Synthesis and Biological properties of Some Novel Schiff Bases derived from coumarin

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Abstract

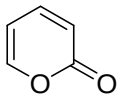
Coumarins are an important class of oxygen heterocycles, which are widespread in plant kingdom and have been extensively reported on. Their chemical structure can be looked upon as arising out of the fusion of a benzene ring to pyran-2-one across the 5 and 6 positions in skeleton

Keywords: Anti-inflammatory, triazole, *Escherichia Coli* and *B. Subtilis*, *A Niger* and *A. sereus.*

INTRODUCTION

1. CHEMISTRY OF COUMARINS

Coumarins are an important class of oxygen heterocycles, which are widespread in plant kingdom and have been extensively reported on. Their chemical structure can be looked upon as arising out of the fusion of a benzene ring to pyran-2-one **1**, across the 5 and 6 positions in skeleton.



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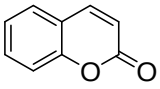

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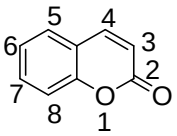
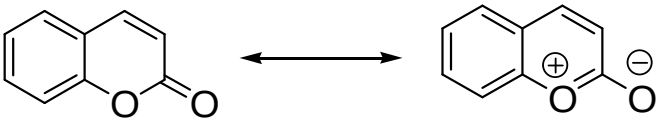


3

The parent coumarin **2** was first isolated by Vogel in 19th century from Tonka beans[1] and even to this date finds itself still in use as perfumery and flavoring agent. Figure **3** represent the numbering system used in coumarin skeleton.[2]

2. STRUCTURE AND REACTIVITY

Aromatic nature of heterocyclic ring of coumarin is disputable, because coumarin shows some reactions of aliphatic compounds and other characteristics of aromatic compounds. The complete aromaticity in coumarin can be only realized if O-CO function contributes two electrons to form 10л electron system. This means that coumarin should be a resonance hybrid, to which contribution from canonical form **4** is significant. However, no evidence is found in the spectra of coumarin to suggest that contribution from betaine form **4** is considerable

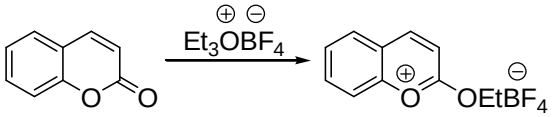


2 **4**

The infrared absorption spectrum of coumarin shows an absorption band at 1710 cm^{-1} which is attributed to lactone carbonyl group but not a betain from. In the ^{1}H NMR spectrum of coumarin[3], the signal due to protons of C3 and C4 appears in the region of 6.45 □ ppm and 7.80 □ ppm with coupling constants of 9.8 Hz. These values are typical of *cis* alkene rather than an aryl ring[4]. Finally the ^{13}C NMR spectra of coumarins[5] are consistant with an essentially aliphatic heterocyclic ring. The chemical shifts of C2, C3 and C4 in coumarin remarkably close to the values for the corresponding carbons in □-pyrone and are given below

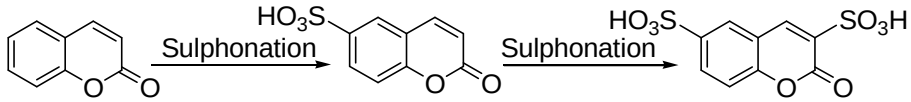
Compound	C2	C3	C4
□-Pyrone	162.0	116.7	144.3
Coumarin	160.4	116.4	143.4

But coumarin does show aromatic character in its pattern of reactivity. The carbonyl oxygen can be alkylated by powerful agents to give stable pyrillium salts **5**



2 **5**

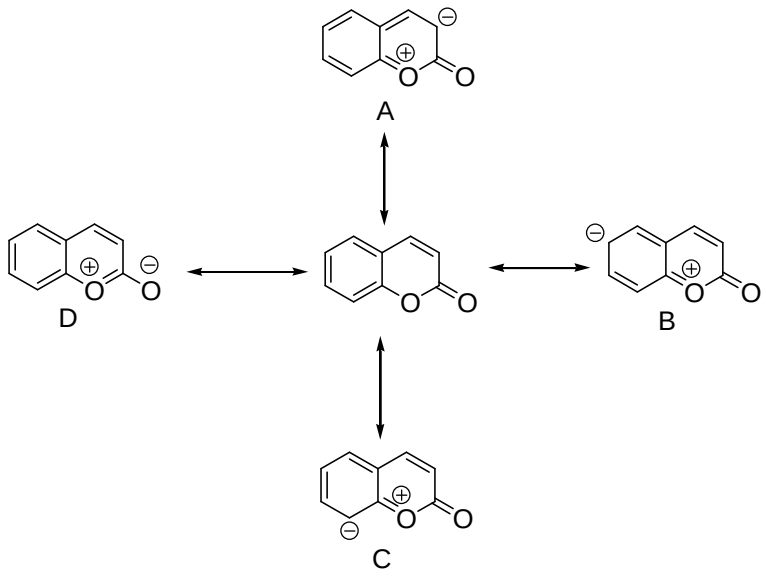
Coumarin nucleus is susceptible to electrophilic substitution.[6] Sulphonation takes place initially in the carbocyclic ring at C6, to give **6**, but under more forcing conditions one more SO_3H group can be introduced at C3, to obtained coumarin-3, 6-disulphonic acid **7**.



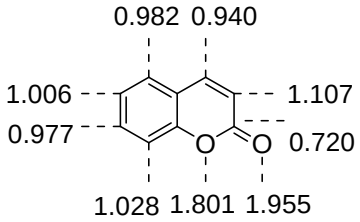
2 **6** **7**

As in case of simple pyrones the properties of heterocyclic ring of coumarin are greatly influenced by the presence of substituents.

Anantatakrishanan[7] discussed the "Mills-Nixon effect" in which the reactivity of coumarin was rationalized based on the comparative studies of bromination and nitration of coumarin, naphthalene and benzene. By considering the possible electron movements in coumarin molecule, Thakur and Shah[8] predicted that C6 and C8 as the most reactive centres. The electron movements are as shown below.

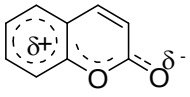


Greater electron densities can be seen on C6 and C8 from the resonating structures B and C. Out of these two, C6 seems to be more reactive because of its proximity to the oxygen atom, similar to the reactivity of para position of phenol. Structure A though imparts more electron density to the C3 position, the electrophilic substitution at C3 is less, probable due to its closeness to the electron withdrawing carbonyl group. Infact the л electron densities calculated by Song and Gorden[9] are quite close to the resonance picture of the molecule. The structure **8** represents the л electron densities for the ground state of coumarin.



8

By considering the structure's B, C and D Bassingnan and Cogrossi[10] have proposed structure **9** which is according to them represents the hybrid or resonating state of molecule.



9

However the contributing structure of the type (D) does not have strong spectral evidences, the position of the carbonyl frequency in the IR spectrum (1710 cm^{-1}) is more in favor of an enol lactone.[11] Hence the contribution from such type of structures is negligible and the resonating state **9** appears to be less probable.

The structural features of meso-ionic compounds have been of interest to medicinal chemist. A wide spectrum of biological activity has been claimed for a variety

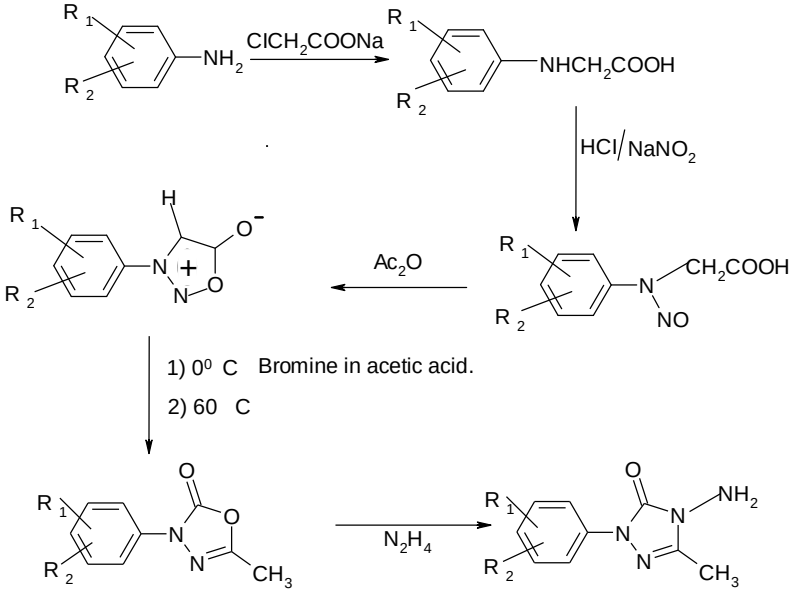
of meso-ionic compounds [12]. Their potential value as biological active substances can be explained by their dipolar structure. These rings systems are composed of delocalized electrons, which have been appreciably perturbed. As a result of perturbation of electrons in meso-ionic system there is an oppositely charged dipolar segment at the extreme of a four atom chain. The presence of oppositely charged dipolar segment in meso-ionic systems is of tremendous value to the medicinal chemist [13]. Its significance perhaps lies in its ability to electrostatically interact with two complementary partially charged positions on receptor macromolecule, such as a protein helix. Another structural feature of the meso-ionic system is their highly charged, yet net neutral electrical character. Therefore, they are soluble to a much greater extent in non polar or lipoid solvents [14]. Thus in vivo, the meso-ionics can cross lipid barrier even though they are internally appreciably ionic. On the contrary some quaternary salts and molecules rich in polar groups such as carbohydrates cannot pass this lipid barrier. The comparatively small size of meso-ionic ring, their planar aromatic character and variation of electron density around the rings eliminates conformational problems and permitting the relatively close approach of all ring atoms to a receptor surface. Meso-ionic compounds have been screened for various biological activities [15]. In continuation of our work on synthetic biologically active sydnones [16,17] and oxadiazolines [18]. Novel 4-amino-2-aryl-5-methyl-2,4-dihydro-3H-1,2,4-triazole-3-ones, by one pot ring conversions of 3-aryl-5-methyl-1,3,4-oxadiazoline-2-ones with hydrazine hydrate which were difficult to synthesize and were inaccessible by other methods have reported recently from our laboratory [19]. The prime synthetic evidence, spectral and antimicrobial studies reported from our laboratory have triggered the new routes in triazole synthetic chemistry. Schiff bases play an important role in many bio-chemical reactions, because of the imine linkage. Imines are to possess antibacterial and more antifungal properties.

In continuation of work, in the present investigation we focused our attention on the synthesis of 3-aryl-[(1-isocyano-4-methyl-7-hydroxy coumarin)]-5-methyl-1,3,4-triazoline-2-one from 1,2,4-triazoles-3-ones and 8-formyl-7-hydroxy-4-methyl-coumarin Schiff base (scheme-3). The aim of this work came from the observation that triazoles contain a potential free primary amino group, which could be used for variety of synthetic studies. It was interesting to study the influencing biological behaviors with various substituted triazoles. Therefore, we felt it of interest to study the chemical reactivity of these heterocyclic coumarin moieties.

PRESENT WORK

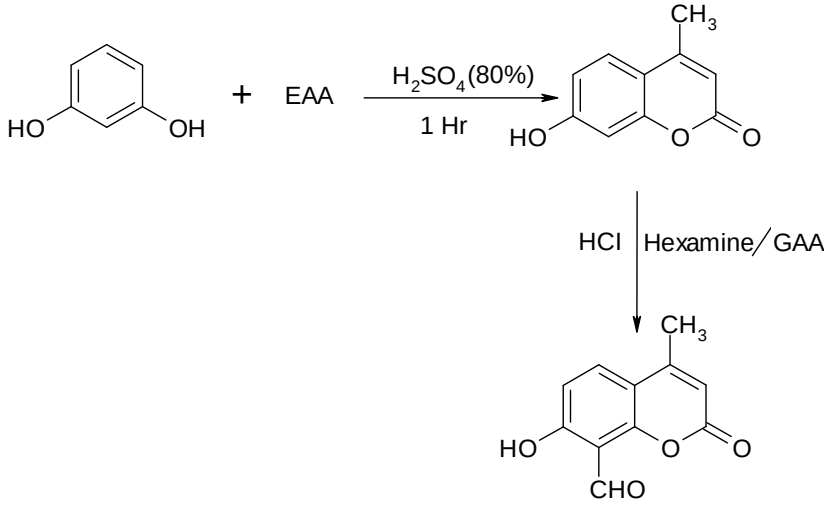
In continuation of work, in the present investigation we focused our attention on the synthesis of 3-aryl-[(1-isocyano-4-methyl-7-hydroxy coumarin)]-5-methyl-1,3,4-triazoline-2-one from 1,2,4-triazoles-3-ones and 8-formyl-7-hydroxy-4-methyl-coumarin Schiff base (scheme-3). The aim of this work came from the observation that triazoles contain a potential free primary amino group, which could be used for variety of synthetic studies. It was interesting to study the influencing biological behaviors with various substituted triazoles. Therefore, we felt it of interest to study the chemical reactivity of these heterocyclic coumarin moieties.

Synthesis of 3-aryl sydnones, oxadiazolines and triazoles derivatives by slight modification in our reported literature methods (Scheme 1)



Scheme 1. Systematic scheme for preparation of 3-aryl sydnones, oxadiazolines and triazoles

A mixture of resorcinol and ethylacetoacetate in sulphuric acid solution was heated on a water bath. The separated bright yellow colored solid was washed with excess of cold water, dried and crystallized from methanol to get the pure product.

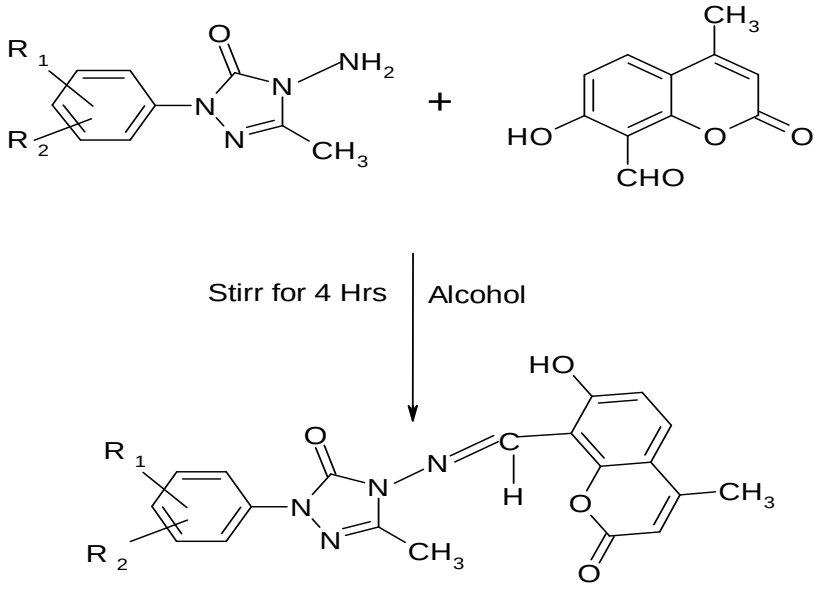


Scheme 2. Systematic scheme for preparation of coumarin derivative.

A mixture of 7-hydroxy-4-methyl-coumarin and Hexamethylene tetramine in glacial acetic acid was heated on a water bath. The hexamine adduct so formed was hydrolyzed with HCl and the mixture was heated for another 30 min. After cooling, the reaction mixture was extracted with diethyl ether, the ether layer was evaporated and the pale yellow colored solution was poured to crushed ice to get the pale yellow solid of 8-

formyl-7-hydroxy-4-methyl coumarin which was crystallized from ethanol and dioxan mixture. The Scheme of the work is represented in Scheme 2.

The desired compound is prepared by equimolar concentrations of substituted 4-amino-2-aryl-5-methyl-2,4-dihydro-3H-1,2,4-triazoles-3-ones (0.01mol) and 8-formyl-7-hydroxy-4-methyl coumarin were stirred for 4 hrs at room temperature using alcohol as a solvent by adding a few drops of acetic acid. The solid obtained was filtered, washed with water and crystallized from ethanol. The scheme of the work is represented in Scheme 3.



Scheme 3. Systematic scheme for preparation of Schiff bases.

RESULTS AND DISCUSSION

The molecular formula of the synthesized compounds, their structural substitutions, yield in percentage, solvent used for recrystallisation, melting point and the C, H and N analysis with the calculated and found values are represented in (Table-1).

The IR spectra of the compounds were recorded in 4000-400 cm^{-1} range [20]. The compounds show the characteristic band of $V_{(O-H)}$ in the range 3410-3440 cm^{-1} [21]. The compounds exhibited bands at casually 1745 cm^{-1} and 1640 cm^{-1} for coumarin lactone carbonyl and aldehyde respectively [22] and 1727 cm^{-1} for triazolinone. The band at 1580-1600 cm^{-1} are assigned to $V_{(C=C)}$ stretching [23]. The azomethine group being exhibited in the range 1617-1625 cm^{-1}.

The ^{1}H NMR spectrum of the ligand was recorded in chloroform using TMS as an internal reference. The data is given in Table-2.

Table 1. Elemental Analysis of the compounds

Compound	R	R'	M.P ^{0}C	Yield (%)	Mol. form	Elemental analysis Found (Calc) % C	H	N
I	H	H	178-79	71	$C_{11}H_8O_4$	64.70 (64.67)	3.92 (3.95)	31.37 (31.35)
II	m-Cl	H	268-69	65	$C_{20}H_{15}N_4O_4Cl$	58.47 (58.30)	3.65 (3.68)	13.6 (13.4)
III	P-C1	H	265-66	67	$C_{20}H_{15}N_4O_4Cl$	58.47 (59.02)	3.65 (3.04)	13.6 (13.4)
IV	P-OCH_3	H	270-71	66	$C_{21}H_{18}N_4O_5$	62.06 (62.96)	4.43 (4.23)	13.8 (13.7)
V	P-CH_3	H	256-57	69	$C_{21}H_{18}N_4O_4$	64.61 (64.02)	4.61 (4.20)	14.3 (14.1)
VI	P-COOH	H	276-77	71	$C_{21}H_{16}N_4O_6$	60.00 (60.23)	3.80 (3.28)	13.3 (13.5)
VII	3-C1	4-CH_3	282-83	82	$C_{21}H_{17}N_4O_4Cl$	59.37 (58.84)	4.00 (3.82)	13.2 (13.1)
VIII	3-NO_2	4-C1	275-76	68	$C_{21}H_{14}N_4O_6Cl$	52.69 (51.92)	3.07 (3.24)	12.3 (12.2)

EXPERIMENTAL

The melting points were determined by open capillaries on a Buchi-apparatus and are uncorrected. The IR spectra were recorded on a Nicolet-Impact-410 FT-IR spectrometer, using KBr pellets.^{1}HNMR and ^{13}CNMR spectra were recorded on a Bruker AC-300F, 300MHz, spectrometer in $CDCl_3$ and DMSO-d_6 using TMS as an internal standard and the values are expressed in δ ppm. The mass spectra were recorded using EI-MS (at CRDI, Lucknow). The elemental analysis was carried out using Heraus CHN rapid analyzer. All the new compounds have given CHN analysis within ±0.4% of the theoretical values. The homogeneity of the compounds was described by Thin Layer Chromatography on aluminum silica gel $60F_{254}$ (merck) detected by UV light (254 nm) and iodine vapors. All the chemicals purchased were of analytical reagent grade, and were used without further purification unless otherwise stated.

Synthesis of 3-aryl sydnones, oxadiazolines and triazoles derivatives by slight modification in our reported literature methods.

Synthesis of 7-hydroxy-4-methyl coumarin

A mixture of resorcinol (0.1 mol) and ethylacetoacetate (0.1 mol) in 50 ml sulphuric acid solution (85%) was heated on a water bath for 3 h. The resulting reddish brown colored solution was decomposed with 500 gm of crushed ice. The separated bright yellow colored solid was washed with excess of cold water, dried and crystallized from methanol to get the pure product.

Nature: Dark brown crystalline solid (methanol); Yield: 80%; m.p. 180-182ºC; IR (KBr, cm^{-1}): 3423 (ν_{OH}), 1733 ($\nu_{C=O}$), 1555 ($\nu_{C=C}$); ^{1}H NMR (300MHz, $CDCl_3$ + TFA, δppm): 2.49 (s, 3H, C4-CH_3), 6.31 (s, 1H, C3-H), 6.92-6.95 (d, 1H, C6-H, J=9 Hz), 6.94 (s, 1H, C8-H), 7.57-760 (d, 1H, C5-H, J=9 Hz);

***Synthesis of 8-formyl-7-hydroxy-4-methyl coumarin* (I)**

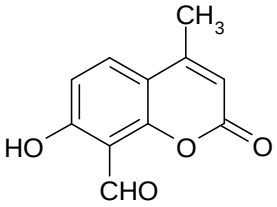
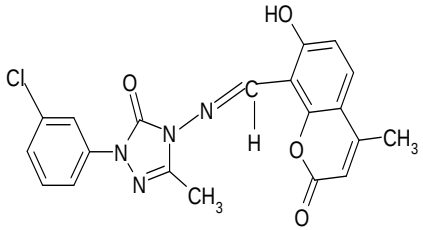
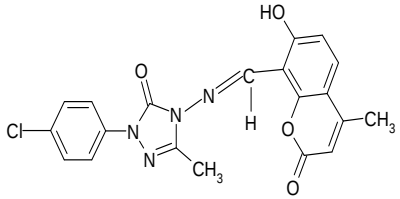
A mixture of 7-hydroxy-4-methyl-coumarin (5 gm) and Hexamethylene tetramine (10 gm) in glacial acetic acid (40 ml) was heated on a water bath for 6 hr. The hexamine adduct so formed was hydrolyzed with 20% HCl (75 ml) and the mixture was heated for another 30 min. After cooling, the reaction mixture was extracted with diethyl ether, the ether layer was evaporated and the pale yellow colored solution was poured to crushed ice to get the pale yellow solid of 8-formyl-7-hydroxy-4-methyl coumarin which was crystallized from ethanol and dioxan mixture. The Scheme of the work is represented in Fig.2

Nature: Pale yellow crystalline solid (Ethanol + dioxan); Yield: 22%; m.p. 176-178ºC; IR (KBr, cm^{-1}): 3446 (ν_{OH}), 1742 ($\nu_{C=O,}$ lactone), 1644 ($\nu_{C=O,}$ aldehyde), 1594 ($\nu_{C=C}$); ^{1}H NMR (300MHz, $CDCl_{3,}$ δppm): 2.44 (s, 3H, C4-CH_3), 6.22 (s, 1H, C3-H), 6.90-6.93 (d, 1H, C6-H, *J*=9 Hz), 7.73-7.76 (d, 1H, C5-H, *J*=9 Hz), 10.63 (s, 1H, HCO), 12.28 (s, 1H, OH);

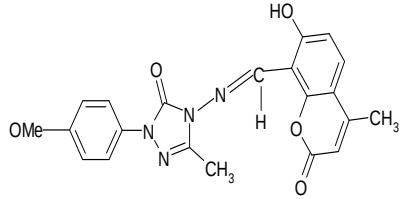
Synthesis of Schiff base, 3-aryl-[(1-isocyano-4-methyl-7-hydroxy coumarin)]-5-methyl-1,3,4-triazoline-2-one from 1,2,4-triazoles-3-ones. (general procedure)

Equimolar concentrations of substituted 4-amino-2-aryl-5-methyl-2,4-dihydro-3H-1,2,4-triazoles-3-ones (0.01mol) and 8-formyl-7-hydroxy-4-methyl coumarin (0.01mol) were stirred for 4 hrs at room temperature using alcohol as a solvent by adding a few drops of acetic acid. The solid obtained was filtered, washed with water and crystallized from ethanol. The scheme of the work is represented in Scheme 3.

Table 2. Spectral data of the compounds

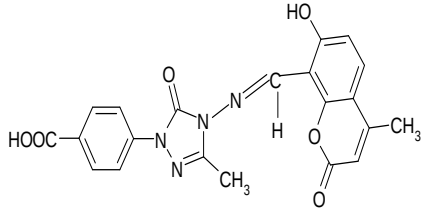
Compound	Structure	Spectral data NMR Characterization
I		IR (KBr, cm^{-1}): 3446 (ν_{OH}), 1742 ($\nu_{C=O,}$ lactone), 1644 ($\nu_{C=O,}$ aldehyde), 1594 ($\nu_{C=C}$); ^{1}H NMR (300MHz, $CDCl_3$, δppm): 2.44 (s, 3H, C4-CH_3), 6.22 (s, 1H, C3-H), 6.90-6.93 (d, 1H, C6-H, *J*=9 Hz), 7.73-7.76 (d, 1H, C5-H, *J*=9 Hz), 10.63 (s, 1H, HCO), 12.28 (s, 1H, OH).
II		IR (KBR) cm^{-1}: 3410 (ν_{OH}), 1745 cm^{-1} (Coumarin lactone carbonyl), 1727 cm^{-1} ($\nu_{C=O}$ of triazolinone), 1585 cm^{-1} ($\nu_{C=C}$),1617 cm^{-1} ($\nu_{C=N}$). ^{1}H NMR (300 MHz, $CDCl_3$): d (ppm) 2.5 (t, 1H, CH), 2.6 (d, 2H, CH_2),6.8-7.6 (m, 7H, ArH), δ 2.37 (3H, s, CH_3),Coumarin (C4 7.80 δ ppm *J*= 9.8 Hz.), δ 10.0 (s, br, 1H) OH Proton (D_2O exchanged).
III		IR (KBR) cm^{-1}: 3430 (ν_{OH}), 1735 cm^{-1} (Coumarin lactone carbonyl), 1725 cm^{-1} ($\nu_{C=O}$ of triazolinone), 1590 cm^{-1} ($\nu_{C=C}$),1620 cm^{-1} ($\nu_{C=N}$). ^{1}H NMR (300 MHz, $CDCl_3$): d (ppm) 2.5 (t, 1H, CH), 2.6 (d, 2H, CH_2),6.8-7.6 (m, 7H, ArH), δ 2.37 (3H, s, CH_3),Coumarin (C3 6.45 δ ppm, C4 7.80 δ ppm *J* =9.8 Hz.), δ 10.0 (s, br, 1H) OH Proton (D_2O exchanged).

IV



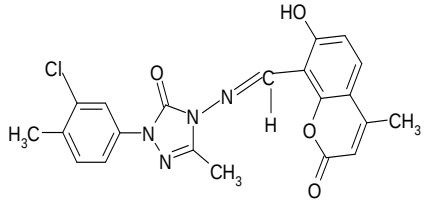
IR (KBR) cm^{-1}: 3410 (ν_{OH}), 1715 cm^{-1} (Coumarin lactone carbonyl), 1727 cm^{-1} ($\nu_{C=O}$ of triazolinone), 1587 cm^{-1} ($\nu_{C=C}$),1618 cm^{-1} ($\nu_{C=N}$).
^{1}H NMR (300 MHz, $CDCl_3$):δ(ppm) 2.5 (t, 1H, CH), 2.6 (d, 2H, CH_2),6.8-7.6 (m, 7H, ArH), δ 2.20 (3H, s, $COCH_3$),Coumarin (C3 6.45 δ ppm, C4 7.80 δ ppm *J* =9.8 Hz.), δ 10.0 (s br 1H) OH Proton (D_2O exchanged).

VI



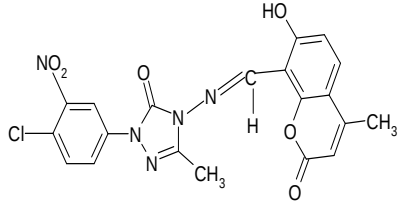
IR (KBR) cm^{-1}: 3418 (Coumarin ν_{OH}), 3346 (Arm ν_{OH}), 1745 cm^{-1} (Coumarin lactone carbonyl), 1727 cm^{-1}; 1724 cm^{-1} ($\nu_{C=O}$ of Carboxylic),($\nu_{C=O}$ of triazolinone), 1585 cm^{-1} ($\nu_{C=C}$),1617 cm^{-1} ($\nu_{C=N}$).
^{1}H NMR (300 MHz, $CDCl_3$): d (ppm) 2.5 (t, 1H, CH), 2.6 (d, 2H, CH_2),6.8-7.6 (m, 7H, ArH), δ 2.37 (3H, s, CH_3),Coumarin (C3 6.45 δ ppm, C4 7.80 δ ppm *J*= 9.8 Hz.),11.9 (1H, s, COOH), δ 10.0 (s, br, 1H) OH Proton (D_2O exchanged).

VII



IR (KBR) cm^{-1}: 3430 (ν_{OH}), 1736 cm^{-1} (Coumarin lactone carbonyl), 1724 cm^{-1} ($\nu_{C=O}$ of triazolinone), 1589 cm^{-1} ($\nu_{C=C}$),1623 cm^{-1} ($\nu_{C=N}$).
^{1}H NMR (300 MHz, $CDCl_3$): d (ppm) 2.5 (t, 1H, CH), 2.6 (d, 2H, CH_2),6.8-7.6 (m, 7H, ArH), δ 2.37 (3H, s, CH_3),Coumarin (C3 6.45 δ ppm, C4 7.80 δ ppm *J*= 9.8 Hz.),7.86-7.88 (2H, d, *j*=8.7, Ar-H), δ 10.0 (s, br, 1H) OH Proton (D_2O exchanged).

VIII



IR (KBR) cm^{-1}: 3417 (ν_{OH}), 1738 cm^{-1} (Coumarin lactone carbonyl), 1724 cm^{-1} ($\nu_{C=O}$ of triazolinone), 1589 cm^{-1} ($\nu_{C=C}$),1625 cm^{-1} ($\nu_{C=N}$).
^{1}H NMR (300 MHz, $CDCl_3$): d (ppm) 2.5 (t, 1H, CH), 2.6 (d, 2H, CH_2),6.8-7.6 (m, 7H, ArH), δ 2.37 (3H, s, CH_3),Coumarin (C3 6.45 δ ppm, C4 7.80 δ ppm *J*= 9.8 Hz.), δ 10.0 (s br 1H) OH Proton (D_2O exchanged).

BIOLOGICAL STUDIES

All the compounds were screened for their antimicrobial activity by cup plate method [24] at 100 µg/ml concentration in DMF against the *Escherichia Coli* and *B. Subtilis* and also against *A Niger* and *A. sereus* fungi, using Norfloxacin and Griseofulvin as the reference drugs respectively. All these compounds were less active against the bacterial strains, but some of them showed selective fungal inhibitory activity [25,26] (Table-3).

Table-3 Anti-microbial activities of compounds

Compound Code	Antibacterial		Antifungal	
	E.coli	*B. subtilis*	*A. niger*	*C. Albicans*
I	15	16	17	16
II	19	18	19	23
III	17	16	14	18
IV	15	14	22	21
V	16	14	24	22
VI	15	13	18	17
VII	14	14	17	18
VIII	19	18	19	21
Norf	22	22	--	--
Gris	--	--	26	26
DMF	04	04	04	04

Conclusions

The work has approached towards the synthetic and biological approach of these wonder molecules. Anti-bacterial property of the synthesized compounds has exhibited average inhibition, but the systematic substitution at various position and other derived compounds have shown remarkable antifungal properties. The compounds **II**, **IV** and **V** have exhibited outstanding activity towards *A.Niger* and C. *Albicans* the remaining compounds have shown poor antifungal activity indicating less biological importance for a synthetic chemist.

Figure 4.Antibacterial activity of Schiff bases.

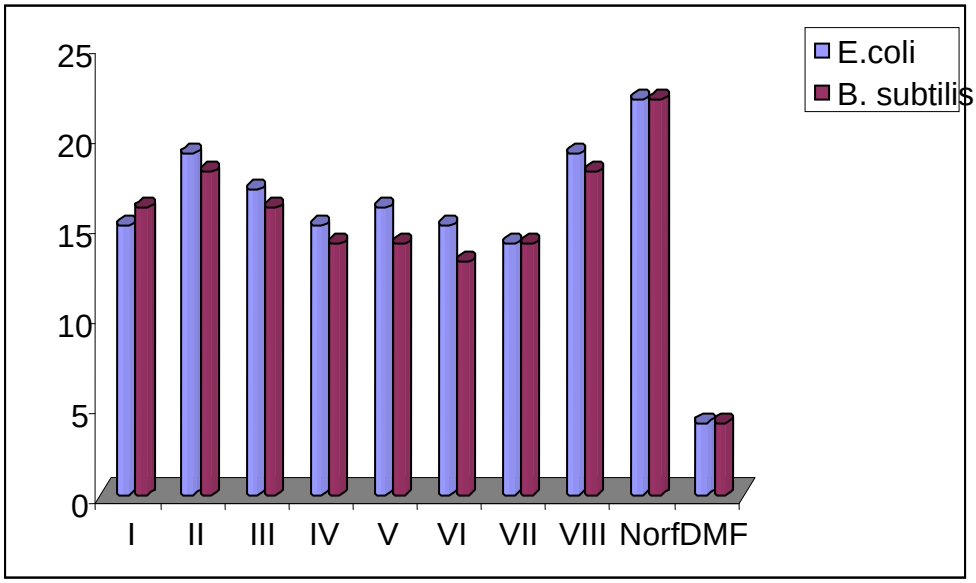
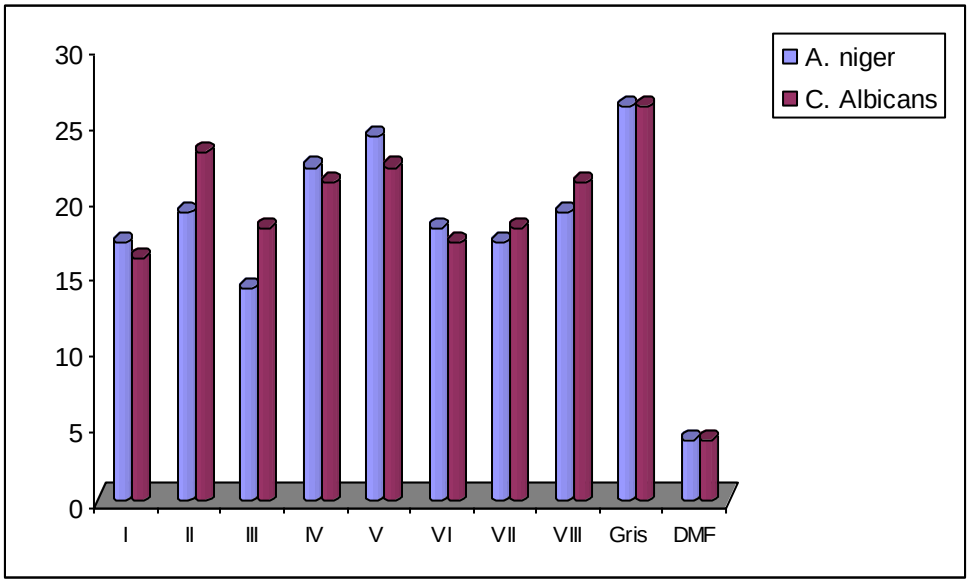


Figure 5. Antifungal activity of Schiff bases.



Efforts are under progress in evaluation of these synthesized compounds for in-vivo studies especially the acute toxicity, analgesic and anti-inflammatory agents and the results will be published in later communications.

This class of compounds has a great scope compared to other organic moieties because of their mesoionic nature, solubility and high sensitiveness towards the biological behaviors.

REFERENCES

1. G. Feuer In *"Progress in Medicinal Chemistry"*Edited by G.P.Ellis and G.B.West North Holland (NY), **1974**, *10*, 86.
2. S. Wawzonek in *"Heterocyclic compounds"* Edited by R. C. Elderfield John.Wiely (NY), **1951**, P217.
3. M J. Cook, A. R. Katitzky and P. Linda. *Adv.Het.Chem*., **1944**, *17*, 321.
4. S. S. Dharmatti, G. Govil, C. R. Kanekar and Y. P. Virmani. *Proc.Ind.Acad.Sci*., **1962**, *56*, 71.
5. W. V. Turner and W. H. Pirkle. *J.Org.Chem*., **1974**, *39*, 1935.
6. W. H. Pirkle and M. Dines. *J.Het.Chem*., **1969**, *61*, 1.
7. S. Y. Anantakrishanan.*Curr.Sci*., **1947**, *16*, 141.
8. V. M. Thakur and N. M. Shah. *J.Uni.Bombay*., **1947**, *16A*, 38.
9. P. S. Song and W. H. Gordon. *J.Phy.Chem*., **1970**, *74*, 4234.
10. P. Bassignan and C. Cogrossi. *Tettrahydron*., **1964**, *20*, 2859.
11. J. Stauton. in *"Comprehensive Organic Chemistry"* Edited by P.G.Sommes, Pergamon Press Oxford., **1979**, *4*, 629.
12. Kavali, J.R.; Badami, B.V. *IL Farmaco*. **2000**, 55, 406-409.
13. Mallur, S.G.; Badami, B.V. *IL Farnaco.* **2000**,55,65-67.
14. Hosamani, C.K.; Mallur, S.G.; Badami, B.V.*Indian J.Heterocycl. Chem.* **1996**, 6, 107.
15. Hiremath, U.S.; Yelamaggad, C.Y.; Badami, B.V.; Puranik, G.S. *J.Chem.Res. (s).* **1994**, 502.
16. Badami, B.V.; Puranik, G.S. *Indian J. chem.* **1974**, 12, 671.
17. Badami, B.V.; Puranik, G.S. *Rev. Roumaine chem.* **1982**, 27, 281.
18. Kavali J R, Kotresh O and Badami B V *J. Chem Res. (S).*,2003, 275.
19. Mohta and Kato H, In Nonbenzenoid. Aromatics, ed. Snyder J P, Academic press. New York, 1969, 117.
20. Earl J C and Mackney A W, *J. chem. Soc*. 1935, 899.
21. Kametani T, Sota K and Shio M, *J. Het. Chem.*, 1970, **7**, 821-829.
22. Rupe H and Gebhardt H, *Ber***,** 1899, **32,** 10.
23. Mallur S G and Badami B V, *IL Farmaco*, 2000, **55**, 65.
24. Chohan Z H, Arif M, Akhar M A and Supuran C T, *Bioinorganic Chemistry and Applications*, 2006, 1-13.
25. Sahu N P, Pal C and Mandal N B, *Bioorganic & Medicinal Chemistry*, 2002, **10(6)**, 1687.
26. Kolvaria E, Ghorbani-Choghamaranib A, Salehic P, Shirinid F and Zolfigol M A, *J. Iran. Chem. Soc.*, 2007, **4**(2**)**, 126.