. 1. To up-date the literature survey pertaining to study the synthesis of Schiff bases by using Ketone with aniline and substituted anilines.
2. To synthesize and characterize the Schiff bases from the 5-Chloro-2-hydroxy-4-methyl acetophenone with Aniline, 3,4-Dimethyl aniline, 2,4,5-Trichloro-aniline, 4-Methyl-2-nitro-aniline, 4-Methoxy-2-nitro-aniline, 2,3-Dichloro-aniline and 4-Chloro-2-nitro-aniline.
3. To study the purification and characterization of the Schiff bases by using elemental analysis, physical constant, TLC and colour with varied spectroscopic methods such as UV-Vis, FTIR.
4. To determine the Antifungal activities of Schiff base derivatives.
5. To synthesize the Thiazolidinone derivatives from the prepared Schiff bases.
6. To determine the Antifungal activities of Thiazolidinone derivatives.

METHODOLOGY:

PREPARATION OF COMPOUNDS

In the First year the synthesis of the Schiff base from 5-Chloro-2-hydroxy-4-methyl acetophenone to its anil and the other derivatives were completed alongwith their purification (by column chromatography) and were analyzed by (analytical - elemental, TLC, spectral - UV and FTIR).

Structures of these compounds were confirmed based on the analytical data.

These Schiff bases were screened for their antifungal activities on four strains of fungi *S. cerevisiae, C. albicans, Alternaria alternata, Aspergillus niger* and *Penicillum notatum* using disk diffusion method.

Antifungal Activity of Synthesized Schiff Bases

1) Among the Schiff bases studied for the MIC for fungal strain, ***S. cerveace***, of the Schiff base, M-IV was found more.
2) Among the fungal strain for ***P. nonatum*** Schiff bases has shown negative response.
3)

ACHIEVEMENTS FROM THE PROJECT:-

1. The literature on the synthesis of Schiff bases by using Ketone with aniline and substituted anilines is updated.
2. Synthesize and characterize the Schiff bases from the 5-Chloro-2-hydroxy-4-methyl acetophenone with Aniline, 3,4-Dimethyl aniline, 2,4,5-Trichloro-aniline, 4-Methyl-2-nitro-aniline, 4-Methoxy-2-nitro-aniline, 2,3-Dichloro-aniline and 4-Chloro-2-nitro-aniline.
3. Schiff bases were purified and characterized by elemental analysis, physical constant, TLC and colour with varied spectroscopic methods such as UV-Vis, FTIR.
4. The Antifungal activities of Schiff base derivatives were determined.
5. The Thiazolidinone derivatives were synthesized from the synthesized Schiff bases.
6. The antifungal activities of Thiazolidinone derivatives were determined.
7. Based on the observed data of antifungal properties, some comments about the synthesized organic compounds are made.

CONTRIBUTION TO THE SOCIETY:-

1. Society will get the work done based on this topic and may be helpful in technical aspects either the one way or other.
2. A drug designer/ biochemist or a medicinal chemist may take the help of the results of antifungal of study in the present work or the suggested the strains which may be active.
3. Same study may be used by chemists to develop some newer compounds of future use which will serve the society in their development.

NO. OF PUBLICATIONS OUT OF THE PROJECT:-Two Published

1) C. J. Patil and C. A. Nehete, Studies on Synthesis of Aromatic Schiff Bases. Part-IV. Synthesis and Characterization of Ketimines from 5-Chloro-2-hydroxy-4-methyl acetophenone with substituted anilines, (Der. Chemica Sinica, commun.-2015)
2) C. A. Nehete and C. J. Patil, Synthesis of Thiazolidinone from Schiff Bases . part-II Synthesis of Thiazolidinones of Schiff Bases derived from 5-Chloro-2-hydroxy-4-methyl acetophenone. (commun.-2015).

Conclusions:

This study can be extended, for the study of similar varied schiff intermediates, thiazolidinones and their antifungal actives against strain of fungi *S. cerevisiae, C. albicans, Alternaria alternata, Aspergillus niger* and *Penicillum notatum* using disk diffusion method.

Antifungal Activity of Synthesized Schiff Bases

4) Among the Schiff bases studied for the MIC for fungal strain, ***S. cerveace***, of the Schiff base, M-IV was found more.
5) Among the fungal strain for ***P. nonatum*** Schiff bases has shown negative response.
6) MIC activity for the *C. albicans* were comparatively lower than *S. cerveace.*
7) Synthesized Schiff bases were shown very weak response in case of ***A. alternate.***

In the Second year the synthesis of the thiazolidinone from Schiff base were synthesized and their antifungal activities were screened.

Antifungal Activity of Synthesized Thiazolidinones:

1) The Thiazolidinone, MT-I is not active for all the studied strains of the fungus.
2) The Thiazolidinone, MT-II is active for the *Aspergillus niger* (*1000* µg/ml).
3) The Thiazolidinone, MT-III is active for the *Saccharomyce cerevisiae and Aspergillus niger.* (500 and *1000* µg/ml).
4) The Thiazolidinone, MT-IV is active for the *Candida albicans (*500 and *1000* µg/ml) *and Aspergillus niger.* (500 µg/ml).
5) The Thiazolidinone, MT-V is active for the *Saccharomyce cerevisiae*(500 and *1000* µg/ml) *and Candida albicans (*500 µg/ml).
6) The Thiazolidinone, MT-VI, MT-VII is not active for all the studied strains of the fungus.
7) *Saccharomyce cerevisiae* is active for the Thiazolidinone, MT-III and MT-V (500 and 1000 µg/ml) only.
8) *Candida albicans,* is active for the Thiazolidinone, MT-IV and MT-V only.
9) *Penicillum notatum and Alternaria alternate* are not active for the studied Thiazolidinones.
10) *Aspergillus niger,* is active for the Thiazolidinone, MT-II, MT-III and MT-IV only.

11) The MT-III and MT-V were high activity against *Saccharomyce cerevisiae* and MT-II (*Aspergillus niger*) and MT-IV (*Candida albicans*) derivatives are showing low activity.

References:

1) Hugo Schiff, Ann., 131,118 (1864).
2) a) A. K. Day. J. Sci. Ind. Res., 33, 76 (1974); b) R. W. Layer, Chem. Bull., 63, 489, (1963) and c) W. F. Smith, Org. Chem. Bull., 35(1), 6, (1963).
3) E. H. Cordes and W. P. Jencks, J. M. Chem. Soc., 84, 832, (1962)
4) E. H. Cordes and W. P. Jencks, J. M. Chem. Soc., 85, 2834, (1963)
5) C. J. Patil, A. S. Madhava, G. Ramchandriah and D. N. Vyas, Bull. Electrochem., 9 (2&3) (1993) 95-98; Ind. J. Chem., 33A (1994) 1037-1041.
6) D. M. Krasoritskii and N. I. Mal'tseva, Opt.Spetrosk,22(3),397,(1967); C.A., 6748781(1967)
7) M. D. Cohen and Mrs. S. Flavian, J. Chem. Soc., (B) 317 (1967)
8) G. Dudek and E. P. Dudek, Tetrahedron, 23 (8), 3245 (1967)
9) G. O. Dudek and E. P. Dudek, J. Am. Chem. Soc., 86, 4283 (1964).
10) Olcay Bekircan and Hakan Bektas, Molecules, 13, (2008) 2126, and Internal references.
11) Y. N. Beokon, a. g. Bulychev, M. I. Maleev, M. Oorth, I. L. Malfanov and S. Nikolai, Mendeleev Commum., (2004) 249, CA 143 (2005) 277531.
12) Y. D. Zhao, D. W. Pang, Z. Zong, J. K. Cheng, Z. F. Luo, C. J. Feng H. Y. Shen and X. C. Zhung, Huaxe Xuebao, 56 (1988) 178, CA 128 (1988) 252661.
13) R. S. George, R. Joseph and K. E. George, Int. J. Polym. Mater, 23 (1993) 17.
14) a) C. H. Rhodes, J. Med. Chem., 74 (1996) 497; b) C. P. Hutter, C. Djerassi, W. L. Beears, R. L. Mayer and C. R. Scholz, J. Am. Chem. Soc., 68 (1946) 1999.
15) J. Dehnert and W. Juchemann, Ger. Offen 3,337,591.
16) a) A. Fakhari, Khorrami, R. Afshin and H. Naeim, Talanta, 66 (2005) 813. b) Z. Cimerman, N. Galic and B. Bosner, J. Anal. Chim. Acta., 343 (1997) 145.
17) E. M. Hodnett and W. J. Dunn, J. Med. Chem., 15(3) (1977) 339.
18) A. S. Madhava, C. J. Patil. D. N. Vyas and G. Ramachandriah, Bull. Electctrochem., 7 (1991) 283.
19) J. M. HILL AND P. J. G. MANN, The Oxidation of Schiff Bases of Pyridoxal and Pyridoxal Phosphate with Amino Acids by manganous lons and Peroxidase, Biochem. J. 99 (1966) 454.
20) D. E. Metzler, J. E. Longenecker and E. E. Snell, J. Am. Chem. Soc., 71 (1949) 228.
21) J. Olivard, D. E. Metzler and E. E. Snell , J. Biochem., 199 (1953) 669.
22) T. Jeewoth, M. Bhowan and G. Kam, Trans. Met. Chem., 24 (1999) 435.
23) A. A. Jarrahpour, M. Motamedifar and K. Pakshir, Molecules., 9 (2004) 815.
24) B. E. Perry, A. E. Bezzer and R. J. Miles, J. Microbios., 45 (1986) 181.
25) J. D. Modi, S. S. Sabnis and C. V. Deliwala, J. Med. Chem., 13 (1970) 935.
26) R. C Sharma and D Kumar , J. Ind. Chem. Soc., 2000, 77, 942.

27) a) H. D Joshi, A R Sawale, R D Ingle and R A Mane, Ind. J. Chem., 2000, 39, 967 and b) M. Rai et. al., JICS 63 (1986) 705.
28) a) V. S Ingle, A R Sawale, R D Ingle, and R A Mane, Ind. J. Chem., 2001, 40, 124; b) P. C. Joshi et. al., JICS 61 (1984) 560.
29) S. H. Rosenblum, J. Huyah, A. Adriano, H. R. Davis, J. W. Cladiler and D. A. Burned, J. Med. Chem., 41 (1998) 973.
30) S. Grasso, A. Chimirri, P. Manforte, G. Fencho, M. Zappalar and A. M. Monforte , Farmaco Ed. Sci., 43 (1988) 857, CA 110 (1989) 50734c.
31) a) A. E. Abdel-Rahman, A. M. Mahmoud, G. M. El-Naggar, H. A. El-Sherif, Pharmazie, 38, (1983) 589; b) R. K. Shikkargol, N. N. Mallikarjuna and S. D. Angadi, Nat. Sci. Acad. Lett. (India), 24 (2001) 39, CA 138 (2011) 116763.
32) D. J. Kaneria, N. J. Datta and H. H. Parekh 2003, Ind. J. Het. Chem., 12,277.
33) J. H. Rex, M. I. Pfaller, T. J. Walsh, V. Chaturvdei, A. Espinel-Ingroff, M. A. Ghannoum, L. L. Gosey, F. C. Odds, M. G. Rinaldi, D. G. Sheehan, D. W. Warnock, Clin. Microbiol. Rev. 2001, 14, 643.
34) S. G. Kucukguzel, F. E. Oruc, S. Rollas, F. Sahin, A. Ozbek, Eur. J. Med. Chem., 13 (2002) 197.
35) R. K. Rawal, Y. S. Prabhakar, S. B. Katti, E. De Clercq, Bioorg. Med. Chem., 13 (2005) 6771.
36) M. G. Vigorita, R. Ottana, F. Monforte, R. Maccari, A. Trovato, M. T. Monforte and M. F. Tuviano, Bioorg. Med. Chem. Lett., 11 (2001) 2791.
37) B. Geol, T. Ram, R. T. Ram, R. Tyagi, E. Bansal, A. Kumar, D. Mukharjee and J. N. Sinha, Eur. J. Chem., 34 (1999) 265.

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