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Synthesis and Microbial Screening of (2-Propyl-Benzimidiazole-1-yl) Acetic Acidbenzylidene Hydrazide

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ABSTRACT

In the present work, a simple convenient and high yielding synthetic route has been employed for the synthesis of targeted molecules (2-propyl-benzoimidazol-1-yl)-acetic acid benzylidene-hydrazid (1a-d) and 4-(Benzylidene-amino)-5-(2-propyl-benzoimidazol-1-ylmethyl)-4H-[1,2,4]triazole-3-thiol(2a-d). The structures were confirmed by Fourier Transform Infrared Spectroscopy (FT-IR), Proton Nuclear Magnetic Resonance (H^1NMR) and physical properties. The synthesized compounds were screened for anti-microbial analysis against Bacillus subtilis, Staphylococcus aureus, Candida albicans and Escherichia coli, Aspergillus niger. The compounds are found to be highly active, hence forth, could be attractive lead molecules for developing new therapeutics against tested microorganisms.

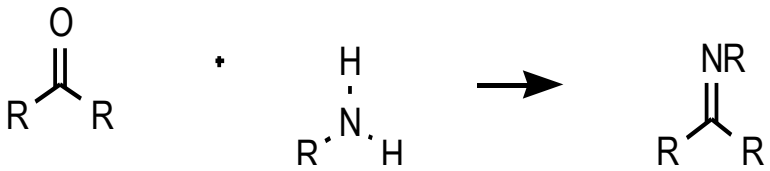
Keywords: 2-Propyl-benzimidiazole-carbohydrazide, Benzaldehyde, Iodine, Schiff bases synthesis, Antimicrobial

INTRODUCTION

Schiff's bases, named after the German chemist Hugo Schiff (1834-1915) are those compounds having a formula RR'C=NR″ where R is an aryl group, R' is a hydrogen atom and R″ is either an alkyl or aryl group. However, usually compounds where R″ is an alkyl or aryl group and R' is an alkyl or aromatic group are also counted as Schiff bases. The Schiff base class is very versatile as compounds can have a variety of different substituents and they can be unabridged or *N*,*N*'-bridged. Most common Schiff bases have NO or N_2O_2-donor atoms but the oxygen atoms can be replaced by sulfur, nitrogen, or selenium.

N-substituted imines, also known as Schiff bases represent one of the most widely used families of organic compounds. In general, they are easily prepared by the condensation reaction of primary amines with carbonyl compounds. The first reports of this kind of reaction have been published by Hugo Schiff in the 1864.

The synthesis and structural research of Schiff bases derived from the aldehydes and amines bearing various alkyl and aryl *N*-substituent's, as well as their metal complexes have been of interest in our research group for over two decades in various proportions and employing a range of solvents. The formation of Schiff bases is generally favored by making use The synthesis and structural research of Schiff bases derived from the aldehydes and amines bearing various alkyl and aryl *N*-substituent's, as well as their metal complexes have been of interest in our research group for over two decades in various proportions and employing a range of solvents. The formation of Schiff bases is generally favored by making use of dehydrating agents. A great care should be taken for the purification of Schiff bases as they are degradable.



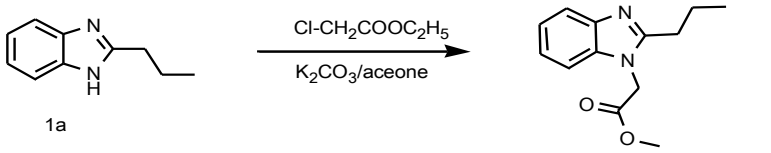
The acid/base catalysis or heating is employed for the synthesis of Schiff bases as their reactions are mostly reversible. The Schiff bases are formed by the reaction of amines with carbonyl compounds but it does not follow simple nucleophilic addition. The compound thus obtained is unstable and loses water molecule. The dehydration step during formation of Schiff base is actually the rate determining step and the reaction shown in scheme is catalyzed by acid. The removal of product or separation of water from the reaction mixture assists the formation of product. The aqueous acids or bases may hydrolyze Schiff bases towards their respective aldehydes or ketones and amines as well.

The Schiff- bases possess antiviral [1], anti-cancer [2], antibacterial [3] activities. Condensation of 2-methoxy-5-methyl phenyl azo salicyaldehyde with different malonanilic acid [4]. Variety of Schiff bases [5-8] were reported showing interesting activities like antitubercular, bacteriostatic, anticancer. Schiff bases are prepared by condensing N,N-bis (4-ethoxy phenyl) malonamide with 4-nitroaniline and are characterized by spectral analysis [9].

A number of Schiff bases [10] were reported in literature which shows different biological activities. New series of Schiff bases have been synthesized from 2-amino-3-(N-tolyl-caroxamide)-4,5,6,7-tetrahydro benzothiophenes with different substituted aldehydes [11]. Schiff bases complexes play a vital role in designing metal complexes related to synthetic and neutral oxygen carriers. In organic compounds the presence of –C=N– along with other functional groups form more stable complexes compared to compounds with only –C=N moiety. Coumarin containing a Schiff's base is expected to have antitumor and other biological activities [12].

EXPERIMENTAL AND SPECTRAL STUDIES

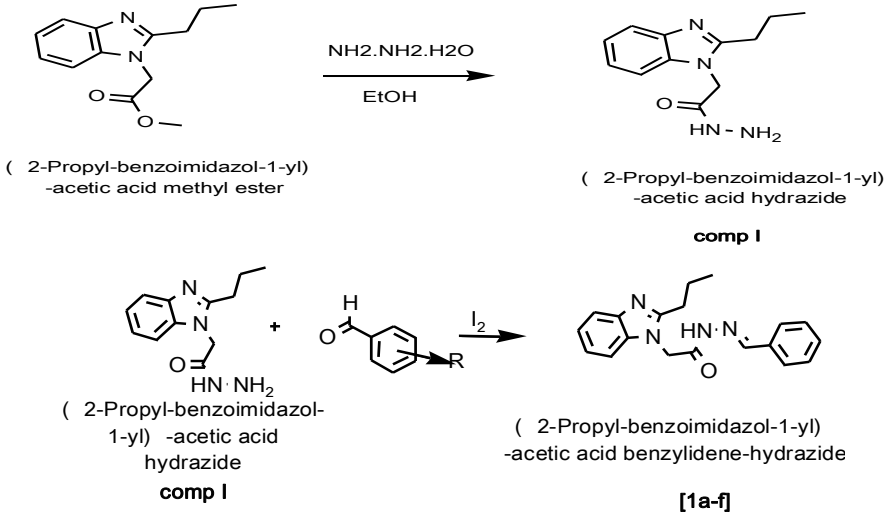
Synthesis of (2-propyl-benzimidiazol-1-yl)-acetic acid methyl ester (1)



1a

(2-Propyl-benzoimidazol-1-yl) -acetic acid methyl ester

Synthesis of (2-propyl-benzimidiazol-1-yl) acetohydrazide (2)



(2-Propyl-benzoimidazol-1-yl) -acetic acid methyl ester

(2-Propyl-benzoimidazol-1-yl) -acetic acid hydrazide

comp I

(2-Propyl-benzoimidazol-1-yl) -acetic acid hydrazide

comp I

(2-Propyl-benzoimidazol-1-yl) -acetic acid benzylidene-hydrazide

[1a-f]

R=2-chloro, 2-nitro, 4-nitro, 4-chloro, 4-methoxy, etc.

Schiff's base

Scheme I

Synthesis of hydrazone (Schiff's bases) from carbohydrazide

A mixture of (2-propyl-benzimidiazol-1-yl) acetic acid hydrazide (0.01 mol) and corresponding substituted benzaldehyde (0.01 mol) in ethanol (25 ml) in presence of iodine crystal was refluxed for 2 h then cool, then the reaction is monitored by Thin Layer Chromatography (TLC), after completion of reaction the mixture transfer to ice cold water containing sodium thiosulfite, clear the solution then the solid precipitate was filtered and crystallized from ethanol (Table 1).

Table 1: Elemental analysis of synthesized compounds (1a-f)

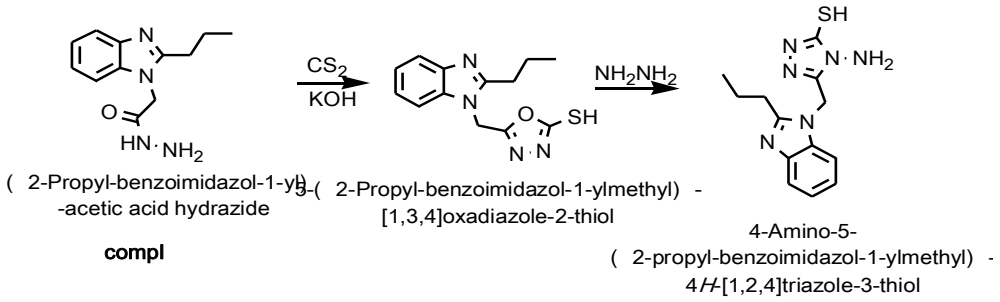
Compound	R	Molecular form/mol.wt	C	H	N	Cl	O
1a	H	$C_{19}H_{20}N_4O$/320	71.23	6.29	17.49	-	04.99
1b	4-OCH_3	$C_{20}H_{23}N_4O_2$/350	68.56	6.33	15.99	-	09.13
1c	4-NO_2	$C_{19}H_{21}N_5O_3$/365	62.46	5.24	19.17	-	13.14
1d	4-Cl	$C_{19}H_{19}N_4OCl$/354	64.31	5.40	15.79	9.99	04.51
1e	2-NO_2	$C_{19}H_{19}N_4O_3$/320	62.46	5.24	19.17	-	13.14
1f	2-Cl	$C_{19}H_{19}N_4OCl$/354	64.31	5.40	15.79	9.99	04.51

Spectral data for newly synthesized compounds

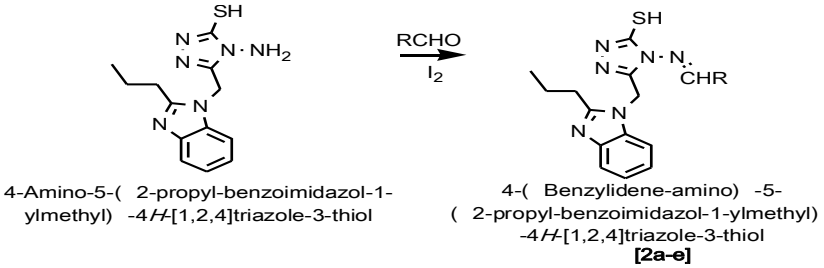
Compounds (R) Spectral data: (1a) H NMR - δ_{ppm}=4H(s) 7.1, δ 2H (t) 2.60, 2H (m) 2.1, 3H (t) 1.3, IR Ar NO_2 (N=O) 1570 cm^{-1}, γ C-H 2970 cm^{-1}, γ C=H 1940, γ C=O 1690 cm^{-1} C=C 1650 cm^{-1}, γ C-O-C 1150 cm^{-1}, (1b) OCH_3, IR -γ O-C 1408 cm^{-1}, γ C=H 1940 cm^{-1}, (1c) NO_2 IR-Ar – NO_2 (N=O) 1570 cm^{-1}, γ C-H 2970 cm^{-1}, γC=H 1940, γ C=O 1690 cm^{-1}, γ N-H3500 cm^{-1}, γ C=C1050 cm^{-1}, γ N-N 3300 cm^{-1}, γ C-O-C 1150 cm^{-1}, (1d) Cl, γ C-Cl 800 cm^{-1}.

Scheme II

Synthesis of 4-amino-5-(2-propyl-benzimidiazol-yl-methyl)-4H- [1,2,4]triazole-3-thiol (1)



Synthesis of hydrazone [2a-e] (2)



R=methoxy, o-chloro benzaldehyde, benzaldehyde

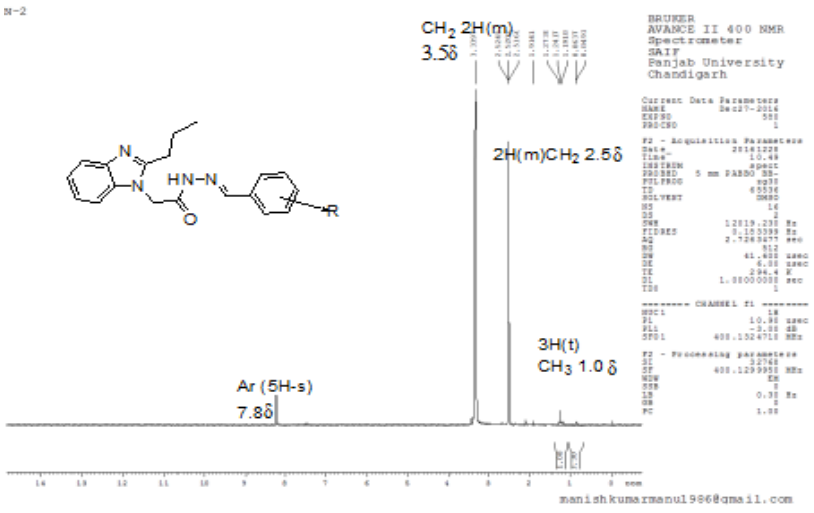
A mixture of 4-(benzylidene-amino)-5-(2-propyl-benzimidiazol-1-ylmethyl)-4H-[1,3,4] triazole-3-thiol (0.01 mol) and corresponding substituted benzaldehyde (0.01 mol) in ethanol (25 ml) in presence of iodine crystal was refluxed for 2 h then cool it. Then the reaction is monitored by TLC and after completion of the reaction the mixture was transfer to ice cold water containing sodium thiosulfite solution, clear the solution then the solid precipitate was filtered and crystallized from ethanol (Table 2).

Table 2: Elemental analysis of synthesized compounds (2a-e)

Compound	R	M.P	%Yield	%C	%H	%O	%N	%S	%Cl	Molecular form/M.wt
2a	H	190	83%	63.81	5.35	8.52	22.32			$C_{20}H_{20}N_6O$/376
2b	4-Cl	182	74%	58.46	4.66	7.80	20.45		8.63	$C_{20}H_{19}N_6OCl$/410
2c	2-NO_2	112	70%	56.99	4.54	7.59	23.26	7.61		$C_{20}H_{19}N_7O_2S$/421
2d	4-NO_2	142	68%	56.99	4.54	7.59	23.61	7.67		$C_{20}H_{19}N_7O_2S$/421
2e	OCH_3	137	62%	62.05	5.45	3.91	20.67	7.89		$C_{21}H_{22}N_6O$ S/406

Spectral data for newly synthesized compounds

Compounds (R) Spectral data: (2a) H NMR NHR-δ=3H (t) 0.93 δ=2H (m)1.6, δ=2H(t) 2.42, 1H(s)4.1,4H (s) 7.2H (s) 2.8 2H (s) 3.0, IR (KBr, cm^{-1}): IR γ N-H 1750 cm^{-1}, γ C=C 1675, γ C-H 3080, γ C-H 2820, γ S-H 2250 cm^{-1}, (2b) Cl NMR δ=3H (t)=0.93, 2H(s), 1.6 2H(t) 2.42, 1H (s) (S-H) 4.1 4H, (aromatic) 7.2, 2H, (-N=CH) 2.9, 2H(N-CH_3)3.0, IR (KBr, cm^{-1}): 2995(C-H), 1663(C=N) 746 (C-Cl), (2c) 2-NO_2 NMR (N-CH_2) 2H (s) 2.65, IR (KBr, cm^{-1}): NO_2, 1325 cm^{-1}, (2d) 3-NO_2, IR NO_2 1325 cm^{-1}, (2e) OCH_3 NMR (OCH_3) δ=3H (s) 1.3, IRγ(O-C)1705 cm^{-1}, S-H 2535 cm^{-1}.



Spectral data for newly synthesized compounds

RESULT AND DISCUSSION

Here in the view of synthesis of some new hydrozone (Schiff's bases) we have chosen multistep sequential steps. First we have synthesized different substituted hydrozone, by the reaction of carbohydrazide [(2-propyl-benzimidiazol-1-yl)-acetic acid hydrazide] and substituted benzaldehyde in presence of Iodine used as a catalyst and the reaction mixture was heated for 2 h. After completion of reaction the reaction mixture monitored by TLC and then the mixture was transferred in ice cold water containing sodium thiosulfite, the excess of Iodine was removed; the precipitate solid was filtered, washed with water and recrystallized from alcohol.

In the present work (comp I) [(2-propyl-benzimidiazol-1-yl)-acetic acid hydrazide] which was previously prepared by one of us was used as the key intermediate for further synthesis. [(2-propyl-benzimidiazol-1-yl)-acetic acid hydrazide] was treated with CS_2/KOH form 4-amino-5-(2-propylbenzimidiazol-1-ylmethyl)-4H-[1,3,4]triazole-3-thiol was obtained. A benzimidazole moiety was converted into triazole moiety was synthesized by the reaction of 4-amino-5-(2-propylbenzimidiazol-1-ylmethyl)-4H[1,3,4]triazole-3-thiol with hydrazine hydrates (99%) in ethyl alcohol absolute, which afforded 4-(benzylidiene-amino)-5-(2-propyl-benzimidiazol-1yl)-4H-[1,3,4]triazole-3-thol.

A number of arylidenes hydrazones were synthesized with the help of aromatic aldehyde namely p-methoxy benzaldehyde, o-chloro benzaldehyde and in presence of iodine and absolute alcohol afforded the corresponding Schiff's bases or hydrazones respectively.

Biological screening antimicrobial activity

The synthesized Schiff bases were screened for antibacterial and antifungal activity. The bacterial cultures for *Bacillus subtilis, S. aureus*, *Candida albicans* and *Escherichia coli* were incubated at 30 ± 0.1°C for 24 h by inoculation into nutrient agar. Schiff bases were stored dry at room temperature and dissolved 20 mg/ml in Dimethyl sulfoxide (DMSO). Antibacterial activities of each compound were evaluated by the agar disc-diffusion method. Mueller Hinton agar media (15 cm^3) kept at 45°C was poured in the petri dishes and allowed to solidify. Poured petri plates (9 cm) were incubated with 50 µl of normal saline solution of above culture media (105-106 bacteria per ml). Discs injected with prepared Schiff bases (50 µl) were applied on the solid agar medium by pressing tightly. The Petri plates were placed at 37°C for 24 h. At the end of period the inhibition zones formed on media were measured with a zone reader in millimeters. Antifungal activities of each compound were evaluated by the agar disc-diffusion method.

Sabarod's agar media (15 cm^3) kept at 45°C was poured in the petri-dishes and allowed to solidify. Sterile, filter paper discs of 10 mm diameter were impregnated with prepared Schiff bases (50 µl) and were placed on to the media, seeded with fungus. The plates were then incubated at 27°C for 1-7 days. At the end of period the inhibition zones formed on media were measured with a zone reader in millimeters.

The results of the antibacterial screening of the Schiff bases at a concentration of 20 mg/ml against all bacteria have been found. The results of antimicrobial screening, indicate that Schiff bases show significant activity against *E. coli, B. subtilis* than *Aspergillus niger* and *C. albicans* while compound 2c, 2d and 3b, 3d were found to be more active against all tested bacterial strains because of the presence of chloro group in the aldehydic group which itself is active against microbes (Table 3). Antibacterial activity of these compounds show ascending order. When we increase concentration, area of inhibited growth also increased. From the results obtained by the antifungal activity it is found that the benzimidazole Schiff bases are more inactive against all tested fungi.

Table 3: Results of antimicrobial activity of the tested compounds

Compound	*Bacillus subtilis*	*Escherichia coli*	*Candida albicans*	*Aspergillus niger*
Gentamycin	+++	+++	_	_
Ampicillin	+++	+++	_	_
2c	+++	++	_	_
2d	+++	++	_	_
3b	+++	++	_	_
3d	+++	++	_	_

Highly active=+++ (inhibition zone>12 mm); Moderately active=++ (inhibition zone 9-12 mm); Slightly active=+ (inhibition zone 6-9 mm)

CONCLUSION

Heterocyclic compounds play key role in all major arena of science and technology. The existence of wide classes of heterocyclic compounds (monocyclic, fused ring etc.) renders them tunable to the demand of application. Thus the vast applicability of heterocyclic compounds needs continuous exploration on the design of newer compounds. This extensive potentiality of heterocyclic compounds in both medicinal and material domain of chemistry was the motivation to undertake this work. The present study is focused on the synthesis of some potentially bioactive heterocyclic compounds by new synthetic protocols and possible applications of some heterocyclic compounds.

Schiff bases of 2-propyl benzimidiazoyl carbohydrazide, and 4-amino-5-(2-Propyl-benzoimidazol-1-ylmethyl)-[1,3,4]oxadiazole-2-thiol were synthesized and characterized by analytical and spectral techniques. These compounds exhibited significant activity against all the tested microorganisms. The hydrazone derivatives studied in this work have shown the importance of their amoebicidal activity. The presence of nitro group enhances the activity increases. Finally, it is important to know the mechanism of action of these kinds of compounds to provide a new lead family of molecules in the treatment of this parasitic disease and other diseases that could be susceptible to the same activity mechanism.

ACKNOWLEDMENTS

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