Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 101 (2013) 254–263

Contents lists available at SciVerse ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

An efficient one pot syntheses of aryl-3,3′-bis(indolyl)methanes and studies on their spectral characteristics, DPPH radical scavenging-, antimicrobial-, cytotoxicity-, and antituberculosis activity

G.S. Suresh Kumar [a], S. Kumaresan [a,*], A. Antony Muthu Prabhu [b], N. Bhuvanesh [c], P.G. Seethalakshmi [d]

[a] Department of Chemistry, Manonmaniam Sundaranar University, Tirunelveli 627 012, Tamilnadu, India
[b] Department of Chemistry, Annamalai University, Annamalai Nagar, Tamilnadu, India
[c] Department of Chemistry, Texas A & M University, College Station, TX 77842, USA
[d] Department of Chemistry, APC Mahalakshmi College for Women, Toothukkudi 628 002, Tamilnadu, India

HIGHLIGHTS

- An efficient one-pot synthesis of BIMs esters using potash alum as a catalyst.
- Single crystal XRD of acid and ester BIMs have different H-bonding pattern.
- Absorption spectra show solvent independent, but diminished emission intensities in polar solvents.
- BIMs display better radical scavenging-, moderate antimicrobial-, and less cytotoxicity.

GRAPHICAL ABSTRACT

ARTICLE INFO

Article history:
Received 13 July 2012
Received in revised form 18 September 2012
Accepted 20 September 2012
Available online 5 October 2012

Keywords:
Formylphenoxyaliphatic acid
Indole
3,3′-Bis(indolyl)methanes
Potash alum
Esterification
DPPH radical scavenging

ABSTRACT

An efficient one-pot syntheses of aryl-3,3′-bis(indolyl)methanes (BIMs) from indole/2-methylindole and formylphenoxyaliphatic acid(s) is described. Esterification of carboxylic acid and aromatic electrophilic substitution reactions are achieved simultaneous in the presence of potash alum as a catalyst. This catalyst could be recovered and reused without substantial loss in its catalytic activity and the methodology could be applied on a range of closely related substrates. The solvation characteristics in ground and excited states of the compounds by monitoring the absorbance and fluorescence band maxima have been studied. The fluorescence studies in protic and aprotic solvents were rationalized on the basis of solute–solvent interaction and substituents effect on these photophysical processes analyzed. The compounds prepared showed efficient antimicrobial effect against human pathogens, cytotoxicity against A431 cell line, and DPPH radical scavenging effect. Single crystal XRD studies have been carried out for a few compounds synthesized in this work.

Introduction

Bis(indolyl)methanes (BIMs) and their derivatives have received more attention due to their presence in natural products [1]. BIMs exhibit antimicrobial-, antifungal- [2], antibiotic- [3], antibacterial-, antiangiogenic- [4], cytotoxic- [1], antimetastatic- [5,6], anti-inflammatory-, analgesic- [7], radical scavenging- [8], growth promoting- [9], etc., activity. The oxidized forms of BIMs are utilized as dyes [10] and colorimetric sensors [11]. Due to the versatile application possibilities of BIMs, there is a vast search for more proficient methods for the synthesis of indole derivatives [12].

Use of potash alum [$KAl(SO_4)_2{\cdot}12H_2O$] in many organic syntheses has been reported [13–16]. Recently esterification of formylphenoxyaliphatic acid(s) with aliphatic alcohol(s) using potash alum was reported by us [17]. In continuation of our work, we

* Corresponding author.
E-mail address: skumarmsu@yahoo.com (S. Kumaresan).

1386-1425/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.saa.2012.09.046

extended esterification of carboxylic acid and condensation of indole with formylphenoxyaliphatic acids using potash alum in alcohol for the synthesis of phenoxyaliphatic acid esters *via* one-pot synthesis.

A thorough literature survey indicated that there are no reports regarding the use of potash alum as a catalyst for the one-pot synthesis of phenoxyaliphatic acid ester of 3,3′-BIMs *via* simultaneous esterification and condensation of indole and formylphenoxyaliphatic acid(s). In the present work, we report an efficient green approach for the synthesis of phenoxyalkyl esters of BIMs using potash alum as a catalyst. The fluorescence activity in different solvents, DPPH radical scavenging, antimicrobial-, cytotoxicity-, and antituberculosis activity properties of these newly synthesized compounds are also reported herein.

Experimental

General methods

Melting points were measured in open capillary tubes and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ scale) and the coupling constants in Hertz. Infrared spectra were recorded on a JASCO FT-IR Model 410 spectrophotometer (in KBr pellet). Band positions are reported in reciprocal centimetres (cm^{-1}). Absorption measurements were carried out with a Shimadzu UV 1601 PC model UV–Visible spectrophotometer and fluorescence measurements were made by using a Shimadzu spectrofluorimeter model RF-5301. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of hexanes and ethyl acetate as eluent. The electrospray (ESI) mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap mass spectrometer. Samples (10 μl) (dissolved in solvent such as methanol/acetonitrile/water) were introduced into the ESI source through Finnigan surveyor autosampler. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer.

Synthesis of esters of BIMs

Indole (10 mmol) and formylphenoxyaliphatic acid(s) (5 mmol) in ethanol (25 ml) were stirred at 80 °C. Potash alum (20 mol%) was added to the reaction mixture. After 24 h heating, the excess ethanol was evaporated. The pasty solid was washed with diethyl ether (20 ml) for removing excess indole and aldehyde(s). Then the solid was dissolved in hot ethanol and filtered. Recrystallization was done in the absence of light. The product BIMs, thus obtained were found to be pure upon TLC.

Ethyl 2-(2-formylphenoxy)acetate (1)

Brown semi-solid; FT-IR (KBr): ν_{max} 1752, 1683, 1594 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 1.32 (t, J = 12.9 Hz, 3H), 4.03 (q, J = 21.3 Hz, 2H), 4.76 (s, 2H), 6.87 (d, J = 8.4 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 10.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 61.5, 65.6, 112.6, 121.8, 125.4, 128.5, 135.6, 160.1, 168.1, 189.5; DART–MS: 209.08 $(M+H)^+$; Anal. Calcd. for $C_{11}H_{12}O_4$: C 63.45, H 5.81%. Found: C 63.42, H 5.83%.

2-{2-[Bis(1H-indol-3-yl)methyl]phenoxy}acetic acid (2a)

Pink solid; FT-IR (KBr): ν_{max} 3402, 1723 cm^{-1}; ^{1}H NMR (500 MHz, δ ppm): 4.53 (s, 2H), 6.41 (s, 1H), 6.46–9.16 (m, 14H), 9.16 (s, 2H); ^{13}C NMR (125 MHz, δ ppm): 32.4, 66.1, 101.7, 111.1, 111.3, 112.3, 118.5, 118.7, 119.3, 119.9, 120.4, 121.2, 121.4, 124.0, 124.5, 127.0, 127.2, 130.0, 133.6, 136.8, 155.5, 171.1; ESI-MS: 395.50; Anal. Calcd. for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07%. Found: C, 75.72; H, 5.06; N, 7.10%. Crystal data for $C_{27}H_{28}N_2O_5$ (CCDC875573), M = 460.51, Monoclinic, space group P2(1)/c, a = 8.7947(14) Å, b = 15.312(3) Å, c = 17.512(3) Å, volume 2299.3(7) Å^3, Z = 4, T = 110(2) K, 13,091 reflections measured, 3404 unique reflections, Goodness-of-fit on F^2 is 1.057, $R1$ = 0.0708, $wR2$ = 0.1252.

Ethyl 2-[2-{bis(1H-indol-3-yl)methyl}phenoxy]acetate (3a)

Pale pink solid; 68% yield; FT-IR (KBr): ν_{max} 3401, 1749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 1.22 (t, J = 12.9 Hz, 3H), 4.18 (q, J = 12.9 Hz, 3H), 4.58 (s, 2H), 6.43 (s, 1H), 6.55–7.44 (m, 14H), 7.84 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.0, 32.5, 61.0, 66.2, 110.8, 112.0, 119.0, 119.4, 120.1, 121.5, 121.7, 123.5, 127.0, 127.2, 130.0, 133.2, 136.8, 155.8, 169.1; ESI-MS: 423.2; Anal. Calcd. for $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.70; N, 6.60%. Found: C, 76.45; H, 5.7; N, 6.55%, Compound (CCDC 873676) crystallizes in the triclinic system, space group P-1, with a = 9.6067(11) Å, b = 13.9907(15) Å, and c = 16.2903(18) Å, and α = 90°, β = 95.9170(10)° and γ = 90°, volume 2177.8(4) Å^3, Z = 4, T = 110(2) K, 24,448 reflections measured, 4955 unique reflections, with a Goodness-of-fit on F^2 is 1.099, $R1$ = 0.0508, $wR2$ = 0.1014.

Ethyl 2-[2-{bis(1H-indol-3-yl)methyl}phenoxy]propionate (3b)

Pale pink solid; 70% yield; FT-IR (KBr): ν_{max} 3419, 1700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 1.11 (t, J = 11.4 Hz, 3H), 2.65 (t, J = 12.6 Hz, 2H), 3.92 (q, J = 11.4 Hz, 2H), 4.23 (t, J = 12.6 Hz, 2H), 6.27 (s, 1H), 6.66–7.39 (m, 14H), 7.87 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 13.9, 32.4, 34.7, 60.4, 64.1, 110.8, 111.9, 119.0, 119.4, 119.9, 120.8, 121.6, 123.4, 127.1, 127.2, 129.6, 132.9, 136.7, 155.8, 171.0; ESI-MS: 437.2; Anal. Calcd. for $C_{28}H_{26}N_2O_3$: C, 76.69; H, 5.98; N, 6.39%. Found: C, 76.78; H, 6.03; N, 6.43%.

Ethyl 2-[2-{bis(1H-indol-3-yl)methyl}-6-methoxyphenoxy] acetate (3c)

Pale pink solid; 78% yield; FT-IR (KBr): ν_{max} 3419, 3354, 1741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.15 (t, J = 7.0 Hz), 3.80 (s, 3H), 4.04 (q, J = 7.0 Hz, 2H), 4.26 (s, 2H), 6.44 (s, 1H), 6.60–7.41 (m, 13H) 7.87 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 33.16, 55.69, 60.80, 69.87, 110.36, 110.93, 119.07, 119.23, 120.07, 121.69, 121.75, 123.60, 124.00, 127.04, 136.64, 138.06, 145.18, 152.10, 169.62; ESI-MS 452.2 Anal. Calcd. For $C_{28}H_{26}N_2O_4$: C, 73.99; H, 5.77; N, 6.16; Found C, 73.96; H, 5.81; N, 6.20.

Ethyl 2-[4-{bis(1H-indol-3-yl)methyl}phenoxy]acetate (3d)

Pale pink solid; 72% yield; FT-IR (KBr): 3397, 3344, 1747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 1.32 (t, J = 14.1 Hz, 3H), 4.29 (q, J = 14.1 Hz, 2H), 4.59 (s, 2H), 5.83 (s, 1H), 6.46–7.40 (m, 14H), 7.81 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.0, 39.2, 61.3, 65.4, 111.0, 114.3, 119.0, 119.5, 119.8, 121.7, 123.6, 126.9, 129.6, 136.6, 137.4, 156.0, 169.2; ESI-MS: m/z 423.2; Anal. Calcd. for $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.70; N, 6.60%, Found: C, 76.28; H, 5.69; N, 6.63%.

Ethyl 2-[4-{bis(1H-indol-3-yl)methyl}phenoxy]propionate (3e)

Pale pink solid; 74% yield; FT-IR (KBr): ν_{max} 3419, 3368, 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 1.24 (t, J = 14.1 Hz, 3H), 2.74 (t, J = 12.9 Hz, 2H), 4.12–4.20 (m, 4H), 5.80 (s, 1H), 6.53–7.36 (m, 14H), 7.81 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.1, 34.7, 39.3, 60.7, 63.4, 111.0, 114.3, 119.1, 119.8, 119.9, 121.8, 123.5, 127.0, 129.6, 136.5, 136.7, 156.8, 171.2; ESI-MS: m/z 437.2; Anal. Calcd. for $C_{28}H_{26}N_2O_3$: C, 76.69; H, 5.98; N 6.39%. Found: C, 76.73; H, 6.03; N, 6.46%.

Ethyl 2-[4-{bis(1H-indol-3-yl)methyl}-2-methoxyphenoxy]acetate (3f)

Pale pink solid; 78% yield; FT-IR (KBr): ν_{max} 3385, 1743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.23 (t, J = 12.3 Hz, 3H), 3.65 (s, 3H), 4.21 (q, J = 12.3 Hz, 2H), 4.60 (s, 2H), 5.77 (s, 1H), 6.45 (s, 2H), 6.61–7.34 (m, 13H), 7.89 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.1, 39.7, 55.7, 61.2, 66.5, 111.1, 112.8, 113.8, 119.0, 119.4, 120.4, 121.7, 123.6, 126.9, 136.6, 138.5, 145.4, 149.2, 169.3; ESI-MS: *m/z* 453.2; Anal. Calcd. for $C_{28}H_{26}N_2O_4$: C, 73.99, H 5.77, N 6.16%. Found: C, 74.03; H, 5.81; N, 6.21%.

Ethyl 2-[4-{bis(1H-indol-3-yl)methyl}-2-methoxyphenoxy]propionate (3g)

Pale pink solid; 78% yield; FT-IR (KBr): ν_{max} 3414, 3370, 1739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.22 (t, J = 12.6 Hz, 3H), 2.78 (t, J = 13.2 Hz, 2H), 3.66 (s, 3H), 4.12 (q, J = 12.6 Hz, 2H), 4.23 (t, J = 13.2 Hz, 2H), 5.78 (s, 1H), 6.51–7.36 (m, 13H), 7.87 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.1, 34.6, 39.7, 55.8, 60.6, 64.7, 111.0, 112.9, 113.8, 119.0, 119.6, 119.8, 120.7, 121.7, 123.6, 126.9, 136.6, 137.7, 146.2, 149.2, 171.2; ESI-MS: 467.3; Anal. Calcd. for $C_{29}H_{28}N_2O_4$: C, 74.34; H, 6.02; N, 5.98%. Found: C, 74.39; H, 5.98; N, 5.93%.

Ethyl 2-[2-{bis(2-methyl-1H-indol-3-yl)methyl}phenoxy] acetate (3h)

pink solid, 82% yield; FT-IR (KBr): 3406, 3369, 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.18 (t, J = 14.4 Hz, 3H), 2.05 (s, 6H), 4.14 (q, J = 14.4 Hz, 2H), 4.39 (s, 2H), 6.33 (s, 1H), 6.72–7.23 (m, 12H), 7.68 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 12.2, 14.1, 33.4, 60.9, 66.4, 109.8, 112.3, 113.1, 118.9, 119.3, 120.3, 121.5, 127.2, 129.3, 130.6, 131.7, 133.3, 135.0, 156.3, 169.3; ESI-MS: *m/z* 451.2; Anal. Calcd. for $C_{29}H_{28}N_2O_3$: C, 76.97; H, 6.24; N, 6.19%. Found: C, 77.02; H, 6.20; N, 6.23%.

Ethyl 2-[2-{bis(2-methyl-1H-indol-3-yl)methyl}phenoxy] propionate (3i)

pink solid; 85% yield; FT-IR (KBr): 3395, 3383, 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.26 (t, J = 14.4 Hz, 3H), 1.98 (s, 6H), 2.75 (t, J = 12.6 Hz, 2H), 4.13–4.21 (m, 4H), 5.91 (s, 1H), 6.74–7.26 (m, 12H), 8.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 12.2, 14.1, 34.7, 38.4, 60.6, 63.6, 110.0, 113.4, 114.3, 118.8, 119.2, 120.3, 128.9, 129.9, 131.9, 135.1, 136.4, 156.7, 171.1; ESI-MS: *m/z* 465.2; Anal. Calcd. for $C_{30}H_{30}N_2O_3$: C, 77.23; H, 6.48; N, 6.00%. Found: C, 77.26; H, 6.52; N, 5.97%.

Ethyl 2-[2-{bis(2-methyl-1H-indol-3-yl)methyl}-6-methoxyphenoxy] acetate (3j)

Pink solid; 65% yield; FT-IR (KBr): 3393, 3375, 1752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.18 (t, J = 7.0 Hz, 3H), 2.07 (s, 6H), 3.79 (s, 3H), 3.94 (s, 2H), 4.04 (q, J = 7.0 Hz, 2H), 6.37 (s, 1H), 6.81–7.21 (m, 11H), 7.71 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.24, 14.18, 33.70, 55.75, 60.51, 69.20, 109.90, 110.67, 113.11, 119.05, 119.43, 120.42, 122.39, 123.69, 129.11, 131.84, 135.01, 138.04, 145.75, 152.15, 169.65; ESI-MS *m/z*: 481.2; Anal. Calcd. For $C_{30}H_{30}N_2O_3$: C, 74.67; H, 6.27; N, 5.18; Found C, 74.60; H, 6.21; N, 6.20.

Ethyl 2-[4-{bis(2-methyl-1H-indol-3-yl)methyl}phenoxy] acetate (3k)

pink solid; 70% yield; FT-IR (KBr): 3419, 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.25 (t, J = 12.3 Hz, 3H), 2.01 (s, 6H), 4.25 (q, J = 12.3 Hz, 2H), 4.58 (s, 2H), 5.92 (s, 1H), 6.76–7.24 (m, 12H), 7.72 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 12.3, 14.1, 38.4, 61.2, 65.7, 109.9, 113.5, 114.3, 119.0, 119.3, 120.5, 128.9, 130.0, 131.7, 135.0, 137.1, 156.2, 169.1; ESI-MS: *m/z* 451.2; Anal. Calcd. for $C_{29}H_{28}N_2O_3$: C, 76.97; H, 6.24; N, 6.19%. Found: C, 76.98; H, 6.26; N, 6.22%.

Ethyl 2-[4-{bis(2-methyl-1H-indol-3-yl)methyl}phenoxy] propionate (3l)

pink solid; 72% yield; FT-IR (KBr): 3398, 3325, 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.26 (t, J = 11.7 Hz, 3H), 1.98 (s, 6H), 2.75 (t, J = 12.6 Hz, 2H), 4.13–4.21 (m, 4H), 5.91 (s, 1H), 6.74–7.26 (m, 12H), 8.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 12.2, 14.1, 34.7, 38.4, 60.6, 63.6, 110.0, 113.4, 114.3, 118.8, 119.2, 120.3, 128.9, 129.9, 131.9, 135.1, 136.4, 156.7, 171.1; ESI-MS: *m/z* 465.2; Anal. Calcd. for $C_{30}H_{30}N_2O_3$: C, 77.23; H, 6.48; N, 6.00%. Found: C, 77.28; H, 6.46; N, 6.03%.

Ethyl 2-[4-{bis(2-methyl-1H-indol-3-yl)methyl}-2-methoxyphenoxy] acetate (3m)

pink solid, 74% yield, FT-IR (KBr): 3419, 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.20 (t, J = 7.0 Hz, 3H), 2.03 (s, 6H), 4.25 (q, J = 7.0 Hz, 2H), 4.59 (s, 2H), 5.92 (s, 1H), 6.76–7.24 (m, 11H), 7.72 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ:12.3, 14.1, 38.4, 61.3, 65.7, 109.9, 113.5, 114.3, 119.0, 119.3, 120.5, 128.9, 130.0, 131.7, 135.0, 137.0, 156.1, 169.1; ESI-MS: *m/z* 481.2; Anal. Calcd. for $C_{30}H_{30}N_2O_3$: C, 74.67; H, 6.27; N, 5.81%. Found: C, 74.70; H, 6.26; N, 5.85%.

Ethyl 2-[4-{bis(2-methyl-1H-indol-3-yl)methyl}-2-methoxyphenoxy] propionate (3n)

pink solid, 78% yield; FT-IR (KBr): 3391, 1727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.25 (t, J = 12.6 Hz, 3H), 2.33 (s, 6H), 2.83 (t, J = 11.4 Hz, 2H) 3.65 (s, 3H), 4.16 (q, J = 12.6 Hz, 2H), 4.28 (t, J = 11.4 Hz, 2H), 5.93 (s, 1H), 6.70–7.25 (m, 11H), 7.72 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 12.4, 14.2, 34.7, 38.8, 56.0, 60.7, 64.9, 109.9, 113.5, 113.9, 119.0, 119.3, 120.5, 128.9, 131.7, 135.0, 137.4, 146.2, 149.5, 171.2; ESI-MS: *m/z* 495.2; Anal. Calcd. for $C_{29}H_{28}N_2O_3$: C, 74.98; H, 6.50; N, 5.64%. Found: C, 75.00; H, 6.56; N, 6.60%.

Methyl 2-(2-(di(1H-indol-3-yl)methyl)phenoxy)acetate (4a)

Pink solid, 72% yield, FT-IR (KBr): 3390, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 3.70 (3H, s), 4.60 (2H, s), 6.43 (1H, s), 6.68–7.46 (14H, m), 7.86 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): 32.5, 51.8, 66.1, 110.8, 112.1, 119.0, 119.3, 120.0, 121.7, 123.5, 127.1, 127.2, 130.0, 133.3, 136.7, 155.4, 169.5; ESI-MS: *m/z* 409.2; Anal. Calcd. for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N, 6.82%. Found: C, 76.05; H, 5.42; N, 6.84%.

Butyl 2-(2-(di(1H-indol-3-yl)methyl)phenoxy)acetate (4b)

Rosy solid, 64% yield, FT-IR (KBr): 3383, 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.87 (3H, J = 14.7 Hz, t), 1.29 (2H, m), 1.56 (2H, m), 4.13 (2H, J = 6.6 Hz, t), 4.57 (2H, s), 6.41 (1H, s), 6.60–7.44 (14H, m), 7.78 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): 13.6, 18.9, 30.5, 32.4, 65.0, 66.0, 110.9, 111.8, 118.9, 119.2, 120.0, 121.5, 121.7, 127.2, 130.0, 133.1, 136.6, 155.3, 169.3 ESI-MS: *m/z* 451.1; Anal. Calcd. for $C_{29}H_{28}N_2O_3$: C, 76.97; H, 6.24; N, 6.19%. Found: C, 76.92; H, 6.20; N, 6.23%. Compound (CCDC 882631) crystallizes in the orthorhombic system, space group Pca2(1), with a = 22.851(3) Å, b = 8.2624(9) Å, and c = 12.1785(14) Å, and α = 90°, β = 90° and γ = 90°, volume 2299.3(4) $Å^3$, Z = 4, T = 110(2) K, 25,016 reflections measured, 5243 unique reflections, with a Goodness-of-fit on F^2 is 0.918, $R1$ = 0.0345, $wR2$ = 0.0879.

DPPH free radical scavenging activity

The free-radical scavenging activity of the compounds 3a–3l was measured by the decrease in absorbance of methanolic solution of DPPH. A stock solution of DPPH (33 mg/l) was prepared in methanol and 5 ml of this solution was added to 1 ml of each compound at different concentrations (25, 50 μg/ml). After 30 min,

absorbance was measured at 517 nm. Scavenging activity was expressed as the percentage inhibition.

Antibacterial activity

Microorganisms were obtained from the Rajah Muthiah Medical College and Hospital, Annamalai Nagar, Chidambaram, Tamilnadu, India. Five bacterial strains – *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Salmonella typhi,* and *Vibrio cholerae* and five fungal strains – *Aspergillus flavus, Aspergillus fumigatus, Candida albicans, Penicillium* sp. and *Rhizopus* sp. were investigated.

Media preparation and antibacterial activity

Antibacterial susceptibility test was followed by Bauer's agar diffusion method. Agar medium was prepared by pouring 20 ml of Muller Hinton Agar supplemented with 4% sodium chloride and allowed to solidify. Plates were dried and 0.1 ml of standardized inoculum suspension poured and uniformly spread. The excess inoculum was drained and the plates were allowed to dry for 5 min. About 6 mm paper discs (Whatmann No. 1) were impregnated with 20 μl of the each compound dissolved in 5% dimethyl sulphoxide (DMSO) at the concentration of 50 mg/ml to obtain 500 μg/disc. Tetracycline (30 μg/disc) was used as a positive control. About 5% DMSO was used as negative control.

Media preparation and antifungal activity

Antifungal activity was determined against five fungi. The stock culture was maintained in glucose peptone yeast and sucrose (GPYS) medium. Fungal inoculum (0.2 ml) of 48 h old culture was distributed uniformly onto the surface of agar plates containing GPYS medium with the help of a sterile cotton swab. Culture medium was prepared by adding dextrose (20 g/l), peptone (10 g/l) and agar (25 g/l) in distilled water and was sterilized in an autoclave at a pressure of 15 lb/in.^{2} and a temperature of 120 °C. At the time of inoculation, the disc impregnated with each compound (100 g/disc of 10 mm dia) was placed and the plates were incubated for 48 h at 37 °C. For each fungal strain, controls were maintained where pure solvents were used instead of the extract. The antimicrobial activity was measured in terms of inhibition zone diameter. The experiment was done thrice and the mean values were reported.

In vitro anticancer activity

The human skin epithelial cell carcinoma cell line (A431) was obtained from National Centre for Cell Science (NCCS), Pune and grown in Dulbeccos Modified Eaglesl Medium (DMEM) containing 10% fetal bovine serum (FBS). All cells were maintained at 37 °C, 5% CO_2, 95% air, and 100% relative humidity. Maintenance cultures were passaged weekly and the culture medium was changed twice a week [18].

Cell treatment procedure

The monolayer cells were detached with trypsin-ethylenediaminetetraacetic acid (EDTA) to make single cell suspensions and viable cells were counted using a hemocytometer and diluted with medium containing 5% FBS to a give final density of 1×10^5 cells/ml. One hundred microlitres per well of cell suspension were seeded into 96-well plates at a plating density of 10,000 cells/well and incubated to allow for cell attachment at 37 °C, 5% CO_2, 95% air, and 100% relative humidity. After 24 h, the cells were treated with serial concentrations of the extracts and fractions. They were initially dissolved in DMSO and further diluted in serum free medium to produce five concentrations. One hundred microlitres per well of each concentration was added to plates to obtain final concentrations of 300, 150, 75, 37.5 and 18.75 μM. The final volume in each well was 200 μl and the plates were incubated at 37 °C, 5% CO_2, 95% air and 100% relative humidity for 48 h. The medium without samples were served as control. Triplicate was maintained for all concentrations.

MTT assay

MTT is a yellow water soluble tetrazolium salt. A mitochondrial enzyme in living cells, succinate-dehydrogenase, cleaves the tetrazolium ring, converting the MTT to an insoluble purple formazan. Therefore, the amount of formazan produced is directly proportional to the number of viable cells.

After 48 h of incubation, 15 μl of MTT (5 mg/ml) in phosphate buffered saline (PBS) was added to each well and incubated at 37 °C for 4 h. The medium with MTT was then flicked off and the formazan crystals formed were solubilized in 100 μl of DMSO and then measured the absorbance at 570 nm using micro plate reader. The % cell inhibition was determined using the following formula.

$$\% \text{ cell inhibition} = 100 - \text{Abs (sample)}/\text{Abs (control)} \times 100.$$

Nonlinear regression graph was plotted between % cell inhibition and Log_{10} concentration and IC50 was determined using GraphPad Prism software.

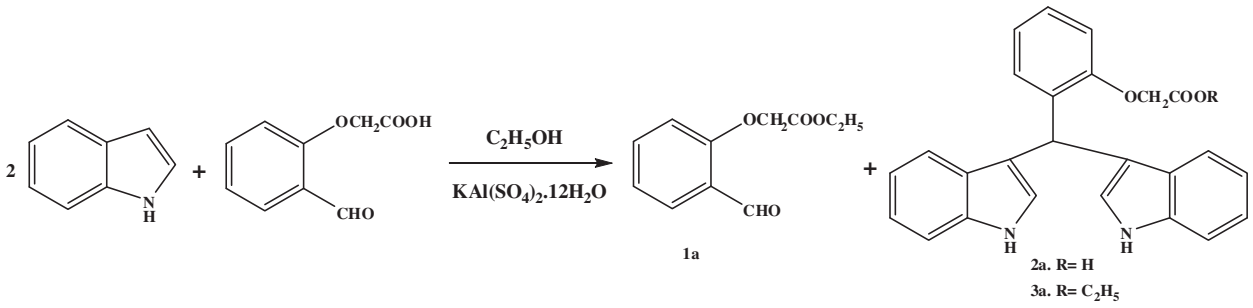
In-vitro antimycobacterial activity screening by resazurin microplate assay (REMA)

The anti-TB activity of the compounds was tested by resazurin microplate assay (REMA) as per Martin et al. [19] with slight modification. Resazurin, a redox dye, is blue in its oxidized state. In the presence of viable cells it is reduced into resorufin, which is pink in color. *M. tuberculosis* H37Rv was grown in Middlebrook 7H9 broth (Difco BBL, Sparks, MD, USA) supplemented with 10% OADC (Becton Dickinson, Sparks, MD, USA) and 0.5% glycerol. The optical density of the bacterial culture was adjusted to McFarland 1.0 unit and 50 μl from this suspension was used as the inoculum. Stock solutions of the test compounds were prepared in dimethyl formamide (DMF) and were added to fresh medium in the wells of a 96-well microplate to which 50 μl inoculum was added making the total assay volume 200 μl. The final concentrations of the test molecules were 1, 10 and 100 μg/ml. Growth control wells contained medium and *M. tuberculosis* H37Rv alone. Rifampicin (1.0 μg/ml) served as a positive control for inhibition of growth. Negative control wells contained the highest volume of DMF in test wells in the absence of any compound. After incubation at 37 °C for 7 days, 15 μl of 0.01% resazurin (Sigma, St. Louis. MO, USA) solution in sterile water was added to the first growth control wells and incubated for 24 h. Once the first set of growth controls turned pink, the dye solution was added to the second set of growth controls and the test wells and incubated for 24 h at 37 °C. Blue color in the wells containing the test compounds would indicate inhibition of growth and pink would indicate lack of inhibition of growth of *M. tuberculosis*.

Results and discussion

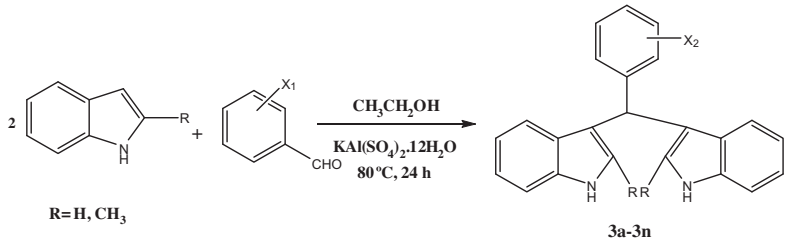
Syntheses of phenoxyaliphatic acid esters of 3,3′-BIMs

We synthesized formylphenoxyaliphatic acids from phenolic aldehydes and the appropriate chlorocarboxylic acids [20]. We studied the model reaction for the synthesis of ethyl 2-[2-{bis(1*H*-indol-3-yl)methyl}phenoxy]acetate (3a) from the condensation of indole with 2-[2-formylphenoxy]acetic acid using potash alum.



Scheme 1. Reaction between indole and 2-formylphenoxyacetic acid in absolute ethanol.

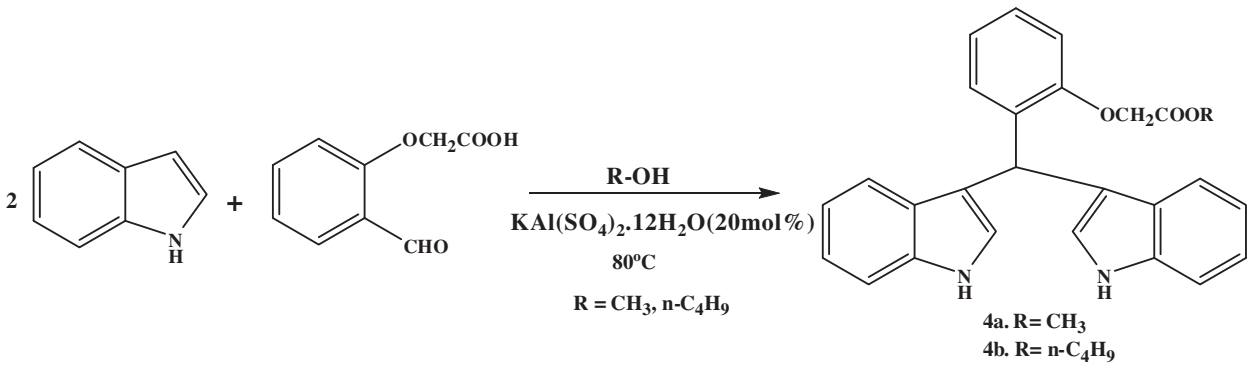
Table 1
Syntheses of 3,3′-bis(indolyl)methanes (BIMs).



Sl. No.	X_1	R	X_2	Yield (%)
1.	2-OCH_2COOH	H	2-$OCH_2COOCH_2CH_3$	68 (**3a**)
2.	2-OCH_2CH_2COOH	H	2-$OCH_2CH_2COOCH_2CH_3$	70 (**3b**)
3.	2-OCH_2COOH, 3-OCH_3	H	2-$OCH_2COOCH_2CH_3$, 3-OCH_3	62 (**3c**)
4.	4-OCH_2COOH	H	4-$OCH_2COOCH_2CH_3$	72 (**3d**)
5.	4-OCH_2CH_2COOH	H	4-$OCH_2CH_2COOCH_2CH_3$	74 (**3e**)
6.	4-OCH_2COOH, 3-OCH_3	H	4-$OCH_2COOCH_2CH_3$, 3-OCH_3	78 (**3f**)
7.	4-OCH_2CH_2COOH, 3-OCH_3	H	4-$OCH_2CH_2COOCH_2CH_3$, 3-OCH_3	78 (**3g**)
8.	2-OCH_2COOH	CH_3	2-$OCH_2COOCH_2CH_3$	70 (**3h**)
9.	2-OCH_2CH_2COOH	CH_3	2-$OCH_2CH_2COOCH_2CH_3$	72 (**3i**)
10.	2-OCH_2COOH, 3-OCH_3	CH_3	2-$OCH_2COOCH_2CH_3$, 3-OCH_3	65 (**3j**)
11.	4-OCH_2COOH	CH_3	4-$OCH_2COOCH_2CH_3$	74 (**3k**)
12.	4-OCH_2CH_2COOH	CH_3	4-$OCH_2CH_2COOCH_2CH_3$	78 (**3l**)
13.	4-OCH_2COOH, 3-OCH_3	CH_3	4-$OCH_2COOCH_2CH_3$, 3-OCH_3	82 (**3m**)
14.	4-OCH_2CH_2COOH, 3-OCH_3	CH_3	4-$OCH_2CH_2COOCH_2CH_3$, 3-OCH_3	85 (**3n**)

Experiments were carried out in various solvents like hexanes, benzene, toluene, acetonitrile, DMF, ethanol, aqueous ethanol (1:1), and water using potash alum (50 mol%) as a catalyst for 12 h under reflux. The reaction did not occur in hexanes, benzene, and toluene to give 2a but proceeded smoothly in acetonitrile, DMF, aqueous ethanol, and water to give 2a. With absolute ethanol, compounds 1a, 2a and 3a were observed. Subsequently, further optimization of the reaction conditions, including reaction temperature, reaction time, and volume of absolute ethanol was investigated.

We initially carried out the reaction between indole (5.0 mmol) and 2-formylphenoxyacetic acid (2.5 mmol) in absolute ethanol



Scheme 2. Synthesis of methyl and n-butyl esters of phenoxyacetic acid 3,3′-BIM.

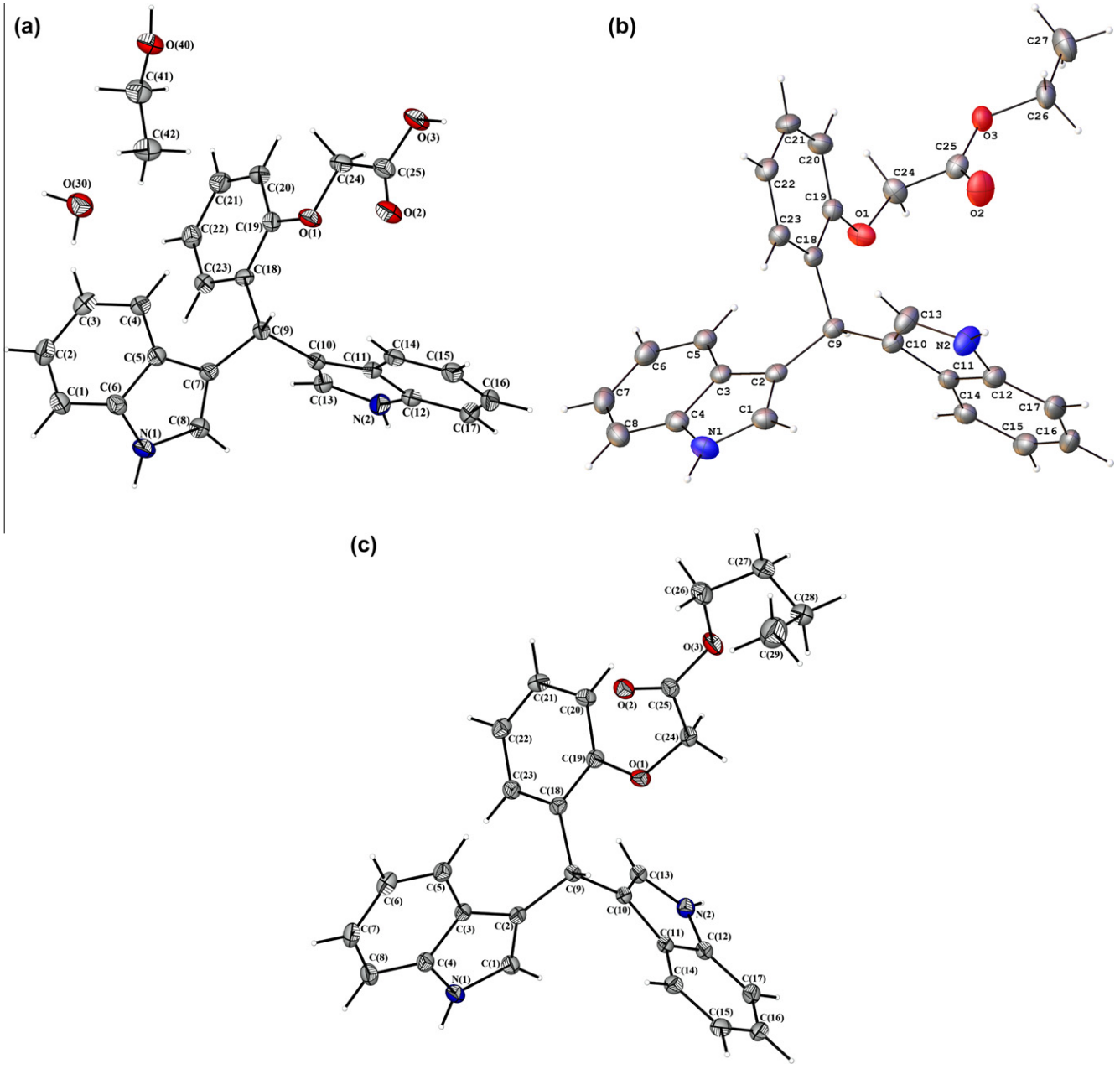


Fig. 1. ORTEP view for (a) 2a, (b) 3a and (c) 4b.

(20 ml) using potash alum (50 mol%) under reflux. After 30 min, we observed ethyl 2-formylphenoxyacetate (1), 2-[2-{bis(1*H*-indol-3-yl)methyl}phenoxy]acetic acid (2a), and ethyl 2-[2-{bis (1*H*-indol-3-yl)methyl}phenoxy]acetate (**3**a) (Scheme 1). TLC monitoring indicated that the starting materials completely got converted into both 2a (25%) and 3a (66%) after 12 h. No significant improvement in conversion was observed either with a higher catalyst loading (up to 1 equivalent) or extension of reaction time (48 h). We could obtain the best result from 20 mol% of potash alum with 5 ml/mmol of alcohol at 80 °C for the synthesis of 3a.

To extend the scope of the reaction as a general and practical procedure for the one-pot syntheses, we carried out the reaction of different formylphenoxyaliphatic acids with indole in absolute ethanol at 80 °C in the presence of potash alum (20 mol%) for 24 h. The results are presented in Table 1.

The results indicate that the *o*- and *p*-isomers of formylphenoxyacetic acid and formylphenoxypropionic acid afforded the corresponding BIMs in moderate yields. Esterification with methanol and n-butanol reveals that the yield of methyl ester was higher than that of n-butyl ester of BIM (Scheme 2).

After completion of the reaction, the reaction mixture was filtered. Potash alum was collected, washed with excess of ethanol, and dried well. The recovered catalyst was reused for the synthesis of 3. The yields of the products 3 were not affected by the use of recovered catalyst. Purity of the recovered potash alum was checked with the IR spectrum of fresh potash alum.

Single crystal XRD studies

2a was crystallized using aqueous ethanol (1:1) whereas 3a and 4b were crystallized using ethanol under slow evaporation in the absence of light. The compounds have been characterized by single crystal X-ray diffraction studies (*vide* supporting information for crystal details). The ORTEP views of the compounds are shown in

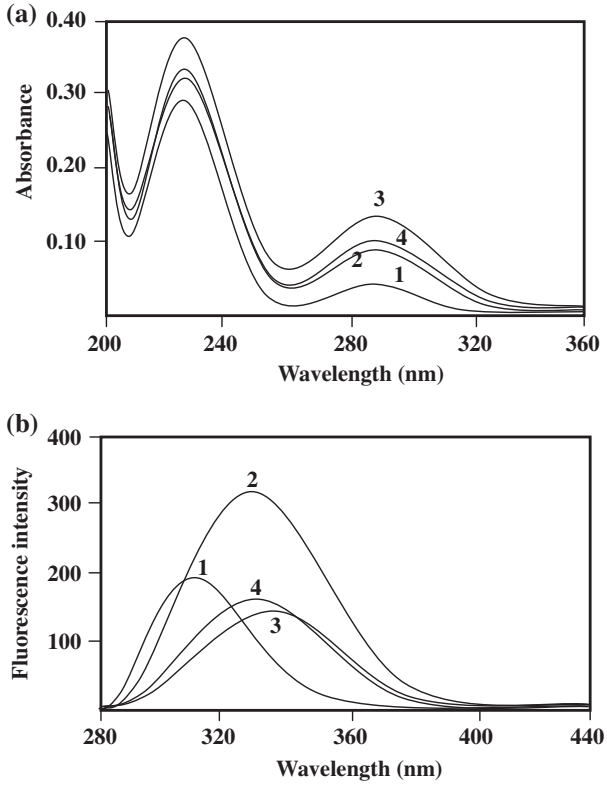


Fig. 2. Absorption and fluorescence spectra of **3h** in selected solvents: 1. cyclohexane, 2. acetonitrile, 3. methanol, and 4. water.

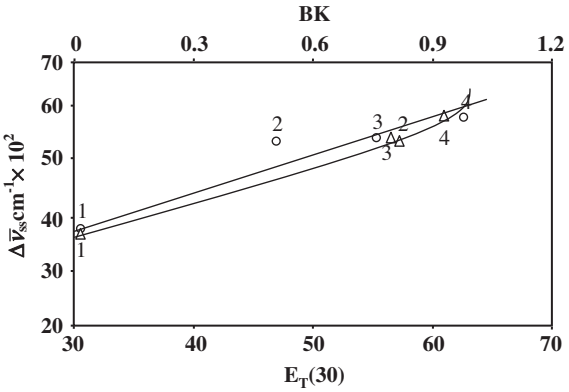


Fig. 3. Plot of Stokes shifts (cm^{-1}) of BIM vs. $E_T(30)$ and BK solvent parameters: 1. cyclohexane, 2. acetonitrile, 3. methanol, and 4. water.

Fig. 1. Acid BIM (2a, Fig. 1a) was crystallized as a monoclinic system. It is connected with a molecule of water and a molecule of ethanol through hydrogen bonding [O3—H3···O40, Ow—H1w···O2]. This leads to the formation of a ring with Etter's graph set designator $R_3^3(8)$. Two such systems join together to form a dimer. In the formation of the dimmer, the oxygen of the carbonyl group of —COOH (O_2 of C_{25}=O_2) forms bifurcated H-bonding with two water molecules. In the dimerization, a new square motif with graph set notation $R_4^2(8)$ is formed (Fig. s1, *vide* supporting information). The molecule of 3a exists as a dimer through the H-bonding, N1—H1···O2, formed by indole N—H with the oxygen of ester carbonyl (C_{25}=O_2). This H-bond formation leads to the formation a ring motif with a graph set notation R^2_2 (22). The crystal is made up of discrete dimers (Fig. s2, *vide* supporting information). Crystal 4b displays association of the molecules through the H-bonding, N1—H1···O2. It leads to the formation of infinite chain with Etter's graph set designator C(11) (Fig. s3, *vide* supporting information). The dihedral angles between the two indole rings in 2a, 3a, and 4b are 60.95°, 78.41°, and 78.98° respectively. No π–π interaction was observed in 2a, 3a, and 4b as the shortest distance is found to be greater than 4.1 Å. 2a, 3a, and 4b have C—H···π and N—H···π interactions. Similar interactions are found in 3,3′-BIMs derivatives [21], other indole derivatives [22], and globular proteins [23]. These interactions may afford stability and contribute to the folding process or have a functional role in proteins.

Solvent effects on absorption and fluorescence spectrum

Hydrogen bonding and solvent polarity are the key factors in controlling pathways of energy dissipation followed by electronic excitation [24]. Solvent-moderated shifts of the energy levels may enhance or inhibit radiationless transitions to the ground state *via* the "proximity effect" [25]. Hydrogen bond formation has a different effect on the energies of various excited states; in an extreme case, hydrogen bonding may cause the reversal of close lying n, π^* and π, π^* states [26].

The indole derivatives are supposed to exhibit photophysical behavior in homogeneous environments [27]. Therefore we extended our study to understand the photophysical behavior of synthesized aryl-3,3′-BIMs. The absorption and emission spectra of BIMs 3h, 3i, 3k, 3l, 3m, and 3n have been studied in various solvents of different polarity and are shown in Fig. 2. The absorption and emission maxima of BIMs are presented in Table 2. The absorption maxima of BIMs in different solvents are dominated by two strong absorption bands at 290 and 224 nm, which can be related with the strong π–π^* transitions. The absorption maximum of BIMs has no significant effect with increasing polarity of solvents.

The fluorescence spectra of the indole derivatives excited at 290 nm have showed a single fluorescence emission maximum in the region of 330–350 nm on going from cyclohexane to water.

Table 2
Spectral properties of compounds **3**.

Solvent	3h			3i			3k			3l			3m			3n		
	λ_{max}	λ_{flu}	Stokes shift	λ_{max}	λ_{flu}	Stokes shift	λ_{max}	λ_{flu}	Stokes shift	λ_{max}	λ_{flu}	Stokes shift	λ_{max}	λ_{flu}	Stokes shift	λ_{max}	λ_{flu}	Stokes shift
Cyclohexane	290 219	328	3994	291 226	329	3969	291 226	327	3783	290 219	328	3994	291 226	329	3969	291 226	330	4061
Acetonitrile	290 236	348	5747	290 229	340	5070	290 229	340	5070	290 236	348	5747	290 229	340	5070	289 229	344	5532
Methanol	291 234	349	5710	291 234	345	5378	290 230	344	5412	291 234	349	5710	291 234	345	5378	289 230	350	6030
Water	290 230	350	5911	290 230	350	5911	289 230	350	6030	290 230	350	5911	290 230	350	5911	289 230	351	6112

Table 3
DPPH radical scavenging activity of 3a–3l.

Concentration (μg/ml)	DPPH radical scavenging (%)														
	BHC	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	3l	3m	3n
25	93.81 ± 0.01	84.37 ± 0.02	76.22 ± 0.04	75.85 ± 0.05	42.22 ± 0.03	40.12 ± 0.05	65.85 ± 0.03	48.50 ± 0.05	54.02 ± 0.01	48.50 ± 0.05	45.25 ± 0.02	54.02 ± 0.01	48.50 ± 0.05	42.22 ± 0.03	51.50 ± 0.05
50	90.85 ± 0.89	85.82 ± 0.03	78.40 ± 0.07	76.50 ± 0.03	44.23 ± 0.03	41.15 ± 0.05	69.11 ± 0.02	50.50 ± 0.05	66.03 ± 0.02	60.43 ± 0.04	59.52 ± 0.03	66.03 ± 0.02	60.48 ± 0.03	57.18 ± 0.02	52.45 ± 0.05

Values are mean ± SD of triplicate values.

The shift in the fluorescence maxima over absorption maxima suggests that the emitting states of the compounds are more polar than the ground state. The absorption and emission spectral shape of all the compounds were the same in the solvents. The red shift on the fluorescence spectra on changing the solvent from cyclohexane to water indicates the effect of hydrogen bonding in the excited state of the compounds [28].

The absorption and emission spectra of the reported BIMs mainly originate from the indole rings. The presence of a methine group in between the two indole rings and substituted phenyl ring prevents the extension of conjugation. The absorption and emission maxima are thus very close to that of an individual indole ring.

Correlation of solvatochromic shift with the solvent polarity

The Stokes shifts $[\bar{\nu}_{abs}(\max) - \bar{\nu}_{flu}(\max)]$ increases with an increase in the polarity of H-bonding of the solvents indicating that the dipole moment of the molecules increases upon excitation. The increase in the dipole moment in the S_1 state suggests all molecules are more polar in the S_1 state. Empirically or theoretically derived solvent parameters like BK [29] and $E_T(30)$ [30] which are accurate parameters of the solvent polarity have been used to correlate the molecular spectroscopic properties. Among these parameters, BK are taken into account of solvent polarity alone, whereas $E_T(30)$ incorporates both solvent polarity and hydrogen bonding effects. Correlation of Stokes shifts with any one of these parameters gives an idea about which type of solute–solvent interaction occurs between them. The solvatochromic shifts reveal that the hydrogen bonding interactions are present along with dipole interactions. In order to confirm this, we have used the above solvent parameters and the values are compared with Stokes shifts of all compounds (Table 2). Fig. 3 shows the plots of Stokes shifts vs. BK and $E_T(30)$ parameters (shown in one graph). The increase in Stokes shifts from cyclohexane to water is found to be more in accordance with $E_T(30)$ than with other parameters. As mentioned earlier, $E_T(30)$ parameter incorporates both solvent polarity and H-bonding effects, whereas the BK parameter represents only the solvent polarity effects. Since H-bonding interactions are predominant in the solvatochromic shifts, $E_T(30)$ gives a good correlation than the BK parameter.

DPPH radical scavenging assay

The antioxidant activity of compounds (**3**) was evaluated using 'DPPH radical scavenging method'. Table 3 revealed no significant improvement even when the concentration of BIMs were increased from 25 to 50 μg/ml. Acetic acid esters were found to be more active than propionic acid esters in which the *ortho* isomers had nearly twice the activity than the *para* isomers. Unsubstituted indole derivatives displayed higher activity than 2-methylindole derivatives. Among these compounds, 3a showed the highest free radical scavenging activity 84.37 ± 0.02 and 85.82 ± 0.03 at concentrations of 25 and 50 μg/ml respectively.

In-vitro antimicrobial assay

BIMs showed better antimicrobial activity. In the present study, antimicrobial activities of compounds (3) were tested against five bacterial and five fungal strains. Among the 12 compounds reported, the highest antibacterial effect was observed with compound 3f against *Staphylococcus aureus* (20 mm), and moderate effect against *Klebseilla pneumonia, Salmonella typhi*, and *Vibrio cholera* (Table 4). On the other hand, compounds 3a and 3f showed highest antifungal activity against *Candida albicans* (20 mm) but did not exhibit any antifungal activity against *Aspergillus fumigatus, Penicillium* sp., and

Table 4
Antibacterial activity of **3**.

Microorganism	Zone of inhibition (mm)														
	Tetracycline (standard)	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	3l	3m	3n
Escherichia coli	13	18	16	16	16	15	17	17	16	15	14	12	12	14	14
Staphylococcus aureus	12	17	18	17	19	19	20	18	17	16	15	12	16	15	15
Klebseillapneumoniae	13	14	15	13	14	16	12	14	10	11	11	10	11	10	13
Salmonella typhi	15	12	13	12	12	13	14	12	14	15	15	14	16	12	14
Vibrio cholerae	14	13	11	11	10	10	11	10	12	10	12	10	10	11	11

Table 5
Antifungal activity of **3**.

Microorganism	Zone of inhibition (mm)														
	Tetracycline (standard)	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	3l	3m	3n
Aspergillusflavus	14	18	16	16	16	15	17	16	12	13	12	11	10	13	12
Aspergillusfumigatus	12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Candida albicans	10	20	19	18	18	19	20	18	16	18	16	14	15	16	15
Penicillium sp.	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rhizopus sp.	17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

* NA = no activity.

Table 6
Calculation of IC50 using% growth inhibition against Log10 Concentration (μM).

Compounds	2a	3a	3b	3c	3d	3e	4a	4b
IC50 (μM)	94.81	209.6	280.0	303.9	126.5	305.8	37.42	>350

Rhizopus sp. (Table 5). The unsubstituted indole derivatives were found to be more active than 2-methylindole derivatives.

In-vitro anticancer activity

We screened the growth inhibition or antiproliferative effects of BIMs 2a, 3a, 3b, 3c, 3d, 3e, 4a and 4b on the cancer cell line A431, AGS, and U373MG using MTT assay. These BIMs have IC50 more than 300 μM on AGS, and U373MG cell line. They have lower antiproliferative effects on A431 cell line. The data showed that 4a had lower IC50 than other compounds (Table 6). As the chain length of ester increases, the IC50 also increases.

In-vitro antituberculosis activity

The antituberculosis activity of the compounds (**3**) were tested by resazurin microplate assay (REMA) as per Martin et al. [19] with slight modification. The results indicate that the compounds have no inhibition against *M. tuberculosis* H37Rv growth up to 100 μM concentration.

Conclusion

An efficient one-pot synthesis of BIM esters from indole and formylphenoxyaliphatic acid(s) in alcohol using potash alum has been developed. This is the first report for simultaneous esterification and condensation of indole with formylphenoxyaliphatic acids in alcohol using potash alum catalyst. The photophysical properties of BIMs showed that the presence of a methine group in between the two indole rings and substituted phenyl ring prevents the extension of conjugation. The radical scavenging activity of BIMs was lower than that of the standard though 3a showed to be a better radical scavenger. BIMs have better activity against *Staphylococcus aureus* and *Candida albicans*, and moderate effect against *Klebseilla pneumonia, Salmonella typhi*, and *Vibrio cholera*. BIMs have poor cyctotoxicity against A431 cell line and revealed an increase in IC50 value with an increase in the ester side chain length. Compounds 3 did not display any inhibition on *M. tuberculosis* H37Rv.

Acknowledgements

One of the authors (G.S. Suresh Kumar) thanks CDRI, Lucknow, India for mass analysis and Madurai Kamaraj University, Madurai, India for the NMR spectral data. The author A. Antony Muthu Prabhu is thankful to Dr. N. Rajendiran, Associate Professor, Department of Chemistry, Annamalai University for introducing in this field.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.saa.2012.09.046.

References

[1] (a) J.K. Porter, C.W. Bacon, J.D. Robbins, D.S. Himmelsbach, H.C.J. Higman, Agric. Food Chem. 25 (1977) 88;
(b) T. Osawa, M. Namiki, Tetrahedron Lett. 24 (1983) 4719;
(c) G. Bifulco, I. Bruno, R. Riccio, J. Lavayre, G.J. Bourdy, *Nat. Prod.* 57 (1994) 1254;
(d) R. Bell, S. Carmeli, N.J. Sar, Nat. Prod. 57 (1994) 1587;
(e) T.R. Garbe, M. Kobayashi, N. Shimizu, N. Takesue, M. Ozawa, H.J. Yukawa, *Nat. Prod.* 63 (2000) 596.
[2] G. Sivaprasad, P.T. Perumal, V.R. Prabavathy, N. Mathivanan, Bioorg. Med. Chem. Lett. 16 (2006) 6302.
[3] A. Kamal, M.N.A. Khan, K.S. Reddy, Y.V.V. Srikanth, S.K. Ahmed, K.P. Kumar, U.S.N.J. Murthy, Enzyme Inhib. Med. Chem. 24 (2009) 559.
[4] M. Kobayashi, S. Aoki, K. Gato, K. Matsunami, M. Kurosu, I. Kitagawa, Chem. Pharm. Bull. 42 (1994) 2449.
[5] (a) G. Giannini, M. Marzi, M.O. Tinti, C. Pisano, International Patent 2000, WO0236597.;
(b) G. Giannini, M. Marzi, M.O. Tinti, C. Pisano, Chem. Abstr. 136, 355230.;
(c) L. Valeria, M. Ernesto, 1998, EP0887348.
[6] L. Valeria, M. Ernesto, O. Ambrogio, G. Frank, K. Hans-Willi, 2000, EP0991645.
[7] K. Sujatha, P.T. Perumal, D. Muralidharan, M. Rajendran, Indian J. Chem. 48B (2009) 267.
[8] S.H. Benabadji, R. Wen, J. Zheng, X. Dong, S. Yuan, Acta Pharmacol. Sin. 25 (2004) 666.
[9] C. Pal, S. Dey, S.K. Mahato, J. Vinayagam, P.K. Pradhan, V.S. Giri, P. Jaisankar, T. Hossain, S. Baruri, D. Raya, S.M. Biswas, Bioorg. Med. Chem. Lett. 17 (2007) 4924.

[10] (a) M. Freund, G. Lebach, Chem. Ber. 36 (1903) 308;
(b) J.R. Majer, Tetrahedron 9 (1960) 106;
(c) J.R. Majer, Tetrahedron 9 (1960) 111;
(d) H. Budzikiewicz, H. Eckau, M. Ehrenberg, Tetrahedron Lett. 13 (1972) 3807;
(e) T.J. Novak, D.N. Kramer, H. Klapper, L.W. Daasch, B.L. Murr, J. Org. Chem. 41 (1976) 870;
(f) T.V. Stupnikova, L.A. Reybenko, Z.M. Skorobogotova, A.K. Sheinkman, Khim. Geterotsikl. Soedin. 3 (1978) 416.
[11] (a) X. He, S. Hu, K. Liu, Y. Guo, J. Xu, S. Shao, Org. Lett. 8 (2006) 333;
(b) R. Martinez, A. Espinosa, A. Tarraga, P. Molina, Tetrahedron 64 (2008) 2184;
(c) J.L. Zhang, H. Wang, Ganguang Kexue yu Guanghuaxue 25 (2007) 257;
(d) Z. Li, D.S. Guo, H.X. Li, Y. Liu, Chem. J. Chin. Univ. 29 (2008) 2545;
D. Bedekovic, I.J. Fletcher, U.S. Patent 4, 1986, 343.
[12] M. Shiri, M.A. Zolfigol, H.G. Kruger, Z. Tanbakouchian, Chem. Rev. 110 (2010) 2250.
[13] (a) J. Azizian, A.A. Mohammadi, A.R. Karimi, M.R. Mohammadiazadeh, Appl. Catal. A: General 300 (2006) 85;
(b) M. Dabiri, M. Baghbanzadeh, S. Kiani, Y. Vakilzadeh, *Monatsh. Chem.* 138 (2007) 997.
[14] S. Kumar, I.S. Grover, J.S. Sandhu, Indian J. Chem. 48B (2009) 585.
[15] S.S. Sonar, S.A. Sadaphal, A.H. Kategaonkar, R.U. Pokalwar, B.B. Shingate, M.S. Shingare, Bull. Korean Chem. Soc. 30 (2009) 825.
[16] O. Benjamin, B.H. Aderemi, A. Hameed, Appl. Catal. A 370 (2009) 54.
[17] G.S. Suresh Kumar, S. Kumaresan, J. Chem. Sci. 124 (4) (2012) 857.
[18] (a) T. Mosmann, J. Immunol. Methods 65 (1983) 55;
(b) A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Lonley, P. Cronise, A. Vaigro-Wolff, M. Gray-Goodrich, H. Cmpbell, J. Mayo, M. Boyd, J. Natl. Cancer Inst. 83 (1991) 757.
[19] (a) A. Martin, M. Camacho, F. Portaels, J.C. Palomino, Antimicrob. Agents Chemother. 47 (11) (2003) 3616;
(b) A. Martin, J.C. Palomino, Drug Susceptibility Testing for Mycobacterium Tuberculosis, Institute of Tropical Medicine, Belgium, Procedure manual Version 03, 2009.
[20] B.S. Furniss, A.J. Hannaford, P.W.G. Smith, R. Austin, Vogel's Textbook of Practical Organic Chemistry, 5th ed., Longman, Scientific & Technical, 1989. pp. 1160.
[21] (a) D. Maciejewska, I. Szpakowska, I. Wolska, M. Niemyjska, M. Mascini, M. Maj-Zurawska, Bioelecterochemistry 69 (2006) 1;
(b) D. Maciejewska, I. Wolska, M. Niemyjska, P. Zero, J. Mol. StrucT. 753 (2005) 53;
(c) M. Rasztawicka, D. Maciejewska, M. Niemyjska, I. Wolska, M. Wlostowski, M. Rasztawicka, Z. Naturforsch 59(b) (2004) 1137.
[22] (a) R. Krishna, D. Velmurugan, G. Babu, P.T. Perumal, Acta Crystallogr. C55 (1999) 75;
(b) R. Krishna, D. Velmurugan, S. Shanmuga Sundara, *Acta Crystallogr.* C55 (1999) IUC9900084.
[23] M. Crisma, F. Formaggio, G. Valle, C. Toniolo, M. Saviano, R. Lacovino, L. Zaccaro, E. Benedetti, Biopolymers 42 (1997) 1.
[24] N.J. Turro, Modern Molecular photochemistry, Menlo Park, CA, Benjamin/Cummings, 1978.
[25] E.C. Lim, J. Phys. Chem. 90 (1986) 6770.
[26] M.J. van der Burgt, L.M.G. Jansen, A.H. Huizer, C.A.G.O. Varma, Chem. Phys. 201 (1995) 525.
[27] R. Martınez, A. Espinosa, A. Tarraga, P. Molina, Tetrahedron 64 (2008) 2184.
[28] A. Sarkar, P. Banerjee, Sk.U. Hossain, S. Bhattacharya, S.C. Bhattacharya, Spectrochim. Acta 72A (2009) 1097.
[29] L. Bilot, A. Kawski, Z. Naturforsch. 18A (1962) 621.
[30] C. Reichardt, K. Dimroth, Fortschr. Chem. Forsch. 11 (1968) 1.