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Synthesis of curcumin based imidazo[2,1-*b*]thiazole derivatives and their biological evaluation as antiproliferative agents

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Motivated by the antiproliferative potential of curcumin and imidazothiazoles, a series of curcumin based imidazo[2,1-*b*] thiazole derivatives have been prepared, characterized and evaluated for their anticancer activity against various human cancer cell lines. These synthesized compounds have been found to have appreciable to moderate activity. Consequently, compounds **8a** and **8g** display noteworthy cytotoxicity with IC_{50} values of 7.2 μM and 4.7 μM, respectively, against A549 cell line. Furthermore, compounds **8a**, **8b** and **8g** exhibit substantial cytotoxicity with IC_{50} values ranging between 9.1 μM to 9.9 μM respectively, against HeLa cell line. Interestingly, compounds **8a** and **8g** exhibit appreciable cytotoxicity with IC_{50} values ranging between 7.5 μM to 8.7 μM respectively, against DU145 cancer cell line. Overall, four compunds (**8a, 8b, 8g** and **8h**) demonstrate IC_{50} values less than 10 μM against selected human cancer cell lines. They could be taken further for investigation of their mode of action and other parameters.

Keywords: Curcumin, Imidazo[2,1-*b*]thiazole, cytotoxicity, antiproliferative activity

Curcumin (Figure 1) is the active curcuminoid of Indian spice turmeric, at first isolated from the rhizomes of Curcuma longa. The derivatives of this naturally occurring curcuminoid exhibit diverse medicinal properties like antibacterial, anti-tumor, antioxidant, anti-inflammatory and anti-HIV activities. Interestingly, curcumin demonstrates curative potential in prostate cancer by causing cell cycle arrest, change in cell propagation, and augmentation of tumor blood vessels *via* down-regulation of androgen receptor as well as epidermal growth factor receptor[1,2].

Unfortunately, curcumin demonstrates certain limitations like poor systemic bioavailability and extremely metabolically unstable which avert its application in the clinical[3]. As a result, widespread research is being carried out to explore novel curcumin analogues/mimics with enhanced effectiveness and safety pharmacokinetic profile[4]. Fascinatingly, the structure characteristic of Curcumin moiety acts as a Michel acceptor and possesses remarkable antioxidant activity by scavenging reactive oxygen species (ROS) which are involved in many kinds of cancers[5-7] along with their ability to influence multiple cancer targets and pathways such as kinases, growth factors, enyzmes and apoptosis[8-10]. Due to the diverse of pharmacological activities of Curcumin scaffold, a large group of medicinal chemists across the world have been successful in development of bioactive agents with different properties possessing this moiety[11-15].

On the contrary, Imidazo[2,1-*b*]thiazole/its analogues have engrossed significant consideration owing to their synthetic as well as successful biological implication[16,17]. Compounds containing this structural feature exhibit a plethora of pharmacological activities such as immune-modulating[18], anticancer[19] analgesic and anti-inflammatory[20], antimicrobial[21,22], anti-hypertensive[23], antioxidant[24] and antimycobacterial[25]. Therapeutically appealing drugs in the clinic; for instance, Levimasole (Figure 2) is known to contain Imidazo[2,1-*b*]thiazole nucleus.

In the recent years, there has been a renewed interest in the progress of new molecular hybrids consisting of two phamacophores in a solitary entity to augment the usefulness of the newer hybrids. The gifted biological activity exhibited by these

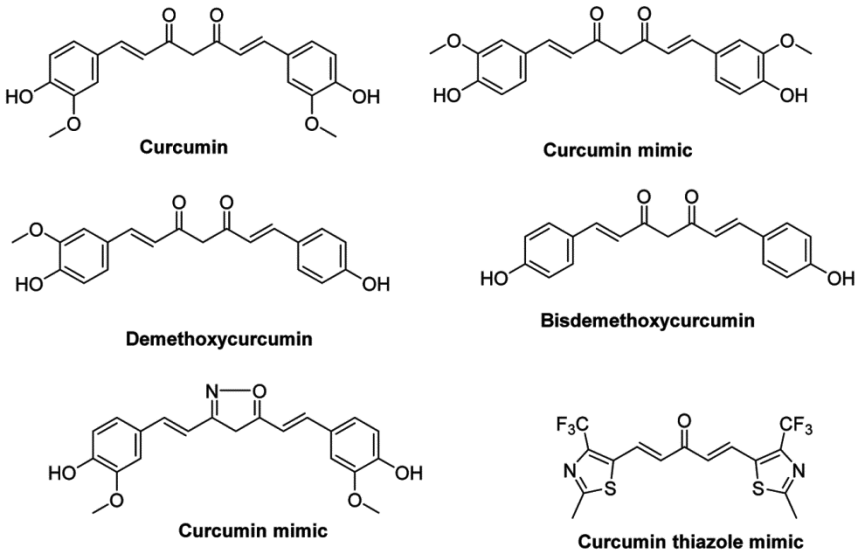

Figure 1 — Structures of curcumin and its analogues

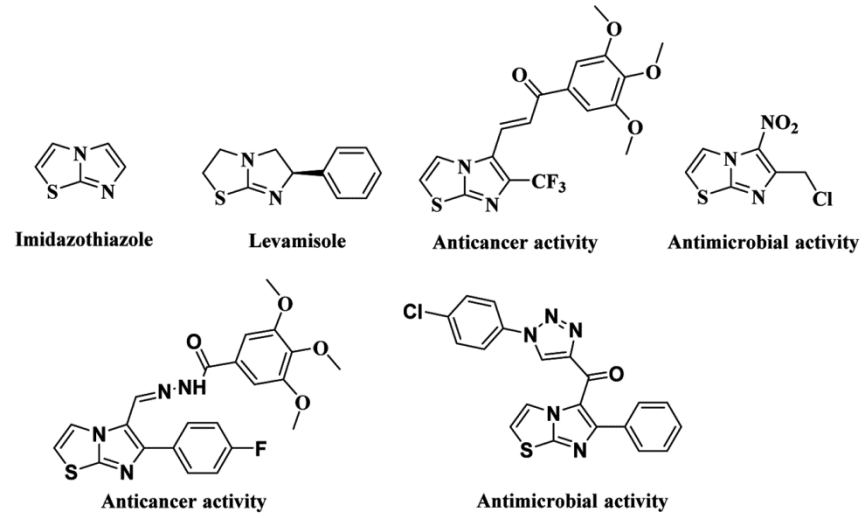

Figure 2 — Structures of Imidazo[2,1-*b*]thiazole and its analogues

hybrids enthused us to develop some newer hybrid molecules by linking the curcumin pharmacophore with Imidazo[2,1-*b*]thiazole scaffold (Figure 3) we considered of interest to synthesize curcumin based Imidazo[2,1-*b*]thiazoles **8(a-o)** to explore the biological activity.

Results and Discussion

Chemistry

The hypothesized compounds, (**8a-o**, Figure 4) were synthesized as outlined in Scheme I. At first, Chalcones **3a-e** were prepared by NaOH-catalysed Claisen-Schmidt condensation of substituted benzaldehydes **1a-e** with acetone[26]. Similarly, 2-aminothiazole **(5)** and appropriate phenacyl bromides **4a-c** were subjected to reflux conditions for 6-8h to get the Imidazo[2,1-*b*]thiazoles intermediates **6a-f** which up on formylation yielded the corresponding Imidazo[2,1-*b*]thiazoles aldehydes[27] **7a-c**. Finally, substituted imidazothiazole aldehydes **7a-c** reacted with Chalcones **3a-e** under Claisen-Schmidt condensation reaction conditions to furnish the desired hybrids **8a-o** in appreciable yields.

Biological activity

In vitro cytotoxicity studies

The newly prepared compounds **8a-o** were first examined for their *in vitro* antiproliferative property against a choice of human cancer cell lines, that is, HeLa (cervical carcinoma), A549 (non-small cell lung

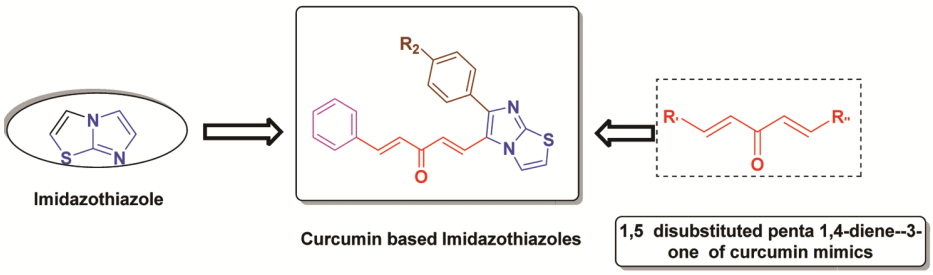

Figure 3 — Design strategy of curcumin based imidazothiazoles

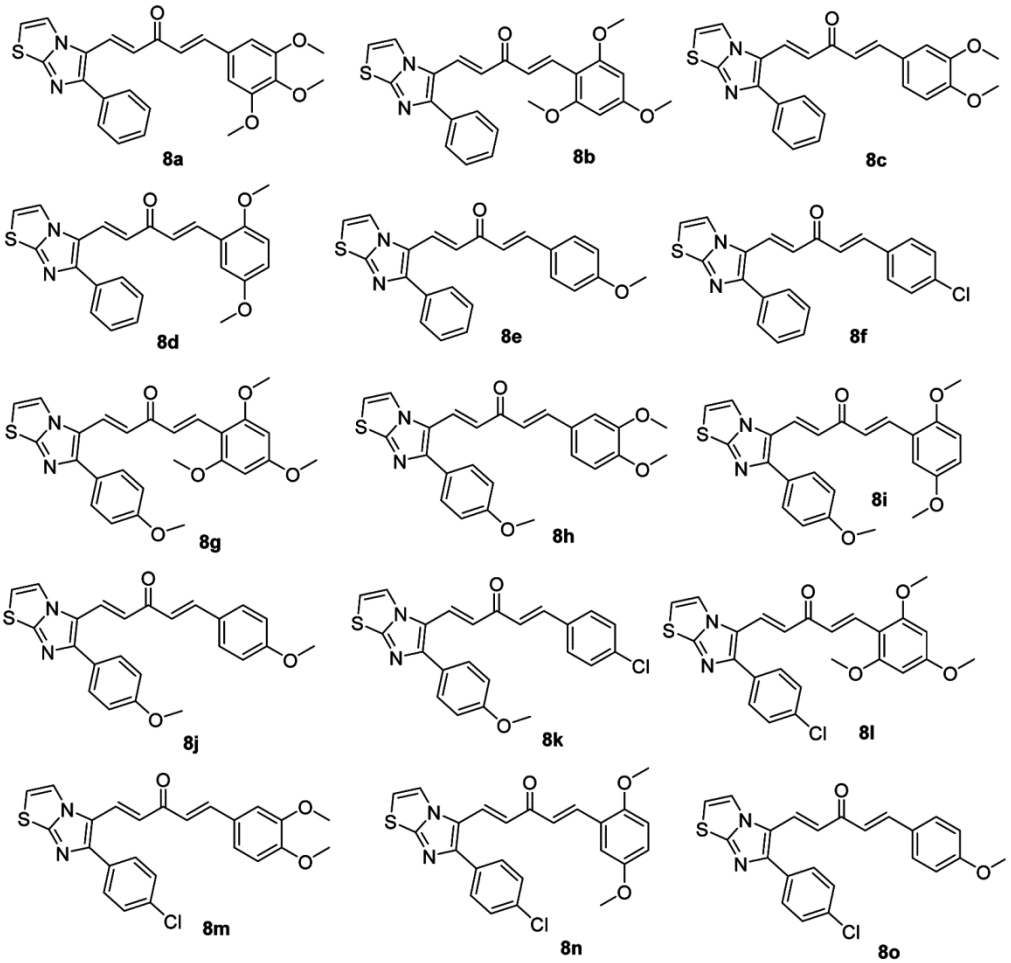

Figure 4 — Structures of novel Curcumin based Imidazo[2,1-*b*]thiazoles **8a-o**

cancer) and DU145 (human prostate cancer) cell lines by by means of MTT assay[28]. IC_{50} values represented in μM as Mean ± SD depicted in Table I. The results unravel that the bulk of the evaluated compounds demonstrated appreciable to moderate antiproliferative activity. Interstingly, compounds **8a** and **8g** displayed noteworthy cytotoxicity with IC_{50} values of 7.2 μM and 4.7 μM, respectively, against A549 cell line. Furthermore, Compounds **8a**, **8b** and **8g** exhibited substantial cytotoxicity with IC_{50} values ranging between 9.1 μM to 9.9 μM respectively, against HeLa cell line. In addition, Compounds **8a** and **8g** exhibited good cytotoxicity with IC_{50} values ranging between 7.5 μM to 8.7 μM respectively, against DU145 cancer cell line.

Experimental Section

All solvents were purified and dried using standard methods prior to use. Commercially available reagents

Table I — Antiproliferative activity of Curcumin based Imidazo[2,1-*b*]thiazoles **8a-o**

Compd	IC_{50} values[a] against various human cancer cell lines		
	HeLa	A549	DU-145
8a	9.3± 0.3	7.2± 0.4	8.7 ± 0.4
8b	9.9± 0.3	11.2±0.3	18.3 ± 0.6
8c	42.6±0.9	32.0± 0.4	42.7 ± 0.7
8d	39.7±0.7	41.2± 0.	29.1 ± 0.2
8e	18.9±0.6	20.2± 0.5	47.2 ± 0.5
8f	28.0±0.4	42.8± 0.8	>50
8g	9.1±0.4	4.7± 0.3	7.5 ± 0.4
8h	16.1 ±0.2	9.6± 0.4	13.6 ± 0.6
8i	28.6±0.5	23.8± 0.7	17.3 ± 0.3
8j	28.1±0.7	35.2± 0.3	30.3 ± 0.3
8k	39.4±0.3	36.2± 0.5	20.0 ± 0.2
8l	26.9±0.2	23.5± 0.2	32.7 ± 0.8
8m	12.5±0.3	21.6± 0.9	14.6 ± 0.5
8n	19.2 ±0.1	15.5± 0.4	27.8 ± 0.4
8o	21.2±0.4	41.6± 0.9	30.2 ± 0.5
Doxorubicin	2.6 ±0.1	3.0 ± 0.1	1.9 ± 0.1

were used without further purification. The reactions were monitored by thin layer chromatography (TLC), using Merck pre-coated silica gel 60-F254 aluminum plates. Visualization of spots on TLC plates was done by UV light. Column chromatography with 60-120 mesh silica gel was used as separation and purification method. Ethyl acetate and hexane were used as eluent. Melting points were obtained on Stuart digital melting-point apparatus/SMP 30 and were uncorrected. ^{1}H NMR spectra were recorded on an Advance NMR instrument operated at 500 MHz ^{13}C NMR spectra were recorded on an Advance NMR instrument operated at 125 MHz Chemical shift values were reported in ppm with TMS as an internal reference and *J* values were given in Hertz. The following abbreviations were used for ^{1}H NMR spectra to indicate the signal multiplicity: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). HRMS were determined with Agilent QTOF mass spectrometer 6540 series instrument and were performed in the ESI techniques at 70 eV.

General procedure for the synthesis of intermediates, 3a-e

To a stirred solution of benzaldehyde **1a-e** (1 mmol) in ethanol (3 mL) was added 0.5 mL of acetone and 15% aqueous NaOH (1 mL) solution at 0°C. The reaction was allowed to stir at room temperature till it was completed. The reaction mixture was evaporated to dryness, extracted twice with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (Silica gel, 60-120 mesh, 9:1 hexane/ethyl acetate) to obtain the desired chalcone **3a-e**.

General procedure for the synthesis of compounds 6a-c

Initially, 2-bromo-1-(substituted)ethanones (**4a-c**, 1.0 equiv) and thiazol-2-amine (**5**, 1.0 equiv) and $NaHCO_3$ (3.0 equiv) were dissolved in Ethanol and the reaction mixture was refluxed till it was completed. The reaction mixture was evaporated to dryness, extracted twice with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (Silica gel, 60-120 mesh, 9:1 hexane/ ethyl acetate) to obtain the desired compounds **6a-c**.

6-Phenylimidazo[2,1-*b*]thiazole, 6a

The titled compound was prepared according to the general method described above, employing 2-bromo-1-phenylethan-1-one (**1a**, 1.0 equiv) and thiazol-2-amine (**2**, 1.0 equiv) to obtain the pure product **3a** as a white solid (80% yield). m.p. 148–150°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.85 (d, *J* = 4.34 Hz, 1H), 7.29 (d, *J* =7.36 Hz, 1H), 7.37–7.46 (m, 3H), 7.74 (s, 1H), 7.83 (d, *J* = 7.17 Hz, 2H); ESI-MS: *m/z* 201 [M+H]+.

6-(4-Methoxyphenyl)imidazo[2,1-*b*]thiazole, 6b

The titled compound was prepared according to the general method described above, employing 2-bromo-1-(4-methoxyphenyl)ethan-1-one (**1c**, 1.0 equiv) and thiazol-2-amine (**2**, 1.0 equiv) to obtain the pure product **3c** as a white solid (82% yield). m.p. 176–177°C; ^{1}H NMR ($CDCl_3$,300 MHz): δ 3.83 (s, 3H), 6.78 (d, *J*= 3.9 Hz, 1H), 6.93 (d, *J*= 8.5 Hz, 2H), 7.40 (d, *J*= 4.6 Hz, 2H), 7.63 (s, 1H), 7.74 (d, *J*= 8.5 Hz, 1H); ESI-MS: *m/z* 231 [M+H]+.

6-(4-Chlorophenyl)imidazo[2,1-*b*]thiazole, 6c

The titled compound was prepared according to the general method described above, employing 2-bromo-1-(4-chloroyphenyl)ethan-1-one (**1b**, 1.0 equiv) and thiazol-2-amine (**2**, 1.0 equiv) to obtain the pure product **3b** as a white solid (84% yield). m.p. 163-164°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.84 (d, *J* = 4.53 Hz, 1H), 7.43 (d, *J* = 4.53 Hz, 1H), 7.52 (d, *J* = 8.49 Hz, 2H), 7.71 (t, *J* = 8.49 Hz, 3H); ESI-MS: *m/z* 235 [M+H]+.

General procedure synthesis of compounds, 7a-c

Vilsmeier reagent was prepared by addition of $POCl_3$ (5.0 equiv) to a stirred solution of DMF

(5.0 equiv) in $CHCl_3$ (10 mL) at 0–5°C. To this reagent, compounds **6a-c** (1.0 equiv) in chloroform (20 mL) was added while maintaining cold conditions. After complete addition, the reaction mixture was stirred at room temperature for 3 h and at reflux conditions for 10–12 h. After completion of the reaction, as indicated on TLC, chloroform was removed under reduced pressure and the resulting oily liquid was poured onto ice. The obtained aldehydes were collected by filtration and crystallised from EtOH (5 mL) to obtain the desired products **7a-c** as solids respectively.

7a: White solid (83% yield). m.p. 139–141°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 4.4 Hz, 1H), 7.46–7.57 (m, 3H), 7.79–7.82 (m, 2H), 8.40 (d, *J* = 4.4 Hz, 1H), 9.91 (s, 1H); ESI-MS: *m/z* 229 $[M+H]^+$.

7b: Brown solid (78% yield). m.p. 138-140°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.89–7.10 (m, 3H), 7.73–7.77 (m, 2H), 8.37–8.38 (m, 1H), 9.88 (s, 1H); ESI-MS: *m/z* 259 $[M + H]^+$.

7c: White solid (82% yield). m.p. 157–158°C;^{1}H NMR ($CDCl_3$,400 MHz): δ 7.09 (d, *J* = 4.4 Hz, 1H), 7.48–7.52 (m, 2H), 7.73–7.77 (m, 2H), 8.40 (d, *J* = 4.4 Hz, 1H), 9.90 (s, 1H); ESI-MS: *m/z* 263 [M+H]+.

General procedure for the synthesis of titled compounds, 8a-o

To a stirred solution of chalcone, **3a-e** (1 mmol) in ethanol (3 mL) was added 0.5 mL of acetone and 15% aqueous NaOH (1 mL) solution at 0°C. The reaction was allowed to stir at room temperature till it was completed. The reaction mixture was evaporated to dryness, extracted twice with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was filtered and recrysrallized with cold ethanol to obtain the pure compounds **8a-o** in good yields.

8a: Yellow solid; yield 76%. m.p.173°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 3H), 3.91 (s, 6H), 6.79 (d, 1H, *J* = 15.8 Hz), 6.82 (s, 2H), 6.92 (d, 1H, *J* = 15.7 Hz), 7.06 (d, 1H, *J* = 4.5 Hz), 7.41–7.46 (m, 1H), 7.44 (d, 2H, *J* = 7.3 Hz), 7.62 (d, 1H, *J* = 15.7 Hz), 7.73 (d, 2H, *J* = 7.1 Hz), 7.88 (d, 1H, *J* = 4.5 Hz), 8.01 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.1, 60.9, 105.4, 113.9, 119.5, 120.2, 124.7, 128.7, 128.9, 129.4, 130.1, 133.4, 140.2, 142.9, 153.3, 187.6; HRESI-MS *m/z* for $C_{25}H_{23}N_2O_4S$ Calcd *m/z*: 447.13935. Found *m/z*: 447.1373.

8b: Yellow solid; yield 79%. m.p.175°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 3.88 (s, 6H), 6.13 (s, 2H), 6.81 (d, 1H, *J* = 16.1 Hz), 7.04 (d, 1H, *J* = 4.4 Hz), 7.39–7.45 (m, 2H), 7.46–7.52 (m, 2H), 7.74 (d, 2H, *J* = 7.0 Hz), 7.89 (d, 1H, *J* = 4.5 Hz), 7.92 (d, 1H, *J* = 15.6 Hz), 8.18 (d, 1H, *J* = 15.6 Hz); ^{13}C NMR (120 MHz, $CDCl_3$) δ 55.3, 55.6, 90.4, 106.2, 113.5, 120.4, 121.9, 124.6, 128.2, 128.8, 133.7, 152.4, 153.1, 161.5, 189.8; HRESI-MS *m/z* for $C_{25}H_{23}N_2O_4S$ Calcd *m/z*: 447.1373. Found *m/z*: 447.1398.

8c: Yellow solid; yield 82%. m.p.170°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (s, 6H), 6.80 (d, 1H, *J* = 15.8 Hz),), 6.87–6.93 (m, 2H), 7.06 (d, 1H, *J* = 4.2 Hz), 7.12 (d, 1H, *J* = 7.2 Hz), 7.18 (d, 1H, *J* = 7.7 Hz), 7.44 (d, 1H, *J* = 7.3 Hz), 7.48–7.53 (m, 2H), 7.67 (d, 1H, *J* = 15.7 Hz), 7.73 (d, 2H, *J* = 7.1 Hz), 7.88 (d, 1H, *J* = 4.4 Hz), 8.00 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 109.7, 111.0, 113.9, 119.5, 120.3, 123.1, 123.3, 127.7, 128.7, 128.9, 133.5, 143.0, 149.1, 151.3, 153.4, 187.8; HRESI-MS *m/z* for $C_{24}H_{21}N_20_3S$ Calcd *m/z*: 417.1267. Found *m/z*: 417.1284.

8d: Yellow solid; yield 84%. m.p.165°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.86 (s, 3H), 6.83 (d, 2H, *J* = 16.1 Hz),), 6.87–6.95 (m, 2H), 7.06 (d, 1H, *J* = 4.0 Hz), 7.11 (s, 1H), 7.40–7.46 (m, 1H), 7.50–7.54 (m, 2H), 7.73 (d, 2H, *J* = 7.0 Hz), 7.89 (d, 1H, *J* = 4.5 Hz), 8.00 (d, 2H, *J* =14.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 56.0, 112.3, 113.3, 117.3, 119.5, 120.3, 124.2, 126.2, 128.7, 128.9, 133.5, 138.1, 153.1, 153.4, 188.5; HRESI-MS *m/z* for $C_{24}H_{21}N_20_3S$ Calcd *m/z*: 417.1217. Found *m/z*: 417.1284.

8e: Yellow solid; yield 81%. m.p.163°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.79 (d, 1H, *J* = 16.0 Hz), 6.88–6.95 (m, 3H), 7.06 (d, 1H, *J* = 5.1 Hz), 7.44 (d, 1H, *J* = 16.1 Hz), 7.50 (d, 2H, *J* = 7.4 Hz), 7.69 (d, 1H, *J* = 15.7 Hz), 7.73 (d, 2H, *J* = 7.1 Hz), 7.87–7.89 (m, 1H), 8.00 (d, 2H, *J* = 15.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.3, 113.8, 114.3, 119.5, 120.4, 123.1,, 128.6, 128.8, 130.0, 133.5, 142.7, 153.3, 153.5, 161.5, 187.8; HRESI-MS *m/z* for $C_{23}H_{18}N_2O_2S$ Calcd *m/z*: 387.1161. Found *m/z*: 387.1179.

8f: Yellow solid; yield 80%. m.p.186°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, 1H, *J* = 16.0 Hz), 6.99 (d, 1H, *J* = 16.0 Hz), 7.07 (d, 1H, *J* = 4.2 Hz), 7.36–7.40 (m, 2H), 7.45 (d, 1H, *J* = 7.1 Hz), 7.48–7.55 (m, 4H), 7.65 (d, 1H, *J* = 15.8 Hz), 7.72

(d, 2H, *J* = 7.6 Hz), 7.87 (d, 1H, *J* = 4.2 Hz), 8.01 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.0, 119.5, 120.0, 125.6, 128.7, 129.1, 129.4, 133.4, 136.2, 141.3, 141.9, 153.3, 187.5; HRESI-MS *m/z* for $C_{22}H_{15}ClN_2OS$ Calcd *m/z*: 391.2818. Found *m/z*: 391.2858.

8g: Yellow solid; yield 68%. m.p.175°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 6H), 3.89 (s, 6H), 6.13 (s, 2H), 6.77(d, 1H, *J* = 16.1 Hz), 7.05 (d, 1H, *J* = 4.3 Hz), 7.47 (d, 1H, *J* = 7.4 Hz), 7.50–7.55 (m, 4H), 7.87 (d, 1H, *J* = 4.1 Hz), 7.95 (d, 1H, *J* = 16.1 Hz), 8.12 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 55.7, 90.5, 113.2, 114.1, 119.6, 120.0, 121.3, 124.8, 126.3, 128.4, 130.2, 133.1, 152.6, 153.2, 161.3, 163.0, 189.8 ; HRESI-MS *m/z* for $C_{26}H_{24}N_2O_5S$ Calcd *m/z*: 477.1478. Found *m/z*: 477.1500.

8h: Yellow solid; yield 76%. m.p.171°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 3.94 (s, 6H), 6.77 (d, 1H, *J* = 15.8 Hz), 6.88 (s, 1H), 6.91 (d, 1H, *J* = 7.3 Hz), 7.01–7.05 (m, 3H), 7.12 (d, 1H, *J* = 7.4 Hz), 7.18 (d, 1H, *J* = 8.3 Hz), 7.66 (d, 1H, *J* = 4.1 Hz), 7.69 (d, 2H, *J* = 8.1 Hz), 7.87 (d, 1H, *J* = 4.5Hz), 7.99 (d, 1H, *J* = 15.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 55.9, 109.8, 111.1, 113.6, 114.2, 123.1, 125.6, 126.1, 127.6, 130.2, 142.8, 149.2, 151.3, 160.1 187.9 ; HRESI-MS *m/z* for $C_{25}H_{23}N_2O_4S$ Calcd *m/z*: 447.1373. Found *m/z*: 447.1394.

8i: Yellow solid; yield 74%. m.p.185°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.85 (d, 1H, *J* = 15.7 Hz), 6.89 (s, 1H), 6.92–6.96 (m, 1H), 7.04–7.10 (m, 2H), 7.11 (d, 1H, *J* = 7.5 Hz), 7.16–7.21 (m, 2H), 7.68–7.72 (m, 2H), 7.88 (d, 1H, *J* = 4.5 Hz), 7.93 (d, 1H, *J* = 16.0 Hz), 7.99 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 56.0, 112.3, 113.3, 114.0, 115.7, 117.3, 119.4, 120.2, 124.1, 126.3, 128.9, 138.2, 152.2, 153.1, 153.4, 188.4 ; HRESI-MS *m/z* for $C_{25}H_{23}N_2O_3S$ Calcd *m/z*: 417.1267. Found *m/z*: 417.12852.

8j: Yellow solid; yield 77%. m.p.181°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.88 (s, 3H), 6.76 (d, 1H, *J* = 16.1 Hz), 6.91 (d, 2H, *J* = 11.1 Hz), 6.93 (d, 2H, *J* = 8.5 Hz),7.56 (d, 2H, *J* = 8.5 Hz), 7.69 (d, 2H, *J* = 15.6 Hz), 7.87 (d, 1H, *J* = 4.5 Hz), 7.89 (d, 1H, *J* = 16.0 Hz), 7.99 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 113.6, 114.2, 119.9, 5, 119.9, 123.2, 126.0, 127.4, 129.3, 130.2, 142.6, 153.3, 160.1, 161.5, 187.8; HRESI-MS *m/z* for $C_{24}H_{21}N_2O_3S$ Calcd *m/z*: 417.1267. Found *m/z*: 417.1286.

8k: Yellow solid; yield 82%. m.p.192°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.74 (d, 1H, *J* = 15.8 Hz), 6.98 (d, 1H, *J* = 15.8 Hz), 7.02 (d, 1H, *J* = 4.5 Hz), 7.04 (d, 1H, *J* = 8.6 Hz), 7.36–7.39 (m, 2H), 7.50–7.55 (m, 2H), 7.66 (d, 3H, *J* = 8.5 Hz), 7.85 (d, 1H, *J* = 4.5 Hz), 7.99 (d, 1H, *J* = 15.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 113.7, 114.2, 119.4, 119.8, 125.8, 129.1, 129.4, 130.2, 133.3, 136.2, 141.2, 141.9, 153.9, 160.2, 187.5; HRESI-MS *m/z* for $C_{23}H_{18}ClN_2O_2S$ Calcd *m/z*: 421.0772. Found *m/z*: 421.07910.

8l: Yellow solid; yield 69%. m.p.201°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 3.88 (s, 6H), 6.13 (s, 2H), 6.83 (d, 1H, *J* = 16.0 Hz), 7.04 (d, 1H, *J* = 4.5 Hz), 7.39 (d, 1H, *J* = 16.0 Hz), 7.44–7.47 (m, 2H), 7.65–7.68 (m, 2H), 7.94 (d, 3H, *J* = 16.0 Hz), 8.18 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 55.7, 90.5, 106.2, 113.8, 120.2, 122.3, 124.8, 127.7, 128.8, 130.1, 132.2, 134.7, 150.9, 153.1, 161.6, 163.1, 189.7; ; HRESI-MS *m/z* for $C_{24}H_{20}N_20_30_3S$ Calcd *m/z*: 481.0983. Found *m/z*: 481.1003.

8m: Yellow solid; yield 84%. m.p.190°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 6H), 6.81 (d, 1H, *J* = 15.0 Hz), 6.90 (s, 2H), 7.10 (d, 2H, *J* = 8.4 Hz), 7.23 (d, 2H, *J* = 8.8 Hz), 7.48 (d, 2H, *J* = 14.8 Hz), 7.68 (d, 3H, *J* = 7.8 Hz), 7.88 (d, 1H, *J* = 15.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 109.7, 111.0 114.1, 119.4, 120.5, 123.2, 123.4, 127.6, 128.7, 130.1, 132.0, 134.7, 143.2, 149.2, 151.4, 153.6, 187.6; HRESI-MS *m/z* for $C_{24}H_{20}ClN_2O_3S$ Calcd *m/z*: 451.0877. Found *m/z*: 451.0896.

8n: Yellow solid; yield 76%. m.p.198°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.86 (s, 3H), 6.85 (d, 1H, *J* = 15.7 Hz), 6.90–6.93 (m, 2H), 7.06 (d, 1H, *J* = 8.4 Hz), 7.08–7.10 (m, 1H), 7.12 (d, 1H, *J* = 4.1 Hz), 7.17–7.23 (m, 2H), 7.69–7.72 (m, 2H), 7.88 (d, 1H, *J* = 4.8 Hz), 7.94 (d, 1H, *J* = 16.0 Hz), 8.00 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 56.0, 112.4, 113.3, 114.1, 117.4, 119.4, 120.4, 124.1, 12.8, 128.9, 130.1, 132.0, 134.7, 138.3, 151.8, 153.1, 153.5, 188.4; HRESI-MS *m/z* for $C_{24}H_{20}ClN_2O_3S$ Calcd *m/z*: 451.0812. Found *m/z*: 451.0898.

8o: Yellow solid; yield 71%. m.p.213°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.79 (d, 1H, *J* = 15.8 Hz), 6.91 (d, 1H, *J* = 15.8 Hz), 6.98 (d, 2H, *J* = 8.8 Hz), 7.08 (d, 1H, *J* = 4.5 Hz), 7.19–7.22 (m, 2H), 7.56 (d, 2H, *J* = 8.8 Hz), 7.69 (d, 1H, *J* = 70 Hz), 7.71–7.72 (m, 2H), 7.88 (d, 1H, *J* = 4.5 Hz), 7.94

(d, 1H, J = 15.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 114.1, 115.9, 119.4, 120.0, 125.8, 129.2, 129.9, 133.2, 136.3, 141.5, 152.8, 153.8, 161.9, 164.3, 187.4; HRESI-MS *m/z* for $C_{23}H_{18}ClN_2O_4S$ Calcd *m/z*: 421.0772. Found *m/z*: 421.07911.

Biological studies

Cell culture

Human cancer cells were grown in DMEM medium supplemented with 10% heat-inactivated fetal bovine serum along with 1% penicillin-streptomycin antibiotic solution. Cells were maintained at 37°C in a humidified atmosphere (RH 85%) containing 5% CO_2.

Cytotoxicity assay

Cytotoxicity of all the synthesized compounds was determined on the basis of measurement of *in vitro* growth inhibition of tumor cell lines in 96-well plates by cell mediated reduction of tetrazolium salt to water insoluble formazan crystals using doxorubicin as a standard (positive control) and DMSO acted as a negative control. The cytotoxicity was assessed against a panel of different human tumor cell lines: HeLa derived from human cervical carcinoma cells, A549 derived from human lung cancer cells and DU-145 derived from human prostate cancer cells using the MTT assay (Mosmann, 1983).

Cells were grown in Dulbecco's Modified Eagle's Medium (DMEM) with 10% Fetal Bovine Serum (FBS) 1% penicillin-streptomycin antibiotic solution. The optimum confluent cells were trypsinized and the cells were seeded at a density of 5600 cells/100 µl in each well of the 96-well plate and incubated in the CO_2 incubator for 24 h. After 24 h, the media was flicked off and 100 µl of different doses of test compounds in fresh media was added to the cells in microtitre plates and kept for incubation at 37 ºC in 5% CO_2 incubator for 24 h and after the specified period of drug exposure, 20 µl of MTT reagent (0.5 mg/ml) was added to each well. The plates were further incubated for 4 h at 37 ºC in the incubator. The media was removed and 200 µl of DMSO or acidic isopropanol was added, and the plates were gently shaken to dissolve the formed formazan crystals. The absorbance was measured using a microplate ELISA reader at a wavelength of 570 nm. Dose–response curves were plotted for the test compounds and controls after correction by subtracting the background absorbance from that of the blanks. The antitumor potency of the compounds indicated by the IC_{50} values (50% inhibitory concentration) was calculated from the plotted absorbance data for the dose–response curves.

IC_{50} values (in µM) are expressed as the average of three independent experiments which was calculated using the statistical tool available in Microsoft Excel program. The percentage cell viability was calculated using the formula below:

% cell viability = (At-Ab)/(Ac-Ab)×100

Where,

At= Absorbance value of test compound

Ab= Absorbance value of blank

Ac=Absorbance value of control

Conclusion

In conclusion, new Curcumin based Imidazothiazole derivatives were prepared, characterized and evaluated for their anti-proliferative activity. They demonstrated good to appreciable activity against the tested cell lines. Among all, compounds **8a** and **8g** exhibited good anti-proliferative potential with IC_{50} values of 7.2 µM and 4.7 µM, respectively, against A549 cell line. Furthermore, Compounds **8a**, **8b** and **8g** exhibited substantial cytotoxicity with IC_{50} values ranging between 9.1 µM to 9.9 µM respectively, against HeLa–Human cervical carcinoma cell line. Interestingly, Compounds **8a** and **8g** exhibited good cytotoxicity with IC_{50} values ranging between 7.5 µM to 8.7 µM respectively, against DU145 cell line. Overall, four compunds (**8a**, **8b**, **8g** and **8h**) exhibited appreciable to moderate antiproliferative activity with IC_{50} values less than 10 µM against selected human cancer cell lines. They could be taken further for investigation of their mode of action and other parameters.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/58776.

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