CURCUMIN-BASED IMIDAZO[2,1-B]THIAZOLE DERIVATIVES ARE SYNTHESISED, AND THEY ARE BIOLOGICALLY TESTED AS ANTIPROLIFERATIVE DRUGS

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ABSTRACT

Inspired by the antiproliferative potential of curcumin and imidazothiazoles, a variety of curcumin-based imidazo[2,1-b] thiazole derivatives have been synthesised, described, and assessed for their anticancer efficacy against a number of different human cancer cell lines. It has been discovered that the chemicals that were produced exhibit activity ranging from significant to moderate. As a result, compounds 8a and 8g exhibit significant cytotoxicity against the A549 cell line, with IC50 values of 7.2 M and 4.7 M, respectively. In addition, compounds 8a, 8b, and 8g have been shown to have a significant amount of cytotoxicity when tested against the HeLa cell line, with their individual IC50 values ranging from 9.1 to 9.9 microM. It is interesting to note that compounds 8a and 8g both show significant cytotoxicity against the DU145 cancer cell line, with IC50 values ranging between 7.5 and 8.7 microM, respectively. In all, four different compounds (8a, 8b, 8g, and 8h) have been shown to have IC50 values that are lower than 10 M when tested against certain human cancer cell lines. They might be examined more thoroughly in order to learn more about their method of action and several other aspects.

Keywords:*Cytotoxicity and antiproliferative activity are some of the keywords that have been associated with curcumin.*

I.INTRODUCTION

The active curcuminoid of the Indian spice turmeric is called curcumin (Figure 1), and it was first extracted from the rhizomes of the plant known as Curcuma longa. The compounds of this naturally occurring curcuminoid demonstrate a wide variety of therapeutic qualities, including actions against germs, tumours, free radicals, inflammation, and HIV. Curcumin has been shown to have the potential to cure prostate cancer, which is quite interesting. It does this by inhibiting cell proliferation, stopping the cell cycle, and increasing the number of blood vessels in the tumour. This is accomplished by down regulating the androgen receptor as well as the epidermal growth factor receptor1,2.

However, curcumin has a number of limitations, including a low bioavailability throughout the body and a high degree of metabolic instability, both of which prevent its use in clinical settings3. As a consequence of this, a substantial amount of research is now being conducted to investigate the possibility of developing new curcumin analogues or mimics that have an improved therapeutic efficacy and pharmacokinetic profile. 4. The structure that is characteristic of the curcumin moiety is fascinating because it acts as a Michel acceptor and possesses remarkable antioxidant activity by scavenging reactive oxygen species (ROS), which are involved in many different types of cancers 5-7 along with their ability to inhibit the growth of cancer cells. affect a variety of

cancer targets and pathways, including kinases, growth factors, enzymes, and apoptosis8-10. A big number of medicinal chemists from all over the globe have been successful in developing bioactive compounds with a variety of features that comprise this moiety11-15. This success may be attributed to the wide range of pharmacological activities that are shown by the curcumin scaffold.

On the other hand, imidazo[2,1-b]thiazole and its analogues have attracted a lot of attention recently due to the fact that they have both a successful synthetic application and a successful biological application16,17. Compounds that contain this structural feature exhibit a wide variety of pharmacological activities, including those that modulate the immune system (18), fight cancer (19), relieve pain and inflammation (20), fight microbes (21, 22), lower blood pressure (23), fight mycobacteria (24) and act as antioxidants (24, 25). therapeutically attractive compounds in the clinic; for example, Imidazo[2,1-b]thiazole nucleus is known to be present in Levimasole (Figure 2), which is known to contain it.

In recent years, there has been a renewed interest in the progression of new molecular hybrids consisting of two phamacophores in a single entity to augment the usefulness of the newer hybrids. This interest is due to the fact that these new molecular hybrids are expected to be more useful than older hybrids. The extraordinarily endowed biological activity shown by these

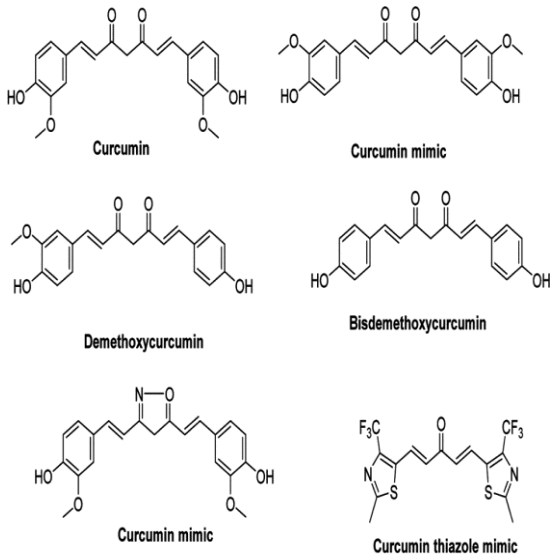


Figure 1 — Structures of curcumin and its analogues

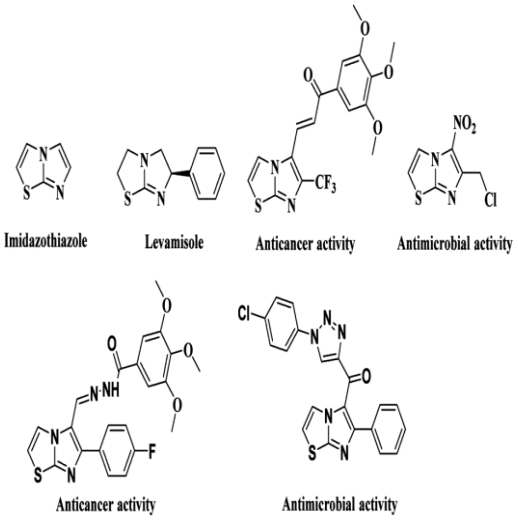


Figure 2 — Structures of Imidazo[2,1-*b*]thiazole and its analogues

By joining the curcumin pharmacophore with the imidazo[2,1-b]thiazole scaffold (Figure 3), we were inspired to create some fresh hybrid compounds. We thought it would be interesting to synthesis the curcumin-based imidazo[2,1-b]thiazoles 8(a-o) to investigate the biological activity.

II.Results and Discussion

Chemistry

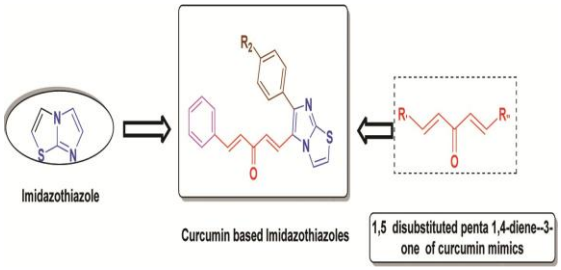
The hypothesized compounds, (**8a-o**, Figure 4) were synthesized as outlined

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



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.

Figure 3 — Design strategy of curcumin based imidazothiazoles

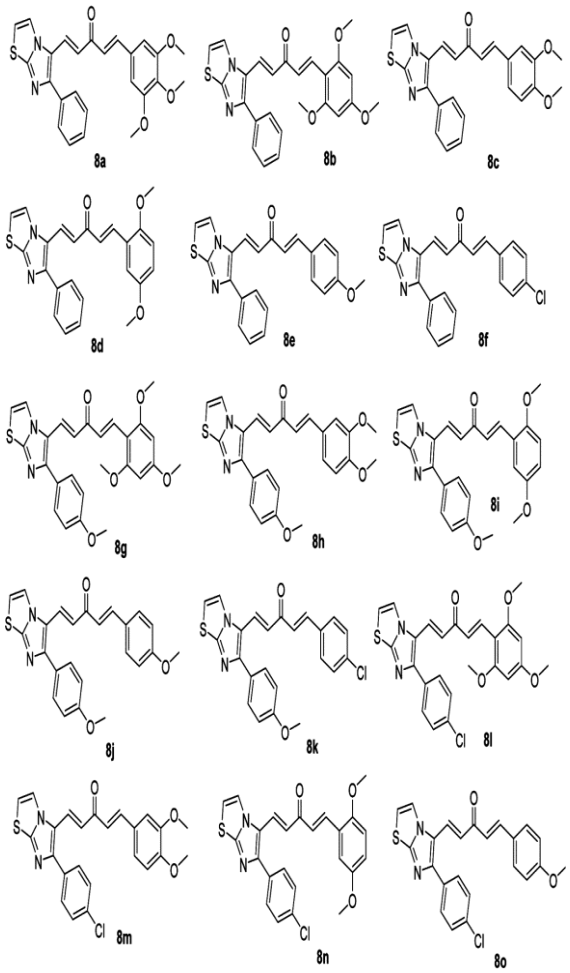


Figure 4 — Structures of novel Curcumin based Imidazo[2,1-*b*]thiazoles **8a-o**

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**

IC_{50} values[a] against various human cancer cell lines

Compd	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 titledcompounds, 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* = 7.3Hz), 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 $C_{24}H_{20}N_20_3S$ 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

To summarise, novel curcumin-based Imidazothiazole compounds were synthesised, described, and tested for their ability to inhibit cell proliferation. They shown considerable to excellent levels of activity against the various cell lines that were examined. Compounds 8a and 8g, out of all of them, had a strong anti-proliferative potential against the A549 cell line with IC50 values of 7.2 M and 4.7 M, respectively. In addition, Compounds 8a, 8b, and 8g displayed significant cytotoxicity against the HeLa– Human cervical cancer cell line, with IC50 values ranging between 9.1 and 9.9 microM, respectively. Compounds 8a and 8g, which were tested on the DU145 cell line, revealed interestingly high levels of cytotoxicity, with IC50 values ranging between 7.5 and 8.7 microM, respectively. Overall, four compounds (8a, 8b, 8g, and 8h) displayed considerable to moderate antiproliferative activity against a selection of human cancer cell lines with IC50 values of less than 10 M. They might be studied some further for more research into their method of action and several other aspects.

Supplementary Information

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

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