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ORIGINAL ARTICLE

Synthesis of formazans from Mannich base of 5-(4-chlorophenyl amino)-2-mercapto-1,3,4-thiadiazole as antimicrobial agents

Pramilla Sah *, Pratibha Bidawat, Manu Seth, Chandra Prakash Gharu

Department of Chemistry, J.N.V. University, Jodhpur 342 005, Rajasthan, India

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KEYWORDS

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Abstract 5-(4-Chlorophenyl amino)-2-mercapto-1,3,4-thiadiazole (**I**) was refluxed with formaldehyde and ammonium chloride in ethanol yielding the Mannich base 5-(4-chloro phenyl amino)-3-aminomethyl-2-mercapto-1,3,4-thiadiazole (**II**). Esterification with 4-chloro-(2,6-dinitro phenoxy)-ethyl acetate (**III**) under anhydrous conditions gave the intermediate (**IV**). Subsequent hydrazinolysis with hydrazine hydrate gave the corresponding hydrazide 3-amino methyl-5-(4-chloro phenyl amino)-2-mercapto-4′-(2′,6′-dinitro phenoxy)-acetyl hydrazide (**V**). The hydrazide was converted into the Schiff bases ($\mathbf{VI_{a-b}}$) by reacting with 2-chlorobenzaldehyde and 3-methoxy-4-hydroxy benzaldehyde in presence of methanol containing 2–3 drops of acetic acid. Diazotisation with aromatic amines, sulphanilic acid and sulphur drugs gave the formazans ($\mathbf{VII_{a-g}}$) respectively. Chemical structures have been established by elemental analysis and the spectral techniques of FTIR, ^{1}H NMR and mass. Antimicrobial activity (*in vitro*) was evaluated against the two pathogenic bacterial strains. *Escherichia coli* and *Salmonella typhi*, three fungal strains *Aspergillus niger*, *Penicillium* species and *Candida albicans*. The compounds have shown moderate activity.

1. Introduction

Thiadiazole system is a cyclic analogue of thiosemicarbazide having the toxophoric N═C═S linkage. This heterocyclic system is responsible for a broad spectrum of biological activities, i.e. antimicrobial (Akhtar et al., 2007), antidepressant (Bahadur and Singh, 1980), antitubercular (Bauer et al., 1966), antioxidant (British Pharmacopeia, 1953), antidiabetic (Giri and Singh, 1967), antileishmanial (Haydon et al., 2009), anti-HIV (Jamode et al., 2008), anti-inflammatory (Joshi et al., 2008), etc.

Formazan derivatives have been synthesized by blocking the reactive hydrogen of a Schiff base or a hydrogen with diazotised

* Corresponding author. Tel.: +91 0291 2642340.
E-mail address: pramilla_s@yahoo.co.uk (P. Sah).
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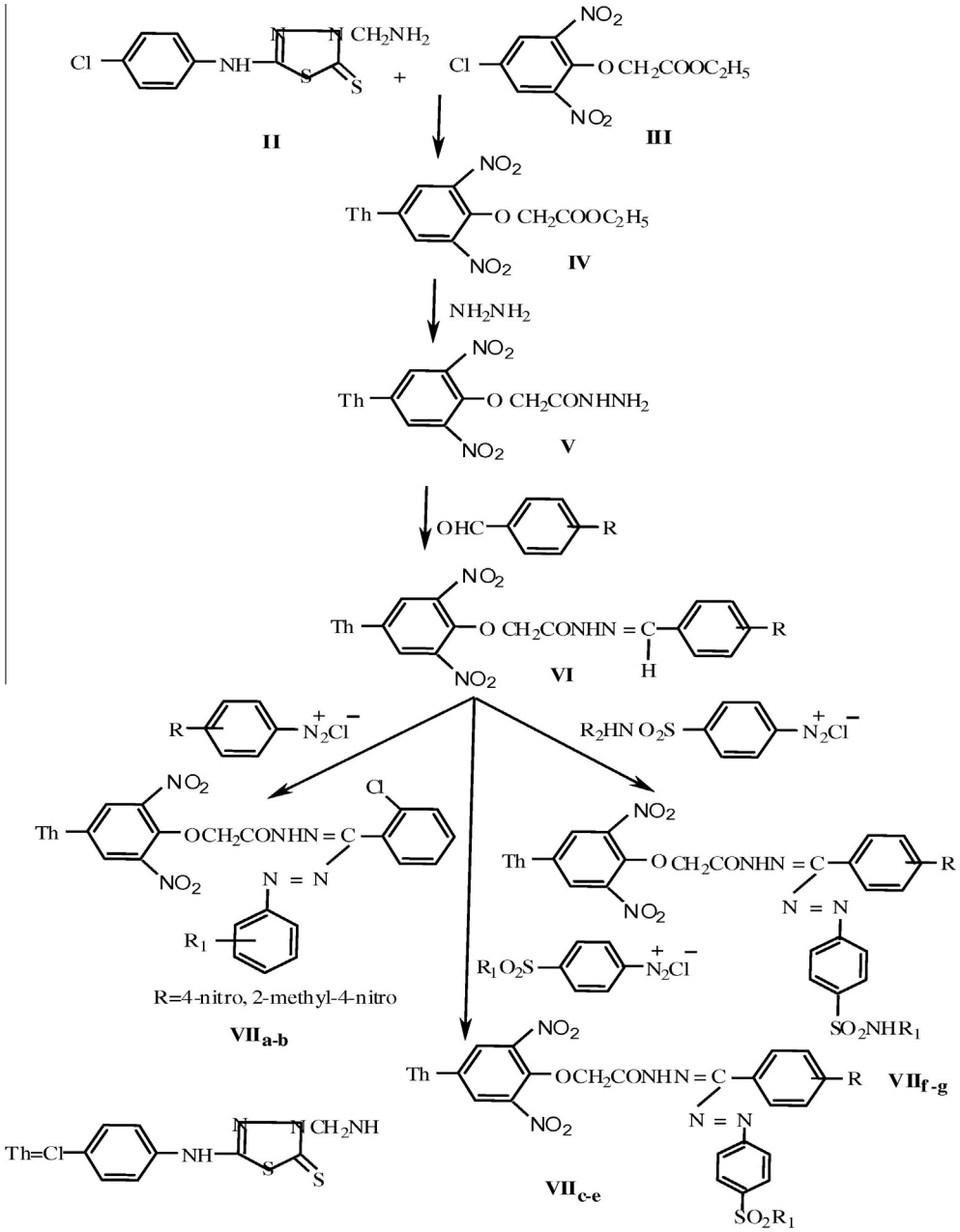
solution of aromatic amines and sulpha drugs. These coloured compounds have been reported to possess antibacterial and antiviral activities against Gomphrena Mossaic Virus (GMV), Sunhemp Rosette Virus (SRV) *in vitro* and *in vivo* (Kumar et al., 2008, 2007; Manoj Kumar et al., 2008; Mishra et al., 1978; Mukherjee and Shukla, 1981). The Sulphon-amides were the first effective chemotherapeutic agents to be employed systematically for the prevention and cure of the bacterial infection in the human beings and also used to treat some urinary tract infections, leprosy and in combination with other drugs in fungal diseases such as toxoplasmosis (Paria et al., 1982; Pattan et al., 2008). It is also reported that benzenesulphonamide substituted on the nitrogen of sulphonamido group such as sulphathiazole, sulphadiazine, and sulphaguanidine are known to possess antimicrobial activities (Pattanayak et al., 2009; Rustagi et al., 2003; Sah and Sinha, 2006).

Insecticidal activity has also been reported by quinazolin substituted formazans (Sah et al., 2010).



VI_a : R = 2-chloro, VI_b : R = 3-methoxy, 4-hydroxy
VII_{a-b} : R = 2-chloro, R_1 = 4-nitro, 2-methyl-4-nitro
VII_{c-e} : R = 2-chloro, R_1 = hydroxyl, amino, guanidino
VII_{f-g} : R = 3-methoxy, 4-hydroxy, R_1 = pyrimidinyl, 4,6–dimethyl pyrimidinyl

Scheme 1

Table 1 Physical and analytical data of Compounds ($\mathbf{VII_{a-g}}$).

Compd. No.	R	R_1	Yield (%)	M.P. (°C)	Molecular Formula	Elemental analysis [Found% (Calcd.%)]			
						C	H	N	S
$\mathbf{VII_a}$	2-Chloro	4-Nitro	60	95	$C_{30}H_{21}N_{11}O_8S_2Cl_2$	45.11 (44.98)	2.63 (2.75)	19.29 (19.19)	8.02 (8.14)
$\mathbf{VII_b}$	2-Chloro	2-Methyl, 4-nitro	70	100	$C_{31}H_{23}N_{11}O_8S_2Cl_2$	45.81 (45.79)	2.83 (2.79)	18.96 (19.15)	7.88 (7.92)
$\mathbf{VII_c}$	2-Chloro	Hydroxyl	70	125	$C_{30}H_{22}N_{10}O_9S_3Cl_2$	43.21 (43.17)	2.64 (2.62)	16.80 (16.75)	11.52 (11.50)
$\mathbf{VII_d}$	2-Chloro	Amino	55	120	$C_{30}H_{23}N_{11}O_8S_3Cl_2$	43.26 (43.27)	2.76 (2.80)	18.50 (18.47)	11.53 (11.55)
$\mathbf{VII_e}$	2-Chloro	Guanidino	65	110	$C_{31}H_{27}N_{13}O_9S_3Cl_2$	41.70 (41.69)	3.02 (3.10)	20.40 (20.45)	10.76 (10.82)
$\mathbf{VII_f}$	3-Methoxy-4-hydroxy	Pyrimidinyl	60	125	$C_{35}H_{28}N_{13}O_{10}S_3Cl$	45.57 (45.54)	3.03 (2.87)	19.75 (19.77)	10.41 (10.47)
$\mathbf{VII_g}$	3-Methoxy-4-hydroxy	4,6-Dimethyl pyrimidinyl	70	90	$C_{37}H_{32}N_{13}O_{10}S_3Cl$	46.76 (46.68)	3.37 (3.31)	19.16 (19.36)	10.11 (10.21)

Table 2 Antibacterial activity.[a]

Compound	*E. coli*	*S. typhi*
$\mathbf{VII_a}$	±	+
$\mathbf{VII_b}$	+	±
$\mathbf{VII_c}$	±	–
$\mathbf{VII_d}$	±	–
$\mathbf{VII_e}$	±	±
$\mathbf{VII_f}$	±	–
$\mathbf{VII_g}$	–	–

Disc size: 5 mm
Duration: 24 h.
Control: DMSO.
Standard: ampicillin, streptomycin (20–25 mm).
++: Highly active (20–25 mm).
+: Active (15–19 mm).
±: Moderately active (8–12 mm).
–: No activity.
[a] Concentration: 500 µg/disc.

In view of these observations, we have synthesized thiadiazole substituted formazans in a single molecular framework as possible antimicrobial agents.

2. Materials and methods

Melting points were determined in open capillary tubes in a 'Neolab' electrical apparatus and are uncorrected. FTIR was carried out on Schimadzu 8101 spectrophotometer in KBr pellets. ^{1}H NMR was recorded on a DPX 300 MHz Brucker spectrophotometer in DMSO and Mass spectra on JEOL SX 102/DA 6000 Mass spectrophotometer data system using Argon/Xenon (6 kV, 10 MA) as the FAB gas.

5-(4-Chlorophenyl amino)-2-mercapto-1,3,4-thiadiazole (**I**) was synthesized by the known procedure (Shashikant et al., 2008), while 4-chloro-2,6-dinitrophenoxy ethyl acetate (**III**) was prepared by our earlier method (Srivastava et al., 1983). The sulpha drugs obtained from the local market were purified by reported methods (Srivastava and Mishra, 1988).

*2.1. 5-(4-Chlorophenyl amino)-3-amino methyl-2-mercapto-1,3,4-thiadiazole (**II**)*

Equimolar ratio of 5-(4-chlorophenyl amino)-2-mercapto-1,3,4-thiadiazole, ammonium chloride and formaldehyde were refluxed in ethanol (10 ml) for 5–6 h. On cooling, a solid separated out which was filtered, dried and recrystallized from ethanol. Yield 60%; M.P. 125 °C; Molecular Formula $C_9H_9N_4S_2Cl$;% Calcd. (Found); C% = 39.63 (39.70); H% = 3.30 (3.34); N% = 20.55 (20.58); S% = 23.48 (23.45).

FTIR (KBr, cm^{-1}): 3415 ($-NH_2$), 3219 (–NH), 1380 (N═C═S), 1223 (N–N═C), 1170 (C–S–C), 739 (–Cl); ^{1}H NMR (DMSO, δ ppm, 300 MHz), 3.39 (s, 2H, CH_2), 4.11 (s, 2H, NH_2), 7.52–7.80 (m, 4H, ArH), 9.22 (s, 1H, NH).

*2.2. 3-Aminomethyl-[5-(4-chlorophenyl amino)-2-mercapto-1,3,4-thiadiazol-5-yl]-4′-(2″,6″-dinitrophenoxy)-ethyl acetate (**IV**)*

Mannich base (0.01 mol) (**II**) and 0.001 mol of the ester (**III**) were refluxed in dry acetone (10 ml) and 0.002 mol of anhy-

drous potassium carbonate for 5–6 h. The unreacted potassium carbonate was removed by decantation. Excess acetone was distilled off and the solution on cooling gave a solid which was filtered, dried and recrystallized from methanol.

Yield 70%; M.P. 120 °C; Molecular Formula $C_{19}H_{17}N_6O_7S_2Cl$; % Calcd. (Found); C% = 42.18 (42.22); H% = 3.14 (3.17); N% = 15.54 (15.50); S% = 11.84 (11.92).

FTIR (KBr, cm^{-1}): 3310 (–NH), 1710 (>C═O), 1530 ($–NO_2$), 1380 (N═C═S), 1223 (N–N═C), 740 (–C–Cl).

*2.3. 3-Aminomethyl-[5-(4-chlorophenyl amino)-2-mercapto-1,3,4-thiadiazol-5-yl]-4′-(2″,6″-dinitrophenoxy)-acetyl hydrazide (**V**)*

0.01 mol of (**IV**) and 0.07 mol (5 ml) of hydrazine hydrate (80%) were refluxed in absolute ethanol (8–10 ml) for about 4–5 h. Excess ethanol was distilled off. The solution was cooled and left overnight. A solid separated out which was filtered, dried and recrystallized from ethanol.

Yield 75%; M.P. 125 °C; Molecular Formula $C_{17}H_{15}N_8O_6S_2Cl$; % Calcd. (Found); C% = 38.74 (38.80); H% = 2.84 (2.92); N% = 21.27 (21.31); S% = 12.15 (12.09).

FTIR (KBr, cm^{-1}): 3325, 3420 ($NHNH_2$), 3310 (–NH), 1645 (>C═O), 1528 ($–NO_2$), 1382 (N═C═S), 1221 (N–N═C), 742 (–C–Cl).

*2.4. 3-[Aminomethyl-5-(4-chlorophenyl amino)-2-mercapto-1,3,4-thiadiazol-5-yl]-4′-[(2″,6″-dinitrophenoxy)]-methyl amido-2‴-chloro-benzylidene imine (**VI$_a$**)*

Equimolar ratio of the hydrazide (**V**) and 2-chloro benzaldehyde were refluxed for 6 h in presence of methanol (10 ml) containing 2–3 drops of acetic acid. Excess solvent was distilled off and the solution was left overnight in a refrigerator. A solid separated out which was filtered, dried and recrystallized by repeated washing with petroleum ether (60–80°) (Scheme 1).

Yield 70%; M.P. 110 °C; Molecular Formula $C_{24}H_{18}N_8O_6S_2Cl_2$; % Calcd. (Found); C% = 44.37 (44.41); H% = 2.77 (2.80); N% = 17.25 (17.19); S% = 9.86 (9.79).

FTIR (KBr, cm^{-1}): 3310 (–NH), 1648 (>C═O), 1625 (–N═C), 1525 ($–NO_2$), 1385 (N═C═S), 1220 (N–N═C), 742 (–C–Cl). ^{1}H NMR (DMSO, δ ppm, 300 MHz), 3.38 (s, 2H, CH_2), 4.26 (s, 2H, OCH_2), 5.18 (s, 1H, N═CH), 7.51–7.94 (m, 10H, ArH), 8.11 (s, 1H, CONH), 8.46 (s, 1H, CH_2-NH), 9.12 (s, 1H, C_6H_4NH).

VI$_b$: Yield 65%; M.P. 120 °C; Molecular Formula $C_{25}H_{21}N_8O_8S_2Cl$; % Calcd. (Found); C% = 45.42 (45.39); H% = 3.71 (3.11); N% = 16.95 (16.89); S% = 9.68 (9.71).

FTIR (KBr, cm^{-1}): 3320 (–NH), 3242 (OHbonded), 1642(>C═O), 1625 (–N═C), 1525 ($–NO_2$), 1385 (N═C═S), 1220 (N–N═C), 742 (–C–Cl).

*2.5. 1-(4‴-nitro phenyl)-3-(chloro phenyl)-5-[(3′-amino methyl)-(2″,6″-dinitro phenoxy acetyl)-5′-(4-chlorophenyl amino)-2′-mercapto-1′,3′,4′-thiadiazol-5′-yl]-formazan (**VII$_a$**)*

4-Nitro aniline (0.015 mol) was dissolved in 3 ml glacial acetic acid and stirred with 2 ml con. HCl at 0 °C. A solution of 1 gm sodium nitrite in 4 ml H_2O was then added drop wise with constant shaking, maintaining the temperature below 0–5 °C. The diazotised product was then added gradually with stirring to a cold solution of 0.01 mol of compound (**VI$_a$**) initially dissolved in 0.01 mol sodium acetate in minimum quantity of ethanol. The reaction product was allowed to stand at room temperature overnight and decomposed by pouring in ice cold water. The solid obtained was filtered, repeatedly washed with cold water, dried and recrystallized with petroleum ether (60–80 °C).

The same procedure was followed for compound **VII$_b$**.

*2.6. 1-(N′-(sulphanilamido)-3-(2-chloro phenyl)-5-[(3′-aminomethyl)-(2″,6″-dinitro phenoxy acetyl)-5′-(4-chlorophenyl amino)-2′-mercapto-1′,3′,4′-thiadiazol-5′-yl]-formazan (**VII$_c$**)*

Sulphanilic acid (0.01 mol) was initially dissolved in con. HCl (3 ml) and cooled in an ice bath. An aqueous solution of sodium nitrite (0.01 mol) was added gradually with constant shaking, maintaining the temperature below 0–5 °C. The diazotised product was further treated with an equimolar ratio of the Schiff base (**VI$_a$**) initially dissolved in an ethanolic solution of sodium acetate (0.01 mol). The contents were left for 24 h at room temperature and then poured into crushed ice. A solid separated out which was filtered, repeatedly washed with cold water dried and recrystallized with petroleum ether (60–80 °C).

The other formazans **VII$_d$**–**VII$_g$** were synthesized by the same method.

The physical and analytical data of the synthesized formazans are given in Table 1.

VII$_a$: FTIR (KBr, cm^{-1}): 3340 (–NH), 1637 (>C═O), 1620 (C═N), 1600 (N═N), 1532 (NO_2), 741 (–C–Cl). ^{1}H NMR (DMSO, δ ppm, 300 MHz), 3.38 (s, 2H, CH_2), 4.09 (s, 2H, OCH_2), 7.49–7.84 (m, 14H, ArH), 8.20 (s, 1H, CONH), 8.41 (s, 1H, CH_2NH), 9.23 (s, 1H, C_6H_4NH). Mass spectra: M^+. 798; 800 (M + 2); 802 (M + 4).

VII$_b$: FTIR (KBr, cm^{-1}): 3338 (–NH), 1641 (>C═O), 1620 (C═N), 1615 (N═N), 1535 ($–NO_2$), 740 (–C–Cl).

VII$_c$: FTIR (KBr, cm^{-1}): 3424 (–OH), 1642 (>C═O), 1600 (N═N), 1540 (NO_2), 1375, 1125 (SO_2, $\sqrt{}$asym, $\sqrt{}$sym), 730 (–Cl). ^{1}H NMR (DMSO, δ ppm, 300 MHz), 3.27 (s, 2H, CH_2), 4.11 (s, 2H, OCH_2), 7.25–7.73 (m, 14H, ArH), 8.14 (s, 1H, CONH), 8.32 (s, 1H, CH_2NH), 9.13 (s, 1H, C_6H_4NH), 10.19 (s, 1H, OH), Mass spectra: M^+. 833, 837 (M + 2), 842 (M + 4).

Table 3 Antifungal activity.[a]

Compound	*Aspergillus niger*	*Penicillium* sp.	*Candida albicans*
VII$_a$	+	+	±
VII$_b$	±	+	±
VII$_c$	–	±	–
VII$_d$	–	±	–
VII$_e$	±	–	–
VII$_f$	–	±	±
VII$_g$	–	–	–

Duration: 72 h.
Control: DMSO.
Standard: griseofulvin, gentamycin.
Medium: PDA (potato dextrose agar).
++: No growth, no fungal colony (highly active).
+: 0–20% Growth, 1–2 fungal colony (active).
±: 20–40 Growth, 2–4 fungal colony (moderately active).
–: >40% Growth, more than four fungal colonies (no activity).
[a] Concentration: 500 μg/disc.

VII_d: FTIR (KBr, cm^{-1}): 3445 (NH_2, broad), 1639 (>C=O), 1590 (N=N), 1530 ($-NO_2$), 1370, 1115 (SO_2, √asym, √sym), 740 (–Cl).

VII_e: FTIR (KBr, cm^{-1}): 3441 (NH_2, broad), 1638 (>C=O), 1595 (N=N), 1525 ($-NO_2$), 730 (–Cl), 1375, 1125 (SO_2, √asym, √sym).

VII_f: FTIR (KBr, cm^{-1}): 3350 (–NH), 3242 (–OH), 1641 (>C=O), 1600 (N=N), 1535 ($-NO_2$), 1370, 1120 (SO_2, √asym, √sym), 735 (–Cl). ^{1}H NMR (DMSO, δ ppm, 300 MHz), 2.5 (s, 1H, SO_2NH), 3.25 (s, 2H, CH_2), 4.18 (s, 2H, OCH_2), 4.56 (s, 3H, OCH_3), 7.42–7.97 (m, 16H, ArH), 8.20 (s, 1H, CONH), 8.48 (s, 1H, CH_2NH), 9.15 (s, 1H, C_6H_4NH), 10.11 (s, 1H, OH), Mass spectra: M^+. 921.5, 924 (M + 2).

VII_g: FTIR (KBr, cm^{-1}): 3355 (–NH), 3242 (–OH), 1645 (>C=O), 1590 (N=N), 1540 ($-NO_2$), 1379, 1125 (SO_2, √asym, √sym), 732 (–Cl).

3. Antimicrobial screening

Antimicrobial screening of the formazans was done following the disc diffusion technique (Tripathi and Mishra, 2007). All the compounds (**VII_{a-g}**) were screened for their *in vitro* antibacterial activity against *Escherichia coli* and *Salmonella typhi* at 500 µg/disc with Streptomycin and Ampicillin as the standard drugs. Antifungal activity was conducted against *Aspergillus niger*, *Penicillium* sp. and *Candida albicans* at the same concentration (500 µg/disc) using Griseofulvin and Gentamycin as the standard drugs. The zone of inhibition was recorded in mm after incubation of plates for 24 h (antibacterial) and 72 h (antifungal) at 37 °C (see Tables 2 and 3).

4. Results and discussion

The FTIR spectrum of compound **II** gave a distinct vibration at 3415 cm^{-1} which was characterised as the amino group vibrations. The ^{1}H NMR spectrum gave two singlets at δ 3.39 and another slightly downfield at δ 4.11 integrating for two protons each. These were identified as the methylene and the amino group protons. Conversion of this Mannich base into the ester (**IV**) gave two new stretching vibrations at 1710 cm^{-1} and 1530 cm^{-1} in its IR spectra which indicated the presence of a carbonyl and nitro group supporting the process of esterification.

Hydrazinolysis led to the formation of the hydrazide (**V**). Stretching vibrations at a slightly lower field around 1645 cm^{-1} were visualized which were the carbonyl group vibrations part of an amido group. Two new vibrations at 3325 and 3420 cm^{-1} indicated the presence of an $NHNH_2$ group.

The hydrazide on reacting 2-chloro benzaldehyde gave the substituted benzylidene imine (**VI_a**). A new vibrational mode at 1625 cm^{-1} was characterised for the C=N group. The ^{1}H NMR gave two singlets for two protons each at δ 3.38 and δ 4.26 while another singlet for one proton at δ 5.18, respectively. The signal for the single proton was that of a methine proton supporting and confirming the formation of the Schiff base.

The Schiff base when treated with the aromatic amine gave the formazan (**VII_a**). The FTIR spectra gave an extra vibration at 1600 cm^{-1} for the azo group. The ^{1}H NMR showed the absence of signal at δ 5.18 while a multiplet integrating for fourteen aromatic protons was visible between δ 7.49 and 7.84. When diazotised solution of sulphanilic acid was taken the

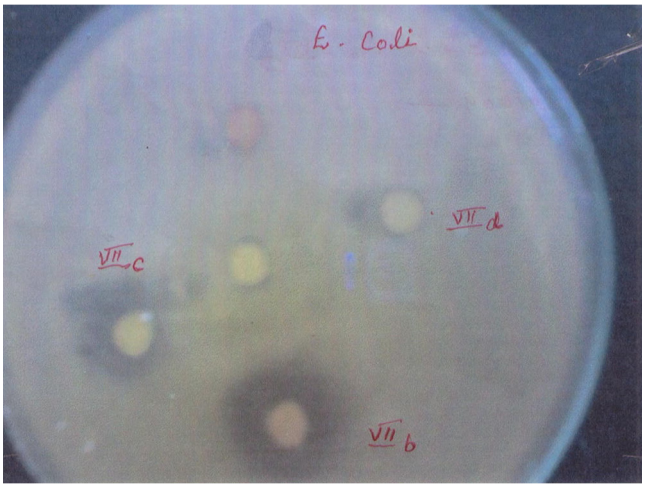


Figure 1 Activity shown by *E. coli*.

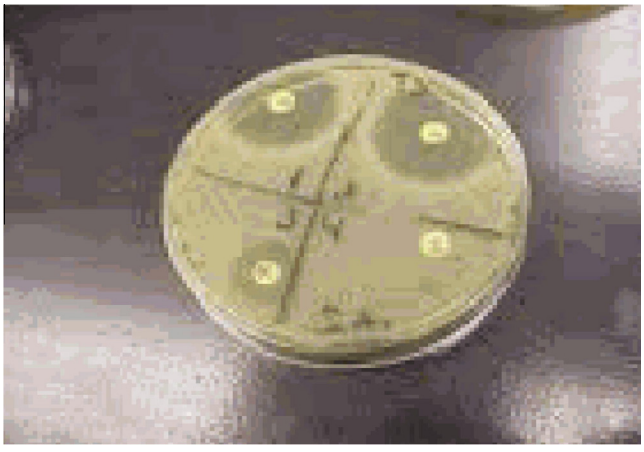


Figure 2 Activity shown by *A. niger*.

FTIR spectrum gave two vibrations at 1125 cm^{-1} and 1375 cm^{-1} which were the symmetric and asymmetric vibrations of the $-SO_2$ group. Band at 3424 cm^{-1} was also observed identified as that of a free hydroxyl group. Presence of the hydroxy group was also indicated by the appearance of a very downfield signal at δ 10.19 in its ^{1}H NMR spectrum.

The mass spectra of compound **VII_a** gave the molecular ion peak at M^+ 798, with two isotopic peaks at 800 (M + 2) and 802 (M + 4) respectively indicating the presence of two halogen atoms. The mass spectra of two other formazans, i.e. **VII_c** and **VII_f** were taken. The molecular ion peaks were visible at M^+ 833 with isotopic peaks at 837 and 842 in compound **VII_c** while the molecular ion peak in **VII_f** was visible at M^+ 921.5 and the isotopic peak at 924 (M + 2), respectively. These mass fragments were in concordance with the molecular weight of the formazans, hence supporting their chemical structures (see Fig. 3).

4.1. Antibacterial activity

Compound (**VII_b**) showed maximum activity (15–19 mm) zone size against *E. coli* while all other compounds showed moderate activity (see Fig. 1).

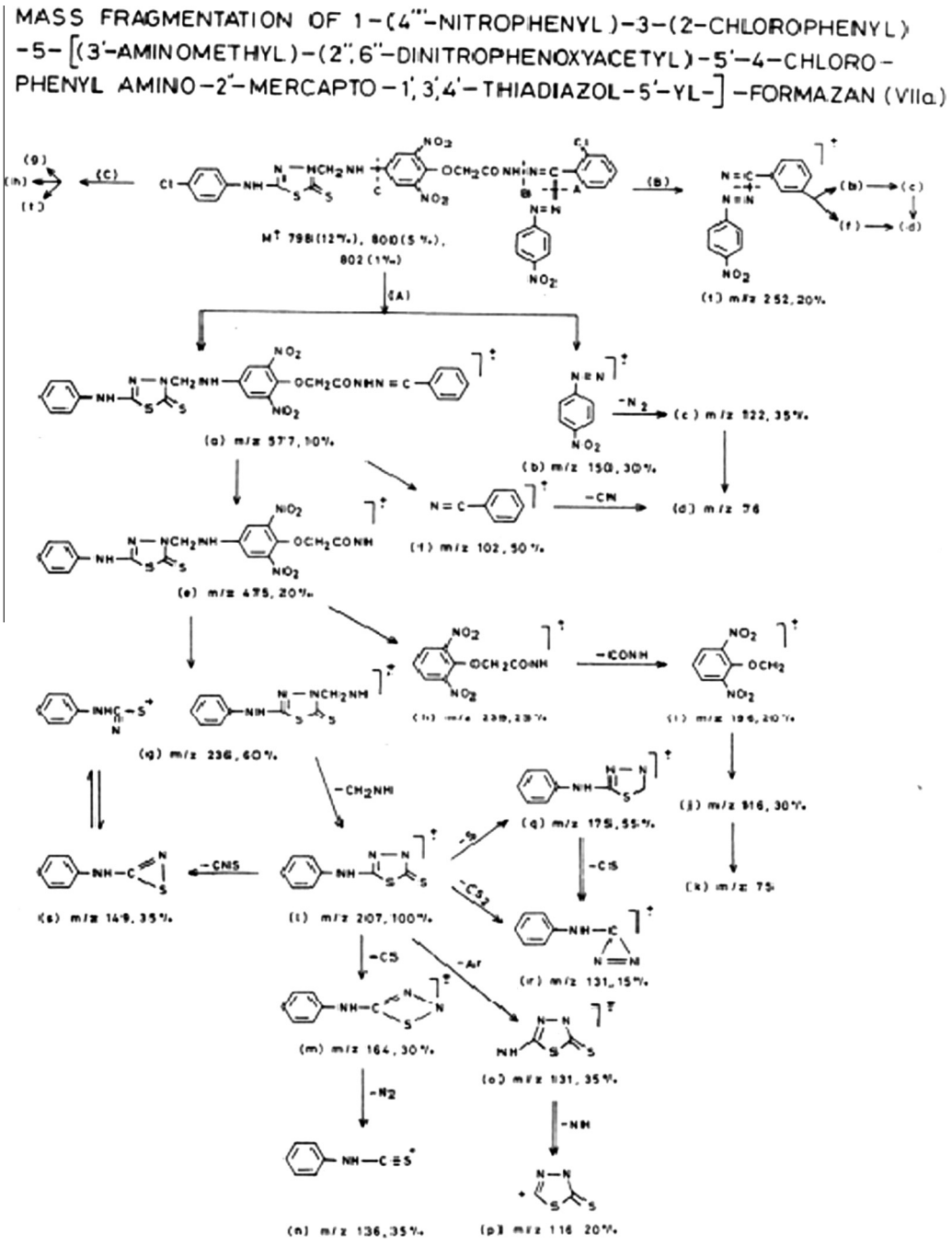


Figure 3 Mass spectra.

Against *S. typhi*, only one derivative ($\mathbf{VII_a}$) showed the maximum inhibition while two formazans compound ($\mathbf{VII_b}$, -$\mathbf{VII_e}$) showed moderate activity (see Fig. 2).

4.2. Antifungal activity

Among the substituted formazans, compound ($\mathbf{VII_a}$) was active against all two fungal strains, i.e. *A. niger* and *Penicillium* species with the development of 1–2 fungal colonies after 72 h incubation followed by $\mathbf{VII_b}$ which was active only against *Penicillium*.

Against *C. albicans* only three derivatives $\mathbf{VII_a}$, $\mathbf{VII_b}$ and $\mathbf{VII_f}$ were moderately active.

It shows that *Penicillium* species was the most inhibited by the formazans among the three fungal strains.

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