Silver triflate catalyzed synthesis of 3-aminoalkylated indoles and evaluation of their antibacterial activities

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Abstract
An efficient, one-pot synthesis was developed for 3-aminoalkylated indoles by three-component coupling reaction of aldehydes, N-methylanilines, and indoles using AgOTf as a catalyst. A series of twenty 3-aminoalkylated indoles was evaluated for their antibacterial activities against both Gram negative and Gram positive bacteria. Compounds 4b and 4r showed good antibacterial activity against both Gram positive and Gram negative strains. However, inversing the property of substituent (from 4r to 4q) resulted in the significant fall in the magnitude of antibacterial activity against Escherichia coli.

Keywords: 3-Substituted indole, one-pot synthesis, silver triflate, antibacterial agents, multicomponent reactions

Introduction
Antimicrobial resistance continues to grow quickly among key microbial pathogens and has become a severe global problem in recent years. Bacterial resistance to almost all available antibacterial agents has been reported [1]. Because of this many infectious diseases, such as HIV infection, staphylococcal infection, tuberculosis, influenza, gonorrhea, candida infection, and malaria, are becoming difficult to treat. Thus, along with trying to control bacterial resistance there is an urgent need for new potent classes of antibiotics with novel modes of action.

The indole scaffold is a prominent and privileged structural motif which is embodied in a myriad of natural products and molecules of pharmaceutical interest in a variety of therapeutic areas [2,3]. They possess a wide spectrum of biological activities such as antibacterial [4], anticonvulsant, and antihypertensive activity. bis-Indole-based compounds have been reported to have broad-spectrum antibacterial activities against antibiotic-resistant strains and are currently being pursued as topical agents (Figure 1) [5-7]. 1,2,3,4-Tetrahydropyrazino [1,2] indoles [8] and triazino [8],6-b) indoles [9] have been reported to have antifungal properties. Hapalindole A isolated from the blue green algae Hapalosiphon fontinalis is a 3-substituted indole derivative. It exhibits potent antibacterial and antymycotic activities [10]. The antibacterial activity of 3-substituted indole derivatives has not been much studied. Owing to interesting chemical and biological properties of indole molecules, development of efficient methods that allow rapid access to functionalized indoles with different substitution patterns constitutes an emerging area in organic synthesis.

Multicomponent reactions have received a great attention of organic chemists as they can provide drug-like molecules with several degrees of structural diversity in a one-pot operation and offer significant advantages over conventional linear-type syntheses such as high atom economy and E-factors, low cost, reduction in overall reaction time, and operational simplicity. There are only a few methods available for the synthesis of 3-aminoalkylated indoles which have been found in many natural products. Recently, a one-pot multicomponent method was developed for the synthesis of 3-aminoalkylated indoles by the reaction of aldehyde, amine, and indole [11-14]. The reaction requires longer time, high temperature, and is generally accompanied by formation of bis-indolyl compound. Thus, there is still high need for the development of an efficient and straightforward method for the synthesis of 3-substituted indole
derivatives. In continuation to our interest in novel reaction methodologies under environmentally friendly conditions [15,16], we herein report an efficient silver triflate catalyzed synthesis of 3-aminoalkylated indoles and their antibacterial activities.

**Experimental**

**General**

Melting points were determined in open capillary tubes on a MPA120-Automated Melting Point apparatus and are uncorrected. The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Heaven 11400 (400 MHz) spectrometer using TMS as internal standard and the chemical shifts are expressed in ppm. All the metal triflates, indole, and the mixture was allowed to stir for an additional 90 min. The progress of reaction was monitored by TLC. After completion of the reaction, solvent was removed under reduced pressure. To the residue, diethyl ether was added and filtered. The filtrate was dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by column chromatography on silica gel (100-200 mesh) using ethyl acetate/hexane as eluents to yield a pure product (4a-4r). All the compounds were characterized by ESI-MS,$^{1}$H NMR, and $^{13}$C NMR spectroscopic data.

$\text{N-[(4-Chlorophenyl)(1H-indol-3-yl)methyl]-N-methylbenzenamine (4a)}$

Brown solid, m.p. 183-185°C;$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.98 (s, 1H), 7.37 (d, $J$ = 4.0 Hz, 2H), 7.27-7.16 (m 5H), 7.03 (d, $J$ = 8.0 Hz, 3H), 6.57 (d, $J$ = 8.0 Hz, 3H), 5.55 (s, 1H), 2.83 (s, 3H);$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 147.5, 141.6, 137.0, 135.5, 132.9, 129.8, 129.1, 129.0, 127.3, 124.2, 121.9, 120.8, 120.2, 119.3, 113.1, 111.2, 47.6, 31.0, 21.1; ESI-MS ($m/z$): 346.9975 [M + H]$^+$.  

$\text{N-[(1H-Indol-3-yl)(p-tolyl)methyl]-N-methylbenzenamine (4b)}$

Brown solid, m.p. 136-138°C;$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.62 (s, 1H), 7.31 (d, $J$ = 8.0 Hz 1H), 7.07-6.98 (m, 7H), 6.92-6.90 (m, 1H), 6.62-6.61 (m, 1H), 6.43 (d, $J$ = 8.4 Hz, 2H), 5.46 (s, 1H), 5.40 (s, 1H), 4.92-4.84 (m, 3H), 2.24 (s, 1H);$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 147.6, 141.7, 136.7, 135.4, 133.2, 129.7, 128.9, 128.8, 127.2, 123.9, 121.9, 120.1, 119.3, 112.4, 111.0, 47.6, 31.0, 21.1; ESI-MS ($m/z$): 327.0665 [M + H]$^+$.  

$\text{N-[(1H-Indol-3-yl)(4-methoxyphenyl)methyl]-N-methylbenzenamine (4c)}$

Brown solid, m.p. 177-179°C;$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.93 (s, 1H), 7.42-7.26 (m, 3H), 7.16 (d, $J$ = 7.6 Hz, 3H), 7.06-6.98 (m, 3H), 6.83 (d, $J$ = 7.6, 2H), 6.56 (d, $J$ = 8.0 Hz, 3H), 5.54 (s, 1H), 3.80 (s, 3H), 2.83 (s, 3H);$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 168.98, 157.90, 147.56, 136.99, 133.29, 129.85, 129.65, 127.13, 123.90, 121.97, 120.16, 119.27, 113.56, 112.40, 110.97, 55.21, 47.13, 30.95; ESI-MS ($m/z$): 343.0446 [M + H]$^+$.  

$\text{N-[(1H-Indol-3-yl)(phenyl)methyl]-N-methylbenzenamine (4d)}$

Brown solid, mp 189-191°C;$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.01 (s, 1H), 7.57 (s, 1H), 7.35 (d, $J$ = 8.0 Hz, 1H), 7.26-7.20 (m, 4H), 7.17-7.14 (m, 2H), 7.09-6.86 (m, 3H), 6.60 (d, $J$ = 2.0 Hz, 3H), 5.53 (s, 1H), 2.79 (s, 3H);$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 147.7, 144.9, 133.0, 130.1, 129.8, 129.0, 128.2, 127.2, 124.0, 122.0, 120.7, 120.1, 119.3, 112.4, 111.0, 48.0, 31.0; ESI-MS ($m/z$): 313.0450 [M + H]$^+$.  

$\text{N-[(1H-Indol-3-yl)(4-hydroxy phenyl)methyl]-N-methylbenzenamine (4e)}$

Brown solid, m.p. 139-140°C;$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.929 (s, 3H), 7.41-7.01 (m, 7H), 6.75-6.57 (m,
Brown solid, m.p. 187-189°C; 1H NMR (400 MHz, CDCl3): δ 7.97 (s, 1H), 7.38-7.19 (m, 4H), 7.08-6.93 (m, 5H), 6.59 (s, 3H), 5.50 (s, 1H), 2.84 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 150.3, 147.6, 138.5, 136.9, 132.0, 129.7, 129.6, 127.0, 123.9, 123.6, 122.6, 122.1, 119.9, 119.4, 115.7, 112.6, 111.1, 110.1, 46.9, 31.0; ESI-MS (m/z): 406.9101 [M + H]+.

**N-(4-Hydroxy-3-bromophenyl)(1H-indol-3-yl)methyl-N-methylbenzenamine (4f)**

Brown solid, m.p. 136-139°C; 1H NMR (400 MHz, CDCl3): δ 7.939 (s, 2H), 7.43-7.22 (m, 3H), 7.20-7.17 (m, 3H), 7.08-6.86 (m, 2H), 6.84-6.81 (m, 2H), 6.57 (d, J = 7.6 Hz, 2H), 5.56 (s, 1H), 3.75 (s, 3H), 2.83 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 159.5, 148.5, 147.6, 146.5, 145.8, 136.7, 132.9, 129.7, 127.1, 123.9, 126.2, 120.6, 120.1, 120.0, 115.0, 112.5, 111.2, 110.1, 55.4, 58.0, 31.0; ESI-MS (m/z): 343.0968 [M + H]+.

**N-(1H-Indol-3-yl)(3-methoxyphenyl)methyl-N-methylbenzenamine (4g)**

Brown solid, m.p. 123-126°C; 1H NMR (400 MHz, CDCl3): δ 7.91 (s, 1H), 7.34-7.27 (m, 2H), 7.16-6.92 (m, 4H), 6.57-6.37 (m, 4H), 5.59 (s, 1H), 3.79 (s, 6H), 2.83 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 159.9, 157.9, 147.3, 136.8, 130.2, 130.0, 129.7, 125.7, 125.0, 123.9, 121.8, 120.2, 119.1, 112.4, 112.3, 110.9, 103.8, 95.6, 55.7, 55.3, 39.1, 31.1; ESI-MS (m/z): 373.0427 [M + H]+.

**N-Methyl-N-(1-methyl-1H-indol-3-yl)(phenyl)methyl benzenamine (4i)**

Brown solid, m.p. 193-194°C; 1H NMR (400 MHz, CDCl3): δ 8.13-8.07 (m, 3H), 7.59 (d, J = 8.0 Hz, 1H), 7.46-7.38 (m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.06-7.02 (m, 3H), 6.66-6.57 (m, 3H), 5.68 (s, 1H), 2.84 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 148.1, 147.8, 146.8, 136.5, 134.9, 130.9, 129.4, 128.8, 126.4, 123.8, 123.5, 121.1, 119.4, 119.1, 112.3, 112.2, 111.0, 47.5, 30.6; ESI-MS (m/z): 358.007 [M + H]+.

**N-((5-Bromo-1H-indol-3-yl)(phenyl)methyl)-N-methylbenzenamine (4m)**

Brown solid, m.p. 207-209°C; 1H NMR (400 MHz, CDCl3): δ 8.07 (s, 1H), 7.39 (s, 1H), 7.27-7.23 (m, 7H), 7.02 (d, J = 8.0 Hz, 2H), 6.58 (d, J = 8.0 Hz, 3H), 5.52 (s, 1H), 2.83 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 147.5, 144.3, 135.4, 132.7, 129.7, 128.9, 128.3, 126.2, 125.2, 125.0, 120.4, 112.7, 115.7, 47.7, 31.1; ESI-MS (m/z): 390.9823 [M + H]+ and 392.9105 [M + 2 + H]+.

**N-((5-Methoxy-1H-indol-3-yl)(4-methoxyphenyl)methyl)-N-methylbenzenamine (4n)**

Brown solid, m.p. 203-205°C; 1H NMR (400 MHz, DMSO-d6): δ 10.62 (s, 1H), 7.24-7.20 (m, 3H), 7.09 (d, J = 4.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 2H), 6.77 (s, 1H), 6.70-6.66 (m, 3H), 6.60-6.53 (m, 1H), 6.43 (d, J = 8.0 Hz, 1H), 5.66 (s, 1H), 3.68 (s, 3H), 3.44 (s, 3H), 3.48 (s, 3H); 13C NMR (100 MHz, DMSO-d6): δ 157.8, 153.1, 137.7, 132.3, 129.9, 129.7, 129.4, 127.4, 124.7, 118.5, 113.8, 112.5, 111.9, 111.0, 102.0, 55.7, 55.4, 47.0, 30.4; ESI-MS (m/z): 373.1681 [M + H]+.

**N-((5-Methoxy-1H-indol-3-yl)(p-tolyl)methyl)-N-methylbenzenamine (4o)**

Brown solid, m.p. 197-199°C; 1H NMR (400 MHz, DMSO-d6): δ 10.60 (s, 1H), 7.21 (d, J = 4.0 Hz, 3H), 7.06 (d, J = 8.0 Hz, 3H), 6.91 (d, J = 4.0 Hz, 1H), 6.77 (s, 1H), 6.69-6.66 (m, 3H), 6.59-6.52 (m, 1H), 6.42 (d, J = 8.0 Hz, 1H), 5.66 (s, 1H), 3.57 (s, 3H), 2.48 (s, 3H), 2.23
6.67 (s, 1H), 6.43 (d, 2H), 6.89 (d, J = 4.0 Hz, 1H), 7.11 (d, J = 4.0 Hz, 1H), 7.08-7.00 (m, 4H), 6.89 (d, J = 4.0 Hz, 2H), 6.75 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 4.0 Hz, 1H), 6.42 (d, J = 8.0 Hz, 2H), 5.39 (d, J = 4.0 Hz, 1H), 2.48 (s, 3H), 2.22 (s, 3H); 13C NMR (100 MHz, DMSO-6.73-6.55 (m, 3H), 6.53 (d, J = 10.0 Hz, 2H), 5.47 (s, 1H), 3.61 (s, 3H); 13C NMR (100 MHz, DMSO-d6): δ 154.7, 148.3, 141.3, 132.3, 130.9, 129.3, 128.9, 128.7, 128.2, 123.4, 117.5, 112.5, 112.3, 112.1, 110.7, 109.5, 55.3; ESI-MS (m/z): 363.21 [M + H]+, 365.20 [M + H +2]+.

**4-Chloro-N-((4-chlorophenyl)(5-methoxy-1H-indol-3-yl)methyl)benzenamine (4q)**

Brown solid, m.p. 195-197°C; 1H NMR (400 MHz, DMSO-d6): δ 11.02 (s, 1H), 7.29 (d, J = 4.0 Hz, 1H), 7.19 (d, J = 4.0 Hz, 1H), 6.89 (d, J = 4.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 3H), 6.67 (s, 1H), 6.43 (d, J = 4.0 Hz, 1H), 6.02 (d, J = 8.0 Hz, 2H), 3.69 (s, 3H), 2.47 (s, 3H); 13C NMR (100 MHz, DMSO-d6): δ 157.8, 148.6, 137.4, 135.8, 131.7, 129.4, 129.2, 128.7, 126.0, 123.9, 121.7, 119.4, 114.0, 112.0, 111.3, 47.0, 30.4, 21.1; ESI-MS (m/z): 405.0683 [M + H]+ and 407.072 [M + 2 + H]+.

**N-((5-Bromo-1H-indol-3-yl)(p-tolyl)methyl)-N-methylbenzenamine (4p)**

Brown solid, m.p. 190-191°C; 1H NMR (400 MHz, DMSO-d6): δ 11.02 (s, 1H), 7.29 (d, J = 4.0 Hz, 1H), 7.19 (d, J = 4.0 Hz, 1H), 7.11 (d, J = 4.0 Hz, 1H), 7.07 (d, J = 4.0 Hz, 2H), 6.89 (d, J = 4.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 3H), 6.67 (s, 1H), 6.43 (d, J = 4.0 Hz, 1H), 5.39 (s, 1H), 3.69 (s, 3H), 2.47 (s, 3H); 13C NMR (100 MHz, DMSO-d6): δ 153.2, 148.9, 144.6, 132.3, 131.2, 130.8, 130.6, 129.5, 128.4, 127.3, 125.3, 125.2, 124.8, 117.7, 112.6, 112.0, 111.1, 55.7, 47.3, 30.3; ESI-MS (m/z): 377.1223 [M + H]+.

**N-((4-Chlorophenyl)(5-methoxy-1H-indol-3-yl)methyl)-N-methylbenzenamine (4r)**

Brown solid, m.p. 190-191°C; 1H NMR (400 MHz, DMSO-d6): δ 11.02 (s, 1H), 7.29 (d, J = 4.0 Hz, 1H), 7.19 (d, J = 4.0 Hz, 1H), 7.11 (d, J = 4.0 Hz, 1H), 7.07 (d, J = 4.0 Hz, 2H), 6.89 (d, J = 4.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 3H), 6.67 (s, 1H), 6.43 (d, J = 4.0 Hz, 1H), 5.39 (s, 1H), 3.69 (s, 3H), 2.47 (s, 3H); 13C NMR (100 MHz, DMSO-d6): δ 153.2, 148.9, 144.6, 132.3, 131.2, 130.8, 130.6, 129.5, 128.4, 127.3, 125.3, 125.2, 124.8, 117.7, 112.6, 112.0, 111.1, 55.7, 47.3, 30.3; ESI-MS (m/z): 377.1223 [M + H]+.

**Results and discussion**

Chemistry

Initially, we investigated reaction of indole benzaldehyde and N-methylaniline to give 4a as acetonitrile using different Lewis acid catalysts (Table 1). Among different catalysts studied AgOTf gave highest yield of 4a (Table 1, entry 2). Among other catalysts, Ce(OTf)3, Yb(OTf)3 and pTSA gave good yield of 4a (Table 1, entries 7, 10, and 12). Formation of bis(indolyl)methane (5-32%) as side product was observed with most of the catalyst studied except with AgOTf, Ce(OTf)3, and Yb(OTf)3.

Subsequently, we investigated different solvents such as DCM, DMSO, DMF, THF, acetonitrile, and ionic liquid [bmim][BF4] for the model reaction. Acetonitrile was found to give highest yield of 4a among all the screened solvent. In case of ionic liquid [bmim][BF4] imine was major product. In other solvents substrate didn’t consume completely and there was mixture of starting material, imine, and 4a. For further studies we selected AgOTf (10 mol%) as catalyst and acetonitrile as reaction medium of choice.
After determining the optimized reaction conditions, we next studied the substrate scope by taking indoles, aldehydes, and N-methyl anilines bearing different substituent for the synthesis of 3-aminoalkylated indoles (4). The results are summarized in Table 2. The structure of the synthesized compounds was confirmed by $^1$H NMR, $^{13}$C NMR, and mass spectroscopic data. A wide range of structurally diverse aldehydes gave the corresponding product 4 in good to excellent yields. Aromatic aldehyde having an electron-donating group gave higher yield as compared to aromatic aldehydes with electron withdrawing group (entry 12, Table 2). The reaction was equally effective for N-methylindole and 5-unsubstituted indoles affording the desired 3-aminoalkylated indoles in almost equally high yields (entries 13-18, Table 2). However, poor yield of corresponding 3-substituted indole was obtained from aniline (entry 19, Table 1). When aliphatic amines were used it did not result in 3-substituted indole under these conditions.

Then, we investigated the possibility of recycling of the catalyst. After the first cycle for model reaction, the solvent was concentrated under vacuum. Diethyl ether was added to the residue obtained and filtered leaving behind AgOTf. The recovered AgOTf was again taken in a round bottom flask and charged with 4-chlorobenzaldehyde (1a), N-methyl aniline (3), and acetonitrile and allowed to react for 30 min followed by the addition of indole and reaction was allowed to continue for additional 90 min. The above sequence was repeated four times to give 4a in good yields (88, 85, 83, and 80%) without much loss in catalytic activity of catalyst.

The reaction is assumed to proceed through two-step domino sequence. The first step is believed to be formation of iminium ion after reaction of the benzaldehyde and N-methyl aniline. The next step is nucleophilic attack of indole on iminium ion followed by proton loss to give a 3-substituted indole. The structure of product is consistent with the synthesis of 3-aminoalkylated indoles via multicomponent condensation reaction of indoles, aldehyde, and amines [11-14].

### Anti-bacterial activity
An array of 20 diversely substituted indoles was evaluated for in vitro antibacterial activity against both Gram positive and Gram negative bacteria. The results of antibacterial activity of compounds (4a-r) are shown in Table 2. The compounds indicating notable antibacterial activity are indicated in bold (Table 2). Compounds 4q, 4r, 4i, and 4b showed significant antibacterial activity against Gram positive bacteria and 4r, 4b, 4o, and 4l was added to the residue obtained and filtered leaving behind AgOTf. The recovered AgOTf was again taken in a round bottom flask and charged with 4-chlorobenzaldehyde (1a), N-methylaniline (3), and acetonitrile and allowed to react for 30 min followed by the addition of indole and reaction was allowed to continue for additional 90 min. The above sequence was repeated four times to give 4a in good yields (88, 85, 83, and 80%) without much loss in catalytic activity of catalyst.

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### Table 1 Optimization of reaction condition for model reaction generating 4a

| Number | Catalyst (Catalyst mol %) | Solvent | Time (h) | Yield (%) |
|--------|---------------------------|---------|----------|-----------|
| 1      | AgOTf 1                   | CH3CN   | 4        | 58        |
| 2      | AgOTf 5                   | CH3CN   | 4        | 78        |
| 3      | AgOTf 10                  | CH3CN   | 4        | 86        |
| 4      | Sc(OTf)3 10               | CH3CN   | 4        | 43        |
| 5      | Ga(OTf)3 10               | CH3CN   | 4        | 45        |
| 6      | Zn(OTf)2 5                | CH3CN   | 4        | 52        |
| 7      | Ce(OTf)3 5                | CH3CN   | 4        | 71        |
| 8      | Cu(OTf)2 5                | CH3CN   | 4        | 68        |
| 9      | Ba(OTf)2 5                | CH3CN   | 4        | 50        |
| 10     | Yb(OTf)3 5                | CH3CN   | 4        | 72        |
| 11     | FeCl3 5                   | CH3CN   | 2        | 59        |
| 12     | pTSA 5                    | CH3CN   | 3        | 71        |
| 13     | BF3.OEt2 5                | CH3CN   | 5        | 34        |
| 14     | Mont. K-10                | CH3CN   | 6        | 15        |
| 15     | SiO2 10                   | CH3CN   | 6        | 30        |
| 16     | AgOTf 10                  | DCM     | 10       | 67        |
| 17     | AgOTf 10                  | DMSO    | 10       | 72        |
| 18     | AgOTf 10                  | DMF     | 10       | 62        |
| 19     | AgOTf 10                  | THF     | 10       | 58        |
| 20     | AgOTf 10 [bmim][BF4]      | 12       | 31        |
| 21     | AgOTf 10 [bmim][BF4]      | H2O     | 12       | 4         |

*Isolated yield.
*100 mg mole of benzaldehyde
*Imine was formed as major product
*No product formation was observed.

### Table 2 Synthesis of 3-aminoalkylated indoles (4a-t) catalyzed by AgOTf

| Number | R R | R’ | R” | R’’ | Product | Yield (%) |
|--------|-----|----|----|-----|---------|-----------|
| 1      | H   | H  | 4-Cl| CH3 | 4a      | 86        |
| 2      | H   | H  | 4-CH3| CH3 | 4b      | 85        |
| 3      | H   | H  | 4-CH3O| CH3 | 4c      | 84        |
| 4      | H   | H  | H   | CH3 | 4d      | 76        |
| 5      | H   | H  | 4-OH| CH3 | 4e      | 77        |
| 6      | H   | H  | 3-Br, 4-OH| CH3 | 4f      | 85        |
| 7      | H   | H  | 3-CH3O| CH3 | 4g      | 83        |
| 8      | H   | H  | 2,4-CH3O| CH3 | 4h      | 80        |
| 9      | H   | CH3 | H   | CH3 | 4i      | 77        |
| 10     | H   | CH3 | 4-Cl| CH3 | 4j      | 76        |
| 11     | H   | CH3 | 4-CH3O| CH3 | 4k      | 77        |
| 12     | H   | H  | 3-NO2| CH3 | 4l      | 48        |
| 13     | 5-Br| H   | H   | CH3 | 4m      | 75        |
| 14     | 5-OCH3| H   | 4-OCH3| CH3 | 4n      | 85        |
| 15     | 5-OCH3| H   | 4-CH3| CH3 | 4o      | 82        |
| 16     | 5-Br| H   | 4-CH3| CH3 | 4p      | 80        |
| 17     | 5-Br| H   | 4-OCH3| CH3 | 4q      | 79        |
| 18     | 5-OCH3| H   | 4-Cl| CH3 | 4r      | 81        |
| 19     | 5-OCH3| H   | 4-Cl| H   | 4s      | 45        |

*Isolated yield.
*Yield for four consecutive cycles for recycled AgOTf were 86, 84, 80 and 78, respectively.
against Gram negative bacteria. These results suggest that analog 4b and 4r can be used as potential broad spectrum antibacterial agents as they are potent against both Gram positive and Gram negative bacteria.

Compound 4d (without functional groups) was not showing any antibacterial activity, however, substitution of electron withdrawing groups at phenyl ring (4l, 4f) exhibited increase in antibacterial activity against Gram negative organisms. Interestingly, introduction of electron-releasing group at phenyl ring (4b) showed good activity against both the Gram positive and Gram negative bacterial strains.

Among the compounds 4i-k, the compound 4i showed antibacterial activity against only B. subtilis but substituting the R” position with an electron withdrawing group (4j, chloro) results in relatively less activity. In contrast, introducing an electron-releasing group at R” position (4k, methoxy) made it further ineffective toward B. subtilis but found to be active against other two bacterial strains (Table 3).

**Conclusion**

In conclusion, we have developed an efficient and straightforward synthesis of 3-aminoalkylated indoles by one-pot three-component coupling reaction of a benzaldehyde, N-methylaniline, and indole or N-methyindole using AgOTf as catalyst. Simplicity, easy work up, short reaction time, environment friendly catalyst, and excellent yield are the advantages which will make this a practical method for synthesis of 3-aminoalkylated indoles over existing methods. All the synthesized compounds were evaluated for their antibacterial activities against both Gram negative and Gram positive bacteria. Compounds 4b and 4r showed good antibacterial activity against both Gram positive and Gram negative strains. However, inversing the property of substituent (from 4r to 4q) resulted in the significant fall in the magnitude of antibacterial activity against E. coli. This study provides insights for further optimizing of substituted indoles for the discovery of potent antibacterial agents.

**Acknowledgements**

The financial support in the form of research project No. 39-733/2010 (SR) from University Grant Commission (UGC), New Delhi is highly acknowledged. VKR thanks BITS Pilani for research fellowship.

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**Competing interests**

The authors declare that they have no competing interests.

Received: 15 August 2011 Accepted: 27 September 2011 Published: 27 September 2011

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Cite this article as: Rao et al. Silver triflate catalyzed synthesis of 3-aminoalkylated indoles and evaluation of their antibacterial activities. Organic and Medicinal Chemistry Letters 2011 1:10.