JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Article

pubs.acs.org/JAFC

Identification of Naphthol Derivatives as Novel Antifeedants and Insecticides. 1

Praveen Kumar Kalavagunta,[†] Rajasekharreddy Pala,[‡] Usha Rani Pathipati,[‡] and Narender Ravirala*[,†]

[†]Crop Protection Chemicals Division and [‡]Biology and Biotechnology Division, CSIR-Indian Institute of Chemical Technology, Taranaka, Hyderabad 500 007, India

Supporting Information

ABSTRACT: A series of β-naphthol-derived 2-aminobenzothiazolomethylnaphthol derivatives (**4a**−**4q**) were synthesized and purified in excellent yields (86−94%) using green protocols and screened for their antifeedant and toxic activities against tobacco caterpillar (*Spodoptera litura*) and castor semilooper (*Achaea janata*) using no-choice leaf disk and topical bioassay methods. Four of them, **4d**, **4f**, **4i**, and **4j**, were identified to be potent antifeedants with ED_{50} values of 16.4, 19.3, 7.0, and 5.2 μg/cm^2 against *S. litura* and 13.9, 17.2, 10.2, and 7.7 μg/cm^2 against *A. janata*, respectively, and the mortality rate is >95% for **4i** and **4j** in the case of *S. litura* and **4j** in case of *A. janata* at a dosage of 0.2 μg/insect. Compounds **4d**, **4i**, and **4m** are moderately toxic to *A. janata* only. Overall, this study identified a novel class of synthetic compounds that do not belong to organochlorides, organophosphates, carbamates, or neonicotinoids as strong antifeedants as well as insecticides.

KEYWORDS: *β-naphthol, 2-aminobenzothiazole, Spodoptera litura, Achaea janata, antifeedant activity, insecticidal activity*

INTRODUCTION

The enormous increase of population necessitates the need for growing more food, which depends not only on good cultivation practices but also on the control of pests and diseases of the crops before as well as after harvest. Many novel and alternate methods of pest control have been suggested in recent years, but it appears that the routine use of chemical pesticides is inevitable to curtail crop losses. The major reason for the inability of these newly devised methods to protect crops from insect pests is that they are developing resistance in a rapid manner. Hence, a need occurs for the invention of newer pesticides that can manage pest populations in the field, leaving beneficial species unaffected. Conventional pesticides, most of which are either organochlorides such as DDT, endosulfan, and pentachlorophenol or organophosphates such as chlorpyrifos, monocrotophos, and malathion, are all found to be acutely toxic to birds, wildlife, and humans.[1,2] They are also found to cause several diseases in humans.[3−6] As a result, most of them have been banned in several countries or are about to be banned. Neonicotinoids such as acetamiprid and imidacloprid, which come into play as promising pesticides, also show potential toxicity. A few of them are known for their connection to honeybee colony collapse disorder.[7] Recently the European Union put a restriction on the use of neonicotinoids,[8] The American Bird Conservancy called for a ban on the use of neonicotinoids in seed treatments because of their toxicity to birds, aquatic invertebrates, and other wildlife.[9] As a result, there is increasing research on developing new classes of pesticides that are toxic to selected pests and insects but not to humans and other creatures. In 2007, DuPont introduced chlorantraniliprole, a new class of insecticide, which belongs to the anthranilamides. It selectively binds to ryanodine receptors in insects and controls the release of Ca^{2+} and essential muscle function, which finally leads to paralysis followed by insect death.[10] However, its potential environmental effects are not well understood.

Several natural products such as azadirachtin, gossypol, quercetin, and rutin are potent insecticides/pesticides. Very few of them are known to have a naphthalene ring in their structure. Even though they are fewer in number, most of them are known to possess a 2-hydroxynaphthalene-1-carbaldehyde skeleton in their basic structure. The natural products hemigossypol and methoxyhemigossypol are currently being used as components of insect bait composition[11] and also showing antifungal activity.[12] On the other hand, gossypol (Figure 1), which is a dimer of hemigossypol, a defensive chemical present in cotton, also shows antioxidative,[13]

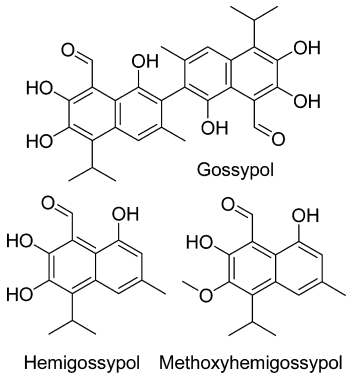


Figure 1. 2-Hydroxynaphthalene-1-carbaldehyde-based natural products with potent biological and insecticidal/pest repellent properties.

Received: April 10, 2014
Revised: June 19, 2014
Accepted: June 23, 2014
Published: June 23, 2014

antibacterial,[14] and antifungal[15] properties and so on. The compound can be used to treat several ailments.[16]

Another natural product, stelladerol (Figure 2), is a strong inhibitor of cyclooxygenase enzyme and phospholipid oxidation.[17] The compound 2-hydroxynaphthalene-1-carbaldehyde itself is known to possess moderate antibacterial property.[18] Naphthol is a precursor for a variety of insecticides and is a well-known component with contact insecticidal properties.[19]

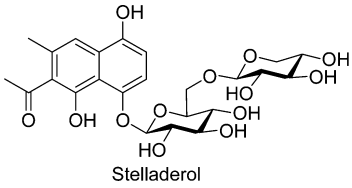


Figure 2. Structure of naphthalene glycoside, stelladerol, which has potential biological activities.

As our group is involved in the synthesis of β-naphthol-based synthetics,[20] we designed and synthesized a series of naphthalene-based hybrid molecules using a novel green protocol to screen them for their dual inhibitory activity as angiotensin converting enzyme inhibitors and calcium channel blockers in treating resistant hypertension. In a recent study Venugopala et al. reported that these compounds show good antimosquito properties.[21] The existing literature and recent studies drove us to screen our compounds for their antifeedant and toxic properties against major agricultural pests. In the present paper we describe the synthesis of 2-aminobenzothiazolomethylnaphthol derivatives using a green protocol and their influence on the feeding behavior and toxicity effects against a major polyphagous pest, *Spodoptera litura*, and a monophagous pest, *Achaea janata* (L).

MATERIALS AND METHODS

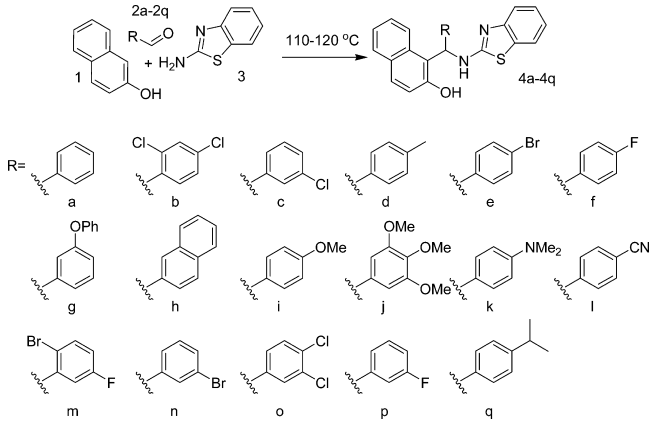
Instruments. Commercially available reagent grade chemicals and solvents were used in all reactions and purification processes. All of the reactions were monitored by TLC on E. Merck Kieselgel 60 F_{254}, with detection by UV light, charring with PMA charring solution, or exposure to I_2 vapors. The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) were recorded on Avance-300 in DMSO-d_6. The spectra were acquired with sufficiently long relaxation delay to ensure quaternary carbon relaxation. Also, more scans were used to obtain reasonable sensitivity of the ^{13}C NMR spectra. Multiplicities arising from ^{13}C−^{19}F couplings were low in intensity and present over a large area, so they were counted independently. Chemical shift values are reported in parts per million relative to DMSO as internal reference. Coupling constant value J is measured in hertz. s (singlet), d (doublet), t (triplet), brs (broad singlet), dd (double doublet), m (multiplet). Mass spectra were recorded on an Agilent LC/MSD trap SL 1100 series spectrometer with a 70 eV ESI probe, and high-resolution mass spectra were obtained by using ESI-QTOF mass spectrometry. Infrared spectra were recorded on a Thermo Nicolet Nexus 670 FT-IR spectrometer.

General Synthesis. To a 10 mL RB flask were added aldehyde (1.0 mmol), 2-aminobenzothiazole (1.0 mmol), and β-naphthol (1.0 mmol); these were mixed thoroughly and heated in preheated oil bath at 110−120 °C for an appropriate time (Table 1). After completion of reaction as indicated by TLC, the reaction mixture was allowed to cool. The so-formed solid was powdered, washed with methanol (8 mL × 3 times for compounds except fluoro and methoxy derivatives, 4 mL × 3 times in the case of fluoro and methoxy derivatives), and dried under vacuum to obtain the corresponding pure 2-aminobenzothiazolomethylnaphthol derivative. However, in the case of fluoro- and methoxy-substituted derivatives, care must be taken during washing or unreacted material present in the reaction mixture may dissolve in methanol and help methanol to dissolve the product, resulting in a decrease in the overall yield. Moreover, the solubility of fluoro and methoxy derivatives is better in methanol when compared to other derivatives. A schematic representation of the reaction is given in Scheme 1.

Table 1. Optimized Reaction Conditions for the Synthesis of Compounds 4a−4q

no.	compd	time, min	temp, °C	yield, %
1	**4a**	40	110	94
2	**4b**	50	120	92
3	**4c**	40	110	93
4	**4d**	45	110	91
5	**4e**	50	110	94
6	**4f**	40	110	95
7	**4g**	45	110	92
8	**4h**	45	110	90
9	**4i**	45	110	91
10	**4j**	45	110	88
11	**4k**	40	110	93
12	**4l**	40	110	92
13	**4m**	50	120	92
14	**4n**	40	110	94
15	**4o**	40	110	94
16	**4p**	40	110	93
17	**4q**	45	110	90

Scheme 1. Schematic Representation for the Synthesis of Compounds 4a−4q



*1. 1-((Benzo[d]thiazol-2-ylamino)(phenyl)methyl)naphthalen-2-ol (**4a**):* white solid; mp = 200−202 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (brs, 1H), 8.78 (d, 1H, J = 7.6 Hz), 7.94−7.74 (m, 3H), 7.66 (d, 1H, J = 7.6 Hz), 7.40−7.13 (m, 10H), 7.0 (t, 1H, J = 7.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.3, 153.2, 152.1, 142.5, 132.1, 130.8, 129.6, 128.6, 128.6, 128.1, 126.2, 126.0, 125.4, 123.8, 122.4, 121.0, 120.9, 118.7, 118.4, 118.1, 53.1; IR (KBr) ν_{max} 3376, 3060, 1598, 1547, 1514, 1444, 1331, 1263, 744 cm^{-1}; ESI-MS m/z 383 (M + H). HRMS calcd for $C_{24}H_{19}N_2OS$, 383.1218; found, 383.1206.

*2. 1-((Benzo[d]thiazol-2-ylamino)(2,4-dichlorophenyl)methyl)-naphthalen-2-ol (**4b**):* white solid; mp = 190−192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.02−9.91 (brs, 1H), 8.88 (d, 1H, J = 7.0 Hz), 8.02 (d, 1H, J = 8.5 Hz), 7.79 (t, 2H, J = 9.3 Hz), 7.70−7.63 (m, 2H), 7.49 (d, 1H, J = 2.1 Hz), 7.46−7.35 (m, 3H), 7.27 (t, 1H, J = 7.6 Hz), 7.23−7.12 (m, 3H), 7.01 (t, 1H, J = 7.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.2, 153.8, 152.1, 139.0, 133.0, 132.7, 131.8, 131.1, 130.7, 130.0, 128.7, 128.3, 126.6, 126.5, 125.5, 122.6, 122.4, 121.1, 120.9, 118.5, 118.3, 115.9, 52.3; IR (KBr) ν_{max} 3378, 3068, 1592, 1542, 1438, 1371, 1331, 1268, 751 cm^{-1}; ESI-MS m/z 451 (M + H). HRMS calcd for $C_{24}H_{17}N_2OSCl_2$, 451.0438; found, 451.0451.

dx.doi.org/10.1021/jf501705u | J. Agric. Food Chem. 2014, 62, 6571−6576

*3. 1-((Benzo[d]thiazol-2-ylamino)(3-chlorophenyl)methyl)-naphthalen-2-ol (**4c**):* white solid; mp = 193−194 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.81 (d, 1H, J = 7.6 Hz), 7.94−7.77 (m, 3H), 7.67 (d, 1H, J = 7.6 Hz), 7.45−7.15 (m, 10H), 7.02 (t, 1H, J = 7.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.1, 153.1, 151.9, 145.3, 132.8, 131.9, 130.8, 130.0, 129.8, 128.6, 128.5, 126.5, 126.1, 125.6, 125.4, 124.8, 123.3, 122.5, 121.1, 120.9, 118.3, 118.2, 118.0, 52.6; IR (KBr) ν_{max} 3360, 3062, 1596, 1573, 1548, 1515, 1444, 1332, 1268, 749 cm^{-1}; ESI-MS m/z 417 (M + H). HRMS calcd for $C_{24}H_{18}N_2OSCl$, 417.0828; found, 417.0809.

*4. 1-((Benzo[d]thiazol-2-ylamino)(p-tolyl)methyl)naphthalen-2-ol (**4d**).* white solid; mp = 180−182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.18−10.11 (brs, 1H), 8.78 (d, 1H, J = 7.6 Hz), 7.91−7.73 (m, 3H), 7.66 (d, 1H, J = 7.4 Hz), 7.39−6.96 (m, 11H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.2, 153.1, 152.1, 139.4, 135.1, 132.1, 130.7, 129.4, 128.6, 128.5, 126.1, 125.9, 125.4, 123.9, 122.4, 120.9, 120.8, 118.7, 118.3, 118.0, 52.9, 20.5; IR (KBr) ν_{max} 3307, 1535, 1441, 1317, 1261, 744 cm^{-1}; ESI-MS m/z 397 (M + H). HRMS calcd for $C_{25}H_{21}N_2OS$, 397.1374; found, 397.1373.

*5. 1-((Benzo[d]thiazol-2-ylamino)(4-bromophenyl)methyl)-naphthalen-2-ol (**4e**):* white solid; mp = 202−204 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.24−10.16 (brs, 1H), 8.82 (d, 1H, J = 7.0 Hz), 7.89−7.75 (m, 3H), 7.67 (d, 1H, J = 7.6 Hz), 7.49−7.36 (m, 4H), 7.30−7.12 (m, 6H), 7.02 (t, 1H, J = 7.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.1, 153.1, 151.9, 142.1, 131.9, 130.9, 130.8, 129.7, 128.5, 128.2, 126.3, 125.3, 123.5, 122.4, 121.0, 120.8, 119.1, 118.3, 118.1, 52.6; IR (KBr) ν_{max} 3373, 1627, 1541, 1442, 1332, 1267, 1206, 1070, 749, 571 cm^{-1}; ESI-MS m/z 461 (M + H). HRMS calcd for $C_{24}H_{18}N_2OSBr$, 461.0323; found, 461.0320.

*6. 1-((Benzo[d]thiazol-2-ylamino)(4-fluorophenyl)methyl)-naphthalen-2-ol (**4f**):* white solid; mp = 178−180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.22−10.13 (brs, 1H), 8.81 (d, 1H, J = 7.4 Hz), 7.93−7.76 (m, 3H), 7.67 (d, 1H, J = 7.7 Hz), 7.42−7.32 (m, 2H), 7.31−7.15 (m, 6H), 7.93−6.95 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.1, 162.2, 159.0, 153.1, 151.9, 138.4, 131.9, 130.7, 129.5, 128.5, 127.9, 127.8, 126.2, 125.3, 123.5, 122.3, 120.9, 120.8, 118.3, 118.0, 114.8, 114.5, 52.6; IR (KBr) ν_{max} 3308, 1537, 1436, 1319, 1286, 1060, 810, 746 cm^{-1}; ESI-MS m/z 401 (M + H). HRMS calcd for $C_{24}H_{18}FN_2OS$, 401.1123; found, 401.1115.

*7. 1-((Benzo[d]thiazol-2-ylamino)(3-phenoxyphenyl)methyl)-naphthalen-2-ol (**4g**):* white solid; mp = 171−173 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.78 (d, 1H, J = 7.4 Hz), 7.89−7.73 (m, 3H), 7.66 (d, 1H, J = 7.0 Hz), 7.43−7.16 (m, 9H), 7.06−6.93 (m, 4H), 6.87 (d, 2H, J = 7.6 Hz), 6.79 (dd, 1H, J_1 = 7.6 Hz, J_2 = 2.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.1, 156.5, 156.0, 153.1, 152.0, 145.0, 132.0, 130.7, 129.7, 128.6, 128.5, 126.2, 125.4, 123.0, 122.4, 121.3, 121.0, 120.8, 118.3, 118.1, 117.9, 116.6, 116.3, 52.7; IR (KBr) ν_{max} 3314, 3052, 1541, 1511, 1451, 1267, 814, 749 cm^{-1}; ESI-MS m/z 475 (M + H). HRMS calcd for $C_{30}H_{23}N_2O_2S$, 475.1480; found, 475.1471.

*8. 1-((Benzo[d]thiazol-2-ylamino)(naphthalen-2-yl)methyl)-naphthalen-2-ol (**4h**):* white solid; mp = 190−192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.21−10.16 (brs, 1H), 8.91 (d, 1H, J = 7.4 Hz), 7.95 (d, 1H, J = 7.9 Hz), 7.89−7.74 (m, 6H), 7.68 (d, 1H, J = 7.9 Hz), 7.53−7.40 (m, 3H), 7.38−7.15 (m, 6H), 7.02 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.2, 153.1, 152.0, 140.1, 132.6, 132.1, 131.7, 130.7, 129.6, 128.5, 128.4, 127.5, 127.3, 126.1, 126.0, 125.4, 125.3, 124.9, 123.8, 123.6, 122.3, 120.9, 120.8, 118.5, 118.3, 118.0, 53.3; IR (KBr) ν_{max} 3313, 3052, 1541, 1442, 1264, 814, 749 cm^{-1}; ESI-MS m/z 433 (M + H). HRMS calcd for $C_{28}H_{21}N_2OS$, 433.1374; found, 433.1387.

*9. 1-((Benzo[d]thiazol-2-ylamino)(4-methoxyphenyl)methyl)-naphthalen-2-ol (**4i**):* white solid; mp = 190−192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.19−10.11 (brs, 1H), 8.79 (d, 1H, J = 7.4 Hz), 7.94−7.84 (brs, 1H), 7.79 (t, 2H, J = 8.7 Hz), 7.66 (d, 1H, J = 7.6 Hz), 7.42−7.12 (m, 9H), 7.0 (t, 1H, J = 7.9 Hz), 6.83 (d, 1H, J = 8.7 Hz), 3.68 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.2, 157.7, 153.0, 152.1, 134.1, 132.1, 130.6, 129.4, 128.6, 128.5, 127.2, 126.1, 125.3, 123.8, 122.3, 120.9, 120.8, 118.7, 118.4, 118.0, 113.5, 54.9, 52.8; IR (KBr) $_{\nu max}$ 3313, 3052, 1541, 1442, 1264, 814, 749 cm^{-1}; ESI-MS m/z 413 (M + H). HRMS calcd for $C_{25}H_{21}N_2O_2S$, 413.1323; found, 413.1319.

*10. 6.1.1.20. 1-((Benzo[d]thiazol-2-ylamino)(3,4,5-trimethoxyphenyl)methyl)naphthalen-2-ol (**4j**):* white solid; mp = 170−172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.42−10.30 (brs, 1H), 8.63−8.37 (brs, 1H), 7.98−7.87 (brs, 1H), 7.75−7.63 (m, 2H), 7.52−7.31 (m, 3H), 7.28−7.15 (m, 3H), 7.11−6.94 (m, 2H), 6.58 (s, 2H), 3.70 (s, 3H), 3.66 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.3, 153.3, 152.4, 137.0, 136.1, 132.0, 129.9, 129.1, 128.6, 128.1, 125.8, 125.1, 123.0, 122.2, 120.8, 120.1, 119.1, 118.8, 117.9, 103.6, 95.6, 59.8, 55.4, 54.3; IR (KBr) ν_{max} 3317, 2923, 2833, 1590, 1538, 1441, 1315, 1248, 1171, 1030, 813, 745 cm^{-1}; ESI-MS m/z 473 (M + H). HRMS calcd for $C_{27}H_{25}N_2O_4S$, 473.1535; found, 473.1527.

*11. 1-((Benzo[d]thiazol-2-ylamino)(4-(dimethylamino)phenyl)-naphthalen-2-ol (**4k**):* white solid; mp = 156−158 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.22−10.04 (brs, 1H), 8.71 (d, 1H, J = 7.4 Hz), 7.93 (d, 1H, J = 7.5 Hz), 7.77 (t, 2H, J = 9.1 Hz), 7.64 (d, 1H, J = 7.4 Hz), 7.39−7.29 (m, 2H), 7.28−7.11 (m, 4H), 7.07 (d, 2H, J = 8.5 Hz), 6.99 (t, 1H, J = 7.9 Hz), 6.63 (d, 2H, J = 8.9 Hz), 2.80 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.2, 153.0, 152.1, 149.0, 132.1, 130.5, 129.5, 129.1, 128.6, 128.4, 126.8, 125.9, 125.3, 122.2, 120.7, 118.9, 118.4, 117.9, 112.2, 53.1, 40.1; IR (KBr) ν_{max} 3315, 2849, 1602, 1538, 1446, 1318, 1264, 1165, 810, 745 cm^{-1}; ESI-MS m/z 426 (M + H). HRMS calcd for $C_{26}H_{24}N_3OS$, 426.1640; found, 426.1639.

*12. 4-((Benzo[d]thiazol-2-ylamino)(2-hydroxynaphthalen-1-yl)-methyl)benzonitrile (**4l**):* white solid; mp = 213−215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.31−10.20 (brs, 1H), 8.85 (d, 1H, J = 7.0 Hz), 7.89−7.78 (m, 3H), 7.76−7.65 (m, 3H), 7.46−7.33 (m, 5H), 7.31−7.17 (m, 3H), 7.03 (t, 1H, J = 7.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.1, 153.2, 151.9, 148.8, 132.0, 130.8, 130.0, 128.6, 128.5, 127.0, 126.5, 125.4, 123.2, 122.5, 121.2, 120.9, 118.8, 118.3, 117.8, 108.9, 53.0; IR (KBr) ν_{max} 3379, 3056, 2226, 1573, 1541, 1437, 1329, 1270, 1026, 751 cm^{-1}; ESI-MS m/z 408 (M + H). HRMS calcd for $C_{25}H_{18}N_3OS$, 408.1170; found, 408.1163.

*13. 1-((Benzo[d]thiazol-2-ylamino)(2-bromo-5-fluorophenyl)-methyl)naphthalen-2-ol (**4m**):* white solid; mp = 198−200 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.92 (brs, 1H), 8.90 (d, 1H, J = 7.4 Hz), 8.05 (d, 1H, J = 8.7 Hz), 7.80 (t, 2H, J = 9.3 Hz), 7.66 (d, 1H, J = 7.7 Hz), 7.61−7.54 (m, 1H), 7.39−7.34 (m, 3H), 7.28 (t, 1H, J = 7.4 Hz), 7.20 (t, 1H, J = 7.6 Hz), 7.14−6.97 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.0, 162.6, 159.4, 153.7, 152.0, 144.2, 144.1, 134.1, 134.0, 132.8, 130.6, 129.9, 128.5, 128.1, 126.5, 125.3, 122.4, 122.3, 121.0, 120.8, 118.5, 118.2, 116.9, 116.7, 116.6, 115.6, 115.3, 54.7; IR (KBr) ν_{max} 3383, 1598, 1543, 1512, 1453, 1431, 1265, 812, 752 cm^{-1}; ESI-MS m/z 479 (M + H). HRMS calcd for $C_{24}H_{17}BrFN_2OS$, 479.0204; found, 479.0190.

*14. 1-((Benzo[d]thiazol-2-ylamino)(3-bromophenyl)naphthalen-2-ol (**4n**):* white solid; mp = 201−203 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.27−10.20 (brs, 1H), 8.84 (d, 1H, J = 7.4 Hz), 7.92−7.77 (m, 3H), 7.68 (d, 1H, J = 7.6 Hz), 7.45−7.15 (m, 11H), 7.02 (t, 1H, J = 7.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.0, 153.1, 151.9, 145.5, 131.9, 130.7, 130.2, 129.8, 129.0, 128.5, 126.4, 125.4, 125.1, 123.3, 122.4, 121.4, 121.0, 120.8, 118.3, 118.1, 118.0, 52.6; IR (KBr) ν_{max} 3377, 3058, 1543, 1511, 1435, 1327, 1268, 747 cm^{-1}; MS-ESI m/z 461 (M + H). HRMS calcd for $C_{24}H_{18}BrN_2OS$, 461.0323; found, 461.0312.

*15. 1-((Benzo[d]thiazol-2-ylamino)(3,4-dichlorophenyl)-naphthalen-2-ol (**4o**):* white solid; mp = 212−214 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.28−10.24 (brs, 1H), 8.87 (d, 1H, J = 7.2 Hz), 7.93−7.79 (m, 3H), 7.69 (d, 1H, J = 7.6 Hz), 7.53 (d, 1H, J = 8.3 Hz), 7.47−7.37 (m, 3H), 7.32−7.15 (m, 5H), 7.03 (t, 1H J = 7.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.0, 153.2, 151.8, 144.0, 131.9, 130.8, 130.6, 130.2, 130.0, 128.6, 128.4, 127.7, 126.6, 126.5, 125.4, 123.1, 122.5, 121.1, 120.9, 118.3, 118.2, 117.6, 52.3; IR (KBr) ν_{max} 3379, 1577, 1540, 11461, 1328, 1268, 1205, 1028, 816, 747 cm^{-1}; ESI-MS m/z 451 (M + H). HRMS calcd for $C_{24}H_{17}Cl_2N_2OS$, 451.0438; found, 451.0439.

*16. 1-((Benzo[d]thiazol-2-ylamino)(3-fluorophenyl)naphthalen-2-ol (**4p**):* white solid; mp = 179−181 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.26−10.19 (brs, 1H), 8.84 (d, 1H, J = 7.4 Hz), 7.90−

7.78 (m, 3H), 7.68 (d, 1H, J = 7.7 Hz), 7.43−7.17 (m, 7H), 7.07−6.96 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.1, 163.7, 160.5, 153.1, 151.9, 145.8, 145.8, 131.9, 130.7, 130.0, 129.9, 129.7, 128.5, 126.3, 125.4, 123.4, 122.4, 122.1, 121.0, 120.8, 118.3, 118.1, 113.0, 112.8, 112.5, 52.7; IR (KBr) ν_{max} 3387, 1587, 1536, 1482, 1439, 1329, 1244, 1053, 749 cm^{-1}; ESI-MS m/z 401 (M + H). HRMS calcd for $C_{24}H_{18}FN_2OS$, 401.1123; found, 401.1118.

*17. 1-((Benzo[d]thiazol-2-ylamino)(4-isopropylphenyl)-naphthalen-2-ol (**4q**):* white solid; mp = 191−193 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17−10.09 (brs, 1H), 8.78 (d, 1h, J = 7.6 Hz), 7.98−7.87 (brs, 1H), 7.79 (t, 2H, J = 7.8 Hz), 7.66 (d, 1H, J = 7.6 Hz), 7.4−7.32 (m, 2H), 7.30−7.10 (m, 8H), 7.00 (t, 1H, J = 8.1 Hz), 2.89−2.74 (m, 1H), 1.14 (dd, 6H, J_1 = 7.0 Hz, J_2 = 1.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.2, 153.0, 152.1, 146.1, 139.6, 132.1, 130.6, 129.3, 128.5, 128.4, 126.1, 126.0, 125.9, 125.3, 123.7, 122.3, 120.8, 120.8, 118.7, 118.4, 118.0, 53.0, 32.9, 23.8, 23.7; IR (KBr) ν_{max} 3314, 3055, 2957, 1540, 1450, 1268, 1060, 746 cm^{-1}; ESI-MS m/z 425 (M + H). HRMS calcd for $C_{27}H_{25}N_2OS$, 425.1687; found, 425.1704.

Test Insects. *S. litura* and *A. janata* larvae used in this study were obtained from a laboratory colony maintained in the Biology and Biotechnology Division, IICT, Hyderabad, India. The culture has been continuously maintained on castor leaves (*Ricinus communis*) at room temperature (26 ± 2 °C), 65 ± 5% relative humidity, and 16:8 L:D photoperiod in the laboratory.

Antifeedant Bioassay. The antifeedant activity of the compounds was tested against tobacco caterpillar, *S. litura* (F.), and castor semilooper, *A. janata* (L.). The experiments were conducted according to the classical no-choice leaf disk method described earlier by Akhtar et al.[22] To study the antifeedant activity of the test compounds, a small circular disk of 4 cm diameter was cut from fresh castor leaves. The leaf disks were treated on their upper surface with individual concentrations of the test compounds; after that, the leaf disks were air-dried at room temperature, and each leaf disk was transferred to a separate Petri plate of 15 cm diameter containing wet filter paper. Control leaf disks were treated with the same volume of the DMSO only. The third-instar larvae of *S. litura* and *A. janata* (starved for 4−5 h prior to the experiment) were allowed to feed to assess antifeedant activity. Progress of the consumption of the leaf area was measured at 6, 12, and 24 h period intervals in both treated and control leaf disks. Areas of control and treated leaf disks consumed were measured after 24 h using a leaf area meter (AM-300, ADC Bioscientific Limited, Hoddesdon, UK). The antifeedant index was then calculated as $(C - T)/(C + T) \times 100$, where C is the consumption of control leaf disks and T is consumption of treated leaf disks.[23] For each concentration, 10 experimental sets were assayed. All tests were replicated three times. The mean of the 30 sets was taken for each compound. Means were subjected to probit analysis.[24]

Topical Bioassay. Toxicity of the test compounds was determined by topical application to the third instar larvae of test insects.[25] Two micrograms of compounds was applied directly to the dorsum of the larva in a 1 μL drop of DMSO using a micro applicator. Insects treated with solvent alone were considered as controls. The treated and control larvae were treated on fresh castor leaves. Mortality was measured daily until 2 days after treatment. Larvae that lost elasticity and heavy water loss from their body and showed no responses when their tails were pinched with forceps were regarded as dead. On the basis of three independent trials, each experiment was conducted in five replicates, leading to 15 replicates with each concentration of compounds. The mean of 15 replicates was taken for each compound, and the percentage of mortality with standard deviation was calculated.

Data Analysis. Antifeedant index was calculated using five different concentrations of each test compound, and data were subjected to probit analysis[24] to determine the ED_{50} value representing the concentrations that caused 50% feeding deterrence along with the 95% fiducial limits. The data were analyzed by completely randomized, one-way analysis of variance (ANOVA), and the means were separated using the Tukey HSD test (Biostat 2008).

RESULTS AND DISCUSSION

Scheme 1 illustrates the general procedure for the synthesis of 2-aminobenzothiazolomethylnaphthol derivatives. The synthesis procedure is completely green, economic, and high-yielding. A total of 17 derivatives were synthesized and screened for their antifeedant effect (Table 2) and toxicity (Table 3) against *S. litura* and *A. janata*.

Table 2. Antifeedant Effect of 2-Aminobenzothiazolomethylnaphthol Derivatives 4a−q against *S. litura* and *A. janata* by No-Choice Leaf Disk Bioassay Method

	antifeedant ED_{50}, μg/cm^2 (95% FL[a])	
compd	*S. litura*	*A. janata*
4a	>300	185.2 (175.0−192.3)
4b	109.9 (96.7−123.1)	204.7 (204.5−204.9)
4c	59.2 (53.9−63.0)	31.7 (21.0−37.6)
4d	**16.4 (16.1−16.7)**	**13.9 (12.7−14.8)**
4e	>300	>300
4f	**19.3 (19.1−19.6)**	**17.2 (13.8−19.6)**
4g	>300	219.0 (216.9−220.8)
4h	201.7 (197.0−205.2)	265.2 (257.6−271.6)
4i	**7.0 (6.3−7.8)**	**10.2 (8.6−10.8)**
4j	**5.2 (4.3−5.8)**	**7.7 (4.0−11.9)**
4k	103.9 (100.0−107.0)	111.2 (58.4−138.4)
4l	31.7 (19.0−38.9)	21.9 (20.9−22.5)
4m	28.0 (27.8−28.2)	43.4 (43.1−43.6)
4n	46.7 (39.7−53.7)	33.4 (29.8−37.3)
4o	73.6 (62.4−80.2)	81.7 (79.23−83.88)
4p	89.2 (80.9−94.4)	76.7 (73.6−79.2)
4q	>300	230.9 (228.8−232.9)
azadirachtin	3.1 (2.0−4.0)	4.7 (3.5−6.0)

[a]Fiducial limits.

The antifeedant activity of the 2-aminobenzothiazolomethylnaphthol derivatives was studied using the no-choice leaf disk method. The results are summarized in Table 2. It is interesting to note that most of the derivatives synthesized have good antifeedancy against *S. litura* and *A. janata*. A few of them, **4d**, **4f**, **4i**, and **4j**, show a high level of antifeedancy even at lower concentrations (5−100 μg/cm^2) against both insects. Derivatives **4d**, **4f**, **4i**, and **4j** showed significant antifeedant activity (ED_{50}) at lower doses of 16.4, 19.3, 7.0, and 5.2 μg/cm^2 against *S. litura* and lower doses of 13.9, 17.2, 10.2, and 7.7 μg/cm^2 against *A. janata*, respectively.

Compounds **4a−q** were primarily screened for their toxicity using topical bioassay method at a dosage of 0.5 μg/insect (Table 3). Compounds **4d**, **4f**, **4i**, and **4j** showed 100% mortality against both species. Interestingly, two compounds, **4l** and **4m**, showed 100% mortality against *A. janata* but were least toxic to *S. litura*. To estimate the mortality rate at a lower dose, we again screened the compounds at a dosage of 0.2 μg/insect (Table 3). Derivative **4j** produced high mortality >95% against the larvae of both *S. litura* and *A. janata*, whereas derivative **4i** showed high mortality, that is, >95%, against *S. litura* but only moderate mortality, that is, >85% and <95% against *A. janata*. On the contrary, derivatives **4d** and **4m** showed moderate mortality against *A. janata*, leaving them least toxic to *S. litura*. Larval death took place soon after exposure to the treatment. Derivatives **4i** and **4j** are very potent in penetrating the larval body through cuticle and cause lethal effects because in these

Table 3. Toxicity Effects of 2-Aminobenzothiazolomethylnaphthol Derivatives 4a−q against *S. litura* and *A. janata* by Topical Bioassay Method

	mortality,[a] %, ± SE		mortality,[b] %, ± SE	
compd	*S. litura*	*A. janata*	*S. litura*	*A. janata*
4a	13.6 ± 0.3	16.6 ± 0.5	6.4 ± 0.5	7.8 ± 0.6
4b	16.0 ± 0.8	14.1 ± 0.4	4.4 ± 0.7	0.0 ± 0.0
4c	67.7 ± 0.8	70.5 ± 1.0	42.2 ± 2.3	56.4 ± 2.7
4d	**100 ± 0.0**	**100 ± 0.0**	84.7 ± 1.1	**88.1 ± 0.9**
4e	3.7 ± 0.3	5.5 ± 0.4	0.0 ± 0.0	0.0 ± 0.0
4f	**100 ± 0.0**	**100 ± 0.0**	70.5 ± 0.8	63.5 ± 1.6
4g	10.5 ± 0.8	6.5 ± 0.4	0.0 ± 0.0	0.0 ± 0.0
4h	27.4 ± 0.5	67.6 ± 0.5	13.2 ± 0.8	47.1 ± 2.0
4i	**100 ± 0.0**	**100 ± 0.0**	**98.6 ± 0.5**	**89.1 ± 1.0**
4j	**100 ± 0.0**	**100 ± 0.0**	**96.3 ± 1.6**	**99.3 ± 0.5**
4k	64.6 ± 2.0	32.3 ± 1.2	43.0 ± 2.7	20.6 ± 1.8
4l	77.7 ± 2.3	**100 ± 0.0**	59.4 ± 1.3	61.6 ± 1.0
4m	80.0 ± 0.9	**100 ± 0.0**	45.5 ± 1.4	**89.1 ± 1.2**
4n	78.8 ± 0.6	69 ± 0.7	60.2 ± 0.9	50.1 ± 1.3
4o	64.2 ± 1.7	**99.7 ± 0.4**	42.5 ± 0.8	64.5 ± 1.3
4p	24.33 ± 1.3	31.7 ± 1.3	0.0 ± 0.0	19.4 ± 1.4
4q	13.3 ± 0.4	17.4 ± 0.3	0.0 ± 0.0	4.3 ± 0.4
azadirachtin	100 ± 0.0	100 ± 0.0	100 ± 0.0	100 ± 0.0

[a]Mortality at a dosage of 0.5 μg/insect. [b]Mortality at a dosage of 0.2 μg/insect.

treatments the feeding was absolutely prevented. It appears, from the results, that derivative **4j** is a strong feeding deterrent and strongly toxic, where as **4i** is a strong feeding deterrent but strongly toxic against *S. litura* and moderately toxic against *A. janata*. On the other hand, compound **4f** is a strong feeding deterrent but least toxic against both *S. litura* and *A. janata*. The treatments could cause desirable impact on larval feeding and survival and could totally achieve the management of these two major crop pests under laboratory conditions. Therefore, these compounds can be used as both antifeedants and pesticides.

It is clear from their structures that the compounds were differently substituted on the phenyl ring, leaving naphthyl and benzothiazole rings unsubstituted. Even though it may not be appropriate to draw a precise structure−activity relationship with the present data, we can observe from the results that the 4-bromophenyl (**4e**) and 4-phenoxyphenyl (**4g**) derivatives are completely nontoxic at a dosage of 0.2 μg/insect, whereas the 3,4,5-trimethoxyphenyl (**4j**) derivative is strongly toxic, leaving the others in between. Fused and bulky substituted phenyl derivatives **4b**, **4e**, **4g**, **4h**, **4k**, and **4q** are inactive or least active along with unsubstituted phenyl derivative **4a**, whereas 3,4,5-trimethoxy-substituted (**4j**) phenyl has strong antifeedancy and toxicity. However, in the case of the 4-methoxy (**4i**) phenyl derivative toxicity increases for *S. litura* and decreases for *A. janata*. The derivatives substituted with chloro, cyano, dimethylamino, dichloro, and fluoro substituents have comparatively low antifeedancy and are least toxic. From the above results we may conclude that the 3,4,5-trimethoxy derivative is strongly antifeedant and toxic, but 4-methoxy derivatives are strong antifeedants with selective toxicity against *S. litura*.

Overall, we identified a novel class of synthetic molecules that do not belong to organochlorides, organophosphates, carbamates, neonicotinoids, and anthranilamides as potent antifeedants and insecticides. These results may enlighten a way to search for natural product inspired synthetic antifeedants and insecticides. Compounds **4i** and **4j** may be useful in protecting crops from the above insects. Derivatives **4d** and **4m** are worth considering as feeding deterrents along with moderate insecticidal properties, and derivative **4f** can be considered as a strong feeding deterrent with least toxicity. Their potential field applicability is yet to be explored.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*(Ravirala Narender) E-mail: ravindra@iict.res.in, raviralanarender@gmail.com. Phone: +91-40-27191538. Fax: +91-40-27193382.

Funding

P.K.K. is thankful to CSIR and R.P. is thankful to ICMR for the award of senior research fellowships.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The support of A. V. Subrahmanya Sarma and T. Prabhakar Rao, Centre for NMR and Structural Chemistry, CSIR-IICT, is greatly acknowledged. Without their support, obtaining a good-quality ^{13}C NMR spectrum might have been difficult. We are also thankful to V. J. Rao, Head, CPC Division, CSIR-IICT, for his constant support and encouragement throughout the work.

■ REFERENCES

(1) Clothianidin − Registration Status and Related Information; http://www.epa.gov/pesticides/about/intheworks/clothianidin-registration-status.html (updated July 27, 2012) (accesssed March 21, 2014).

(2) EXTOXNET − Extension Toxicology Network. A Pesticide Information Project of Cooperative Extension Offices of Cornell University, Michigan State University, Oregon State University, and University of California at Davis; http://pmep.cce.cornell.edu/

profiles/extoxnet/carbaryl-dicrotophos/chlorpyrifos-ext.html (accessed March 21, 2014).
(3) Hayden, K. M.; Norton, M. C.; Darcey, D.; Ostbye, T.; Zandi, P. P.; Breitner, J. C. S.; Welsh-Bohmer, K. A. For the Cache County Study Investigators. Occupational exposure to pesticides increases the risk of incident AD: the Cache County study. *Neurology* **2010**, *74* (19), 1524−1530.
(4) Bouchard, M. F.; Bellinger, D. C.; Wright, R. O.; Weisskopf, M. G. Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. *Pediatrics* **2010**, *125* (6), e1270−e1277.
(5) Velmurugan, G.; Venkatesh, B. D. D.; Ramasamy, S. Prolonged monocrotophos intake induces cardiac oxidative stress and myocardial damage in rats. *Toxicology* **2013**, *307*, 103−108.
(6) Mahendra, P. K.; Abhishek, K. S.; Vivek, K.; Vinay, K. T.; Ritesh, K. S.; Megha, A.; Vinay, K. K.; Sanjay, Y.; Swatantra, K. J.; Aditya, B. P. Monocrotophos induced apoptosis in PC12 cells: role of xenobiotic metabolizing cytochrome P450s. *PLoS One* **2011**, *6*, e17757.
(7) Gill, R. J.; Ramos-Rodriguez, O.; Raine, N. Combined pesticide exposure severely affects individual- and colony-level traits in bees. *Nature* **2012**, *491* (7422), 105−108.
(8) McDonald-Gibson, C. 'Victory for bees' as European Union bans neonicotinoid pesticides blamed for destroying bee population; http://www.independent.co.uk/environment/nature/victory-for-bees-as-european-union-bans-neonicotinoid-pesticides-blamed-for-destroying-bee-population-8595408.html (accesses June 17, 2014).
(9) Mineau, P.; Palmer, C. The impact of the nation's most widely used insecticides on birds; http://www.abcbirds.org/abcprograms/policy/toxins/Neonic_FINAL.pdf (accessed June 17, 2014).
(10) Daniel, W. S. Altacor WG Insecticide (DPX-E2Y45) Introducing a Novel Anthranilic Diamide Insecticide from DuPont; http://ncc.confex.com/ncc/viewHandout.cgi?uploadid=246 (accessed June 17, 2014).
(11) The United States of America as represented by the Secretary of Agriculture. US6773727, 2004.
(12) Puckhaber, L. S.; Dowd, M. K.; Stipanovic, R. D.; Howell, C. R. Toxicity of (+)- and (−)-gossypol to the plant pathogen *Rhizoctonia solani*. *J. Agric. Food Chem.* **2002**, *50*, 7017−7021.
(13) Ilkevych, N. S.; Schroeder, G.; Rybachenko, V. I.; Chotiy, K. Y.; Makarova, R. A. Vibrational spectra, structure and antioxidant activity of gossypol imine derivatives. *Spectrochim. Acta Mol. Biomol. Spectrosc.* **2012**, *86*, 328−335.
(14) Tegos, G.; Stermitz, F. R.; Lomovskaya, O.; Lewis, K. Multidrug pump inhibitors uncover remarkable activity of plant antimicrobials. *Antimicrob. Agents Chemother.* **2002**, *46*, 3133−3141.
(15) Mellon, J. E.; Dowd, M. K.; Beltz, S. B.; Klich, M. A.; Zelaya, C. A. Inhibitory effects of gossypol, gossypolone, and apogossypolone on a collection of economically important filamentous fungi. *J. Agric. Food Chem.* **2012**, *60*, 2740−2745.
(16) Ascenta Therapeutics Inc. WO2008/150506, 2008.
(17) Cichewicz, R. H.; Nair, M. G. Isolation and characterization of stelladerol, a new antioxidant naphthalene glycoside, and other antioxidant glycosides from edible daylily (*Hemerocallis*) flowers. *J. Agric. Food Chem.* **2002**, *50*, 87−91.
(18) Patel, M. N.; Patel, S. H.; Chhasatia, M. R.; Desai, C. R. *Nucleosides Nucleotides Nucleic Acids* **2010**, *29*, 200−215.
(19) Swaine, W. Organic contact insecticide and its use. U.S. Patent Office, New York, 2283471, 1942.
(20) Praveen, K. K.; Satyanarayana, S.; Lakshmi, R. P.; Narasimhulu, G.; Narender, R.; Subba Reddy, B. V. Iodine-catalyzed three-component one-pot synthesis of naphthopyranopyrimidines under solvent-free conditions. *Tetrahedron Lett.* **2012**, *53*, 1738−1741.
(21) Venugopala, K. N.; Krishnappa, M.; Nayak, S. K.; Subrahmanya, B. K.; Vaderapura, J. P.; Chalannavar, R. K.; Gleiser, R. M.; Odhav, B. Synthesis and antimosquito properties of 2,6-substituted benzo[*d*]-thiazole and 2,4-substituted benzo[*d*]thiazole analogues against *Anopheles arabiensis*. *Eur. J. Med. Chem.* **2013**, *65*, 295−303.
(22) Akhtar, Y.; Isman, M. B. Feeding responses of specialist herbivores to plant extracts and pure allelochemicals: effects of prolonged exposure. *Entomol. Exp. Appl.* **2004**, *111*, 201−208.
(23) Murray, B. I.; Opender, K.; Anna, L.; Jerzy, K. Insecticidal and antifeedant bioactivities of neem oils and their relationship to azadirachtin content. *J. Agric. Food Chem.* **1990**, *38*, 1406−1411.
(24) Finney, D. J. In *Probit Analysis*; Cambridge University Press: London, UK, 1971; pp 68−72.
(25) Jamil, K.; Usha Rani, P.; Tyagarajan, G. Water hyacinth a potential new juvenile hormone mimic. *Int. Pest Control* **1984**, *26*, 106−108.