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Solid phase-promoted greener synthesis and antibacterial activity of novel Schiff bases under catalytically free condition

Shaikh Kabeer Ahmed, Vishal A. Patil and Zamir A. Mohammed

Department of Chemistry, Sir Sayyed College, P.B. No. 89, Aurangabad, M.S., India-431001.

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ABSTRACT

Non-traditional method (grinding) was used for the preparation of novel schiff bases from 4-amino-3-methyl phenol / 2-amino-4-methyl phenol and several aldehydes and ketones under catalytically free condition. This procedure constitutes an energy efficient, shorter time, higher yield as well as green synthesis approach. Some synthesized products were characterized by IR, NMR and MASS and also tested for antibacterial (*Escherichia coli, Staphylococcus aureus, Bacillus subtilis, and Klebsiella pneumonae*) activities by disc diffusion method

Introduction

Schiff bases and their derivatives, which usually possess diverse biological activities such as antibacterial [1-4], antifungal [4], anti-inflammatory [5], analgesic [6], CNS depressant [6] anticonvulsant [7], anticancer [8], insecticidal [9], plant growth inhibitor [10], antitubercular[11] and antitumor [12-13].

Schiff bases are also used as a starting material in the preparation of number of industrial and biological active compounds via ring closure, cycloaddition and replacement reaction [14]. At present a broad range of methods for synthesizing imines in the presence of catalysts are available: $ZnCl_2$ [15], $TiCl_2$ [16], K-10 [17-18], $MgSO_4$-PPTL [19], $Mg(ClO_4)_2$ [20] and also SiO_2-$NaHSO_4$ (under MW irradiation condition) [21]. More recently, ultrasound irradiation has been used to give rise to the formation of a series of Schiff bases (aryl-aryl and aryl-alkyl), under solvent-free conditions [22] or using SiO_2 as a catalyst in ethanol [23], with short reaction times (10-20 min) and high yields. But, in recent years, environmentally benign synthetic methods have received considerable attention. Verma et al [24] reported synthesis of enamines and imines under microwave irradiation accompanied with solvent less condition. Kaupp et al [25] reported the synthesis of Schiff bases using water as a solvent.

These wide application and biological data prompted us to synthesize new Schiff bases and to ascertain their microbial activity.

Result and discussion

Chemistry:

In this article, we have prepared thirty new Schiff bases under solvent and catalytically free condition (except 27, 28, 29, 30. Table 1). Initially, the mixture of substituted amines and aldehydes was ground in mortar with a pestle at room temperature under neat condition (Table 1, 1-26). The result demonstrated that, completion of reaction in 2-3 min. but, when the mixture of substituted amines and ketones was ground in mortar with a pestle at room temperature under neat condition. The result demonstrated that the need of catalyst. Thus, we chose inexpensive and efficient HOAc as a catalyst for this reaction. HOAc was used in 20 mol % which, leads to excellent yield of the product (Table 1, 27-30).

Anti-bacterial activity:

For the anti-bacterial activities we chose some selected compounds (Table 2). These compounds were evaluated against various pathogenic (Gram-negative and Gram-positive) bacterial strains viz., *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*), *Bacillus subtilis* (*B. subtilis*) and *Klebsiella pneumonae* (*K. pneumonae*).

The anti-bacterial activities were evaluated by the disc diffusion method. The solvent used for the preparation of compound solution (DMSO) did not show inhibition against the tested organisms (negative control).

The results of anti-bacterial screening of newly synthesized compounds are presented in Table 2. In these compounds 1 and 15 showed good activity (zone of inhibitions 11 and 15 mm at concentration of 250 µg/ml) against *S. aureus.* Compound 6 showed excellent activities (zone of inhibitions 15-19 mm at concentration of 250 µg/ml) against all four bacterial strains. It is interestingly to note that the slight structural difference in 5 and 6 can be observed, but their antibacterial activity is entirely different.

The electric property of the compounds has close relations with biological activity [26, 27] and the weak antibacterial activity of compound 5 compared to compound 6 may be explained by their charge density distribution.

Compound 13 showed good activity (zone of inhibitions 6-16 mm at concentration of 250 µg/ml) against *E. coli, S. aureus and K. pneumonae.* The compound 21 with CH_3 substituent at meta position showed moderate antibacterial activity (zone of inhibitions 11 mm at concentration of 250 µg/ml) against *E. coli.* but the compound 22 with CH_3 substituent at para position did not show any activity against *E. coli, S. aureus, B. subtilis* and *K. pneumonae.*

Tele: 0091-240-2311285, 2313876

E-mail addresses: shaikh_kabeerahmed@rediffmail.com

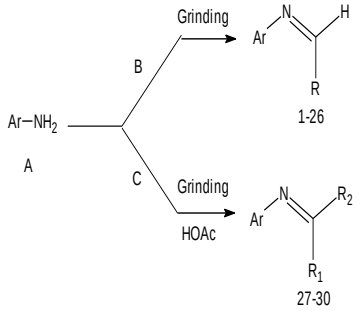
Experimental:

Material and instrumentation:

All the chemicals used for this work were obtained from Merck and Aldrich Chemical Companies. Melting points of the synthesized compounds were determined in open-glass capillaries on a stuart-SMP10 melting point apparatus and are uncorrected. IR absorption spectras were recorded on a Perkin Elmer 1650 FTIR using KBr pellets in the range of 4,000-450 cm^{-1}, ^{1}H-NMR were recorded on a Bruker spectrometer operating at 300 MHz using. The ^{1}H-NMR chemical shifts are reported as parts per million (ppm) downfield from TMS (Me_4Si) used as an internal standard. Mass spectras were recorded on LCQ ion trap mass spectrometer. Purity of the compounds was checked by thin layer chromatography (TLC) on Merck silica gel 60 F254 precoated sheets in benzene/methanol mixture and spots were developed using iodine vapors as visualizing agents.

Synthesis of Schiff bases (1-26):

A mixture of 4-amino-3-methyl phenol/2-amino-4-methyl phenol (1 mmol) and substituted aldehydes (1mmol) was grinded in a mortar with a pestle made of porcelain. Progress of reaction was monitored by TLC. After completion of reaction (2-3 min) the crude product was purified by column chromatography. Synthetic pathway for preparation of title compounds is shown in Scheme 1.



Scheme 1: Synthesis of Schiff bases

A = Substituted Aromatic Amines

B = Substituted Aromatic Aldehydes

C = Substituted Aromatic ketones

4-{[(*E*)-(4-chlorophenyl)methylidene]amino}-3-methylphenol (1)

IR (KBr, cm^{-1}) ν 3387, 3026, 2926, 1601, 1492, 1452, 1370, 1028, 754, 698, 540; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ: 10.01 (s, 1H, OH), 8.33 (s, 1H, CH=N), 7.82 (d, J = 8.7 Hz, 2H),7.45 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.4 Hz, 1H), 6.72 (s, 1H), 6.61 (d, J= 8.4 Hz, 1H), 2.34 (s, 3H); MS (ES): m/z 245 (MH^+), 246 (MH^{+1})

4-{(*E*)-[(4-hydroxy-2-methylphenyl)imino]methyl}benzonitrile (2)

IR (KBr, cm^{-1}) ν 3372, 3026, 2925, 2238, 1601, 1492, 1452, 1330, 1028, 756, 698, 551; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ: 10.12 (s, 1H, OH), 8.43 (s, 1H, CH=N), 7.99 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.7 Hz, 1H), 6.75 (s, 1H), 6.69 (d, J = 8.7 Hz, 1H), 2.39 (s, 3H); MS (ES): m/z 236 (MH^+)

4-{(*E*)-[(4-hydroxy-2-methylphenyl)imino]methyl}benzonitrile (3)

IR: (KBr, cm^{-1}) ν 3372, 3026, 2925, 2238, 1601, 1492, 1452, 1330, 1028, 756, 698, 551; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ: 10.12 (s, 1H, OH), 8.43 (s, 1H, CH=N), 7.99 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.7 Hz, 1H), 6.75 (s, 1H), 6.69 (d, J = 8.7 Hz, 1H), 2.39 (s, 3H); MS (ES): m/z 236.19 (MH^+)

4-{(*E*)-[(4-hydroxy-2-methylphenyl)imino]methyl}benzonitrile (4)

IR: (KBr, cm^{-1}) ν 3378, 3027, 2928, 2240, 1603, 1491, 1451, 1332, 1029, 757, 694, 550; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ: 10.17 (s, 1H, OH), 8.49 (s, 1H, CH=N), 8.01 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.1 Hz, 2H), 7.04 (s, 1H), 6.92 (d, J = 8.7 Hz, 1H), 6.77 (d, J = 8.7 Hz, 1H), 2.40 (s, 3H); MS (ES): m/z 236.16 (MH^+)

3-methyl-4-{[(*E*)-(4-nitrophenyl)methylidene]amino}phenol (5)

IR (KBr, cm^{-1}) ν 3363, 3026, 2925, 1601, 1492, 1452, 1345, 1028, 755, 700, 539; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ 10.17 (s, 1H, OH), 8.48 (s, 1H, CH=N), 8.30 (d, J = 8.7 Hz, 2H), 8.09 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 6.69 (d, J = 8.4 Hz, 1H), 2.40 (s, 3H); MS (ES): m/z 255 (MH^+)

4-methyl-2-{[(*E*)-(4-nitrophenyl)methylidene]amino}phenol (6)

IR (KBr, cm^{-1}) ν 3365, 3026, 2920, 1602, 1493, 1452, 1335, 1028, 755, 699, 539; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ 10.18 (s, 1H, OH), 8.77 (s, 1H, CH=N), 8.39 (d, J = 8.7 Hz, 2H), 8.09 (d, J = 8.7 Hz, 2H), 7.17 (s, 1H), 7.07 (d, J = 9 Hz, 1H), 6.96 (d, J = 9 Hz, 1H), 2.33 (s, 3H); MS (ES): m/z 255 (MH^+)

4-{[(*E*)-(4-fluorophenyl)methylidene]amino}-3-methylphenol (7)

IR: (KBr, cm^{-1}) ν 3324, 3023, 2928, 1601, 1497, 1454, 1374,1180, 1027, 754, 694, 538; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ 9.81 (s, 1H, OH), 8.67 (s, 1H, CH=N), 7.75 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.10 (s, 1H), 7.07 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 2.37 (s, 3H); MS (ES): m/z 229.15 (MH^+)

3-methyl-4-{[(*E*)-thiophen-2-ylmethylidene]amino}phenol (9)

IR (KBr, cm^{-1}) ν 3407, 3025, 2922, 1602, 1492, 1452, 1315, 1028, 758, 697, 540; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ 9.96 (s, 1H, OH), 8.47 (s, 1H, CH=N), 7.48 (t, 1H), 7.14 (d, J = 3.6 Hz, 1H), 7.13 (d, J = 3.6 Hz, 1H), 6.68 (m, 3H), 2.34 (s, 3H); MS (ES): m/z 217 (MH^+)

4-methyl-2-{[(*E*)-thiophen-2-ylmethylidene]amino}phenol (10)

IR: (KBr, cm^{-1}) ν 34010, 3027, 2928, 1601, 1496, 1454, 1317, 1029, 757, 698, 541; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ 10.05 (s, 1H, OH), 8.50 (s, 1H, CH=N), 7.49 (t, 1H), 7.16 (d, J = 3.6 Hz, 1H), 7.15 (d, J = 3.6 Hz, 1H), 6.71 (m, 3H), 2.36 (s, 3H); MS (ES): m/z 217.10 (MH^+)

4-{(*E*)-[(4-hydroxy-2-methylphenyl)imino]methyl}-2-methoxyphenol (11)

IR: (KBr, cm^{-1}) ν 3379, 3028, 2926, 1604, 1498, 1450, 1908, 1194, 1028,7 758, 704; ^{1}HNMR: (DMSO-d^6, 300 MHz), δ: 10.11 (s, 1H, OH), 10.01 (s, 1H, OH), 8.37 (s, 1H, CH=N), 7.21-6.60 (m, 6H), 3.69 (s, 3H), 2.33 (s, 3H); MS (ES): m/z 257.19 (MH^+)

4-{[(*E*)-(2,4-dichlorophenyl)methylidene]amino}-3-methylphenol (13)

IR (KBr, cm^{-1}) ν 3370, 3059, 3026, 2918, 1601, 1492, 1453, 1300, 1028, 754, 698, 539; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ 10.42 (s, 1H, OH), 8.76 (s, 1H, CH=N), 8.20 (d, J = 8.4 Hz, 2H), 7.44 (s, 1H), 7.34 (d, J = 8.4 Hz, 2H), 6.87 (m, 3H), 2.37 (s, 3H); MS (ES): m/z 280.1 (MH^+), 282 (MH^{+2})

2-{[(*E*)-(2,4-dichlorophenyl)methylidene]amino}-4-methylphenol (14)

IR: (KBr, cm^{-1}) ν 3374, 3060, 3027, 2920, 1603, 1491, 1454, 1301, 1029, 756, 699, 538; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ 10.47 (s, 1H, OH), 8.78 (s, 1H, CH=N), 8.24 (d, J = 8.4 Hz, 2H),

7.45 (s, 1H), 7.36 (d, J = 8.4 Hz, 2H), 6.89 (m, 3H), 2.38 (s, 3H); MS (ES): m/z 280.12 (MH^+), 282.46 (MH^{+2})

3-methyl-4-{[(*E*)-pyridin-2-ylmethylidene]amino}phenol (15)

IR: (KBr, cm^{-1}) ν 3342, 3025, 2926, 1603, 1490, 1451, 1371, 1027, 758, 702, 540; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ 10.03 (s, 1H, OH), 8.84 (s, 1H, CH=N), 8.70 (d, J = 4.8 Hz, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.82 (t 1H), 7.41 (t 1H), 7.21 (d, J = 8.1 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.89 (s, 1H), 2.34 (s, 3H); MS (ES): m/z 212.14 (MH^+)

4-methyl-2-{[(*E*)-pyridin-2-ylmethylidene]amino}phenol (16)

IR (KBr, cm^{-1}) ν 3346, 3026, 2924, 1601, 1492, 1452, 1373, 1028, 757, 703, 541; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ 10.10 (s, 1H, OH), 8.81 (s, 1H, CH=N), 8.71 (d, J = 4.5 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.84 (t 1H), 7.40 (t 1H), 7.20 (s, 1H), 7.04 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 2.32 (s, 3H); MS (ES): m/z 212 (MH^+)

2-{[(*E*)-(4-bromophenyl)methylidene]amino}-4-methylphenol (18)

IR (KBr, cm^{-1}) ν 3320, 3026, 2924, 1603, 1493, 1452, 1371,1181, 1028, 754, 695, 539; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ 9.98 (s, 1H, OH), 8.63 (s, 1H, CH=N), 7.77 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.11 (s, 1H), 7.04 (d, J = 8.1 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 2.36 (s, 3H); MS (ES): m/z 290.1 (MH^+)

4-{[(*E*)-(4-hydroxyphenyl)methylidene]amino}-3-methylphenol (21)

IR (KBr, cm^{-1}) ν 3375, 3025, 2923, 1601, 1493, 1452, 1909, 1193, 1028, 758, 701, 538; ^{1}HNMR: (DMSO-d^6, 300 MHz), δ: 10.11 (s, 2H, OH), 8.30 (s, 1H, CH=N), 7.41 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.1 Hz, 1H), 6.89 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.1 Hz, 1H), 6.64 (s, 1H), 2.33 (s, 1H); MS (ES): m/z 227 (MH^+)

4-methyl-2-{[(*E*)-phenylmethylidene]amino}phenol (24)

IR (KBr, cm^{-1}) ν 3358, 3025, 2923, 1600, 1492, 1452, 1375, 1028, 759, 702, 540; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ 10.03 (s, 1H, OH), 8.69 (s, 1H, CH=N), 7.93-7.49 (m, 5H), 7.13 (s, 1H), 7.04 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 2.33 (s, 1H); MS (ES): m/z 211 (MH^+)

Synthesis of Schiff bases (27-30):

A mixture of 4-amino-3-methyl phenol/2-amino-4-methyl phenol (1 mmol) and substituted ketones (1mmol) was grinded in a mortar with a pestle at room temperature and then acetic acid (20 mol%) was added and crushed, progress of reaction was monitored by TLC. After completion of reaction (2-3 min) the crude product was washed with water, dried and purified by column chromatography. Synthetic pathway for preparation of title compounds is shown in Scheme 1.

3-methyl-4-(5*H*-pyrido[3',2':4,5]cyclopenta[1,2-*b*]pyridin-5-ylideneamino)phenol (28)

IR (KBr, cm^{-1}) ν 3378, 3047, 1653, 1593, 1559, 1401, 748, 711; ^{1}HNMR: ($CDCl_3$, 300 MHz), δ 9.84 (s, 1H, OH), 8.74 (m, 2H), 8.37 (dd, 8.7 Hz, 1.2 Hz, 1H), 8.28 (dd, 8.7 Hz, 1.2 Hz, 1H), 7.38 (m, 1H), 7.25 (m, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.77 (s, 1H), 6.64 (d, J = 8.1 Hz, 1H), 2.35 (s, 3H);); MS (ES): m/z 288.1 (MH^+)

Antimicrobial activity assay procedure

Disc diffusion method:

The antimicrobial activity of newly synthesized compounds was evaluated according to the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS, 1997) using the disc diffusion method [28]. Briefly, a 24/48 h-old culture of selected bacteria was mixed with sterile physiological saline (0.85%) and the turbidity was adjusted to the standard inoculum of McFarland scale 0.5 [~106 colony forming units (CFU) per milliliter]. Petri plates containing 20 mL of Nutrient Agar (NA, Hi- Media) were used for all the bacteria tested. The inoculums was spread on the surface of the solidified media and Whatman no. 1 filter paper discs (6 mm in diameter) impregnated with the test compound (20 µL/disc) were placed on the plates. Cephotoxime (10 µg/disc, Hi-Media) and Tetracycline (30 µg/disc, Hi-Media) were used as positive controls for bacteria. A paper disc impregnated with dimethylsulfoxide (DMSO) was used as negative control. Plates inoculated with the bacteria were incubated for 24 h at 37 ºC. The inhibition zone diameters were measured in millimeters. All the tests were performed in triplicate and the average was taken as final reading.

Conclusion:

We have synthesized a series of new Schiff bases under solvent and catalytically free condition. But in this protocol, for synthesis of Schiff bases from ketone requires acetic acid as a catalyst. This protocol furnishes the products very quickly with excellent yields, simplifies the work up and does not harm the environment. The anti-bacterial screening results reveal that the compounds 6 (which bear 4-CH_3 and NO_2), 13 (which bear 3-CH_3 and di-Cl) and 21 (which bear 3- CH_3 and OH) showed excellent to moderate anti-bacterial activity. Probably the electric property of these compounds may be a reason for their biological activity.

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Table 1: Synthesis of schiff bases

P	A	B/C	Time (Min)	Yield (%)	M. P. (C^0)
1	4-amino-3-methyl phenol (a)	*p*-Chlorobenzaldehyde	2-3	85	80-82
2	2-amino-4-methyl phenol (b)	*p*-Chlorobenzaldehyde	2-3	77	74-76
3	(a)	*p*-Cyanobenzaldehyde	2-3	72	188-190
4	(b)	*p*-Cyanobenzaldehyde	2-3	77	54-56
5	(a)	*p*-Nitrobenzaldehyde	2-3	74	106-108
6	(b)	*p*-Nitrobenzaldehyde	2-3	82	202-204
7	(a)	*p*-Fluorobenzaldehyde	2-3	82	86-88
8	(b)	*p*-Fluorobenzaldehyde	2-3	80	108-110
9	(a)	2-Thiophene carboxaldehyde	2-3	90	82-84
10	(b)	2-Thiophene carboxaldehyde	2-3	77	60-62
11	(a)	vanilline	2-3	74	210-212
12	(b)	vanilline	2-3	75	117-119
13	(a)	2,4-Dichlorobenzaldehyde	2-3	78	164-166
14	(b)	2,4-Dichlorobenzaldehyde	2-3	81	121-123
15	(a)	2-Pyrimidine carboxaldehyde	2-3	87	95-97
16	(b)	2-Pyrimidine carboxaldehyde	2-3	80	78-80
17	(a)	*p*-Bromobenzaldehyde	2-3	90	102-104
18	(b)	*p*-Bromobenzaldehyde	2-3	86	82-84
19	(a)	3-Nitrobenzaldehyde	2-3	84	140-142
20	(b)	3-Nitrobenzaldehyde	2-3	76	146-148
21	(a)	*p*-Hydroxybenzaldehyde	2-3	87	190-192
22	(b)	*p*-Hydroxybenzaldehyde	2-3	82	142-144
23	(a)	Benzaldehyde	2-3	80	107-109
24	(b)	Benzaldehyde	2-3	77	75-77
25	(a)	2-Hydroxybenzaldehyde	2-3	93	90-92
26	(b)	2-Hydroxybenzaldehyde	2-3	88	160-162
27#	(a)	4,5-diazafluoren-9-hydrazone	2-3	78	256-258
28#	(b)	4,5-diazafluoren-9-hydrazone	2-3	75	>300
29#	(a)	2-Acetylpyridine	2-3	77	186-188
30#	(b)	2-Acetylpyridine	2-3	72	68-70

P = Schiff base products
# = reaction takes place in presence of acetic acid

Table 2: Anti-bacterial activities of the compounds

Compounds	1	3	5	6	9	13	16	18	21	22	24	S1	S2
E. coli (mm)	-	7	7	16	7	13	-	7	11	-	-	14	13
S. aureus (mm)	11	9	-	19	-	16	15	-	-	-	7	20	15
B. subtilius (mm)	-	-	-	15	-	-	-	-	-	-	-	13	14
K. pneumonia (mm)	11	-	16	10	6	-	-	-	-	-	-	14	16

- : indicates bacteria are resistant to the compounds,
S1 : Cephotoxime used as standard drug at concentration of 10 µg/ml
S2 : Tetracycline used as standard drug at concentration of 30 µg/ml
Compounds tested at concentration of 100 µg/ml