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A NOVEL, EXPEDIENT SYNTHESIS OF THIAZOLO[4,5-*c*]- AND -[5,4-*b*]CARBAZOLES

Manas Chakrabarty,*[a] Nandita Ghosh,[a] and Yoshihiro Harigaya[b]

[a]Department of Chemistry, Bose Institute, 93/1, A.P.C. Road, Kolkata-700009, India (email: manas@bosemain.boseinst.ac.in); [b]School of Pharmaceutical Sciences, Kitasato University, Minato-ku, Tokyo-108, Japan

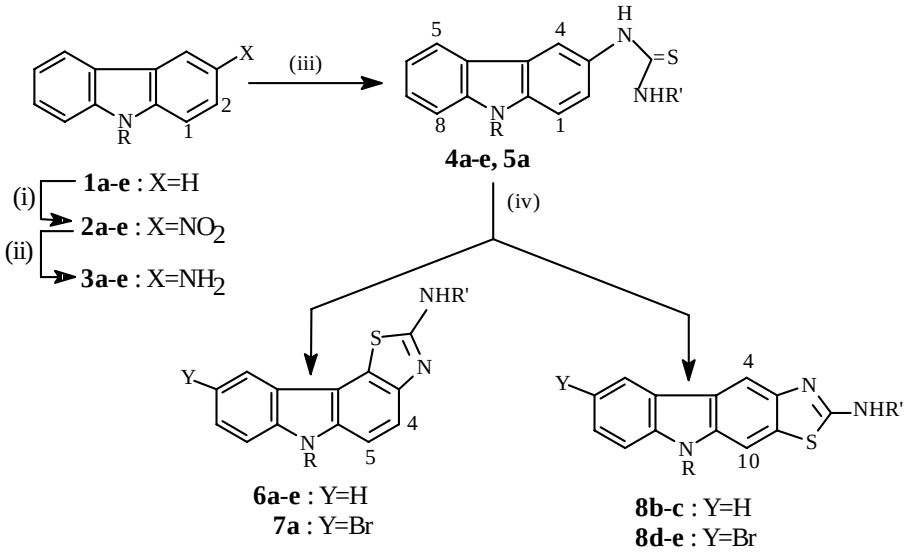
Abstract- A new synthesis of thiazolo[4,5-*c*]- and -[5,4-*b*]carbazoles (**6a**-**e**, **7a**, **8b**-**e**) was accomplished from 3-aminocarbazoles (**3a**-**e**) by separate condensations with methyl and phenyl isothiocyanates, followed by oxidative cyclization of the resulting thioureidocarbazoles (**4a**-**e**, **5a**).

Thiazoles constitute an important class of pharmaceuticals. Vitamin B_1 as well as the coenzyme thiamin pyrophosphate, antibacterial sulfathiazole, antiulcer famotidine and nizatidine, antibiotic cystothiazole A and the Cruciferous indole phytoalexins camalexin and spirobrassinin are some of the notable examples of this class.[1] Annelated thiazoles also display diverse biological activities, which has led to the synthesis of many such compounds, e.g. the antitumor 2-(4-aminophenyl)benzothiazoles,[2] thiazoloacridines,[3] 2-cyanothiazolobenzodioxins[4] and the cytotoxic thiazoloquinazolines.[5] In continuation of our ongoing interest in the development of new synthetic routes to annelated carbazoles, e.g. indolocarbazoles,[6] we have developed a new synthesis of thiazolocarbazoles (TCs), which has been briefly presented in this paper. Pertinently, thiazolocarbazoles, both angular and linear, have previously been synthesized by two routes, viz. the Fischer indolization of the phenylhydrazones of tetrahydrobenzo[*d*]thiazol-5-one and –6-one[7] and the thermal cyclization of (3-carbazolyl)imino-1,2,3-dithiazoles, derived from 3-amino-carbazoles and Appel's salt (4,5-dichloro-1,2,3-dithiazolium chloride).[8]

Our strategy involved the construction of the thiazole nucleus onto the carbazole framework (**1a**-**e**) through the successive intermediacies of 3-nitrocarbazole (**2a**) and its *N*-alkyl derivatives (**2b**-**e**), 3-aminocarbazoles (**3a**-**e**) and 3-(*N*-methyl/phenyl)thioureidocarbazoles (**4a**-**e**, **5a**). Thus, **2a**, prepared from carbazole by ceric ammonium nitrate in presence of silica gel,[9] was reduced by hydrazine hydrate and palladised charcoal[10] to **3a**. Condensation of the latter with methyl and phenyl isothiocyanates separately

efficiently furnished **4a** and **5a,** respectively. Separate treatment of each of them with bromine in acetic acid[11a-c] in cold provided the respective angular isomers, 2-methylaminothiazolo[4,5-*c*]carbazole (**6a**) and 9-bromo-2-anilinothiazolo[4,5-*c*]carbazole (**7a**) in high yields. The presence of two one-proton doublets (H-4, 5), both showing *ortho* couplings (e.g. **6a**: δ 7.508 and 7.397, 1H, d each, *J* 8.5 Hz) consolidated the angular structures (**6a**) and (**7a**) and ruled out the possible alternative linear structures, each of which would have displayed two one-proton singlets for the corresponding protons (H-4, 10). Bromination is reportedly often encountered during cyclization of thioureidobenzenoids by bromine in a suitable solvent.[11a]

For generalization, four 9(*N*)-alkyl-3-(*N*-methylthioureido)carbazoles (**4b**-**e**), prepared from the corresponding 9-alkyl-3-aminocarbazoles (**3b**-**e**) by similar condensations with methyl and phenyl isothiocyanates, were separately treated with bromine in acetic acid. Interestingly, both angular and linear isomers were formed in each case. Thus, from each of 9(*N*)-methylthioureidocarbazole (**4b**) and the corresponding *N*-ethyl derivative (**4c**), both angular TCs (i.e. thiazolo[4,5-*c*]carbazoles) and linear TCs (i.e. thiazolo[5,4-*b*]carbazoles), viz. **6b** and **8b** from **4b**, and **6c** and **8c** from **4c** were formed in overall yields of 70% and 67%, respectively. The linear structures were identified, as before, by the diagnostic multiplicity (singlet) for each of H-4 and H-10. But from the (9)*N*-propyl- and (9)*N*-butylthioureidocarbazoles (**4d** and **4e**, respectively), curiously enough, the unexpected 6-bromo linear



R=H (**a**), Me (**b**), Et (**c**), Pr (**d**), Bu (**e**); R'=Me (**4, 6**, **8**), Ph (**5**, **7**)

(i) CAN/ SiO_2-MeCN; 60-65°C.(ii) $NH_2NH_2.H_2O$, Pd-C, Δ.

(iii) R′NCS, MeOH, Δ. (iv) Br_2/AcOH, 15-20°C

Scheme 1

TCs (**8d**, **e**) were formed in addition to the expected angular TCs (**6d**, **e**) in better overall yields (73/81%) (Scheme 1; Table 1).

Table 1. Yields of angular and linear TCs from thioureidocarbazoles

Thioureidocarbazole (R R')	Angular TC (Y)	Yield (%)	Linear TC (Y)	Yield (%)
4a (H Me)	**6a** (H)	79	---	---
4b (Me Me)	**6b** (H)	36	**8b** (H)	34
4c (Et Me)	**6c** (H)	47	**8c** (H)	20
4d (n-Pr Me)	**6d** (H)	41	**8d** (Br)	32
4e (n-Bu Me)	**6e** (H)	41	**8e** (Br)	40
5a (H Ph)	**7a** (Br)	80	---	---

Noticeably, the linear TCs (**8b**-**e**) are additionally formed only when there is an alkyl group at the carbazolic nitrogen in (**4b**-**e**). But it is not quite clear as to why, in the case of the 2-methylamino-TCs, bromination takes place only for *N*-propyl and *N*-butyl linear isomers (**8d**) and (**8e**), whereas the same occurs in the case of the parent (i.e. *N*-unsubstituted)-2-anilino angular isomer (**7a**).

A comparison of the efficacy of our method with that of the French group[8] is not, strictly speaking, feasible, since the final products were 2-cyano-TCs in their method and 2-methylamino/anilino-TCs in our method. Nevertheless, the overall yields were *ca*. (3-42)% in the method using Appel's salt,[8] as against *ca*. 64-77% in our method, whereas the Fischer indolization method[7] suffers from the shortcoming that it does not allow modulation at the carbazolic nitrogen

In fine, we have developed an expedient and efficacious synthesis of both thiazolo[4,5-*c*]- and -[5,4-*b*]-carbazoles from 3-aminocarbazoles. The prepared TCs did not show any significant antimalarial (against *P. falciparum*) and antiprotozoan (against *Giardia intestinalis*) activity (vide Experimental). However, the potential of the TCs as antitumor agents is yet to be explored.

EXPERIMENTAL

General. Melting points (in Celsius) were determined on a Toshniwal apparatus. IR spectra (KBr disk) were recorded on a Nicolet Impact 410 spectrophotometer, EIMS on AEI MS 30 (LR) or JEOL-JMS AX 505HA (LR, HR) mass spectrometers and ^{1}H and ^{13}C NMR spectra (in $CDCl_3$ for thioureidocarbazoles and in DMSO-d_6 for TCs), both 1D and 2D, on Varian XL-400 or Bruker DRX 500 NMR spectrometers. TLCs, both analytical and preparative, were carried out on silica gel G (Merck, India) plates and spots

were visualized by iodine vapour or 0.5% potassium permanganate in aq. 1N NaOH. Elemental analyses were performed in a Dr. Hans Hoesli Analyser (Type A1; No. 1058).

Synthesis of thioureidocarbazoles: In a typical experiment, a solution of 3-aminocarbazole[10] (**3a**; 1 mmol) in dry methanol (15 mL) containing methyl isothiocyanate (80 mg; 1.1 mmol) was refluxed till (1 h) the aminocarbazole was fully consumed (TLC). The solution was concentrated to about 5 mL and allowed to stand at rt. The resulting crystals of the thioureidocarbazole (**4a**) were filtered under suction, washed first with little water (to get rid of the residual isothiocyanate) and then with 10% aq. methanol and dried. Addition of water to the mother liquor furnished further crops of **4a**. Similar procedures were followed for preparing **4b-e** and **5a**. All the thioureidocarbazoles were recrystallized from methanol as white needles.

4a: Yield: 96%; mp 218-219°; IR: 3396, 3310, 1553, 1341, 751 cm^{-1}; MS: *m/z* 255 (M^+), 224 (100%), 221, 206, 192, 182, 166; ^{1}H NMR: δ 2.89 (3H, d, *J*=4.0 Hz), 7.12 (1H, t, *J*=7.5 Hz), 7.21 (1H, br d, *J*=7.5 Hz), 7.32 (1H, br), 7.36 (1H, t, *J*=7.5 Hz), 7.43 (1H, d, *J*=8.5 Hz), 7.46 (1H, d, *J*=8.0 Hz), 7.95 (1H, s), 8.08 (1H, d, *J*=7.5 Hz), 9.44 (1H, br s), 11.24 (1H, s); ^{13}C NMR: δ 32.3 (CH_3), 111.8 (2×), 118.4, 119.3 (2×), 121.2, 126.5 (all Ar-CH), 123.2, 123.5, 125.0, 138.6, 141.4, 182.5 (all Ar-C); *Anal.* Calcd for $C_{14}H_{13}N_3S$: C, 65.88; H, 5.10; N, 16.47. Found: C, 65.83; H, 5.08; N, 16.51.

4b: Yield: 94%; mp 232-234°; IR: 3376, 3270, 1553, 1248, 744 cm^{-1}; MS: *m/z* 269 (M^+), 238, 235 (100%), 220, 206, 196, 180; ^{1}H NMR: δ 3.10 (3H, d, *J*=5.0 Hz), 3.85 (3H, s), 5.92 (1H, br), 7.26 (1H, t, *J*=7.5 Hz), 7.29 (1H, dd, *J*=2.0, 8.5 Hz), 7.41 (2H, d, *J*=8.5 Hz), 7.52 (1H, dt, *J*=1.0, 7.5 Hz), 7.90 (1H, d, *J*=2.0 Hz), 7.94 (1H, br s), 8.03 (1H, d, *J*=7.5 Hz); ^{13}C NMR: δ 29.7, 32.4 (both CH_3), 109.3, 110.1, 119.3, 119.9, 120.9, 124.9, 127.1 (all Ar-CH), 122.4, 124.0, 127.3, 140.4, 142.0, 182.9 (all Ar-C); *Anal.* Calcd for $C_{15}H_{15}N_3S$: C, 66.91; H, 5.58; N, 15.61. Found: C, 66.82; H, 5.55; N, 15.65.

4c: Yield: 95%; mp 248-250°; IR: 3250, 3138, 1540, 1513, 1381, 738 cm^{-1}; MS: *m/z* 283 (M^+), 252 (100%), 249, 238, 237, 223, 220, 210, 194; ^{1}H NMR: δ 1.43 (3H, t, *J*=7.5 Hz), 3.11 (3H, d, *J*=4.5 Hz), 4.37 (2H, q, *J*=7.5 Hz), 5.92 (1H, br s), 7.25 (1H, t, *J*=7.5 Hz), 7.29 (1H, d, *J*=8.5 Hz), 7.42 (2H, d, *J*=8.5 Hz), 7.51 (1H, t, *J*=7.5 Hz), 7.92 (1H, s), 7.96 (1H, br s), 8.04 (1H, d, *J*=7.5 Hz); ^{13}C NMR: δ 14.2, 32.4 (both CH_3), 38.1 (CH_2), 109.3, 110.1, 119.5, 119.9, 121.0, 124.9, 127.0 (all Ar-CH), 122.6, 124.2, 127.2, 139.4, 140.9, 183.0 (all Ar-C); *Anal.* Calcd for $C_{16}H_{17}N_3S$: C, 67.84; H, 6.01; N, 14.84. Found: C, 67.77; H, 6.0; N, 14.80.

4d: Yield: 94%; mp 184-186°; IR: 3237, 3144, 1540, 1334, 751 cm^{-1}; MS: *m/z* 297 (M^+), 266, 263 (100%), 234, 231, 205; ^{1}H NMR: δ 0.98 (3H, t, *J*=7.5 Hz), 1.91 (2H, sextet, *J*=7.5 Hz), 3.11 (3H, d, *J*=4.5

Hz), 4.28 (2H, t, *J*=7.5 Hz), 5.92 (1H, br s), 7.25 (1H, t, *J*=7.5 Hz), 7.28 (1H, dd, *J*=2.0, 8.5 Hz), 7.43 (2H, d, *J*=8.5 Hz), 7.5 (1H, t, *J*=7.5 Hz), 7.89 (1H, br), 7.92 (1H, d, *J*=1.0 Hz), 8.04 (1H, d, *J*=7.5 Hz); ^{13}C NMR: δ 12.1, 32.5 (both CH_3), 22.7, 45.2 (both CH_2), 109.6, 110.3, 119.4, 119.8, 120.9, 124.8, 127.0 (all Ar-CH), 122.4, 124.1, 127.1, 140.0, 141.5, 183.0 (all Ar-C); *Anal.* Calcd for $C_{17}H_{19}N_3S$: C, 68.68; H, 6.39; N, 14.14. Found: C, 68.71; H, 6.38; N, 14.17.

4e: Yield: 95%; mp 156-158°; IR: 3237, 3158, 1540, 1513, 738 cm^{-1}; MS: *m/z* 311 (M^+), 280, 277, 238 (100%), 209; ^{1}H NMR: δ 0.95 (3H, t, *J*=7.5 Hz), 1.40 (2H, sextet, *J*=7.5 Hz), 1.85 (2H, quintet, *J*=7.5 Hz), 3.11 (3H, d, *J*=4.5 Hz), 4.30 (2H, t, *J*=7.5 Hz), 5.93 (1H, br s), 7.25 (1H, t, *J*=7.5 Hz), 7.29 (1H, dd, *J*=2.0, 8.5 Hz), 7.42 (2H, d, *J*=8.5 Hz), 7.50 (1H, dt, *J*=7.5, 0.5 Hz), 7.92 (1H, d, *J*=2.0 Hz), 7.96 (1H, br), 8.04 (1H, d, *J*=8.0 Hz); ^{13}C NMR: δ 14.2, 32.4 (both CH_3), 20.9, 31.5, 43.4 (all CH_2), 109.5, 110.3, 119.4, 119.8, 121.0, 124.8, 127.0 (all Ar-CH), 122.4, 124.1, 127.1, 139.9, 141.4, 182.9 (all Ar-C); *Anal.* Calcd for $C_{18}H_{21}N_3S$: C, 69.45; H, 6.75; N, 13.50. Found: C, 69.40; H, 6.77; N, 13.45.

5a: Yield: 86%; mp 196-197°; IR: 3396, 3310, 1553, 1341, 751 cm^{-1}; MS: *m/z* 317 (M^+), 283, 224, 192, 182 (100%), 166, 135; ^{1}H NMR: δ 7.10 (1H, t, *J*=8.0 Hz), 7.13 (1H, dt, *J*=1.0, 8.0 Hz), 7.30 (2H, t, *J*=8.0 Hz), 7.35 (1H, d, *J*=8.0 Hz), 7.36 (1H, dt, *J*=1.0, 8.0 Hz), 7.44 (1H, d, *J*=8.0 Hz), 7.46 (1H, d, *J*=8.0 Hz), 7.49 (2H, dd, *J*=1.0, 8.0 Hz), 8.07 (1H, d *J*=8.0 Hz), 8.08 (1H, d, *J*=2.0 Hz), 9.57, 9.74 and 11.26 (1H, br each); ^{13}C NMR: δ 110.6, 110.9, 117.2, 118.4, 120.2, 123.8 (2×), 124.1, 124.2, 125.6, 128.2 (2×) (all Ar-CH), 122.2, 122.3, 130.3, 137.6, 139.6, 140.2, 180.2 (all Ar-C); *Anal.* Calcd for $C_{19}H_{15}N_3S$: C, 71.92; H, 4.73; N, 13.25. Found: C, 71.88; H, 4.74; N, 13.19.

Cyclization of thioureidocarbazoles to TCs. General procedure: A solution of bromine (0.1 mL; 2 mmol) in acetic acid (1 mL) was added dropwise with stirring to an ice-cold solution of the thioureidocarbazole (**4a**-**e**, **5a**; 1 mmol) in acetonitrile (20 mL) and the whole was stirred for 0.5 h, after which it was allowed to come to rt. The solution was then poured into excess 10% aq. sodium thiosulfate, and the resulting precipitate was filtered, washed with water, dried and purified by either crystallization (**6a**, **7a**) or prep. TLC on silica gel (**6b**-**e**, **8b**-**e**). All the TCs (for yields: see Table 1) were crystallized from methanol-ethyl acetate as white micro needles.

6a: Mp 218-220°; IR: 3370, 3224, 1613, 1566, 751 cm^{-1}; MS: *m/z* 253 (M^+; 100%), 238; ^{1}H NMR: δ 2.97 (3H, d, *J*=3.0 Hz), 7.19 (1H, t, *J*=8.0 Hz), 7.38 (1H, t, *J*=8.5 Hz), 7.39 (1H, d, *J*=8.5 Hz), 7.50 (1H, d, *J*=8.5 Hz), 7.52 (1H, d, *J*=8.5 Hz), 7.84-7.75 (2H, d, *J*=7.0 Hz), 11.35 (1H, s); ^{13}C NMR: δ 31.6 (CH_3), 109.6, 111.9, 117.5, 119.4, 121.0, 126.1 (all Ar-CH), 116.1, 121.6, 121.7, 136.4, 140.7, 147.0, 165.7 (all Ar-C); *Anal.* Calcd for $C_{14}H_{11}N_3S$: C, 66.40; H, 4.35; N, 16.60. Found: C, 66.66; H, 4.35; N, 16.67.

6b: Mp 226-228°; IR: 3230, 1613, 1566, 1420, 731 cm^{-1}; MS: *m/z* 267 (M^+; 100%), 252, 238; ^1H NMR: δ 2.98 (3H, d, *J*=4.5 Hz), 3.87 (3H, s), 7.24 (1H, t, *J*=7.5 Hz), 7.46 (1H, t, *J*=7.5 Hz), 7.48 (1H, d, *J*=8.0 Hz), 7.59 (2H, d, *J*=8.5 Hz), 7.84 (1H, d, *J*=8.0 Hz), 7.87 (1H, q, *J*=4.5 Hz); ^{13}C NMR: δ 30.1, 31.6 (both CH_3), 107.8, 110.1, 117.5, 119.6, 121.1, 126.3 (all Ar-CH), 115.6, 121.1, 122.0, 137.3, 141.5, 147.3, 165.8 (all Ar-C) HRMS: *m/z* 267.0834 (M^+); Calcd for $C_{15}H_{13}N_3S$: 267.0830.

6c: Mp 182-184°; IR: 3237, 3177, 1613, 1553, 744 cm^{-1}; MS: *m/z* 281 (M^+; 100%), 266, 252; ^1H NMR: δ 1.29 (3H, t, *J*=7.0 Hz), 2.99 (3H, d, *J*=5.0 Hz), 4.44 (2H, q, *J*=7.0 Hz), 7.24 (1H, dt, *J*=1.0, 8.0 Hz), 7.46 (1H, ddd, *J*=1.0, 7.0, 8.0 Hz), 7.50 (1H, d, *J*=9.0 Hz), 7.59 (1H, d, *J*=8.0 Hz), 7.61 (1H, d, *J*=9.0 Hz), 7.84 (1H, d, *J*=5.0 Hz), 7.85 (1H, d, *J*=8.0 Hz); ^{13}C NMR: δ 13.7, 30.7 (both CH_3), 37.1 (CH_2), 106.9, 109.2, 116.6, 118.7, 120.3, 125.4 (all Ar-CH), 114.9, 120.4, 121.2, 135.3, 139.5, 146.4, 164.9 (all Ar-C); HRMS: *m/z* 281.0981 (M^+); Calcd for $C_{16}H_{15}N_3S$: 281.0986.

6d: Mp 156-158°; IR: 3224, 3184, 1626, 1566, 744 cm^{-1}; MS: *m/z* 295 (M^+), 266 (100%), 250, 219, 149; ^1H NMR: δ 0.85 (3H, t, *J*=7.0 Hz), 1.80 (2H, sextet, *J*=7.0 Hz), 2.98 (3H, d, *J*=4.0 Hz), 4.35 (2H, t, *J*=7.0 Hz), 7.23 (1H, t, *J*=7.5 Hz), 7.44 (1H, t, *J*=7.5 Hz), 7.49 (1H, d, *J*=8.5 Hz), 7.57 (1H, d, *J*=8.5 Hz), 7.63-7.59 (1H, m), 7.87-7.79 (1H, m), 7.83 (1H, d, *J*=7.5 Hz); ^{13}C NMR: δ 12.2, 31.6 (both CH_3), 22.8, 44.8 (both CH_2), 108.0, 110.3, 117.4, 119.6, 121.1, 126.2 (all Ar-CH), 115.6, 121.1, 122.0, 136.7, 141.0, 147.2, 165.9 (all Ar-C); HRMS: *m/z* 295.1132 (M^+); Calcd for $C_{17}H_{17}N_3S$: 295.1144.

6e: Mp 164-166°; IR: 3443, 3237, 1635, 1573, 744 cm^{-1}; MS: *m/z* 309 (M^+), 266 (100%), 250; ^1H NMR: δ 0.83 (3H, t, *J*=7.0 Hz), 1.27 (2H, sextet, *J*=7.0 Hz), 1.71 (2H, quintet, *J*=7.0 Hz), 2.98 (3H, d, *J*=4.0 Hz), 4.36 (2H, t, *J*=7.0 Hz), 7.22 (1H, t, *J*=7.5 Hz), 7.43 (1H, t, *J*=7.5 Hz), 7.47 (1H, d, *J*=8.5 Hz), 7.57 (1H, d, J=8.0 Hz), 7.64-7.56 (1H, m), 7.83 (1H, d, *J*=7.5 Hz), 7.87 (1H, d, *J*=5.0 Hz); ^{13}C NMR: δ 14.5, 31.6 (both CH_3), 20.5, 31.6, 43.3 (all CH_2), 107.9, 110.2, 117.4, 119.6, 121.1, 126.2 (all Ar-CH), 115.6, 121.1, 122.0, 136.7, 140.9, 147.3, 165.8 (all Ar-C); *Anal.* Calcd for $C_{18}H_{19}N_3S$: C, 69.90; H, 6.15; N, 13.59. Found: C, 69.96; H, 6.13; N, 13.62.

7a: Mp 278°; IR: 3416, 3376, 1600, 1546, 744 cm^{-1}; MS: *m/z* 395 (M^++2; 100%), 393 (M^+; 100), 314, 265, 263, 259, 257; ^1H NMR: δ 7.00 (1H, t, *J*=7.5 Hz), 7.37 (2H, t, *J*=7.5 Hz), 7.50-7.55 (3H, m), 7.76 (1H, d, *J*=8.5 Hz), 7.82 (2H, d, *J*=7.5 Hz), 7.94 (1H, s), 10.47 and 11.67 (1H, each br); ^{13}C NMR: δ 110.5, 114.2, 118.3 (2×), 119.4, 122.6, 123.1, 128.7, 129.9 (2×) (all Ar-CH), 111.5, 114.7, 121.8, 123.4, 137.6, 139.4, 141.8, 146.6, 159.9 (all Ar-C); *Anal.* Calcd for $C_{19}H_{12}N_3{}^{79+81}BrS$: C, 57.86; H, 3.04; N, 10.65. Found: C, 58.11; H, 3.04; N, 10.66.

8b: Mp 232-234°; IR: 3230, 1613, 1566, 731 cm^{-1}; MS: *m/z* 267 (M^+; 100%), 252, 238; ^1H NMR: δ 2.77 (3H, d, *J*=4.5 Hz), 3.63 (3H, s), 6.95 (1H, dt, *J*=7.5, 1.0 Hz), 7.21 (1H, dt, *J*=7.5, 1.0 Hz), 7.31 (1H, d, *J*=8.0 Hz), 7.58 (1H, q, *J*=4.5 Hz), 7.68 (1H, s), 7.93 (1H, d, *J*=8.0 Hz), 7.95 (1H, s); ^{13}C NMR: δ 29.9,

31.3 (both CH_3) 101.7, 109.4, 109.6, 119.0, 120.9, 126.2 (all Ar-CH), 121.9, 123.0, 130.9, 137.8, 141.8, 147.3, 165.2 (all Ar-C); HRMS: *m/z* 267.0833 (M^+); Calcd for $C_{15}H_{13}N_3S$: 267.0830.

8c: Mp 242-244°; IR: 3230, 3184, 1633, 1580, 751 cm^{-1}; MS: *m/z* 281 (M^+; 100%), 266, 252; ^1H NMR: δ 1.29 (3H, t, *J*=7.0 Hz), 2.95 (1H, d, *J*=4.5 Hz), 4.38 (2H, q, *J*=7.0 Hz), 7.12 and 7.39 (1H, t each, *J*=7.5 Hz), 7.50 (1H, d, *J*=8.0 Hz), 7.67 (1H, q, *J*=4.5 Hz), 7.88 (1H, s), 8.11 (1H, d, *J*=7.5 Hz), 8.13 (1H, s); ^{13}C NMR: δ 14.3, 31.3 (both CH_3), 37.9 (CH_2), 101.7, 109.5, 109.6, 119.0, 121.0, 126.2 (all Ar-CH), 122.0, 123.1, 130.0, 136.7, 140.7, 147.2, 165.2 (all Ar-C); *Anal.* Calcd for $C_{16}H_{15}N_3S$: C, 68.33; H, 5.34; N, 14.94. Found: C, 68.28; H, 5.36; N, 14.90.

8d: Mp 246-248°; IR: 3230, 3118, 1639, 1613, 744 cm^{-1}; MS: *m/z* 375 (M^++2; 100%), 373 (M^+; 100%), 346, 344, 295, 266; ^1H NMR: δ 0.84 (3H, t, *J*=7.0 Hz), 1.76 (2H, sextet, *J*=7.0 Hz), 2.95 (3H, d, *J*=4.0 Hz), 4.27 (2H, t, *J*=7.0 Hz), 7.47 (1H, d, *J*=8.5 Hz), 7.49 (1H, d, *J*=8.5 Hz), 7.79 (1H, q, *J*=4.0 Hz), 7.91 (1H, s), 8.17 and 8.33 (1H, each s); ^{13}C NMR: δ 12.1, 31.3 (both CH_3), 22.5, 44.8 (both CH_2), 102.2, 109.7, 111.9, 123.4, 128.4 (all Ar-CH), 111.0, 120.8, 125.0, 132.0, 137.5, 140.0, 147.6, 165.4 (all Ar-C); HRMS: *m/z* 373.0267 (M^+); Calcd for $C_{17}H_{16}N_3{}^{79}BrS$: 373.0249.

8e: Mp 220-222°; IR: 3224, 3118, 1639, 1613, 744 cm^{-1}; MS: *m/z* 389 (M^++2; 100%), 387 (M^+; 100%), 346, 344, 309, 266; ^1H NMR: δ 0.84 (3H, t, *J*=7.0 Hz), 1.27 (2H, sextet, *J*=7.0 Hz), 1.70 (2H, quintet, *J*=7.0 Hz), 2.96 (3H, d, *J*=4.0 Hz), 4.30 (2H, t, *J*=7.0 Hz), 7.48 (2H, s), 7.73 (1H, q, *J*=4.0 Hz), 7.90 (1H, s), 8.17 and 8.33 (1H, each s); ^{13}C NMR: δ 14.5, 31.9 (both CH_3), 20.6, 31.3, 43.2 (all CH_2), 102.2, 109.7, 111.8, 123.4, 128.4 (all Ar-CH), 111.0, 120.9, 125.0, 131.8, 137.4, 139.9, 150.1, 165.4 (all Ar-C); HRMS: *m/z* 387.0382 (M^+); Calcd for $C_{18}H_{18}N_3{}^{79}BrS$: 383.0405.

Screening of TCs for bioactivities: All the TCs (in 0.5% DMSO in appropriate culture media) were screened against malarial parasite (*Plasmodium falciparum*) and intestinal protozoa (*Giardia intestinalis*) using chloroquine diphosphate and emetine as the respective control drugs. Lactate dehydrogenase assay was used for anti-malarial screening and the protozoan growth was assessed visually using an inverted microplate. All the TCs were found to be inactive against both the parasites at up to 50 μg/mL.

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