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RESEARCH ARTICLE

SYNTHESIS AND CHARACTERIZATION OF SOME NEW BIOLOGICALLY ACTIVE IMINES DERIVED FROM 3-METHOXY-4-ACETYLOXY-BENZALDEHYDE AND 3-METHOXY-4-*P*-TOLUENE-SULPHONYLOXY-5-ALLYL-BENZALDEHYDE

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ABSTRACT

A new series of imines ((*E*)-4-(((4-substituted-phenyl)imino)methyl)-2-methoxyphenyl-acetate and (*E*)-2-allyl-4-(((4-substituted-phenyl)imino)methyl)-6-methoxy phenyl-4-methyl-benzene-sulfonate) has been synthesized by the condensation of 3-methoxy-4-acetyloxy benzaldehyde and 3-methoxy-4-*p*-toluene-sulphonyloxy-5-allyl-benzaldehyde with several sulfa drugs and characterized by FT-IR, ^{1}H NMR spectra and elemental analysis. The compounds were screened *in-vitro* against *E. coli, P. aeruginosa, B. subtilis, A. niger, A. flavus* using disc diffusion method. The synthesized compounds exhibited promising antimicrobial activity.

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INTRODUCTION

Antibiotic resistance is a problem of deep scientific concern both in hospital and community settings. Resistance of pathogenic organisms to tolerate antibiotics has become a worldwide problem with severe consequences on the treatment of infectious diseases. The heightened use/misuse of antibiotics in human medicine, agriculture and veterinary is primarily contributing to the phenomenon. There is a perturbing increase of antibiotic resistance in bacteria that cause either community infections or hospital acquired infections. Imines are characterized by the -N=CH- linkage. The imines family is composed of natural products with critical pharmacophores (Przybylski *et al*., 2009). It can be used as ideal lead structures to develop agrochemicals and medicines, including fungicide (Aggarwal *et al*., 2009; Isloor *et al*., 2009), bactericide (Shi *et al*., 2007), antiviral agent (Sriram *et al*., 2006), herbicide (Ward *et al*., 1986), insecticide (DeMilo and Redfern, 1979), antioxidant (Gumrukcuoglu *et al*., 2013), antiproliferative (Sztanke *et al*., 2013; Mohana and Mallesha, 2013) and antimicrobial drug (Vijesh *et al*., 2013; Pudota *et al*., 2013). Some imines were reported to possess antibacterial (Sridhar *et al*., 2001; Mladenova *et al*., 2002; Panneerselvam *et al*., 2005; Walsh *et al*., 1996; Pandeya *et al*., 1999; Pandeya *et al*., 1999), antifungal (Panneerselvam *et al*., 2005; Walsh *et al*., 1996; Pandeya *et al*., 1999; Pandeya *et al*., 1999) and antitumor activities (Liu *et al*., 1992; Hodnett and Dunn, 1970). Apart from pharmacological applications, 1,3-dipolar cyclo-addition of imine has been considered to be an efficient and versatile tool for the construction of different heterocycles. In addition imines perform important role in biological systems, where the >C=N- linkage is an essential structural requirement for biological activity (Sengupta, 1964). Many imines exhibited remarkable antibacterial (Shridhar *et al*., 1996; Shkawat, Sabnis and De liwala, 1993) antifungal (Barboiu *et al*., 1996; Pignatello *et al*., 1994), anticancer (Wu *et al*., 2007), diuretic activities (Mereghetti *et al*., 2000) and can also be regarded as mimetic systems for enzyme models (Deshmukh and Doshi, 1995). Sulfa drugs, the first medications effective against bacterial diseases appeared as the "miracle drugs" when death from bacterial infections such as pneumonia and blood poisoning were common (http://www.encyclopedia.com/topic/sulfa_drug.aspx). These are known for antibacterial (Mandell *et al*., 1966; Maren, 1976; Owa and Nagasu, 2000), anti-tumor (Domagk, 1935), diuretic (Boyd, 1988) and anti-thyroid activities (Ogden and Flexner, 2001). The presence of imine and sulfonamide functional group has been considered responsible for biological activity. A group of synthetic organic compounds derived from sulfanilamide, capable of inhibiting bacterial growth and activity. The sulfonamide derivatives are

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widely used in clinical medicine as pharmacological agents with a wide variety of biological actions (Alhassan *et al*., 2004; Cheng *et al*., 2010). Considering all these, it was of importance to synthesize ((E)-4-(((4-substitutedphenyl)imino)methyl)-2-methoxyphenyl acetate and (E)-2-allyl-4-(((4-substituted-phenyl)imino)methyl)-6-methoxyphenyl-4-methylbenzenesul fonate) with a possible antimicrobi- al activity. More importantly, these have the advantage of ease of synthesis without the need for stringent reaction conditions or metal catalysts.

MATERIALS AND METHODS

Chemicals and reagents used

All materials were of commercial grade reagent and purchased from Sigma-Aldrich. All reactions were monitored by Thin-Layer chromatography (TLC) on pre-coated sheets of 25 DS alufolin kieselgel 60 F_{254} silica gel 60 F_{254} (Merck), using UV-vis florescence analysis chamber for detection. Melting points were measured in open glass capillary and are uncorrected. ^{1}H NMR spectra were recorded on a BRUKER AVANCE-II 129 400 MHz FT-NMR spectrometer (Bruker Bio Spin, Switzerland) at 400 and 100 MHz respectively. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer. Elemental analysis was performed on Elementarvario MICRO cube CHN analyzer. All synthesized compound were purified by recrystallization with ethanol.

General procedure for the synthesis of precursors

(a) General procedure for the synthesis of 3-methoxy-4-acetyloxy-benzaldehyde

5.32 g of 3-methoxy-4-hydroxy-benzaldehyde (0.35 N) was dissolved in 25 ml of aqueous (2.5 N) NaOH solution, Crushed ice along with 5.7 ml of acetic anhydride was added in it. The contents were stirred vigorously for one hour. The supernatant obtained is filtered and washed successively with 0.1N NaOH and distilled water. It was then recrystellized with n-hexane. Molecular formula $C_{10}H_{10}O_4$ Yields 84%, m.p. 80^{o}C; Elemental analysis data; Found/required (%) C 61.65 (61.85), H 4.96 (5.19), O 32.85 (32.96); IR Absorption frequencies (cm^{-1})1690.3 C=O (ald.), 1598.7 C=C (Ar), 2846.4 C-H (Ar), 1427.07 C-H (Ar), 1757.8 C=O (ester); ^{1}H NMR-Spectra (DMSO) δppm 3.33 (1HS) Ar-H, 7.32-7.4 1(2HD) Ar-H, 9.993 (1HS) CHO, 3.8 (3HS) OCH_3, 2.28 (3HS) CH_3(ester).

(b) General procedure for the synthesis of 3-methoxy-4-*p*-toluene-sulphonyloxy-5-allyl-benzaldehyde: Synthesis has been done in following three steps:

I. Preparation of 3-methoxy-4-allyloxy-benzaldehyde

A mixture of vanillin (12.16 g), potassium carbonate (10 g), allylbromide (6.8 ml) in DMF (25 ml) was shaken vigorously for one hour, when homogeneous solution obtained. The contents were left overnight, poured in water (150 ml) and acidified with 2.0 N HCl and extracted with ether. The extract was washed, free from vanillin with NaOH (0.1 N), then with water and dried over anhydrous $MgSO_4$. Evaporation of solvent 3-methoxy-4-allyloxy-benzaldehyde was obtained as viscous dark colored liquid.

II. Claisen rearrangement of 3-methoxy-4-allyloxy-benzaldehyde: formation of 3-methoxy, 4-hydroxy-5-allyl-benzaldehyde

3-methoxy-4-allyloxy-benzaldehyde (5.0 g) was heated in an oil bath at 200-220^{o}C for two hours. The viscous liquid on cooling gave pale yellow solid. Recrystellization with ethanol gave 4.6 g (92%) of the pure product.

III. Tosylation of 3-methoxy-4-hydroxy-5-allyloxy-benzaldehyde: formation of 3-methoxy-4-*p*-toluene-sulphonyloxy-5-allyl-benzaldehyd

5.0 g of 3-methoxy-4-hydroxy-5-allyl-benzaldehyde in 100 ml dry acetone was treated with 5.0 g *p*-toluene-sulphonyl-chloride followed by gradual addition of (4.g) Sodium bicarbonate solution in 20 ml of water. After vigorous stirring the reaction mixture was poured in to water. The product was washed with dilute NaOH and water, recrystellized from alcohol.

General procedure for the synthesis of imines (a1-a6)

Solution of 3-methoxy-4-acetyloxy-benzaldehyde (0.005 mol) and sulfathiazole (0.005 mol) were refluxed for eight hours, cooled in ice water and a few drop of sulfuric acid was added. The contents were scratched when solid separated out; it was filtered under suction, washed with water and recrystellized from ethanol/water (1:1) mixture, imines were obtained as light yellow crystals.

General procedure for the synthesis of imines (b1-b6)

Solution of 3-methoxy-4-*p*-toluene-sulphonyloxy-5-allyl-benzaldehyde (0.005 mol) and sulfona- mide (0.005 mol) were refluxed for eight hours, cooled in ice water and a few drop of sulfuric acid was added. The contents were scratched when solid separated out. It was filtered under suction, washed with water and recrystellized from ethanol/water (1:1) mixture; imines were obtained as yellow crystals.

Analytical data

Compound (a1) Molecular formula $C_{24}H_{24}N_2O_6S_2$;Yield; 79%; m.p. 207^{o}C; Elemental analysis data required (found %); C 57.58 (57.41), H 4.83 (4.74), N 5.60 (5.53); IR Absorption Frequencies (cm^{-1}); C=N (imines); 1619.91, C=O (ester); 1707.90, NH; 3378.67, C=C(Ar); 1596.77, OCH_3; 1471.42, C-H (Ar); 2846.4, ^{1}H NMR-Spectra (DMSO) δppm 10.91(NH, 1HS), 6.07-7.46 (Ar-H, 7HM), 3.32 (OCH_3, 3HS), 2.27 (CH_3(ester), 3HS) 2.10(NH, 1HS).

Compound (a2) Molecular formula $C_{26}H_{25}N_2NaO_7S_2$Yield; 79%, m.p. 216^{o}C; Elemental analysis data required (found %); C 55.31 (55.26), H 4.46 (4.39), N 4.96 (4.91); IR Absorption Frequencies (cm^{-1}); C=N (imines); 1619.91, C=O (ester); 1690.90, NH; 3300.67, C=C(Ar); 1596.77, OCH_3; 1420.42, C-H (Ar); 2900.4, ^{1}H NMR-Spectra (DMSO) δppm 10.91(NH, 1HS), 6.07-7.46 (Ar-H, 7HM), 3.32 (OCH_3, 3HS), 2.27 (CH_3(ester), 3HS) 2.00(CH_3, 1HS).

Compound (a6) Molecular formula $C_{19}H_{17}N_3O_5S_2$; Yield; 79%, m.p. 189^{o}C; Elemental analysis data required (found %); C 52.89 (52.70), H 3.97(3.85), N 9.74(9.71); IR Absorption Frequencies (cm^{-1}); C=N (imines); 1619.91, C=O (ester);

Table 1. Physical data of compounds (a1-a6)

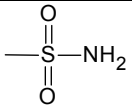
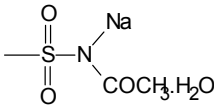
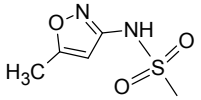
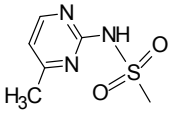
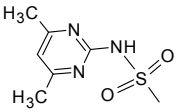
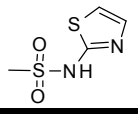
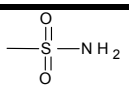
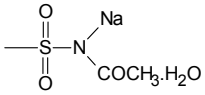
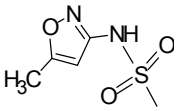
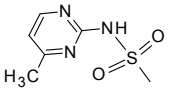
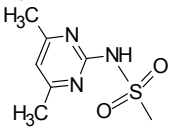
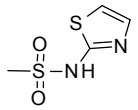
S.N.	Compound	R	m.p.°C	Yield %	Molecular formula
1.	a1		207	69	$C_{16}H_{14}N_2O_4S$
2.	a2		216	60	$C_{18}H_{19}N_2NaO_7S$
3.	a3		191	74	$C_{20}H_{19}N_3O_6S$
4.	a4		195	82	$C_{22}H_{22}N_4O_5S$
5.	a5		211	64	$C_{16}H_{18}N_3O_6SNa$
6.	a6		189	79	$C_{19}H_{17}N_3O_5S_2$

Table 2. Physical data of compounds (b1-b6)

S.N.	Compound	R	m.p.°C	Yield %	Molecular formula
1.	b1		179	68	$C_{24}H_{24}N_2O_6S_2$
2.	b2		194	54	$C_{26}H_{27}N_2NaO_8S_2$
3.	b3		179	71	$C_{28}H_{27}N_3O_7S_2$
4.	b4		186	66	$C_{29}H_{28}N_4O_6S_2$
5.	b5		198	62	$C_{30}H_{30}N_4O_6S_2$
6.	b6		173	72	$C_{27}H_{25}N_3O_6S_3$

1707.90, NH; 3378.67, C=C(Ar); 1596.77, OCH_3; 1471.42, C-H (Ar); 2846.42, ^{1}H NMR-Spectra (DMSO) δppm 10.91(NH, 1HS), 6.07-7.46 (Ar-H, 7HM), 3.32 (OCH_3, 3HS), 2.27 (CH_3(ester), 3HS).

Compound (b1) Molecular formula $C_{16}H_{16}N_2O_5S$; Yield; 79%, m.p. 189°C; Elemental analysis data required (found %); C 55.16 (55.02), H 4.63 (4.54), N 8.04 (7.93); IR Absorption Frequencies (cm^{-1}); C=N (imines); 1619.91, C=O (ester); 1700.90, NH; 3350.67, C=C(Ar); 1596.77, OCH_3; 1471.42, C-H (Ar); 2846.4, ^{1}H NMR-Spectra (DMSO) δppm 9.00(NH, 1HS), 7.07-8.46 (Ar-H, 7HM), 3.82 (OCH_3, 3HS), 2.27 (CH_3(ester), 3HS) 1.90(NH, 1HS).

Compound (b2) Molecular formula $C_{18}H_{17}N_2NaO_6S$; Yield; 79%, m.p. 194°C; Elemental analysis data required (found %); C 52.42 (52.43), H 4.16 (4.09), N 6.79 (6.68); IR Absorption Frequencies (cm^{-1}); C=N (imines); 1600.91, C=O (ester); 1650.90, NH; 3378.67, C=C(Ar); 1550.77, OCH_3; 1450.42, C-H (Ar); 2800.4, ^{1}H NMR-Spectra (DMSO) δppm 9.00(NH, 1HS), 7.07-8.46 (Ar-H, 7HM), 3.82 (OCH_3, 3HS), 2.27 (CH_3(ester), 3HS) 2.40(CH_3, 1HS).

Compound (b6) Molecular formula $C_{27}H_{25}N_3O_6S_3$; Yield; 72%, m.p. 173°C; Elemental analysis data required (found %); C 55.56 (55.47), H 4.32 (4.25), N 7.20 (7.08); IR Absorption Frequencies (cm^{-1}); C=N (imines); 1654.31, CH_3-Ar. 2870.23 CH_2 (allyl group) 2750.67 NH; 3365.53, C=C(Ar); 1548.23, OCH_3; 1476.45, C-H (Ar); 2874.58, ^{1}H NMR-Spectra (DMSO) δppm 8.86. (CH=N, 1HS), 4.90-5.00 (2HD allyl CH_2) 5.87-5.93 (5HM allyl CH), 3.14 (2HD CH_2) 4.00 (1HS NH) 6.02-7.53 (Ar-H, 10HM), 3.71 (OCH_3, 3HS), 2.84 (3HS CH_3-Ar).

Table 3. Results of *in-vitro* antimicrobial activity screening of imines (a1-a6)

S. No.	Compound	Zone of inhibition (mm)				
		E.coli	*P.aeruginosa*	*B.subtilis*	*A.niger*	*A.flavus*
1	a1	10	-	12	10	16
2	a2	12	-	14	12	12
3	a3	14	14	20	14	20
4	a4	10	-	16	10	16
5	a5	-	-	14	10	-
6	a6	14	12	20	14	16
7.	Control	28	24	32	24	36

Concentration =1000 µg/ml, (-) = No effect
Control for bacterial/fungal strain: Chloremphenicol/Fluconazole

Table 4. Results of *in-vitro* antimicrobial activity screening of imines (b1-b6)

S.No.	Compound	Zone of inhibition (mm)				
		E.coli	*P.aeruginosa*	*B.subtilis*	*A.niger*	*A.flavus*
1	b1	16	14	16	12	20
2	b2	14	18	20	14	14
3	b3	12	20	28	16	16
4	b4	14	16	20	12	16
5	b5	16	16	14	12	14
6	b6	18	16	20	14	24
7.	Control	28	24	32	24	36

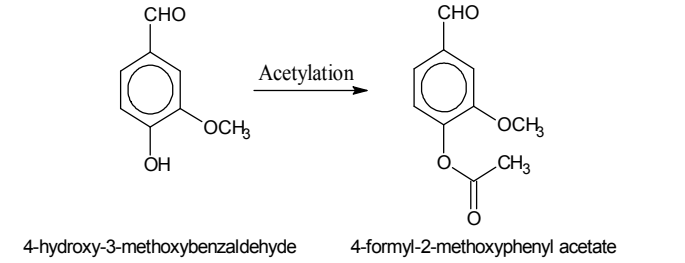
Concentration = 1000 µg/ml, (-) = No effect
Control for bacterial/fungal strain: Chloremphenicol/Fluconazole

Antimicrobial activity

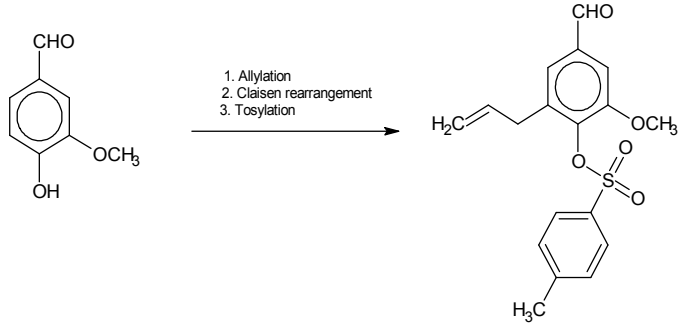
All the synthesized imine analogs (a1-a6 and b1-b6) has been screened *in-vitro* for their antibacterial activity against *E. coli, P. aeruginosa, B. subtilis* and antifungal activity against *A. niger, A. flavus* in order to determine their structure-activity relationship. The Reference antibacterial drug Chloremphenicol and antifungal drug Fluconazole was used for the study.

RESULTS AND DISCUSSION

The synthetic sequence and mechanism of formation of the precursors and synthesized imines has been depicted in **Scheme-1 and Scheme-2** respectively.

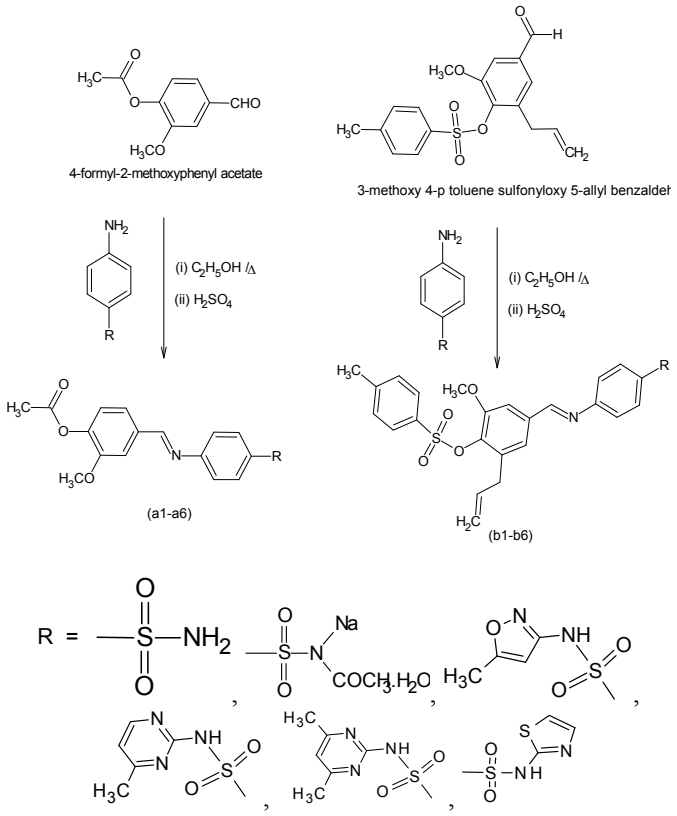


4-hydroxy-3-methoxybenzaldehyde 4-formyl-2-methoxyphenyl acetate



2-allyl-4-formyl-6-methoxyphenyl-4-methylbenzenesulfonate

Scheme – 1



Scheme – 2

Highlights of the results of *in-vitro* antimicrobial activity observed for the synthesized imines (a1-a6) and (b1-b6) through disc diffusion assay are as follows:

- Imine (b3) with allyl, sulphonyloxy and sulfamethoxazole group exhibit better antibacterial activity against *Bacillus subtilis*.
- Imine (b6) with allyl, sulphonyloxy and sulfathiazole group exhibit better antifungal activity against *A.flavus.*

Conclusion

A series of new Imine analogs (a1-a6 and b1-b6) were synthesized and their antibacterial and antifungal activity has been evaluated. Results indicated that synthesized imines exhibited good antimicrobial activity. Imine analog (b3) with allyl sulphonyloxy and sulfamethoxazole group exhibited better antibacterial activity against *Bacillus subtilis*. Imine analog (b6) with allyl sulphonyloxy and sulphathiazole group exhibited better antifungal activity against *A. flavus.*

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