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Microwave-assisted novel and efficient one-pot synthesis of fused steroidal and non-steroidal isothiazoles

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ABSTRACT

An efficient microwave promoted one-pot synthesis of steroidal and non-steroidal isothiazole derivatives from corresponding β-bromo-α,β-unsaturated aldehydes has been described using a sodium thiocyanate-urea system. The β-bromo-α,β-unsaturated aldehydes derivatives are efficiently synthesized from corresponding cyclic ketones using Vilsmeir formylation reaction. The synthetic protocol is also applied for the synthesis of antifungal brassilexin.

Isothiazoles are important class of heterocyclic compounds which have been incorporated into a wide range of biologically active compounds, either as a substituent group or as a replacement of another ring.[1] Isothiazole derivatives are used as chiral auxiliaries for asymmetric synthesis,[2] electrophilic fluorination of enolates[3] and has also been suggested for many industrial applications.[4–6] In addition, the isothiazole moiety constitutes the core structure of many synthetic pharmaceuticals displaying broad spectrum of biological activities.[7] A preliminary biological evaluation of some of the isothiazole 1,1-dioxide and 4,5-dihydroisothiazole 1,1-dioxide derivatives has shown promising pharmacological activities against arterial smooth cell (SMC) proliferation.[8] Additionally, derivatives of isothiazoles are reported as potent inhibitors of VEGF receptors,[9] histone acetyltransferase,[10] and kinase,[11] and also exhibit antiviral activities[12] and brain cholinergic channel activator properties.[13]

Some of the isothiazole bearing derivatives such as, Ziprasidone[14] (**1**) (marketed as Geodon/Zeldox by Pfizer) and Perospirone[15] (**2**) (Lullan) are atypical antipsychotics approved for the treatment of schizophrenia, mania and mixed states associated with bipolar disorders. Similarly, naturally occurring Sinalexin (**3**) and Brassilexin (**6j**) are among the most potent antifungal phytoalexins produced by economically important cruciferous plants (Fig. 1).[16]

The importance of isothiazole pharmacophore in clinical drug molecules has attracted organic chemists to look for new synthetic strategies of their analogs.[17] However, most of these synthetic methodologies are based on annulations of isothiazole moiety to non-steroidal building blocks. On the other hand, the studies on steroidal heterocycles emerge as an important area of research and enormous efforts have been made for the synthesis of novel heterosteroids because of their inherent biological activities.[18] To the best of our knowledge, incorporation of an isothiazole moiety in the steroidal core still received limited attentions. For example, Seldes et al.[19] reported the synthesis of A-ring fused steroidal isothiazole from 5α-cholestan-3-one via a tedious multi-step reaction. On the other hand, Barton[20] synthesized 3β-acetoxycholest-4-eno[6,5,4-*c*,*d*]

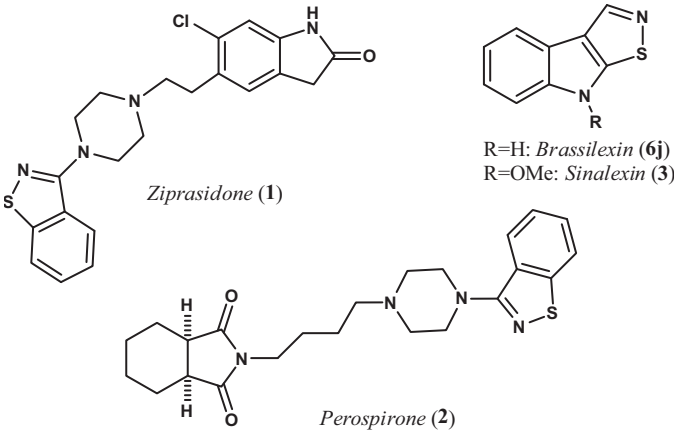

Figure 1. Some important molecule having isothiazole molecular unit.

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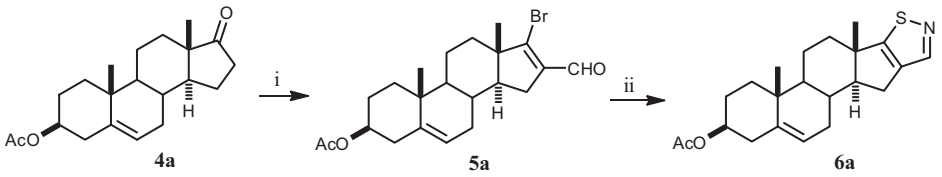
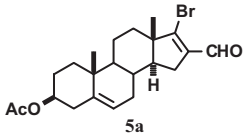
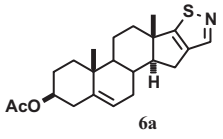
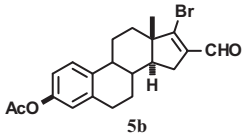
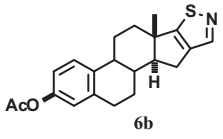
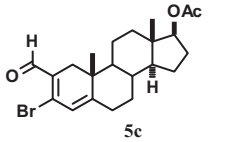
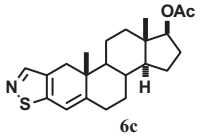
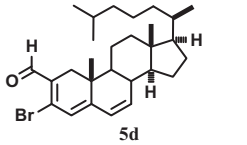
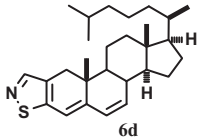
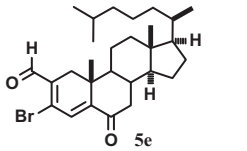
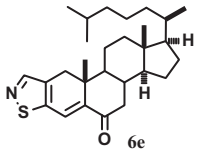
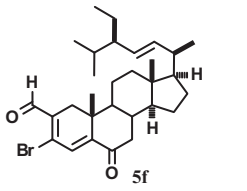
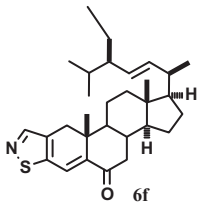
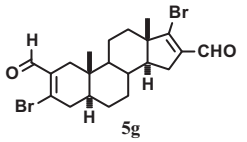
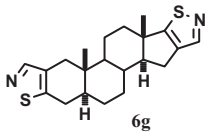
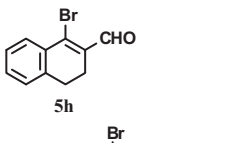
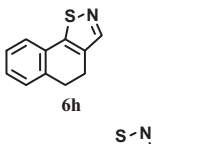
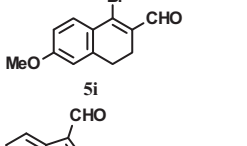
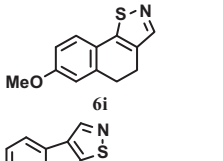
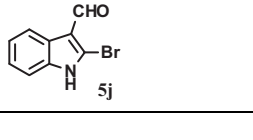
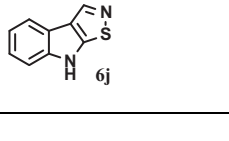


Scheme 1. Reagents and conditions: (i) PBr_3/DMF/$CHCl_3$, 72%; (ii) NaSCN/urea/DMF, MW 360 W, 10 bar 80%.

Table 1
Synthesis of fused steroidal and non-steroidal Isothiazoles (**6a–6j**)

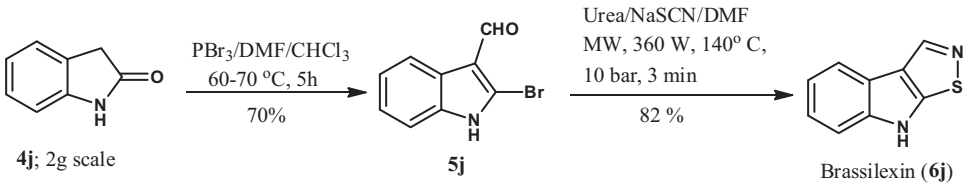
Entry	Substrate (**5a–5j**)	Products (**6a–6j**)	Yield (%)
1			82
2			85
3			87
4			86
5			79
6			81
7			75
8			84
9			86
10			82

isothiazole by the reaction of thiazyl chloride and cholesteryl acetate with very low yield (15%). The β-halo-α,β-unsaturated aldehyde functional group is an interesting organic synthon,[21] however example of its application in the field of steroids is scarce.[22] In continuation of our research interests on A- and D-ring fused heterocycles,[23] we report herein a one-pot synthesis of steroidal isothiazoles from the reaction of easily accessible A- and D-ring annelated β-bromo-α,β-unsaturated aldehydes with a mixture of sodium thiocyanate and urea as an environmentally benign source of ammonia under microwave irradiation (MWI).[24]

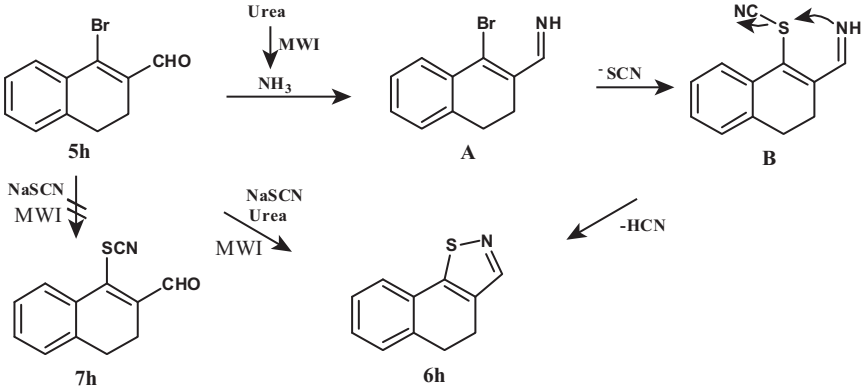
In a typical experimental procedure, a mixture of 3β-acetoxy-17-bromo-16-formyl-androst-5,17-diene (**5a**, 1 mmol), sodium thiocyanate (1.5 mmol), and urea (3 mmol) in DMF (1 ml) was exposed to MWI in a Synthos 3000 (Anton Paar) microwave reactor for 3 min at 140 °C at 10 bar pressure and power at 80% (maximum output 360 W) to afford 3β-acetoxy-5,17-dieno-androst [16,17-*d*]isothiazole **6a** in 82% yield (Scheme 1) (Table 1, entry 1). The product **6a** was characterized by comparison of physical and spectral data.[25] When the same reaction was carried out with chloroformyl steroid, for example, 3β-acetoxy-17-chloro-16-formyl-androst-5,17-diene, we obtained desired product **6a** with lower yield (67%). The starting material **5a** was conveniently prepared from 3β-acetoxy-androst-5-en-17-one (**4a**) using Vilsmeier reagent prepared freshly from a mixture of phosphorous tribromide and *N,N*-dimethylformamide. Similarly, steroidal A- and D-ring annelated β-bromo-α,β-unsaturated aldehydes (**5b–5g**) were accomplished, respectively, from the Vilsmeir reaction of commercially available estrone, testosterone, cholesterol, and stigmasterol.[22c] The reaction of **5b–5f** with sodium thiocyanate and urea afforded corresponding isothiazoles (**6b–6f**) in good yields (Table 1, entries 2–6).[25] The synthesis of A- and D-ring fused steroidal bis-isothiazole **6g** was accomplished from 4-androsten-3,17-dione by initial reduction to dihydroandrost-3,17-dione followed by Vilsmeier formylation reaction to 3,17-dibromo-2,16-diformyl-androst-2,16-diene (**5g**). The reaction of **5g** with sodium thiocyanate and urea in DMF under MWI afforded the desired androst[2,3-*d*][16,17-*d*]bisisothiazole **6g** in 75% yield (Table 1, entry 7). Similarly, the non-steroidal β-bromo-α,β-unsaturated aldehyde analogs, for example, 1-bromo-2-formyldihydronaphthalene (**5h**) reacted with sodium thiocyanate and urea under microwave irradiation to afford 3,4-dihydronaphth[2,1-*d*]isothiazole (**6i**) in 84% yield.

In order to broaden the scope of our reaction, we planned to synthesize antifungal brassilexin (**6j**)[26] using our synthetic strategy. A recent literature report revealed the synthesis of **6j** from indole-2-thione using Vilsmeier formylation and subsequent oxidation, which in general led to undesired by-product 5*H*-thiopyrano[2,3-*b*:6,5-*b*′]diindole.[27] In our strategy, we employed indolin-2-one (**4j**) in place of indole-2-thione to afford corresponding 2-bromo-3-formylindole **5j**[28] using Vilsmeier reaction. The bassilexin **6j** was conveniently synthesized from **5j** using our one-pot synthesis protocol as the major isolable product (Scheme 2).

A plausible mechanism for the one-pot formation of 4,5-dihydronaphtho[2,1-*d*]isothiazole **6h** from 1-bromo-3,4-dihydronaphthalene-2-carbaldehyde **5h** is proposed in Scheme 3. Under microwave heating urea released ammonia[29] and reacted with aldehyde group to form intermediate **A**. The aldimine intermediate



Scheme 2. Microwave-assisted one-pot synthesis of Brassilexin (**6j**).



Scheme 3. Proposed mechanism for the synthesis of fused isothiazole.

A probably facilitated the nucleophilic addition of 'SCN' to form intermediate **B**, which afforded the isothiazole **6h** by nucleophilic substitution at the S-atom. To support the mechanism, we independently attempted to introduce the thiocyanate group under identical condition via substitution reaction of compound **5h** with sodium thiocyanate in DMF in the absence of urea. The reaction did not proceed at all and we failed to isolate the expected product **7h** under MWI as well as conventional heating of compound **5h**. However, the addition of urea to the same reaction pot, smoothly accomplished our desired product 4,5-dihydronaphtho[2,1-*d*]isothiazole **6h** with high yield, thus rendering support to our proposed mechanism. The use of a mixture of sodium thiocyanate and ammonium acetate (in place of urea) under identical condition also led to product **6h**, albeit in lower yield (48%).

In conclusion, we have reported an efficient one-pot strategy for the synthesis of steroidal and non-steroidal isothiazoles from corresponding β-bromo-α,β-unsaturated aldehydes using a simple system of sodium thiocyanate and urea. We could successfully demonstrate the utility of urea as an environmentally benign and safe source of ammonia as well as novel strategy for isothiazole synthesis avoiding alternative use of toxic liquid ammonia. In addition, the synthetic protocol is also conveniently employed for the improved synthesis of brassilexin from 2-bromo-3-formylindole. The advantages of the present procedure are relatively short reaction time, easy work-up procedure, and high yield. Further work on the synthetic potential toward sinalexin and its analogs is in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.021.

References and notes

1. (a) Chapman, R. F.; Peart, B. J. *Comprehensive Heterocyclic Chemistry II*; 1996; Vol. 3, pp 319–372.; (b) Pain, D. L.; Peart, B. J.; Wooldridge, K. R. H. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Cheseman, G. W. H., Eds.; Pergamon: Oxford, 1984; Vol. 6, pp 131–175. Chapter 4.17.
2. Liu, Z.; NorioShibata, N.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **2002**, 302–303.
3. Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708–5711.
4. Bradbury, R.; Moscrop, C.; Meyrick, B. H.; Holbrook, M. B. Br. UK Patent Appl. 2335,924, 31 pp, 2000; *Chem. Abstr.* **2000**, *132*, 51147e.
5. Pasch, N. F. US, Patent 6068,879, 9 pp, 76, 2000; *Chem. Abstr.* **2000**, *132*, 355544k.
6. Turcotte, D. E.; Coffey, A. L. J.; Olsen, A. W.; Dituro, M. A.; Stephens, C. R. US Patent US US 6290,870, 11 pp, 2001; *Chem. Abstr.* **2001**, *135*, 244824u.
7. (a) Cutri, C. C.; Garozzo, A.; Siracusa, M. A.; Sarva, M. C.; Castro, A.; Geremia, E.; Pinizzotto, M. R.; Guerrera, F. *Bioorg. Med. Chem.* **1999**, *7*, 225–230; (b) Varaprasad, C. V. N. S.; Barawkar, D.; Abdellaoui, H. E.; Chakravarty, S.; Allan, M.; Chen, H.; Zhang, W.; Wu, J. Z.; Tam, R.; Hamatake, R.; Lang, S.; Hong, Z. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3975–3980; (c) Machon, Z. *Diss. Pharm. Pharmacol.* **1969**, *21*, 325; (d) Scott, J. W.; Boris, A. *J. Med. Chem.* **1973**, *16*, 512–516; (e) Geronikaki, A.; Eleftheriou, P.; Vicini, P.; Alam, I.; Dixit, A.; Saxena, A. K. *J. Med. Chem.* **2008**, *51*, 5221–5228.
8. (a) Beccalli, E. M.; Clerici, F.; Gelmi, M. L. *Tetrahedron* **1999**, *55*, 2001–2012; (b) Guilloteau, F.; Miginiac, L. *Synth. Commun.* **1995**, *25*, 1383–1389.
9. Kiselyov, A. S.; Semenova, M.; Semenov, V. V. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1195–1198.
10. Stimson, L.; Rowlands, M. G.; Newbatt, Y. M.; Smith, N. F.; Raynaud, F. I.; Rogers, P.; Bavetsias, V.; Gorsuch, S.; Jarman, M.; Bannister, A.; Kouzarides, T.; McDonald, E.; Workman, P.; Aherne, G. W. *Mol. Cancer Ther.* **2005**, *4*, 1521.
11. (a) Beeb, J. S.; Jani, J. P.; Knauth, E.; Goodwin, P.; Higdon, C.; Rossi, A. M.; Emerson, E.; Finkelstein, M.; Floyd, E.; Harriman, S.; Atherton, J.; Hillerman, S.; Soderstrom, C.; Kou, K.; Gant, T.; Noe, M. C.; Foster, B.; Rastinejad, F.; Marx, M. A.; Schaeffer, T.; Whalen, P. M.; Roberts, W. G. *Cancer Res.* **2003**, *63*, 7301; (b) Thompson, N.; Lyons, J. *Curr. Opin. Pharmacol.* **2005**, *5*, 350.
12. (a) Swayze, E. E.; Drach, J. C.; Wotring, L. L.; Townsend, L. B. *J. Med. Chem.* **1997**, *40*, 771; (b) Garozzo, A.; Curti, C. C. C.; Castro, A.; Tempera, G.; Guerrera, F.; Sarva, M. C.; Geremia, E. *Antiviral Res.* **2000**, *45*, 199; (c) Curti, C. C. C.; Garozzo, A.; Siracusa, M. A.; Castro, A.; Tempera, G.; Sarva, M. C.; Guerrera, F. *Antiviral Res.* **2002**, *55*, 357.
13. Garvey, D. S.; Wasicak, J. T.; Elliott, R. L.; Lebold, S.; Hettinger, A.-M.; Carrera, G. M.; Lin, N.-H.; He, Y.; Holladay, M. W.; Anderson, D. J.; Cadman, E. D.; Raszkiewicz, J. L.; Sullivan, J. P.; Arneric, S. P. *J. Med. Chem.* **1994**, *37*, 4455.
14. Howard, H. R.; Lowe, J. A., III; Seeger, T. F.; Seymour, P. A.; Zorn, S. H.; Maloney, P. R.; Ewing, F. E.; Newman, M.; Schmidt, A. W.; Furman, J. S.; Robinson, G. L.; Jackson, E.; Johnson, C.; Morrone *J. Med. Chem.* **1996**, *39*, 143.
15. (a) Shiwa, T.; Amano, T.; Matsubayashi, H.; Seki, T.; Sasa, M.; Sakai, N. *Jpn. J. Pharmacol. Sci.* **2003**, *93*, 114; (b) Matsushita, M.; Egashira, N.; Harada, S.;

Okuno, R.; Mishima, K.; Iwasaki, K.; Nishimura, R.; Fujiwara, M. *Jpn. J. Pharmacol. Sci.* **2005**, *99*, 154.
16. Pedras, M. S. C.; Suchy, M. *Org. Biomol. Chem.* **2005**, *3*, 2002–2007. and references cited there in.
17. (a) Chang, Y.-G.; Cho, H. S.; Kim, K. *Org. Lett.* **2003**, *5*, 507–510; (b) Devarie-Baez, N. O.; Xian, M. *Org. Lett.* **2010**, *12*, 752–754; (c) Lee, D. J.; Kim, B. S.; Kim, K. *J. Org. Chem.* **2002**, *67*, 5375–5377; (d) Fordyce, E. A. F.; Morrison, A. J.; Sharp, R. D.; Paton, R. M. *Tetrahedron* **2010**, *66*, 7192–7197; (e) Hamad Elgazwy, A.-S. S. *Tetrahedron* **2003**, *59*, 7445–7463. and references cited there in.
18. (a) Singh, H.; Jindal, D. P.; Yadav, M. R.; Kumar, M. *Prog. Med. Chem.* **1991**, *28*, 233–300; (b) Hirshmann, R.; Steinberg, N. G.; Buchschacher, P.; Fried, J. H.; Kent, G. J.; Tishler, M. *J. Am. Chem. Soc.* **1963**, *85*, 120–122; (c) Burbiel, J.; Bracher, F. *Steroids* **2003**, *68*, 587–594.
19. Giacopello, S.; Deluca, M. E.; Seldes, A. M. *Tetrahedron Lett.* **1994**, *35*, 6643–6646.
20. Barton, D. H. R.; Bubb, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 916.
21. (a) Okamoto, N.; Sakurai, K.; Ishikura, M.; Takeda, K.; Yanada, R. *Tetrahedron Lett.* **2009**, *50*, 4167; (b) Karthikeyan, P.; Rani, A. M.; Saiganesh, R.; Balasubramanian, K. K.; Kabilan, S. *Tetrahedron* **2009**, *65*, 811–821.
22. (a) Moersch, G. W.; Neuklis, W. A. *J. Chem. Soc.* **1965**, *1*, 788–790; (b) Gupta, R.; Pathak, D.; Jindal, D. P. *Eur. J. Med. Chem.* **1999**, *34*, 659–662; (c) Gogoi, J.; Bezbaruah, P.; Saikia, P.; Goswami, J.; Gogoi, P.; Boruah, R. C. *Tetrahedron Lett.* **2012**, *53*, 1497–1500; (d) Siddiqui, A. U.; Maheshwar Rao, V. U.; Maimirani, M.; Siddiqui, A. H. *J. Heterocycl. Chem.* **1995**, *32*, 353–354; (e) Moreira, V. M. A.; Vasaitis, T. S.; Njar, V. C. O.; Salvador, J. A. R. *Steroids* **2007**, *72*, 939–948; (f) Moreira, V. M. A.; Salvador, J. A. R.; Beja, A. M.; Paixão, J. A. *Steroids* **2011**, *76*, 582–587.
23. (a) Borthakur, M.; Borthakur, M. G.; Boruah, R. C. *Steroids* **2008**, *73*, 539–542; (b) Saikia, A.; Borhtakur, M. G.; Borthakur, M.; Saikia, C. J.; Bora, U.; Boruah, R. C. *Tetrahedron Lett.* **2006**, *47*, 43–46; (c) Borthakur, M. G.; Hasib, A.; Gogoi, J.; Boruah, R. C. *Steroids* **2010**, *75*, 445–449.
24. Loupy, A. *Microwaves in Organic Synthesis*; VCH: Weinheim, Germany, 2002.
25. Spectral and analytical data of selected compounds:
3β-Acetoxy-androst-5,17-dieno[16,17-d]isothiazole (**6a**): Yellow solid, mp 162–65 °C; yield 82%, R_f = 0.3 (10% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (s, 1H), 5.36 (d, J = 5.0 Hz, 1H), 4.53 (m, 1H), 2.64–0.88 (m, 17H), 1.97 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 178.4, 170.6, 152.1, 143.3, 140.0, 121.9, 73.7, 62.6, 49.9, 45.1, 38.1, 36.8, 35.5, 31.3, 30.9, 27.7, 26.8, 21.5, 20.6, 19.3, 19.1 (one peak is missing due to overlap); IR ($CHCl_3$): 2945, 2854, 1732, 1373, 1246, 1033, 756 cm^{-1}; MS(ESI): m/z 311.1 [M$^+$−CH_3COOH]; Anal. Calcd for $C_{22}H_{29}NO_2S$ (371.54): C, 71.12; H, 7.87; N, 3.77%. Found: C, 71.13; H, 7.77; N, 3.69%.
3-Acetoxyestra-1,3,5(10),17-tetraeno[16,17-d]isothiazole (**6b**): White solid, mp 155-57 °C; yield 85%, R_f = 0.3 (20% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (s, 1H), 7.24–7.3 (m, 1H), 6.88–6.8 (m, 2H), 2.951.52 (m, 13H), 2.29 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 178.4, 169.9, 152.2, 148.6, 143.2, 137.9, 137.5, 126.2, 121.7, 119.9, 61.8, 45.5, 44.1, 37.4, 35.5, 29.3, 27.3, 26.6, 26.1, 21.2, 19.3; IR ($CHCl_3$): 3018, 2980, 2931, 2856, 1759, 1493, 1370, 1207, 1014, 755 cm^{-1}; MS (ESI): m/z 353 [M$^+$]; Anal. Calcd for $C_{21}H_{23}NO_2S$ (353.48): C, 71.36; H, 6.56; N, 3.96%. Found: C, 71.35; H, 6.59; N, 3.99%.
Cholest-2,4,6-trieno-[2,1-d]isothiazole (**6d**): White solid, mp 106–10 °C; yield 86%, R_f = 0.4 (15% EtOAc in hexanes): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (s, 1H), 6.28 (s, 1H), 6.08 (dd, J_1 = 2.43 Hz, J_2 = 9.8 Hz, 1H), 5.9 (d, J = 9.7 Hz, 1H), 2.95 (d, J = 15.6 Hz, 1H), 2.5 (d, J = 15.6 Hz, 1H), 2.2–0.86 (m, 32H), 0.74 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 156.2, 156.1, 146.1, 135.9, 130.8, 127.4, 112.3, 56.0, 54.2, 50.7, 43.1, 39.7, 39.5, 38.2, 37.4, 36.1, 35.8, 33.9, 28.2, 28.0, 23.9, 23.8, 22.8, 22.6, 20.9, 18.7, 16.0, 11.8; IR ($CHCl_3$): 2949, 2868, 1466, 1381, 771, 755 cm^{-1}; MS(ESI): m/z 423 [M$^+$]; Anal. Calcd for $C_{28}H_{41}NS$ (423.70): C, 79.37; H, 9.75; N, 3.31%. Found: C, 79.35; H, 9.76; N, 3.31%.
Androst[2,3-d][16,17-d]bisisothiazole (**6g**): White solid, mp 217–20 °C; yield 86%, R_f = 0.4 (30% EtOAc in hexanes): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (s, 1H), 8.18 (s, 1H), 2.9–1 (m, 18H), 1.1 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 178.4, 157.9, 157.2, 152.1, 143.3, 132.9, 62.4, 53.6, 45.2, 42.5, 36.9, 35.9, 35.5, 34.7, 31.2, 28.5, 27.8, 26.8, 20.8, 19.2, 11.6; IR ($CHCl_3$): 2917, 2853, 1444, 1373, 752 cm^{-1}; MS(ESI): m/z 370.1 [M$^+$]; Anal. Calcd for $C_{21}H_{26}N_2S_2$ (370.57): C, 68.06; H, 7.07; N, 7.56%. Found: C, 68.10; H, 7.01; N, 7.55%.
Indolo[3,2-d]isothiazole (Brassilexin **6j**): Brown solid, mp 141–43 °C (literature mp 140–42 °C)[27], yield 70%, R_f = 0.2 (30% EtOAc in hexanes)]: ^{1}H NMR (300 MHz, CD_3OD): δ = 8.30 (s, 1H), 7.45 (dd, J_1 = 1.9, J_2 = 6.1 Hz, 1H), 7.10–6.99 (m, 3H); ^{13}C NMR (90 MHz, CD_3OD): δ = 176.0, 150.4, 138.0, 128.4, 122.7, 121.1, 114.4, 109.1, 107.2; IR ($CHCl_3$): 3063, 3017, 2938, 2891, 1478, 1242, 949, 822, 759 cm^{-1}; MS(ESI): m/z 174 [M$^+$]; Anal. Calcd for $C_9H_6N_2S$ (174.22): C, 62.05; H, 3.47; N, 16.08%. Found: C, 62.09; H, 3.44; N, 16.07%.
26. Pedras, M. S. C.; Okanga, F. I.; Zaharia, I. L.; Khan, A. Q. *Phytochemistry* **2000**, *53*, 161.
27. Pedras, M. S.; Jha, M. *J. Org. Chem.* **2005**, *70*, 1828–1834.
28. The Vilsmeier reaction of 2-bromo-3-formylindole was carried out using 3 mequiv of phosphorous tribromide and dimethylformamide in 2 g scale with 70% yield.
29. (a) Barthakur, M. J.; Borthakur, M.; Devi, P.; Saikia, C. J.; Saikia, A.; Bora, U.; Chetia, A.; Boruah, R. C. *Synlett* **2007**, 223–226; (b) Borthakur, M.; Boruah, R. C. *Steroids* **2008**, *73*, 637–641; (c) Borthakur, M.; Dutta, M.; Gogoi, S.; Boruah, R. C. *Synlett* **2008**, 3125–3128; (d) Borthakur, M.; Gogoi, S.; Gogoi, J.; Boruah, R. C. *Tetrahedron Lett.* **2010**, *51*, 5160–5163.