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Structure–Activity Relationship and Pharmacokinetic Studies of 1,5-Diheteroarylpenta-1,4-dien-3-ones: A Class of Promising Curcumin-Based Anticancer Agents

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Abstract

Forty-three 1,5-diheteroaryl-1,4-pentadien-3-ones were designed as potential curcumin mimics, structurally featuring a central five-carbon dienone linker and two identical nitrogen-containing aromatic rings. They were synthesized using a Horner–Wadsworth–Emmons reaction as the critical step and evaluated for their cytotoxicity and antiproliferative activities toward both androgen-insensitive and androgen-sensitive prostate cancer cell lines and an aggressive cervical cancer cell line. Most of the synthesized compounds showed distinctly better in vitro potency than curcumin in the four cancer cell lines. The structure–activity data acquired from the study validated (1*E*,4*E*)-1,5-dihereroaryl-1,4-pentadien-3-ones as an excellent scaffold for in-depth development for clinical treatment of prostate and cervical cancers. 1-Alkyl-1*H*-imidazol-2-yl, ortho pyridyl, 1-alkyl-1*H*-benzo[*d*]imidazole-2-yl, 4-bromo-1-methyl-1*H*-pyrazol-3-yl, thiazol-2-yl, and 2-methyl-4-(trifluoromethyl)thiazol-5-yl were identified as optimal heteroaromatic rings for the promising in vitro potency. (1*E*,4*E*)-1,5-Bis(2-methyl-4-(trifluoromethyl)thiazol-5-yl)penta-1,4-dien-3-one, featuring thiazole rings and trifluoromethyl groups, was established as the optimal lead compound because of its good in vitro potency and attractive in vivo pharmacokinetic profiles.

Graphical abstract

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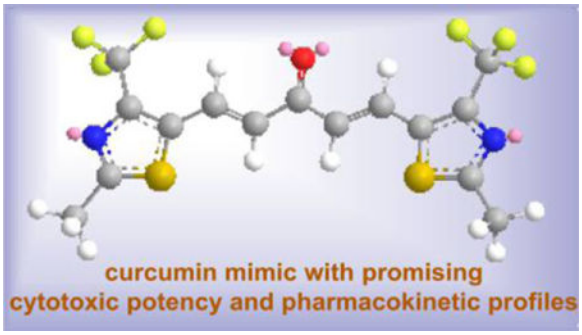
Supporting Information

^{1}H NMR and ^{13}C NMR spetra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.5b00470.

Notes

The authors declare no competing financial interest.



INTRODUCTION

The significant difference in the rate of prostate cancer incidence between Western (120 per 100 000 in Northern America) and East Asian countries (less than 10 per 100 000 in Asia)[1] and the soared risk of prostate cancer in the first generation of Asian men relocating to the United States[2] imply the potential of Asian traditional food in preventing prostate cancer. Turmeric, the rhizomes of *Curcuma longa*, represents a typical Asian diet that has benefited people as a yellow spice used as curry ingredient and as a traditional Indian medicine for centuries. Scientists have identified curcumin (**1**, Figure 1) as the major chemical component responsible for the biological activity of turmeric. Not only having been demonstrated to have capability to prevent prostate cancer,[3] curcumin has also been confirmed in 2000 by both in vitro cell culture systems and in vivo mice models to have potential in treating prostate cancer.[4] Furthermore, its high safety profile in humans has been validated by the U.S. Food and Drug Administration (FDA).[2,5] However, curcumin has difficulty in reaching blood system and its action targets, which has been verified by a phase I human clinical trial.[6] This constitutes the critical problems of curcumin that prevent itself from becoming a clinical chemotherapeutic but has already triggered extensive research in search for curcumin mimics with improved potency and/or better pharmacokinetic profiles for the potential clinical treatment of cancers.[3,7–16] Curcumin analogue 2, differing from curcumin by replacing the seven-carbon β-diketone linker of curcumin with a five-carbon dienone linear linker, showed 5- to 5.5-fold increase in cytotoxic potency relative to curcumin toward PC-3 prostate cancer cell line.[17] Our previous preliminary data showed that 1,5-diheteroarylpenta-1,4-diene-3-ones, represented by compounds **3–5**, is an optimal scaffold for developing curcumin mimics as potential anticancer agents due to their superior in vitro potency (up to 60 times better than curcumin) and potential pharmacokinetic profiles.[16,18] This scaffold of curcumin mimics[16,18] is characteristic of two identical terminal five- or six-membered heteroaromatic rings and a central linear dienone linker. They consistently exhibit enhanced cytotoxic potency than curcumin in androgen-insensitive prostate cancer cell lines (PC-3 and DU-145) but no apparent toxicity against MCF-10A normal mammary epithelial cells. Moreover, they might afford better bioavailability due to the existence of two basic nitrogen-containing heteroaromatic rings. It is therefore very meaningful to launch in-depth investigation of this class of curcumin mimics as potential drug candidates for the treatment of prostate and cervical cancers. Herein, we reported the synthesis and biological evaluation of forty-one new and two known 1,5-diheteroaryl-1,4-pentadien-3-ones, as well as their structure–activity relationship and pharmacokinetic studies.

It is worth noting that dienone moiety was flagged by Baell and Holloway as May Be PAINS (pan assay interference compounds)[19] because the dienone moiety might covalently interact with proteins, which might lead to its nonselective cytotoxicity through interaction with one or more unidentified cellular proteins important for cell viability. However, as suggested by Baell,[20] "with more medicinal chemistry, compound utility can be judged to be firmly in the positive based on clear SAR and optimization to low or mid nanomolar levels of activity." We therefore consider that it is rational to retain compounds containing dienone motif that were apparently clean in our studies based on the following points: (i) our target compounds selectively exhibit cytotoxicity toward cancer cell lines but no apparent cytotoxicity against normal mammary epithelial cells;[18] (ii) the structure–activity relationship studies indicate that our optimal compounds are over 100-fold more potent than compounds **17**, **33**, and **34** in in vitro cytotoxicity toward prostate and cervical cancer cells, and (iii) optimization of our target compounds has resulted in nanomolar level of cytotoxicity.

RESULTS AND DISCUSSION

Encouraged by the potency conferred by the linear dienone linker and the basic aromatic rings,[18] we set out to explore the effect of various heteroaromatic rings on the cytotoxicity of 1,5-diheteroarylpenta-1,4-dien-3-ones against prostate and cervical cancer cell lines. Consequently, forty-three compounds (**6–48**, Table 1 and Scheme 1) containing two identical terminal five-membered, six-membered, or bulky heteroaromatic rings and a central dienone linker have been designed and synthesized as curcumin mimics for cytotoxic and antiproliferative evaluation.

Chemistry

The designed forty-three 1,5-diheteroarylpenta-1,4-dien-3-ones (**6–48**) have been synthesized. All of them are new compounds except for compounds **27** and **29** that were included for systematic structure–activity relationship studies. According to the procedure described in the literature,[21] the potassium carbonate-mediated double aldol condensation of the appropriate aromatic aldehyde with acetone was employed to successfully synthesize eleven 1,5-diheteroarylpenta-1,4-dien-3-ones in our previous study.[18] However, most of target compounds for the current study were hard to obtain through the base-catalyzed aldol condensation. After various explorations, we eventually succeeded in synthesizing compounds **6–48** in good yields through the Hornor–Wadsworth–Emmons reaction of 1,3-bis(diethylphosphonato)acetone with the appropriate aromatic aldehyde[22] (Scheme 1). The key reagent 1,3-bis(diethylphosphonato)acetone (**92**) for the synthesis of 6–48 was readily prepared from carbazic acid methyl ester, 1,3-dichloroacetone, and triethyl phosphite according to the procedure described in the literature.[23] The aromatic carboxaldehydes (**59–77**) were available from commercial sources. 1-Alkyl-1*H*-imidazole-2-carbaldehydes (**49–58**) were synthesized from 1*H*-imidazole-2-carbaldyhyde (**93**) using potassium carbonate as base (Scheme 2) according to the procedure described in the literature.[24] As illustrated in Schemes 3 and 4, benzo[*d*]thiazole-2-carbaldehyde (**78**) and 1-alkyl-1*H*-benzo[*d*]imidazole-2-carbaldehydes (**79–91**) were obtained by oxidation of the corresponding primary alcohols **95** and **98–110** with Dess–Martin reagent.[25–27] (Benzo[*d*]-thiazole-2-yl)methanol (**95**) was synthesized by refluxing 2-aminothiophenol (**94**) with

glycolic acid in hydrochloric acid (4 M) (Scheme 3). 1-Alkyl-1*H*-benzo[*d*]imidazole-2-yl)methanols (**98–110**) were achieved by *N*-alkylation of (1*H*-benzo[*d*]-imidazole-2-yl)methanol (**97**) with the appropriate alkyl halide using potassium carbonate as base and DMF as solvent (Scheme 4). (1*H*-Benzo[*d*]imidazole-2-yl)methanol (**97**) was obtained from benzene-1,2-diamine (**96**) by refluxing with glycolic acid in hydrochloric acid (4 M).

Cytotoxicity toward Prostate and Cervical Cancer Cell Lines

The in vitro cytotoxicity of 1,5-diheteroarylpenta-1,4-dien-3-ones (**6–48**) was determined using trypan blue dye exclusion assay (TB) against a panel of cancer cell lines (PC-3, DU-145, LNCaP, and HeLa). Both PC-3 and DU145 cell lines are androgen-insensitive metastatic prostate cancer cells that cannot express prostate-specific antigen,[28,29] while LNCaP cell line is androgen-sensitive and has capability to express prostate-specific antigen.[30] They are the most common cell-based models for in vitro assessment of potency and efficacy of antiprostate cancer agents. Curcumin and DMSO were used as positive and negative control, respectively.

As shown in Table 2, with few exceptions, exposure of the cancer cells to most of the synthesized 1,5-diheteroarylpenta-1,4-dien-3-ones at 1 and 10 μM concentrations significantly decreases the viability of four cell lines. Among the series of compounds tested, thirty-three (**6–15, 19, 21–26, 28–30**, and **36–48**) out of forty-three compounds displayed markedly improved ability to inhibit the growth of four cancer cell lines at both concentrations, as compared with curcumin. Seven compounds (**16, 18, 20, 27, 31, 32**, and **35**) appeared to be as effective (or slightly more effective) as curcumin. Compounds **17, 33**, and **34** were almost inactive even at 10 μM concentration. The IC_{50} values for fifteen compounds (**10, 12–14, 19, 24, 26, 32, 36**, and **43–48**) in HeLa cells and for seven compounds (**32, 36**, and **43–47**) in PC-3 cells were measured, which exhibit over 11–95 times higher cytotoxic potency than curcumin (Tables 3 and 4).

Antiproliferative Activity toward Prostate and Cervical Cancer Cell Lines

To further determine the in vitro anticancer activity of the synthesized curcumin mimics, those compounds with inhibitory rate greater than 45% at 1 μM toward the four cancer cell lines were selected for further evaluation of their antiproliferative effects using WST-1 cell proliferation assay according to the manufacturer's instruction. To acquire enough data for structure–activity relationship studies, compounds **10, 30**, and **40** were also included on the list even they do not fully meet the criteria. The assay is based on the cleavage of the water-soluble tetrazolium salt WST-1 to formazan catalyzed by the cellular mitochondrial dehydrogenases. The amount of formazan dye yielded directly correlates to the number of live cells in the culture. According to preliminary cytotoxic potency by trypan blue dye exclusion assay, twenty-seven compounds (**6–10, 12–15, 19, 22, 24, 26, 30, 32, 36–41**, and **43–48**) were selected for WST-1 cell proliferation assay using the procedure as described in the Experimental Section in three prostate cancer cell lines and one cervical cancer cell line and their IC_{50} values were determined. Curcumin was used as a positive control for comparison in the parallel experiments, and the results were summarized in Tables 3 and 4. All twenty-seven 1,5-diheteroarylpenta-1,4-dien-3-ones were appraised as promising antiprostate and anticervical cancer agents by comparing their IC_{50} values with that of

curcumin (Table 4). They are 13–121 times, 12–59 times, and 11–95 times, respectively, more potent than curcumin in two androgen-insensitive human prostate cancer cell lines (PC-3 and DU145), the androgen-sensitive human cancer cell line (LNCaP), and the human cervical cancer cell line (HeLa). This validates the promising scaffold containing two identical terminal basic heteroaromatic rings and a central linear dienone linker as novel curcumin mimics with promising cytotoxic and antiproliferative effects against cancer cells.

Structure–Activity Relationships

The below structure–activity relationships of curcumin mimics can be summed up based on the in vitro cell-based experimental data that were derived from efforts focused on the terminal heteroaromatic ring modifications of 1,5-diheteroarylpenta-1,4-dien-3-ones.

i. In prostate and cervical cancer cell models, among fortythree (1*E*,4*E*)-1,5-diheteroarylpenta-1,4-dien-3-ones, only compounds **17, 33**, and **34** did not show increased or similar cytotoxicity against prostate and cervical cancer cell lines, as compared with curcumin (Table 2). This suggests that (1*E*,4*E*)-1,5-diheteroarylpenta-1,4-dien-3-ones represent the optimal scaffold for curcumin mimics with substantially improved cytotoxicity and antiproliferative effect.

ii. 1-Alkyl-1*H*-imidazol-2-yl in compounds **6–15** represent the optimal terminal five-membered heteroaromatic rings for the potency in four cancer cell lines. The pentan-2-yl in compound **12**, as well as the isobutyl in (1*E*,4*E*)-1,5-bis(1-isobutyl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one and the *sec*-butyl in compound **4**,[18] serves as the most favorable alkyl group on the nitrogen atom of 1*H*-imidazol-2-yl for the activity. Other five-membered heteroaromatic rings beneficial to the potency include 4-bromo-1-methyl-1*H*-pyrazol-3-yl in compound **19**, 4-methylthiazol-2-yl in compound **22**, and 2-methyl-4-(trifluoromethyl)thiazol-5-yl in **24**.

iii. Regarding six-membered heteroaromatic rings, it has been reported that ortho pyridyl generally increases the cytotoxic and antiproliferative potency by 7–60 times.[16] The substituent at the meta position is crucial for the potency because compound **26** with an electron donating methyl group at meta position showed better inhibition, while the corresponding analogue **25** with an electron withdrawing bromo group at meta position did not show significantly enhanced activity. No apparent effect can generally be bestowed by meta and para pyridyl (e.g., **27–29**). The enhanced activity of para pyridyl analogue **30** can be attributed to the electron withdrawing group (F) at ortho position. Collectively, the structure–activity relationships acquired for the six-membered analogues revealed that promising activity requires the presence of a nitrogen atom or a substituent at ortho position displaying electron-withdrawing properties.

iv. Among 18 curcumin mimics (**31–48**) with bulky heteroaromatic rings, only those having 1-alkyl-1*H*-benzo[*d*]imidazole-2-yl as heteroaromatic rings (e.g., compounds **36–48**) possessed the enhanced potency. Methyl (in **36**), isopropyl (in **43**), and isobutyl (in **44**) represent the optimal alkyl group on the nitrogen atom for increased potency.

In Vivo Pharmacokinetic Studies

One of the major challenges that this study seeks to address is to improve the pharmaceutical profile of curcumin, known for its poor bioavailability following oral administration.[6,31–33] To this end we have modified the curcumin structure to temper its metabolic instability and water solubility by introducing a shorter dienone linker and replacing the six-membered phenol terminal rings with nitrogen-containing heteroaromatic rings that vary in size and polarity. To evaluate if the curcumin analogues with markedly improved anticancer activities could also possess greater bioavailability, we chose two most promising mimics, **14** and **24**, for pharmacokinetic studies. The two compounds were among the most potent mimics tested in this study, but in particular, compound **24** was selected mainly because it contains thiazole rings and trifluoromethyl groups, two structural moieties generally expected to confer attractive pharmacokinetic profiles. C57 mice were administered with **14, 24**, or curcumin via oral gavage at a single dose of 1 mg/kg, and blood samples were collected at 30 min and 1, 2, 4, and 24 h after the oral administration. Plasma was prepared from the blood samples and was analyzed by HPLC–MS/MS for determination of drug concentrations as described in the Experimental Section. Summarized in Table 5 are the plasma concentrations of **14, 24**, and curcumin at different sampling time points. Compound **14** exhibited slightly improved oral bioavailability showing 2- to 10-fold increase in plasma concentration than curcumin at 30 min, 4 h, and 24 h after treatment. Compound **24**, however, showed significantly increased oral bioavailability with 58-, 21-, 28-, 533-, and 653-fold higher plasma concentration than curcumin at 30 min, 1 h, 4 h, and 24 h after drug administration, respectively. With the peak concentration reaching 61.92 ng/mL, compound **24** affords an AUC value of 892.77 ng mL^{-1} h^{-1} versus 2.43 ng mL^{-1} h^{-1} for curcumin, clearly demonstrating its markedly improved therapeutic potential. Our pharmacokinetic results of curcumin are consistent with previous reports where plasma curcumin levels remain at low (ng/mL) levels in patients, which is insufficient to yield the anticancer benefits of curcumin.[34] Even at a dose 12 000 mg/day, the peak plasma concentration of curcumin was only 57 ng/mL,[35] a level that is considered to be therapeutically effective. Thus, the dose of 1 mg/mL of compound **24** used in mice, when extrapolated to humans, would correspond to a daily dose of 70 mg for a person of 155 lb that will afford a peak plasma concentration of 62 ng/kg, exceeding the level achieved by the high dose of 12 000 mg/day. Considering that compound **24** is 11–36 times more potent than curcumin in the tested cancer cell lines, it is therefore reasonable to conclude that the excellent bioavailability of 24, as shown in its high peak concentration and AUC value, will provide the therapeutic efficacy necessary to be cytotoxic to cancer cells.

CONCLUSION

In a continuing study of curcumin mimics as potential drug candidates to treat prostate cancer, we designed and synthesized forty-one new and two known (1*E*,4*E*)-1,5-diheteroarylpenta-1,4-dien-3-ones. These curcumin mimics were tested for cytotoxicity against androgen-sensitive LNCaP and androgen-insensitive PC-3 and DU-145 human prostate cancer cell lines, as well as HeLa human cervical cancer cells. Thirty-two compounds possessed significantly improved cytotoxicity in the four cancer cell lines. Twenty-six compounds were selected for the evaluation of their antiproliferative activities in

these cancer cell lines. Compared to curcumin, the twenty-six analogues are 12- to 121-fold more potent in inhibiting cancer cell proliferation. The acquired structure–activity relationship data indicated (i) that (1*E*,4*E*)-1,5-diheteroarylpenta-1,4-dien-3-ones represent the optimal scaffold for curcumin mimics with substantially improved cytotoxicity and antiproliferative effect in prostate and cervical cancer cell models and (ii) 1-alkyl-1*H*-imidazol-2-yl, ortho pyridyl, 1-alkyl-1*H*-benzo[*d*]imidazole-2-yl, 4-bromo-1-methyl-1*H*-pyrazol-3-yl, thiazol-2-yl, and 2-methyl-4-(trifluoromethyl)-thiazol-5-yl serve as optimal heteroaromatic rings for increased in vitro potency. Pharmacokinetic studies in mice identified compound **24** as a promising lead compound that is currently under further evaluation as a potential clinical trial candidate for the treatment of prostate and cervical cancers. This study established robust structure–activity relationships (SARs) of (1*E*,4*E*)-1,5-diheteroarylpenta-1,4-dien-3-ones, which will guide future designs of new curcumin mimics with the hope to further improve the therapeutic index for the treatment of cancer.

EXPERIMENTAL SECTION

General Procedures

HRMS results were obtained on an Orbitrap mass spectrometer with electrospray ionization (ESI). NMR spectra were obtained on a Bruker Fourier 300 spectrometer or an Agilent-Varian 400 spectrometer in $CDCl_3$ or DMSO-d_6. The chemical shifts are given in ppm referenced to the respective solvent peak, and coupling constants are reported in Hz. Anhydrous THF and dichloromethane were purified by PureSolv MD 7 solvent purification system from Innovative Technologies (MB-SPS-800). All other reagents and solvents were purchased from commercial sources and were used without further purification. Silica gel column chromatography was performed using silica gel (32–63 μm). Preparative thin-layer chromatography (PTLC) separations were carried out on 1000 μm AnalTech thin layer chromatography plates (lot no. 13401). Curcumin was synthesized by Claisen–Schmidt condensation of aromatic aldehyde with acetylacetone according to the procedure described in the literature.[36] 1,3-Bis(diethylphosphonato)acetone was synthesized using the procedure illustrated in the literature.[23] The purities of biologically tested compounds are ≥95% as determined by HPLC. Specifically, the major peak accounted for ≥95% of the combined total peak area when monitored by a diode array detector (DAD) at 325 ± 100 nm. The HPLC analyses were performed on an Agilent Hewlett-Packard 1100 series HPLC DAD system using a 5 μm C_{18} reversed phase column (4.6 mm × 250 mm) and a diode array detector.

General Procedure for the Synthesis of 1-Alkyl-1*H*-imidazole-2-carbaldehyde.[24]

To a solution of 1*H*-imidazole-2-carbaldehyde (13 mmol) and potassium carbonate (16 mmol) in DMF (13 mL) was added alkyl bromide (16 mmol), and the reaction mixture was stirred at 50 °C for 6 h. The inorganic solids were removed by filtration, and the filtrate was diluted with water and extracted with diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulfate, and the volatile components were evaporated under vacuum to give the respective product.

1-Ethyl-1*H*-imidazole-2-carbaldehyde (49)

Yellow oil, 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.67 (s, 1H), 7.15 (s, 1H), 7.09 (s, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8, 143.0, 131.5, 125.6, 42.8, 16.2.

1-Propyl-1*H*-imidazole-2-carbaldehyde (50)

Yellow oil, 64% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.77 (s, 1H), 7.24 (s, 1H), 7.13 (s, 1H), 4.33 (t, J = 7.2 Hz, 2H), 1.86−1.69 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.1, 143.4, 131.6, 126.4, 49.4, 24.4, 10.9.

1-Butyl-1*H*-imidazole-2-carbaldehyde (51)

Yellow oil, 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (s, 1H), 7.18 (s, 1H), 7.09 (s, 1H), 4.30 (t, J = 7.3 Hz, 2H), 1.73−1.59 (m, 2H), 1.31−1.16 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.9, 143.2, 131.4, 126.3, 47.5, 33.0, 19.5, 13.5.

1-Pentyl-1*H*-imidazole-2-carbaldehyde (52)

Yellow oil, 73% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.74 (s, 1H), 7.21 (s, 1H), 7.11 (s, 1H), 4.32 (t, J = 7.3 Hz, 2H), 1.79−1.64 (m, 2H), 1.35−1.17 (m, 4H), 0.82 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.0, 143.3, 131.5, 126.3, 47.8, 30.7, 28.5, 22.2, 13.9.

1-Hexyl-1*H*-imidazole-2-carbaldehyde (53)

Yellow oil, 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.77 (s, 1H), 7.24 (s, 1H), 7.13 (s, 1H), 4.35 (t, J = 7.3 Hz, 2H), 1.76−1.69 (m, 2H), 1.31−1.23 (m, 6H), 0.84 (t, J = 5.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.1, 143.4, 131.6, 126.3, 47.9, 31.3, 31.1, 26.1, 22.5, 14.0.

1-Heptyl-1*H*-imidazole-2-carbaldehyde (54)

Yellow oil, 73% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.26 (s, 1H), 7.13 (s, 1H), 4.36 (t, J = 7.2 Hz, 2H), 1.82−1.65 (m, 2H), 1.30−1.15 (m, 8H), 0.84 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.0, 143.3, 131.4, 126.3, 48.0, 31.7, 31.1, 28.9, 26.5, 22.6, 14.1.

1-(Pentan-2-yl)-1*H*-imidazole-2-carbaldehyde (55)

Yellow oil, 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.29 (s, 1H), 7.28 (s, 1H), 5.48−5.36 (m, 1H), 1.80−1.62 (m, 2H), 1.43 (d, J = 6.7 Hz, 3H), 1.27−1.07 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.5, 143.3, 132.2, 122.3, 52.6, 39.9, 22.0, 19.2, 13.8.

1-(Pentan-3-yl)-1*H*-imidazole-2-carbaldehyde (56)

Yellow oil, 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.76 (s, 1H), 7.27 (s, 1H), 7.20 (s, 1H), 5.24−5.04 (m, 1H), 1.88−1.54 (m, 4H), 0.71 (t, J = 7.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.5, 144.3, 132.3, 122.3, 59.8, 28.9, 10.2.

1-(Isopentyl)-1*H*-imidazole-2-carbaldehyde (57)

Yellow oil, 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (s, 1H), 7.20 (s, 1H), 7.11 (s, 1H), 4.33 (t, J = 7.4 Hz, 2H), 1.63−1.49 (m, 3H), 0.88 (d, J = 6.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.9, 143.3, 131.5, 126.1, 46.2, 39.9, 25.6, 22.3.

1-(3-Methylbut-2-en-1-yl)-1*H*-imidazole-2-carbaldehyde (58)

Yellow oil, 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.81 (d, J = 1.0 Hz, 1H), 7.26 (s, 1H), 7.16 (s, 1H), 5.37−5.32 (m, 1H), 5.00 (d, J = 7.2 Hz, 2H), 1.773 (s, 3H), 1.770 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.2, 143.2, 138.8, 131.6, 125.5, 118.4, 45.3, 25.7, 18.1.

Synthesis of Benzo[*d*]thiazol-2-ylmethanol (95).[27]

To a mixture of 2-aminobenzenethiol (0.25 g, 2 mmol) and glycolic acid (0.46 g, 6 mmol) was added HCl (4 N, 6 mL). The reaction was allowed to proceed with refluxing at 100 °C for 6 h prior to being quenched with saturated aqueous sodium bicarbonate. The solution was extracted with ethyl acetate (20 mL × 3). The combined extracts was evaporated in vacuo to give the crude product, which was subjected to the PTLC purification using DCM/MeOH (100/2, v/v) as eluent to yield the title compound benzo[*d*]thiazol-2-ylmethanol in 15% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 5.08 (s, 2H), 4.73 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 152.7, 134.6, 126.3, 125.2, 122.6, 121.9, 62.3.

Synthesis of Benzo[*d*]thiazole-2-carbaldehyde (78)

To a solution of benzo[*d*]thiazol-2-ylmethanol (47 mg, 0.28 mmol) in methylene chloride (3 mL) was added DMP (132 mg, 0.31 mmol), and the reaction was allowed to proceed with stirring at cold room (4 °C) for 1 h prior to being quenched with saturated aqueous sodium thiosulfate solution (1 mL). The subsequent mixture was extracted with methylene chloride (5 mL × 3). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated. The crude product obtained was purified by PTLC, eluting with DCM/MeOH (100/1, v/v) to yield the title product benzo[*d*]thiazole-2-carbaldehyde in 56% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.28 (d, J = 8.0 Hz, 2H), 8.02 (d, J = 8.0 Hz, 2H), 7.68−7.53 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.6, 165.5, 153.7, 136.5, 128.6, 127.5, 125.9, 122.8.

Synthesis of (1*H*-Benzo[*d*]imidazole-2-yl)methanol (97).[25]

To a mixture of benzene-1,2-diamine (1.08 g, 10 mmol) and glycolic acid (2.28 g, 30 mmol) was added HCl (4 N, 30 mL). The reaction was allowed to proceed with refluxing at 100 °C for 6 h prior to being quenched with saturated aqueous sodium bicarbonate. The white solid were collected by filtration in 58% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.35 (br s, 1H), 7.50 (dd, J = 5.6, 3.2 Hz, 2H), 7.13 (dd, J = 5.6, 3.2 Hz, 2H), 5.78 (br s, 1H), 4.71 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.2, 138.7, 121.4, 114.9, 57.8.

General Procedure for the Synthesis of (1-Alkyl-1*H*-benzo-[*d*]imidazole-2-yl)methanol

To a solution of (1*H*-benzo[*d*]-imidazole-2-yl)methanol (148 mg, 1 mmol) in DMF (2 mL) were added the appropriate alkyl bromide (2 mmol) and potassium carbonate (690 mg, 5

mmol), and the reaction mixture was stirred at room temperature for 24 h prior to being diluted with methylene chloride (8 mL) and sodium chloride (8 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (8 mL × 2). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo to provide a crude product, which was subjected to PTLC purification using DCM/MeOH (100/5, v/v) as eluent to yield the title compound.

(1-Methyl-1*H*-benzo[*d*]imidazole-2-yl)methanol (98)

Yellow oil, 52% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.64 (m, 1H), 7.34−7.26 (m, 3H), 4.92 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 141.2, 135.8, 123.1, 122.5, 119.1, 109.5, 56.8, 30.0.

(1-Ethyl-1*H*-benzo[*d*]imidazol-2-yl)methanol (99)

Yellow oil, 33% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 6.3 Hz, 1H), 7.41−7.15 (m, 3H), 4.89 (s, 2H), 4.31 (q, J = 7.1 Hz, 2H), 1.47 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 141.6, 134.8, 123.0, 122.3, 119.4, 109.7, 56.7, 38.9, 15.3.

(1-Propyl-1*H*-benzo[*d*]imidazol-2-yl)methanol (100)

Yellow oil, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, J = 6.2, 4.0 Hz, 1H), 7.18−6.99 (m, 3H), 6.74 (br s, 1H), 4.73 (s, 2H), 4.00 (t, J = 7.3 Hz, 2H), 1.73−1.64 (m, 2H), 0.78 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 141.3, 134.9, 122.6, 122.0, 119.0, 109.8, 56.3, 45.3, 23.1, 11.3.

(1-Butyl-1*H*-benzo[*d*]imidazol-2-yl)methanol (101)

Yellow oil, 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.46 (m, 1H), 7.15 (br s, 1H), 7.09−6.98 (m, 3H), 4.70 (s, 2H), 3.96 (t, J = 7.5 Hz, 2H), 1.61−1.53 (m, 2H), 1.18−1.12 (m, 2H), 0.78 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 141.2, 134.7, 122.5, 121.8, 118.8, 109.6, 56.2, 43.5, 31.7, 19.9, 13.5.

(1-Pentyl-1*H*-benzo[*d*]imidazol-2-yl)methanol (102)

Yellow oil, 62% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, J = 5.8, 2.6 Hz, 1H), 7.41−7.18 (m, 3H), 6.14 (br s, 1H), 4.94 (s, 2H), 4.25 (t, J = 7.5 Hz, 2H), 1.98−1.76 (m, 2H), 1.53−1.29 (m, 4H), 0.95 (t, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 141.4, 134.9, 122.7, 122.1, 119.1, 109.8, 56.4, 43.9, 29.6, 29.0, 22.3, 13.9.

(1-*n*-Hexyl-1*H*-benzo[*d*]imidazole-2-yl)methanol (103)

Yellow oil, 91% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.62 (m, 1H), 7.30−7.18 (m, 3H), 4.88 (s, 2H), 4.19 (t, J = 7.5 Hz, 2H), 1.83−1.76 (m, 2H), 1.47−1.15 (m, 6H), 0.89 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 141.4, 135.0, 122.7, 122.1, 119.1, 109.8, 56.4, 44.0, 31.4, 29.9, 26.6, 22.5, 14.0.

(1-Heptyl-1*H*-benzo[*d*]imidazol-2-yl)methanol (104)

Yellow oil, 58% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, J = 5.9, 2.5 Hz, 1H), 7.31−7.15 (m, 3H), 4.87 (s, 2H), 4.16 (t, J = 7.5 Hz, 2H), 1.89−1.70 (m, 2H), 1.39−1.19 (m,

8H), 0.88 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 141.3, 134.9, 122.6, 122.0, 119.0, 109.7, 56.4, 43.9, 31.6, 29.8, 28.8, 26.8, 22.5, 14.0.

(1-Isopropyl-1*H*-benzo[*d*]imidazole-2-yl)methanol (105)

Yellow oil, 29% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.59 (m, 1H), 7.57−7.40 (m, 1H), 7.20−7.17 (m, 2H), 5.02−4.93 (m, 1H), 4.87 (s, 2H), 1.62 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 142.0, 133.4, 122.4, 121.8, 119.5, 112.0, 56.9, 48.3, 21.4.

(1-Isobutyl-1*H*-benzo[*d*]imidazole-2-yl)methanol (106)

Yellow oil, 56% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.63 (m, 1H), 7.26−7.16 (m, 3H), 4.88 (s, 2H), 4.00 (d, J = 7.7 Hz, 2H), 2.30−2.21 (m, 1H), 0.92 (d, J = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 141.4, 135.3, 122.7, 122.1, 119.1, 110.2, 56.5, 51.2, 29.2, 20.2.

(1-sec-Butyl-1*H*-benzo[*d*]imidazole-2-yl)methanol (107)

Yellow oil, 36% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.65 (m, 1H), 7.55−7.46 (m, 1H), 7.25−7.21 (m, 2H), 4.91 (s, 2H), 4.62−4.48 (m, 1H), 2.22−2.12 (m, 1H), 2.03−1.88 (m, 1H), 1.64 (d, J = 6.9 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 141.9, 133.3, 122.4, 121.9, 119.5, 112.0, 56.9, 54.3, 28.1, 19.7, 11.2.

(1-(Pentan-2-yl)-1*H*-benzo[*d*]imidazole-2-yl)methanol (108)

Yellow oil, 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.58 (m, 1H), 7.53−7.39 (m, 1H), 7.18−7.15 (m, 2H), 4.90 (s, 2H), 4.83−4.67 (m, 1H), 2.12−2.07 (m, 1H), 1.88−1.77 (m, 1H), 1.58 (d, J = 6.8 Hz, 3H), 1.07−0.95 (m, 1H), 1.13−0.91 (m, 1H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 141.9, 133.3, 122.3, 121.7, 119.4, 111.9, 56.8, 52.6, 37.1, 19.9, 19.8, 13.7.

(1-(Pentan-3-yl)-1*H*-benzo[*d*]imidazole-2-yl)methanol (109)

Yellow oil, 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.67 (m, 1H), 7.47−7.43 (m, 1H), 7.24−7.17 (m, 2H), 4.89 (s, 2H), 4.29−4.21 (m, 1H), 2.20−2.08 (m, 2H), 2.00−1.90 (m, 2H), 0.78 (t, J = 7.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 141.9, 133.2, 122.3, 121.8, 119.5, 112.0, 60.5, 57.0, 26.7, 11.0.

(1-Isopentyl-1*H*-benzo[*d*]imidazole-2-yl)methanol (110)

Yellow oil, 67% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.59 (m, 1H), 7.22−7.06 (m, 3H), 4.82 (s, 2H), 4.06 (t, J = 7.2 Hz, 2H), 1.68−1.50 (m, 3H), 0.91 (d, J = 5.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 141.2, 134.6, 122.4, 121.7, 118.8, 109.4, 56.1, 42.0, 38.3, 25.7, 22.1.

General Procedure for the Synthesis of 1-Alkyl-1*H*-benzo-[*d*]imidazole-2-carbaldehyde

To a solution of (1-alkyl-1*H*-benzo-[*d*]imidazole-2-yl)methanol (1 mmol) in methylene chloride (10 mL) was added DMP (466 mg, 1.1 mmol), and the reaction was allowed to proceed with stirring at cold room (4 °C) for 1 h prior to being quenched with saturated aqueous sodium thiosulfate solution (3 mL). The subsequent mixture was extracted with

methylene chloride (10 mL × 3). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated. The crude product obtained was purified by PTLC eluting with DCM/MeOH (100/5, v/v) to yield the title product.

1-Methyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde (79)

Yellow oil, 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.11 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.56−7.32 (m, 3H), 4.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 146.3, 142.9, 137.1, 127.0, 124.2, 122.5, 110.6, 31.5.

1-Ethyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde (80)

Yellow oil, 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.48−7.31 (m, 3H), 4.60 (q, J = 6.8 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9, 145.7, 142.9, 136.0, 126.8, 124.1, 122.4, 110.7, 39.8, 15.5.

1-Propyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde (81)

Yellow oil, 46% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.45−7.29 (m, 3H), 4.51 (t, J = 7.3 Hz, 2H), 1.90−1.73 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 146.0, 142.8, 136.5, 126.7, 124.0, 122.4, 111.0, 46.2, 23.6, 11.2.

1-Butyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde (82)

Yellow oil, 47% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.40−7.21 (m, 3H), 4.47 (t, J = 7.3 Hz, 2H), 1.72−1.65 (m, 2H), 1.31−1.23 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 145.8, 142.6, 136.2, 126.5, 123.8, 122.2, 110.8, 44.4, 32.3, 19.8, 13.6.

1-Pentyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde (83)

Yellow oil, 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.44−7.24 (m, 3H), 4.58−4.38 (m, 2H), 1.74 (quin, J = 7.4 Hz, 2H), 1.28−1.25 (m, 4H), 0.81 (t, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9, 145.7, 142.9, 136.0, 126.8, 124.1, 122.4, 110.7, 39.8, 15.5.

1-*n*-Hexyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde (84)

Yellow oil, 42% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.87 (dt, J = 8.2, 0.8 Hz, 1H), 7.44−7.37 (m, 2H), 7.35−7.29 (m, 1H), 4.52 (t, J = 5.6 Hz, 2H), 1.81−1.72 (m, 2H), 1.30−1.22 (m, 6H), 0.82 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 145.8, 142.6, 136.2, 126.5, 123.8, 122.2, 110.8, 44.6, 31.2, 30.1, 26.2, 22.3, 13.8.

1-Heptyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde (85)

Yellow oil, 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.43−7.26 (m, 3H), 4.52 (t, J = 7.4 Hz, 2H), 1.79−1.73 (m, 2H), 1.27−1.21 (m, 8H), 0.81 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 146.0, 142.8, 136.4, 126.7, 123.9, 122.4, 111.0, 44.8, 31.6, 30.4, 28.9, 26.7, 22.5, 14.0.

1-Isopropyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde (86)

Yellow oil, 91% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.46−7.31 (m, 2H), 5.90−5.81 (m, 1H), 1.65 (d, J = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 145.9, 143.6, 135.3, 126.4, 123.8, 122.8, 113.6, 48.4, 21.6.

1-Isobutyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde (87)

Yellow oil, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.82 (dt, J = 8.1, 1.0 Hz, 1H), 7.49−7.13 (m, 3H), 4.28 (d, J = 7.5 Hz, 2H), 2.19−2.04 (m, 1H), 0.82 (d, J = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 146.2, 142.7, 136.7, 126.7, 123.9, 122.3, 111.4, 51.7, 29.8, 20.0.

1-sec-Butyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde (88)

Yellow oil, 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 7.94−7.91 (m, 1H), 7.65−7.60 (m, 1H), 7.43−7.33 (m, 2H), 5.68−5.57 (m, 1H), 2.21−2.10 (m, 1H), 2.00−1.90 (m, 1H), 1.65 (d, J = 7.0 Hz, 3H), 0.75 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.3, 146.6, 143.7, 135.4, 126.4, 123.9, 122.8, 113.7, 54.3, 28.5, 20.0, 11.1.

1-(Pentan-2-yl)-1*H*-benzo[*d*]imidazole-2-carbaldehyde (89)

Yellow oil, 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.91 (dd, J = 6.9, 1.7 Hz, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.44−7.30 (m, 2H), 6.01−5.38 (m, 1H), 2.21−2.02 (m, 1H), 1.94−1.72 (m, 1H), 1.61 (d, J = 7.0 Hz, 3H), 1.30−1.10 (m, 1H), 1.05−0.93 (m, 1H), 0.81 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.3, 146.4, 143.7, 135.4, 126.4, 124.0, 122.8, 113.7, 52.5, 37.4, 20.2, 19.8, 13.7.

1-(Pentan-3-yl)-1*H*-benzo[*d*]imidazole-2-carbaldehyde (90)

Yellow oil, 57% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 7.95−7.89 (m, 1H), 7.58 (d, J = 7.0 Hz, 1H), 7.40−7.32 (m, 2H), 5.79−5.25 (m, 1H), 2.14 (m, 2H), 2.06−1.84 (m, 2H), 0.72 (t, J = 7.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.4, 147.3, 143.8, 135.2, 126.4, 123.9, 122.8, 113.9, 60.5, 27.0, 11.0.

1-Isopentyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde (91)

Yellow oil, 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.30−7.28 (overlapped, 2H), 7.26−7.18 (m, 1H), 4.40 (t, J = 7.4 Hz, 2H), 1.56−1.50 (m, 3H), 0.87 (d, J = 6.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.4, 145.6, 142.6, 136.0, 126.4, 123.7, 122.1, 110.6, 43.0, 38.8, 25.8, 22.2.

General Procedure for the Synthesis (1*E*,4*E*)-1,5-Diarylpenta-1,4-dien-3-one.[22]

A 25 mL flask was charged with 1,3-bis(diethylphosphonato)acetone (0.50 g, 1.51 mmol) and the appropriate heteroaromatic carboxaldehyde (3.02 mmol). A solution of potassium carbonate (2.80 g, 20.3 mmol) in water (2.5 mL) and ethanol (1.5 mL) were added, and the biphasic mixture was stirred rapidly at room temperature for 1 h to overnight. The reaction mixture was extracted with ethyl acetate (10 mL × 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated. The residue was purified over

preparative thin layer chromatography, eluting with dichloromethane/methanol (100:5, v/v), hexanes/ethyl acetate (50:50, v/v), and/or ethyl acetate/methanol (9:1, v/v) to give the respective product.

(1*E*,4*E*)-1,5-Bis(1-ethyl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (6)

This compound was prepared in 91% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 15.2 Hz, 2H), 7.43 (d, J = 15.2 Hz, 2H), 7.17 (s, 2H), 7.04 (s, 2H), 4.10 (q, J = 7.3 Hz, 4H), 1.42 (t, J = 7.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.2, 142.8, 130.9, 127.3, 126.8, 122.2, 41.2, 16.8. IR (KBr): 3104, 2978, 1648, 1616, 1588, 1477, 1441 cm^{-1}. HRMS (ESI), m/z calculated for $C_{15}H_{19}N_4O$ $[M + H]^+$: 271.1559. Found: 271.1558. HPLC purity 97.2% (20 min run of 45−80% CH_3CN in H_2O with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-propyl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (7)

This compound was prepared in 83% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 15.3 Hz, 2H), 7.52 (d, J = 15.3 Hz, 2H), 7.20 (s, 2H), 7.04 (d, J = 0.8 Hz, 2H), 4.05 (t, J = 7.2 Hz, 4H), 1.88−1.74 (m, 4H), 0.93 (t, J = 7.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.2, 143.1, 130.3, 127.8, 126.7, 123.0, 48.1, 24.9, 11.2. IR (KBr): 3105, 2964, 2933, 2875, 1647, 1616, 1589, 1508, 1474, 1443, 1281, 1092 cm^{-1}. HRMS (ESI), m/z calculated for $C_{17}H_{22}N_4O$ $[M + H]^+$: 299.1872. Found: 299.1871. HPLC purity 96.8% (20 min run of 20−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-butyl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (8)

This compound was prepared in 95% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, J = 15.2 Hz, 2H), 7.47 (d, J = 15.2 Hz, 2H), 7.18 (s, 2H), 7.02 (s, 2H), 4.06 (t, J = 7.2 Hz, 4H), 1.81−1.67 (m, 4H), 1.39, 1.26 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.2, 143.0, 130.6, 127.4, 126.8, 122.9, 46.1, 33.5, 19.8, 13.6. IR (KBr): 3104, 2955, 2929, 2859, 1648, 1616, 1589, 1474, 1444, 1091 cm^{-1}. HRMS (ESI), m/z calculated for $C_{19}H_{27}N_4O$ $[M + H]^+$: 327.2185. Found: 327.2183. HPLC purity 96.4% (20 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-pentyl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (9)

This compound was prepared in 80% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 15.3 Hz, 2H), 7.43 (d, J = 15.3 Hz, 2H), 7.14 (s, 2H), 7.00 (s, 2H), 4.02 (t, J = 7.2 Hz, 4H), 1.79−1.65 (m, 4H), 1.33−1.17 (m, 8H), 0.83 (t, J = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.2, 142.9, 130.5, 127.3, 126.7, 122.9, 46.3, 31.1, 28.6, 22.2, 13.9. IR (KBr): 2929, 2859, 1649, 1616, 1588, 1474, 1444, 1134, 1090 cm^{-1}. HRMS (ESI), m/z calculated for $C_{21}H_{30}N_4O$ $[M + H]^+$: 355.2498. Found: 355.2497. HPLC purity 96.4% (25 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-hexyl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (10)

This compound was prepared in 74% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, J = 15.2 Hz, 2H), 7.47 (d, J = 15.2 Hz, 2H), 7.19 (s, 2H), 7.03 (s, 2H), 4.06 (t, J = 7.3 Hz, 4H), 1.34−1.24 (m, 12H), 0.86 (t, J = 6.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.2, 143.1, 130.7, 127.3, 126.9, 122.9, 46.4, 31.5, 31.3, 26.3, 22.5, 14.0. IR (KBr): 3105,

2954, 2927, 2857, 1649, 1617, 1445, 1274, 1096 cm^{-1}. HRMS (ESI), *m*/*z* calculated for $C_{23}H_{35}N_4O$ $[M + H]^+$: 383.2811. Found: 383.2821. HPLC purity 95.3% (25 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-heptyl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (11)

This compound was prepared in 91% yield as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, J = 15.2 Hz, 2H), 7.41 (d, J = 15.2 Hz, 2H), 7.13 (s, 2H), 6.98 (s, 2H), 4.00 (t, J = 7.2 Hz, 4H), 1.78−1.59 (m, 4H), 1.27−1.12 (m, 16H), 0.79 (t, J = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.0, 142.9, 130.5, 127.3, 126.7, 122.8, 46.3, 31.5, 31.4, 28.7, 26.5, 22.5, 14.0. IR (KBr): 3104, 2953, 2925, 2855, 1650, 1617, 1590, 1507, 1474, 1445, 1274, 1093 cm^{-1}. HRMS (ESI), *m*/*z* calculated for $C_{25}H_{39}N_4O$ $[M + H]^+$: 411.3124. Found: 411.3126. HPLC purity 96.9% (25 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-(pentan-2-yl)-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (12)

This compound was prepared in 90% yield as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 15.2 Hz, 2H), 7.49 (d, J = 15.2 Hz, 2H), 7.22 (s, 2H), 7.08 (s, 2H), 4.53−4.42 (m, 2H), 1.72 (q, J = 7.6 Hz, 4H), 1.44 (d, J = 6.7 Hz, 6H), 1.27−1.08 (m, 4H), 0.86 (t, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.3, 143.0, 131.1, 127.6, 126.9, 118.9, 51.9, 40.0, 22.4, 19.4, 13.8. IR (KBr): 3104, 2958, 2931, 2872, 1647, 1641, 1588, 1454, 1422, 1270, 1173, 1091 cm^{-1}. HRMS (ESI), *m*/*z* calculated for $C_{21}H_{31}N_4O$ $[M + H]^+$: 355.2498. Found: 355.2507. HPLC purity 97.5% (25 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-(pentan-3-yl)-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (13)

This compound was prepared in 99% yield as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 15.2 Hz, 2H), 7.50 (d, J = 15.2 Hz, 2H), 7.24 (s, 2H), 7.03 (s, 2H), 4.18−4.08 (m, 2H), 1.91−1.78 (m, 4H), 1.76−1.63 (m, 4H), 0.77 (t, J = 6.6 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.4, 144.1, 131.3, 127.6, 127.0, 118.9, 59.7, 29.2, 10.6. IR (KBr): 3104, 2966, 2934, 2877, 1648, 1615, 1591, 1456, 1293, 1174, 1092 cm^{-1}. HRMS (ESI), *m*/*z* calculated for $C_{21}H_{31}N_4O$ $[M + H]^+$: 355.2498. Found: 355.2505. HPLC purity 97.2% (15 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-isopentyl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (14)

This compound was prepared in 99% yield as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 15.2 Hz, 2H), 7.42 (d, J = 15.2 Hz, 2H), 7.17 (s, 2H), 7.02 (s, 2H), 4.05 (t, J = 7.1 Hz, 4H), 1.68−1.54 (m, 6H), 0.93 (d, J = 6.2 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.1, 143.0, 130.8, 127.4, 126.9, 122.8, 44.7, 40.4, 25.7, 22.3. IR (KBr): 3105, 2955, 2929, 2869, 1649, 1617, 1448, 1276, 1173, 1096 cm^{-1}. HRMS (ESI), *m*/*z* calculated for $C_{21}H_{31}N_4O$ $[M + H]^+$: 355.2498. Found: 355.2503. HPLC purity 96.3% (20 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-(3-methylbut-2-en-1-yl)-1*H*-imidazol-2-yl)-penta-1,4-dien-3-one (15)

This compound was prepared in 60% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 15.3 Hz, 2H), 7.45 (d, J = 15.3 Hz, 2H), 7.18 (s, 2H), 7.03 (s, 2H), 5.29 (t, J = 7.0 Hz, 2H), 4.65 (d, J = 7.0 Hz, 4H), 1.80 (s, 6H), 1.78 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.3, 143.1, 138.5, 130.6, 127.5, 127.1, 122.6, 118.7, 44.3, 25.8, 18.2. IR (KBr): 3107, 2971, 2915, 1649, 1615, 1643, 1377, 1273, 1108 cm^{-1}. HRMS (ESI), m/z calculated for $C_{21}H_{27}N_4O$ $[M + H]^+$: 351.2185. Found: 351.2184. HPLC purity 95.0% (20 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-methyl-1*H*-imidazol-5-yl)penta-1,4-dien-3-one (16)

This compound was prepared in 62% yield as a yellow solid; mp 186−188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, J = 15.6 Hz, 2H), 7.57 (s, 2H), 7.55 (s, 2H), 6.84 (d, J = 15.6 Hz, 2H), 3.75 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.3, 141.4, 144.1, 132.9, 129.5, 123.8, 32.4. IR (KBr): 3109, 1644, 1612, 1578, 1492, 1389, 1278, 1227, 1196, 1123 cm^{-1}. HRMS (ESI), m/z calculated for $C_{13}H_{15}N_4O$ $[M + H]^+$: 243.1246. Found: 243.1247. HPLC purity 100.0% (15 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-methyl-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (17)

This compound was prepared in 60% yield as a yellow solid; mp 150−152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (s, 2H), 7.59 (s, 2H), 7.58 (d, J = 15.9 Hz, 2H), 6.75 (d, J = 15.9 Hz, 2H), 3.92 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.8, 139.0, 133.5, 130.9, 123.7, 119.2, 39.3. IR (KBr): 3106, 2940, 1647, 1615, 1547, 1484, 1447, 1412, 1396, 1263, 1158, 1098 cm^{-1}. HRMS (ESI), m/z calculated for $C_{13}H_{15}N_4O$ $[M + H]^+$: 243.1246. Found: 243.1249. HPLC purity 96.1% (20 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(5-chloro-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (18)

This compound was prepared in 82% yield as a yellow solid; mp 156−158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 16.2 Hz, 2H), 7.11 (d, J = 16.2 Hz, 2H), 3.95 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.4, 140.3 (q, J_{CF} = 37.5 Hz), 130.1, 129.1, 127.1, 120.8 (q, J_{CF} = 268.5 Hz), 112.8, 37.4. IR (KBr): 2964, 1674, 1620, 1589, 1525, 1484, 1411, 1337, 1302, 1110 cm^{-1}. HRMS (ESI), m/z calculated for $C_{15}H_{10}Cl_2F_6N_4O$ $[M + H]^+$: 447.0214. Found: 447.0218. HPLC purity 99.5% (30 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(4-bromo-1-methyl-1*H*-pyrazol-3-yl)penta-1,4-dien-3-one (19)

This compound was prepared in 88% yield as a yellow solid; mp 150−152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 16.1 Hz, 2H), 7.43 (s, 2H), 7.40 (d, J = 16.1 Hz, 2H), 3.93 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.1, 145.5, 132.02, 131.97, 126.7, 96.2, 40.1. IR (KBr): 3127, 2943, 1667, 1624, 1586, 1460, 1425, 1398, 1347, 1254, 1143, 1101 cm^{-1}. HRMS (ESI), m/z calculated for $C_{13}H_{13}Br_2N_4O$ $[M + H]^+$: 398.9456. Found: 398.9463. HPLC purity 99.8% (20 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(oxazol-4-yl)penta-1,4-dien-3-one (20)

This compound was prepared in 74% yield as a yellow solid; mp 128−130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (s, 2H), 7.87 (s, 2H), 7.58 (d, J = 15.5 Hz, 2H), 7.26 (d, J = 15.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.6, 151.8, 140.1, 137.4, 130.7, 127.4. IR (KBr): 3123, 1677, 1636, 1594, 1553, 1523, 1335, 1315, 1207, 1082 cm^{-1}. HRMS (ESI), m/z calculated for $C_{11}H_9N_2O_3$ $[M + H]^+$: 217.0613. Found: 217.0612. HPLC purity 96.4% (15 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(3,5-dimethylisoxazol-4-yl)penta-1,4-dien-3-one (21)

This compound was prepared in 97% yield as a yellow solid; mp 108−110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 16.1 Hz, 2H), 6.69 (d, J = 16.1 Hz, 2H), 2.56 (s, 6H), 2.45 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.6, 170.7, 158.6, 131.8, 125.1, 112.0, 12.2, 12.0. IR (KBr): 2927, 1642, 1579, 1426, 1323, 1266, 1101 cm^{-1}. HRMS (ESI), m/z calculated for $C_{15}H_{17}N_2O_3$ $[M + H]^+$: 273.1239. Found: 273.1237. HPLC purity 96.0% (20 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(4-methylthiazol-2-yl)penta-1,4-dien-3-one (22)

This compound was prepared in 72% yield as a yellow solid; mp 118−120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J = 15.7 Hz, 2H), 7.34 (d, J = 15.7 Hz, 2H), 7.06 (s, 2H), 2.52 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.9, 163.1, 155.6, 134.7, 128.5, 117.2, 17.2. IR (KBr): 2920, 2855, 1650, 1613, 1591, 1506, 1438, 1320, 1110 cm^{-1}. HRMS (ESI), m/z calculated for $C_{13}H_{13}N_2OS_2$ $[M + H]^+$: 277.0469. Found: 277.0473. HPLC purity 99.6% (15 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Di(thiazol-5-yl)penta-1,4-dien-3-one (23)

This compound was prepared in 72% yield as a light yellow solid; mp 153−155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (s, 2H), 8.11 (s, 2H), 7.90 (d, J = 15.6 Hz, 2H), 6.82 (d, J = 15.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.7, 155.0, 147.3, 135.6, 132.8, 127.7. IR (KBr): 3074, 1645, 1614, 1585, 1498, 1387, 1318, 1174 cm^{-1}. HRMS (ESI), m/z calculated for $C_{11}H_9N_2OS_2$ $[M + H]^+$: 249.0156. Found: 249.0157. HPLC purity 100.0% (20 min run of 20−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(2-methyl-4-(trifluoromethyl)thiazol-5-yl)-penta-1,4-dien-3-one (24)

This compound was prepared in 68% yield as a yellow solid; mp 138−140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, J = 15.5 Hz, 2H), 6.72 (d, J = 15.5 Hz, 2H), 2.76 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.1, 168.1, 143.8 (q, J_{CF} = 35.3 Hz), 136.0, 130.5, 130.0, 120.8 (q, J_{CF} = 270.8 Hz), 19.8. IR (KBr): 1655, 1611, 1483, 1364, 1318, 1159, 1124 cm^{-1}. HRMS (ESI), m/z calculated for $C_{15}H_{11}F_6N_2OS_2$ $[M + H]^+$: 413.0217. Found: 413.0217. HPLC purity 96.2% (20 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(6-bromopyridin-2-yl)penta-1,4-dien-3-one (25)

This compound was prepared in 84% yield as a gray yellow solid; mp 208−210 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 16.0 Hz, 2H), 7.61 (d, J = 16.0 Hz, 2H), 7.58 (d, J = 7.4

Hz, 2H), 7.48 (d, J = 7.4 Hz, 2H), 7.43 (t, J = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.1, 154.4, 142.9, 140.6, 139.2, 130.1, 129.0, 123.8. IR (KBr): 2923, 1695, 1657, 1579, 1550, 1434, 1408, 1119 cm^{-1}. HRMS (ESI), m/z calculated for $C_{15}H_{11}Br_2N_2O$ $[M + H]^+$: 392.9238. Found: 392.9247. HPLC purity 97.7% (20 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(6-methylpyridin-2-yl)penta-1,4-dien-3-one (26)

This compound was prepared in 98% yield as a gray yellow solid; mp 208−210 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, J = 15.7 Hz, 2H), 7.62 (t, J = 7.7 Hz, 2H), 7.60 (d, J = 15.7 Hz, 2H), 7.32 (d, J = 7.6 Hz, 2H), 7.15 (d, J = 7.7 Hz, 2H), 2.61 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.9, 159.1, 152.7, 142.6, 137.0, 128.7, 124.3, 121.9, 24.7. IR (KBr): 3056, 2921, 1654, 1600, 1449, 1367, 1183 cm^{-1}. HRMS (ESI), m/z calculated for $C_{15}H_{11}Br_2N_2O$ $[M + H]^+$: 265.1341. Found: 265.1344. HPLC purity 97.6% (15 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Di(pyridin-3-yl)penta-1,4-dien-3-one (27)

This compound was prepared in 58% yield as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, J = 2.2 Hz, 2H), 8.64 (dd, J = 4.8, 1.6 Hz, 2H), 7.93 (dt, J = 8.0, 1.9 Hz, 2H), 7.74 (d, J = 16.0 Hz, 2H), 7.37 (dd, J = 8.0, 4.8 Hz, 2H), 7.14 (d, J = 16.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.8, 151.4, 150.1, 140.3, 134.8, 130.6, 127.0, 124.0. IR (KBr): 3033, 2925, 1700, 1654, 1624, 1585, 1478, 1416, 1342, 1199, 1101, 1025 cm^{-1}. HRMS (ESI), m/z calculated for $C_{15}H_{13}N_2O$ $[M + H]^+$: 237.1028. Found: 237.1031. HPLC purity 97.9% (20 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(6-(trifluoromethyl)pyridin-3-yl)penta-1,4-dien-3-one (28)

This compound was prepared in 97% yield as a light yellow solid; mp 186−188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.95 (s, 2H), 8.10 (d, J = 7.8 Hz, 2H), 7.79 (d, J = 16.0 Hz, 2H), 7.76 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 16.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.9, 149.8, 149.3 (q, J_{CF} = 35.2 Hz), 138.8, 136.1, 128.6, 121.3 (q, J_{CF} = 272.2 Hz), 120.7. IR (KBr): 2923, 1704, 1660, 1600, 1573, 1397, 1337, 1247, 1177, 1086 cm^{-1}. HRMS (ESI), m/z calculated for $C_{17}H_{11}F_6N_2O$ $[M + H]^+$: 373.0776. Found: 373.0784. HPLC purity 95.7% (20 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Di(pyridin-4-yl)penta-1,4-dien-3-one (29)

This compound was prepared in 72% yield as a yellow solid; mp 118−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, J = 4.5 Hz, 2H), 8.67 (d, J = 4.5 Hz, 2H), 7.63 (d, J = 16.0 Hz, 2H), 7.44 (d, J = 4.5 Hz, 2H), 7.43 (d, J = 4.5 Hz, 2H), 7.19 (d, J = 16.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.9, 150.8, 141.8, 141.2, 128.8, 122.1. IR (KBr): 3027, 1658, 1591, 1549, 1412, 1342, 1299, 1179, 1100 cm^{-1}. HRMS (ESI), m/z calculated for C_{15} $H_{12}N_2O$ $[M + H]^+$: 237.1028. Found: 237.1033. HPLC purity 95.9% (15 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(3-fluoropyridin-4-yl)penta-1,4-dien-3-one (30)

This compound was prepared in 81% yield as a yellow solid; mp 104−106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (s, 2H), 8.51 (d, J = 5.0 Hz, 2H), 7.78 (d, J = 16.1 Hz, 2H), 7.50 (t, J = 5.7 Hz, 2H), 7.31 (d, J = 16.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.7, 157.5 (d, J_{CF} = 261 Hz), 146.3, 139.6 (d, J_{CF} = 22.5 Hz), 134.2, 131.1, 129.4, 122.4. IR (KBr): 3032, 1676, 1625, 1590, 1548, 1487, 1413, 1323, 1214, 1196, 1096 cm^{-1}. HRMS (ESI), m/z calculated for $C_{15}H_{11}F_2N_2O$ [M + H]$^+$: 273.0839. Found: 273.0842. HPLC purity 97.9% (15 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Di(quinolin-2-yl)penta-1,4-dien-3-one (31)

This compound was prepared in 88% yield as a yellow solid; mp 162−165 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, J = 8.5 Hz, 2H), 8.15 (d, J = 8.5 Hz, 2H), 7.98 (d, J = 15.9 Hz, 2H), 7.84−7.68 (m, 8H), 7.57 (t, J = 7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.7, 153.6, 148.5, 143.2, 137.0, 130.3, 130.0, 128.3, 127.7, 127.6, 121.0. IR (KBr): 3059, 1651, 1589, 1503, 1428, 1345, 1301, 1192 cm^{-1}. HRMS (ESI), m/z calculated for $C_{23}H_{17}N_2O$ [M + H]$^+$: 337.1341. Found: 337.1342. HPLC purity 98.4% (25 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Di(quinolin-4-yl)penta-1,4-dien-3-one (32)

This compound was prepared in 63% yield as a yellow solid; mp 150−152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.92 (d, J = 4.5 Hz, 2H), 8.46 (d, J = 15.7 Hz, 2H), 8.15 (d, J = 8.6 Hz, 2H), 8.12 (d, J = 8.6 Hz, 2H), 7.79 (t, J = 7.7 Hz, 2H), 7.61−7.58 (overlapped, 4H), 7.31 (d, J = 15.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.6, 150.1, 148.7, 140.4, 138.8, 130.9, 130.4, 130.2, 127.7, 126.4, 123.4, 118.3. IR (KBr): 3060, 1675, 1622, 1595, 1563, 1505, 1462, 1387, 1316, 1114, 1076 cm^{-1}. HRMS (ESI), m/z calculated for $C_{23}H_{17}N_2O$ [M + H]$^+$: 337.1341. Found: 337.1347. HPLC purity 99.0% (30 min run of 20−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(2-chloroquinolin-3-yl)penta-1,4-dien-3-one (33)

This compound was prepared in 99% yield as a yellow solid; mp 220 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.14 (s, 2H), 8.12 (d, J = 8.1 Hz, 4H), 8.11 (d, J = 15.9 Hz, 2H), 8.00 (d, J = 8.1 Hz, 2H), 7.74 (t, J = 7.5 Hz, 2H), 7.61 (d, J = 15.9 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6 + $CDCl_3$): δ 187.6 149.4, 147.3, 137.6, 137.4, 132.0, 129.6, 128.7, 127.9, 127.7, 127.1, 126.9. IR (KBr): 3055, 1655, 1614, 1592, 1580, 1392, 1375, 1342, 1294, 1191, 1133, 1045 cm^{-1}. HRMS (ESI), m/z calculated for $C_{23}H_{15}Cl_2N_2O$ [M + H]$^+$: 405.0561. Found: 405.0577. HPLC purity 96.7% (30 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(4-methyl-5-(pyridin-4-yl)thiazol-2-yl)penta-1,4-dien-3-one (34)

This compound was prepared in 75% yield as a yellow solid; mp 225 °C (decomposed). 1H NMR (300 MHz, $CDCl_3$): δ 8.72 (d, J = 5.9 Hz, 4H), 7.89 (d, J = 15.3 Hz, 2H), 7.79 (d, J = 5.9 Hz, 4H), 6.73 (d, J = 15.3 Hz, 2H), 2.64 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.4, 164.7, 158.7, 150.9, 139.7, 132.5, 131.2, 127.4, 120.4, 16.1. IR (KBr): 3029, 3007, 1671, 1583, 1381, 1314, 1272, 1097 cm^{-1}. HRMS (ESI), m/z calculated for $C_{23}H_{18}N_4OS_2$ [M +

H]$^+$: 431.1000. Found: 431.1005. HPLC purity 95.7% (30 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(benzo[*d*]thiazol-2-yl)penta-1,4-dien-3-one (35)

This compound was prepared in 81% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, J = 8.0 Hz, 2H), 7.99−7.93 (overlapped, 2H), 7.95 (d, J = 15.8 Hz, 2H), 7.58−7.44 (overlapped, 4H), 7. 46 (d, J = 15.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.3, 163.7, 154.2, 136.1, 135.6, 131.3, 127.1, 126.9, 124.3, 122.0. IR (KBr): 3047, 2924, 1668, 1647, 1624, 1583, 1475, 1311, 1162, 1093 cm^{-1}. HRMS (ESI), m/z calculated for $C_{19}H_{12}N_2OS_2$ [M + H]$^+$: 349.0469. Found: 349.0473. HPLC purity 98.9% (40 min run of 45−65% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-one (36)

This compound was prepared in 81% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94−7.81 (m, 6H), 7.38−7.34 (m, 6H), 3.96 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.7, 148.4, 143.4, 136.6, 131.4, 127.9, 124.4, 123.7, 120.5, 110.0, 30.3. IR (KBr): 1676, 1633, 1614, 1599, 1484, 1461, 1403, 1336, 1305, 1093 cm^{-1}. HRMS (ESI), m/z calculated for $C_{21}H_{18}N_4O$ [M + H]$^+$: 243.1559. Found: 243.1570. HPLC purity 97.3% (15 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-ethyl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-one (37)

This compound was prepared in 69% yield as a yellow solid; mp 166−168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J = 15.3 Hz, 2H), 7.88−7.80 (overlapped, 2H), 7.80 (d, J = 15.3 Hz, 2H), 7.48−7.28 (m, 6H), 4.40 (q, J = 7.0 Hz, 4H), 1.49 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.7, 147.6, 143.6, 135.6, 131.5, 127.8, 124.3, 123.7, 120.6, 110.0, 38.8, 16.1. IR (KBr): 3062, 2979, 1654, 1625, 1600, 1410, 1331, 1187, 1094 cm^{-1}. HRMS (ESI), m/z calculated for $C_{23}H_{22}N_4O$ [M + H]$^+$: 371.1872. Found: 371.1872. HPLC purity 97.2% (20 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-propyl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-one (38)

This compound was prepared in 99% yield as a yellow solid; mp 109−112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 15.3 Hz, 2H), 7.87−7.79 (overlapped, 2H), 7.79 (d, J = 15.3 Hz, 2H), 7.42−7.30 (m, 6H), 4.31 (t, J = 7.1 Hz, 4H), 1.98−1.87 (m, 4H), 0.98 (t, J = 7.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.8, 148.1, 143.45, 136.1, 131.5, 128.0, 124.3, 123.6, 120.6, 110.2, 45.4, 24.1, 11.5. IR (KBr): 3061, 2964, 2932, 2875, 1653, 1624, 1599, 1444, 1406, 1330, 1183, 1093 cm^{-1}. HRMS (ESI), m/z calculated for $C_{25}H_{26}N_4O$ [M + H]$^+$: 399.2185. Found: 399.2185. HPLC purity 99.7% (20 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-butyl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-one (39)

This compound was prepared in 92% yield as a yellow solid; mp 128−130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 15.4 Hz, 2H), 7.87−7.79 (overlapped, 2H), 7.79 (d, J = 15.4 Hz, 2H), 7.42−7.30 (m, 6H), 4.33 (t, J = 7.2 Hz, 4H), 1.91−1.78 (m, 4H), 1.42−1.33 (m, 4H), 0.96 (t, J = 7.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.7, 148.0, 143.5, 136.0,

131.5, 128.0, 124.3, 123.6, 120.6, 110.2, 43.8, 32.9, 20.3, 13.8. IR (KBr): 3061, 2957, 2930, 2872, 1654, 1624, 1596, 1464, 1177, 1092 cm^{-1}. HRMS (ESI), *m*/*z* calculated for $C_{27}H_{30}N_4O$ $[M + H]^+$: 427.2498. Found: 427.2499. HPLC purity 99.7% (25 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-pentyl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-one (40)

This compound was prepared in 34% yield as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 15.3 Hz, 2H), 7.87−7.78 (overlapped, 2H), 7.78 (d, J = 15.3 Hz, 2H), 7.43−7.28 (m, 6H), 4.31 (t, J = 7.3 Hz, 4H), 1.93−1.75 (m, 4H), 1.41−1.26 (m, 8H), 0.88 (t, J = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.7, 148.0, 143.4, 136.0, 131.4, 127.9, 124.3, 123.6, 120.5, 110.2, 43.9, 30.5, 29.0, 22.4, 14.0. IR (KBr): 3051, 2956, 2929, 2858, 1655, 1624, 1598, 1445, 1406, 1330, 1092 cm^{-1}. HRMS (ESI), *m*/*z* calculated for $C_{29}H_{34}N_4O$ $[M + H]^+$: 455.2811. Found: 455.2812. HPLC purity 97.0% (40 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-hexyl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-one (41)

This compound was prepared in 66% yield as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 15.2 Hz, 2H), 7.84−7.80 (overlapped, 2H), 7.79 (d, J = 15.2 Hz, 2H), 7.42−7.28 (m, 6H), 4.31 (t, J = 7.3 Hz, 4H), 1.90−1.80 (m, 4H), 1.41−1.25 (m, 12H), 0.86 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.5, 148.0, 143.5, 136.0, 131.5, 127.9, 124.3, 123.6, 120.6, 110.2, 44.0, 31.5, 30.8, 26.7, 22.6, 14.1. IR (KBr): 2954, 2928, 2857, 1654, 1625, 1603, 1466, 1409, 1331, 1183, 1094 cm^{-1}. HRMS (ESI), *m*/*z* calculated for $C_{31}H_{39}N_4O$ $[M + H]^+$: 483.3124. Found: 483.3130. HPLC purity 96.1% (25 min run of 65−90% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-heptyl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-one (42)

This compound was prepared in 85% yield as a yellow solid; mp 171−173 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J = 15.3 Hz, 2H), 7.85−7.80 (overlapped, 2H), 7.80 (d, J = 15.3 Hz, 2H), 7.42−7.30 (m, 6H), 4.33 (t, J = 7.3 Hz, 4H), 1.91−1.80 (m, 4H), 1.45−1.15 (m, 16H), 0.86 (t, J = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.7, 148.0, 143.5, 136.0, 131.5, 128.0, 124.3, 123.6, 120.6, 110.2, 44.0, 31.7, 30.8, 29.0, 27.0, 22.7, 14.2. IR (KBr): 3062, 2926, 2855, 1654, 1625, 1601, 1407, 1331, 1181, 1093 cm^{-1}. HRMS (ESI), *m*/*z* calculated for $C_{33}H_{42}N_4O$ $[M + H]^+$: 511.3437. Found: 511.3431. HPLC purity 100.0% (40 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-isopropyl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-one (43)

This compound was prepared in 63% yield as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J = 15.8 Hz, 2H), 7.85 (d, J = 15.8 Hz, 2H), 7.81 (d, J = 5.2 Hz, 2H), 7.62−7.52 (m, 2H), 7.31−7.28 (m, 4H), 5.06−4.97 (m, 2H), 1.71 (d, J = 6.8 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.8, 147.6, 144.0, 134.5, 131.8, 128.5, 123.9, 123.3, 120.8, 112.2, 48.2, 22.0. IR (KBr): 3053, 2977, 2935, 1653, 1621, 1608, 1456, 1385, 1184, 1104 cm^{-1}. HRMS (ESI), *m*/*z* calculated for $C_{25}H_{26}N_4O$ $[M + H]^+$: 399.2185. Found: 399.2192. HPLC purity 96.0% (20 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-isobutyl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-one (44)

This compound was prepared in 85% yield as a yellow solid; mp 113−115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 15.2 Hz, 2H), 7.83−7.81 (overlapped, 2H), 7.79 (d, J = 15.2 Hz, 2H), 7.41−7.31 (m, 6H), 4.14 (d, J = 7.5 Hz, 4H), 2.31−2.18 (m, 2H), 0.98 (d, J = 6.6 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.7, 148.4, 143.4, 136.4, 131.5, 128.2, 124.3, 123.6, 120.6, 110.5, 51.2, 30.2, 20.4. IR (KBr): 2961, 2931, 2872, 1654, 1625, 1601, 1468, 1369, 1331, 1299, 1186, 1094 cm^{-1}. HRMS (ESI), m/z calculated for $C_{27}H_{31}N_4O$ [M + H]$^{+}$: 427.2498. Found: 427.2510. HPLC purity 99.2% (40 min run of 45−65% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-(sec-butyl)-1*H*-benzo[*d*]imidazol-2-yl)-penta-1,4-dien-3-one (45)

This compound was prepared in 98% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98−7.74 (overlapped, 6H), 7.56−7.53 (m, 2H), 7.37−7.27 (m, 4H), 4.74−4.66 (m, 2H), 2.23−2.15 (m, 2H), 2.10−1.94 (m, 2H), 1.71 (d, J = 6.9 Hz, 6H), 0.80 (t, J = 7.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.7, 148.3, 143.9, 134.6, 131.9, 128.5, 123.9, 123.3, 120.8, 112.2, 54.4, 28.7, 20.4, 11.3. IR (KBr): 3052, 2967, 2933, 2875, 1652, 1620, 1596, 1454, 1407 cm^{-1}. HRMS (ESI), m/z calculated for $C_{27}H_{30}N_4O$ [M + H]$^{+}$: 427.2498. Found: 427.2506. HPLC purity 97.7% (30 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-(pentan-2-yl)-1*H*-benzo[*d*]imidazol-2-yl)-penta-1,4-dien-3-one (46)

This compound was prepared in 76% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05−7.80 (overlapped, 6H), 7.59−7.56 (m, 2H), 7.36−7.29 (m, 4H), 4.87−4.83 (m, 2H), 2.25−2.12 (m, 2H), 2.04−1.87 (m, 2H), 1.72 (d, J = 6.9 Hz, 6H), 1.35−1.18 (m, 2H), 1.14−0.99 (m, 2H), 0.86 (t, J = 7.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.6, 148.0, 143.6, 134.5, 132.0, 128.4, 123.9, 123.4, 120.6, 112.2, 52.7, 37.7, 20.6, 20.0, 13.7. IR (KBr): 2958, 2931, 2872, 1653, 1620, 1599, 1454, 1407, 1382 cm^{-1}. HRMS (ESI), m/z calculated for $C_{27}H_{31}N_4O$ [M + H]$^{+}$: 455.2811. Found: 455.2818. HPLC purity 98.0% (30 min run of 65−90% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-(pentan-3-yl)-1*H*-benzo[*d*]imidazol-2-yl)-penta-1,4-dien-3-one (47)

This compound was prepared in 88% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93−7.80 (overlapped, 6H), 7.53 (d, J = 7.2 Hz, 2H), 7.37−7.27 (m, 4H), 4.44−4.38 (m, 2H), 2.29−2.13 (m, 4H), 2.11−1.97 (m, 4H), 0.78 (t, J = 7.3 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.7, 149.1, 143.9, 134.6, 131.9, 128.5, 123.8, 123.3, 120.7, 112.2, 60.9, 27.2, 11.2. IR (KBr): 2965, 2933, 2875, 1653, 1609, 1454, 1385 cm^{-1}. HRMS (ESI), m/z calculated for $C_{29}H_{35}N_4O$ [M + H]$^{+}$: 455.2811. Found: 455.2819. HPLC purity 95.1% (40 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

(1*E*,4*E*)-1,5-Bis(1-isopentyl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-one (48)

This compound was prepared in 98% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 15.2 Hz, 2H), 7.82−7.78 (overlapped, 2H), 7.77 (d, J = 15.2 Hz, 2H), 7.38−7.24 (m, 6H), 4.27 (t, J = 7.3 Hz, 4H), 1.78−1.60 (m, 6H), 1.00 (d, J = 6.1 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.5, 147.8, 143.3, 135.8, 131.5, 127.7, 124.2, 123.6, 120.5, 110.0,

42.3, 39.5, 26.0, 22.5. IR (KBr): 2956, 2929, 2870, 1654, 1613, 1458, 1409, 1331 cm^{-1}. HRMS (ESI), *m*/*z* calculated for $C_{29}H_{35}N_4O$ $[M + H]^+$: 455.2811. Found: 455.2824. HPLC purity 99.4% (40 min run of 45−80% CH_3CN in H_2O, with 15 min gradient, 1.0 mL/min).

Cell Culture

All cell lines were initially purchased from American Type Culture Collection (ATCC). The PC-3 and LNCaP prostate cancer cell lines and the HeLa cervical cancer cell line were routinely cultured in RPMI-1640 medium supplemented with 10% FBS and 1% penicillin/streptomycin. Cultures were maintained in a high humidity environment supplemented with 5% carbon dioxide at a temperature of 37 °C. The DU-145 prostate cancer cells were routinely cultured in Eagle's minimum essential medium (EMEM) supplemented with 10% FBS and 1% penicillin/streptomycin.

Trypan Blue Dye Exclusion Assay

PC-3 or DU145 or LNCaP or HeLa cells were plated in 24-well plates at a density of 20 000 each well in 10% FBS RPMI-1640 medium. The cells were then treated with curcumin or with synthesized mimics separately at different doses for 3 days, while equal treatment volumes of DMSO were used as vehicle control. Cell numbers were counted with a cell viability analyzer (VI-Cell XR, Beckman Coulter). The ratio of drug treated viable cell numbers to vehicle treated viable cell numbers was defined as percentage viability, and variation between replicate experiments is not greater than 5%. The inhibitory rates in Table 2 were expressed as cell viability reduction rates (percentage viability of untreated cell culture control–percentage viability of drug-treated cell culture). The IC_{50} value is the concentration of each compound that inhibits cell growth by 50% under the experimental conditions and is the average from triplicate determinations that were reproducible and statistically significant. For calculating the IC_{50} values, a linear inhibition was made based on at least five dosages for each compound.

WST-1 Cell Proliferation Assay

PC-3 or DU-145 or LNCaP or HeLa cells were plated in 96-well plates at a density of 3200 each well in 200 μL of culture medium. The cells were then treated with curcumin or with synthesized analogues separately at different doses from 0.1 to 1 μM for 3 days, while equal treatment volumes of DMSO were used as vehicle control. The cells were cultured in a CO_2 incubator at 37 °C for 3 days. Then 10 μL of the premixed WST-1 cell proliferation reagent (Clontech) was added to each well. After mixing gently for 1 min on an orbital shaker, the cells were incubated for additional 3 h at 37 °C. To ensure homogeneous distribution of color, it is important to mix gently on an orbital shaker for 1 min. The absorbance of each well was measured using a microplate-reader (Synergy HT, BioTek) at a wavelength of 430 nm. The IC_{50} value is the concentration of each compound that inhibits cell proliferation by 50% under the experimental conditions and is the average from triplicate determinations that were reproducible and statistically significant. For calculating the IC_{50} values, a linear proliferative inhibition was made based on at least five dosages for each compound.

Pharmacokinetic Study.[37]

Female C57BL/6 mice were used for the pharmacokinetic study of curcumin and compounds 14 and 24. Mice were given oral gavage containing PBS and ethanol-dissolved curcumin, 14, or 24 at a single dose of 1 (mg/kg)/mouse. After oral administration, blood samples were collected from the orbital sinus of the mice at 0.5, 1, 2, 4, and 24 h with each group of five mice subjected to only one sampling. Mice blood was collected with a capillary into 1.5 mL microcentrifuge tubes containing 0.1 mL of 10% EDTA anticoagulant. Plasma was then separated from red cells by centrifugation in a refrigerated centrifuge at 4 °C and transferred to a separate tube. The plasma samples were frozen at −80 °C until analysis. All procedures involving these animals were conducted in compliance with state and federal laws, standards of the U.S. Department of Health and Human Services, and guidelines established by Xavier University Animal Care and Use Committee. The facilities and laboratory animals program of Xavier University are accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care.

High Performance Liquid Chromatography–Tandem Mass Spectrometry (HPLC–MS/MS) for Drug Analysis in Plasma Samples

Plasma samples were extracted with chloroform/methanol (2:1) using traditional Folch method for lipid extraction. Methanol (1 mL) and chloroform (2 mL) were added to each plasma sample followed by addition of 5 ng of trans-tamoxifen-$^{13}C2,^{15}N$ to each sample as the internal standard. The mixtures were stored at −20 °C overnight. Next the samples were sonicated for 5 min and centrifuged with a Thermo Scientific Heraeus Megafuge16 centrifuge. The top layer was transferred to another test tube. The bottom layer was washed with 1 mL of chloroform/methanol (2:1), centrifuged, and the top layer was transferred and combined with the previous top layer. Eight-tenth of a milliliter of HPLC grade water was added to the extracts. After vortexing, the mixture was centrifuged. The bottom layer was dried out with nitrogen and resuspended in 100 μL of HPLC grade acetonitrile. An aliquot of 10 μL of sample was injected onto a Hypersil Gold column (50 mm × 2.1 mm; particle size 1.9 μm, Thermo Scientific) on a Dionex Ultimate 3000 UPLC system equipped with a TSQ Vantage triple quadrupole mass spectrometer for analysis. A binary mobile phase (A, water with 0.05% formic acid; B, acetonitrile with 0.05% formic acid) was used to achieve the gradient of initial 30% B for 1 min and then to 80% B at 8 min, to 100% B at 9 min, and returned to 30% B for 4 min. The flow rate was controlled at 0.6 mL/min. The settings of HESI source were as follows: spray voltage (3200 V); vaporizer temperature (365 °C); sheath gas pressure (45 psi); auxiliary gas pressure (10 psi); capillary temperature (330 °C). Nitrogen was used as the sheath gas and auxiliary gas. Argon was used as the collision gas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

DMP	Dess–Martin periodinane
FBS	fetal bovine serum
PANIS	pan assay interference compounds
TB	trypan blue dye exclusion assay
PTLC	preparative thin-layer chromatography

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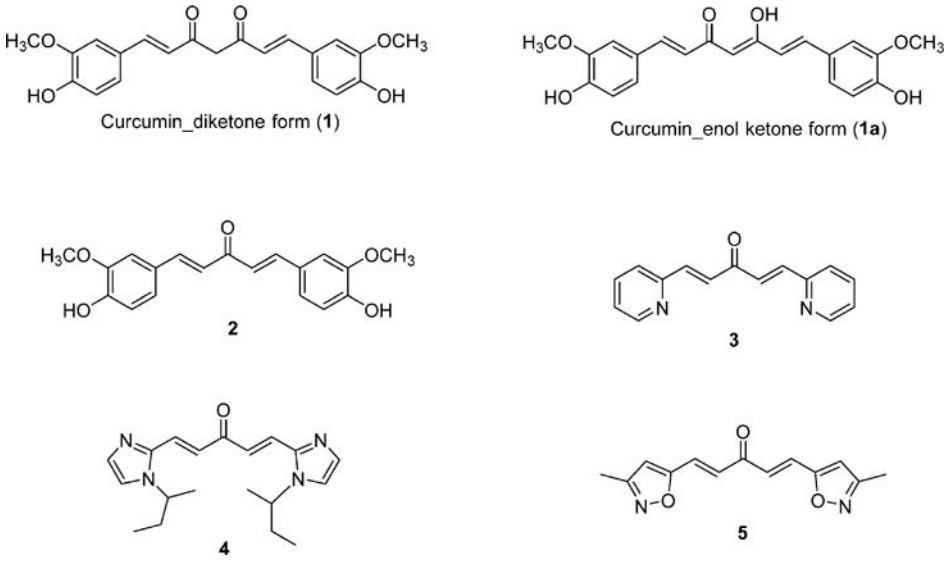
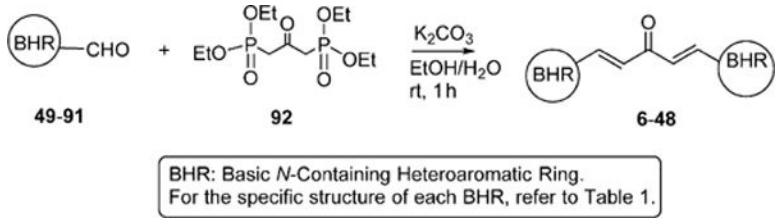
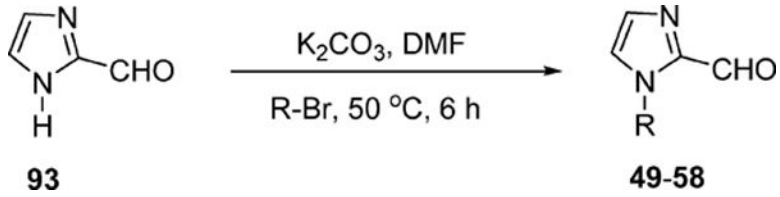


Figure 1.
Structures of curcumin and its representative mimics.



Scheme 1.

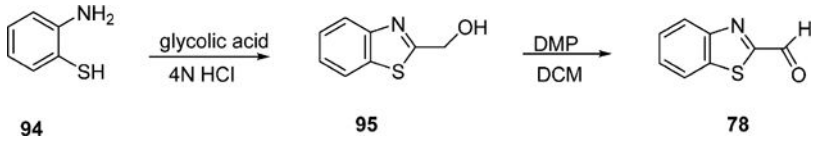
Synthesis of Curcumin-Based Compounds via a Horner–Wadsworth–Emmons Reaction



93 49-58

Scheme 2.

Synthesis of 1-Alkyl-1*H*-imidazole-2-carbaldehydes (49–58)



94 95 78

Scheme 3.

Synthesis of Benzo[*d*]thiazole-2-carbaldehyde (78)

Scheme 4.

Synthesis of 1-Alkyl-1*H*-benzo[*d*]imidazole-2-carbaldehydes (79–91)

Table 1

Structures of Heteroaromatic rings (BHR)

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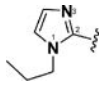
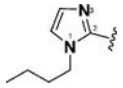
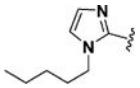
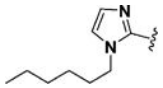
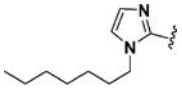
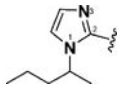
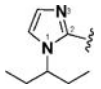
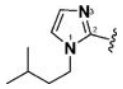
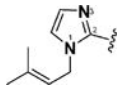
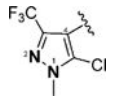
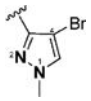
6 & 49		7 & 50		8 & 51	
9 & 52		10 & 53		11 & 54	
12 & 55		13 & 56		14 & 57	
15 & 58		16 & 59		17 & 60	
18 & 61		19 & 62		20 & 63	
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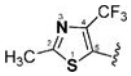
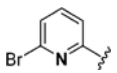
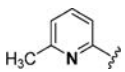
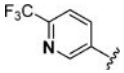
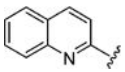
24 & 67		25 & 95		26 & 69	
27 & 70		28 & 71		29 & 72	
30 & 73		31 & 74		32 & 75	

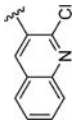
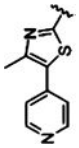
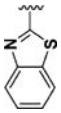
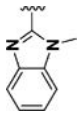
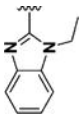
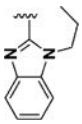
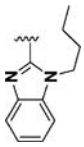
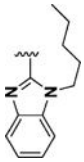
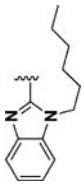
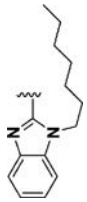
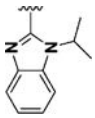
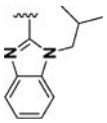
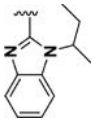
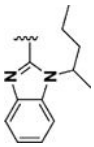
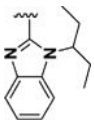
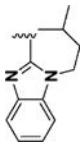
Compd	BHR	Compd	BHR	Compd	BHR
33 & 76		34 & 77		35 & 78	
36 & 79		37 & 80		38 & 81	
39 & 82		40 & 83		41 & 84	
42 & 85		43 & 86		44 & 87	
45 & 88		46 & 89		47 & 90	
48 & 91					

Table 2

Cytotoxicity of 1,5-Diheteroarylpenta-1,4-dien-3-ones

	inhibitory rate (%)							
	PC-3[a]		DU145[b]		LNCaP[c]		HeLa[d]	
compd	10 μM	1 μM	10 μM	1 μM	10 μM	1 μM	10 μM	1 μM
curcumin	55.07	2.45	58.49	7.25	65.45	28.78	50.30	13.75
6	94.34	76.97	84.97	45.75	80.90	53.63	95.13	92.70
7	97.39	84.35	86.93	50.02	78.17	47.27	97.56	94.59
8	93.91	91.30	84.97	65.70	80.90	77.26	96.48	97.83
9	90.87	91.30	83.66	63.74	91.80	50.90	96.75	97.02
10	84.59	87.50	93.39	79.25	72.49	41.66	97.13	96.69
11	92.17	85.22	88.56	35.93	85.44	52.72	98.91	89.73
12	82.83	92.42	89.08	91.70	85.70	77.13	97.25	95.73
13	93.94	89.90	87.77	83.41	88.56	61.42	94.81	97.25
14	90.91	92.93	94.32	84.28	88.56	67.13	95.73	96.03
15	85.52	71.98	90.00	79.55	83.86	51.60	96.34	96.95
16	59.40	0.00	47.18	19.34	58.32	18.52	84.08	18.27
17	27.15	0.00	0.01	0.00	38.70	6.45	20.72	0.00
18	70.76	0.00	84.25	31.48	52.77	9.26	92.69	32.36
19	86.92	80.85	87.27	67.29	83.86	61.28	99.08	96.34
20	87.39	9.37	85.91	0.01	41.93	25.80	97.56	16.15
21	94.55	50.03	85.96	27.25	50.72	31.88	99.18	69.12
22	89.60	69.82	85.11	54.07	68.11	59.07	97.83	68.30
23	89.60	19.33	90.21	23.85	46.37	14.49	98.64	22.75
24	89.47	84.22	90.32	54.86	77.14	64.39	93.67	76.59
25	91.92	13.16	82.97	21.42	64.99	45.71	89.63	14.63
26	84.85	73.75	93.45	69.88	84.99	77.85	96.64	97.25
27	86.71	8.05	77.66	4.76	53.70	15.74	97.65	26.62
28	91.59	37.89	75.47	0.01	68.80	22.58	97.86	33.82
29	87.77	31.97	89.74	31.85	78.69	29.62	95.04	40.19
30	81.92	57.48	90.11	42.13	78.69	26.85	98.17	50.37

compd	inhibitory rate (%)							
	PC-3[a]		DU145[b]		LNCaP[c]		HeLa[d]	
	10 μM	1 μM	10 μM	1 μM	10 μM	1 μM	10 μM	1 μM
31	83.79	0.90	86.53	23.48	66.95	9.61	96.52	21.19
32	60.96	4.20	48.42	4.03	74.10	48.21	96.52	79.75
33	1.64	0.00	6.22	6.22	14.28	11.61	21.51	6.64
34	25.73	14.40	35.23	13.46	23.43	34.37	48.97	22.91
35	69.81	6.29	46.80	18.16	69.52	21.87	96.18	21.34
36	78.84	81.09	90.83	55.32	67.96	45.31	97.97	95.50
37	86.14	84.66	81.95	64.60	91.19	74.71	98.87	92.09
38	85.15	89.60	79.87	67.37	79.11	73.11	98.87	95.48
39	83.17	88.62	87.15	64.95	85.70	68.12	97.74	97.17
40	81.69	89.60	89.58	60.78	90.09	32.96	97.45	98.02
41	82.82	62.00	91.13	79.85	78.21	60.46	96.99	96.29
42	88.12	72.79	86.11	36.46	74.71	42.07	97.45	90.40
43	83.79	79.29	84.82	92.26	88.27	62.49	97.53	96.63
44	84.19	88.46	85.77	84.19	79.42	59.26	89.25	93.12
45	84.69	91.44	87.11	89.11	77.33	70.30	97.08	95.28
46	87.61	69.67	88.54	75.00	67.32	59.25	94.17	90.66
47	91.02	71.97	81.43	79.60	70.55	45.95	97.34	90.66
48	83.34	58.49	80.24	79.40	72.97	54.00	96.64	96.29

[a]Human androgen-insensitive prostate cancer cell line.

[b]Human androgen-insensitive prostate cancer cell line.

[c]Human androgen-sensitive prostate cancer cell line.

[d]Human aggressive cervical cancer cell line.

Table 3

Antiproliferative Activity and Cytotoxicity of Selected 1,5-Diheteroarylpenta-1,4-dien-3-ones

	IC_{50} (μM)[a]					
	PC-3[b]				HeLa[e]	
compd	WST-1	TB	DU145,[c] WST-1	LNCaP,[d] WST-1	WST-1	TB
curcumin	25.43 ± 2.15	12.36 ± 0.04	26.23 ± 0.65	13.61 ± 2.69	12.11 ± 0.67	10.46 ± 1.97
6	1.07 ± 0.38		0.91 ± 0.08	0.59 ± 0.10	0.52 ± 0.25	
7	1.53 ± 0.05		0.66 ± 0.14	0.78 ± 0.12	0.40 ± 0.05	
8	0.68 ± 0.08		0.37 ± 0.02	0.49 ± 0.03	0.23 ± 0.04	
9	0.71 ± 0.06		0.55 ± 0.14	0.59 ± 0.03	0.35 ± 0.04	
10	0.90 ± 0.07		0.85 ± 0.14	1.13 ± 0.07	0.65 ± 0.02	0.59 ± 0.13
12	0.31 ± 0.06		0.29 ± 0.05	0.24 ± 0.05	0.19 ± 0.08	0.15 ± 0.13
13	0.69 ± 0.07		0.62 ± 0.13	0.58 ± 0.17	0.36 ± 0.02	0.25 ± 0.05
14	0.71 ± 0.06		0.71 ± 0.11	0.57 ± 0.17	0.41 ± 0.02	0.23 ± 0.04
15	0.60 ± 0.05		0.53 ± 0.12	0.39 ± 0.11	0.33 ± 0.03	
19	0.51 ± 0.06		0.45 ± 0.13	0.31 ± 0.14	0.14 ± 0.10	0.21 ± 0.03
22	0.84 ± 0.11		0.96 ± 0.02	0.46 ± 0.25	0.67 ± 0.05	
24	0.71 ± 0.04		1.14 ± 0.00	0.60 ± 0.05	0.47 ± 0.26	0.92 ± 0.17
26	0.47 ± 0.08		0.47 ± 0.16	0.23 ± 0.17	0.20 ± 0.01	0.25 ± 0.05
30	0.73 ± 0.20		1.51 ± 0.28	0.67 ± 0.31	0.71 ± 0.15	
32	0.47 ± 0.13	0.41 ± 0.04	0.66 ± 0.20	0.41 ± 0.13	0.42 ± 0.20	0.48 ± 0.15
36	0.21 ± 0.03	0.39 ± 0.13	0.34 ± 0.08	0.27 ± 0.06	0.14 ± 0.04	0.43 ± 0.20
37	0.52 ± 0.01		0.42 ± 0.13	0.38 ± 0.08	0.23 ± 0.01	
38	0.34 ± 0.04		0.45 ± 0.22	0.52 ± 0.12	0.17 ± 0.01	
39	0.40 ± 0.04		0.51 ± 0.14	0.58 ± 0.15	0.20 ± 0.04	
40	0.37 ± 0.04		0.70 ± 0.22	0.86 ± 0.20	0.32 ± 0.04	
41	0.64 ± 0.22		1.83 ± 0.33	1.16 ± 0.23	0.59 ± 0.10	
43	0.23 ± 0.02	0.14 ± 0.01	0.53 ± 0.10	0.45 ± 0.02	0.16 ± 0.02	0.14 ± 0.05
44	0.22 ± 0.01	0.21 ± 0.07	0.43 ± 0.03	0.38 ± 0.07	0.14 ± 0.02	0.15 ± 0.02
45	0.34 ± 0.10	0.24 ± 0.06	0.83 ± 0.14	0.79 ± 0.10	0.23 ± 0.02	0.23 ± 0.07
46	0.30 ± 0.06	0.70 ± 0.24	0.89 ± 0.04	0.70 ± 0.08	0.27 ± 0.03	0.69 ± 0.13

	IC$_{50}$ (μM)[a]					
	PC-3[b]				HeLa[e]	
compd	WST-1	TB	DU145,[c] WST-1	LNCaP,[d] WST-1	WST-1	TB
47	0.26 ± 0.03	0.93 ± 0.22	0.83 ± 0.15	0.54 ± 0.12	0.18 ± 0.02	0.93 ± 0.29
48	0.79 ± 0.20		>2	0.92 ± 0.07	0.54 ± 0.12	0.84 ± 0.26

[a] IC_{50} is the drug concentration effective in inhibiting 50% of the cell viability measured by WST-1 cell proliferation assay (WST-1) or trypan blue exclusion assay (TB) after 3 days exposure.

[b] Human androgen-insensitive prostate cancer cell line.

[c] Human androgen-insensitive prostate cancer cell line.

[d] Human androgen-sensitive prostate cancer cell line.

[e] Human aggressive cervical cancer cell line.

Table 4

Relative Potency of Curcumin Mimics

	IC_{50}(curcumin)/IC_{50}(compd)[a]					
	PC-3[b]				HeLa[e]	
compd	WST-1	TB	DU145,[c] WST-1	LNCaP,[d] WST-1	WST-1	TB
curcumin	1	1	1	1	1	1
6	24		29	23	23	
7	17		40	17	30	
8	37		71	28	53	
9	36		48	23	35	
10	28		31	12	19	
12	82		90	57	64	75
13	37		42	24	34	42
14	36		37	24	30	46
15	42		49	35	37	
19	50		58	44	87	51
22	30		27	30	18	
24	36		23	23	26	11
26	54		56	59	61	43
30	35		17	20	17	
32	54	30	40	33	29	22
36	121	32	77	50	87	24
37	49		63	36	53	
38	75		66	26	71	
39	64		51	24	61	
40	69		38	16	38	
41	40		14	12	21	
43	111	90	50	30	76	75
44	116	58	61	36	87	95
45	75	53	32	17	53	45
46	85	18	30	19	45	15

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compd	IC_{50}(curcumin)/IC_{50}(compd)[a]							
	PC-3[b]		DU145,[c] WST-1	LNCaP,[d] WST-1	HeLa[e]	
	WST-1	TB			WST-1	TB
47	98	13	32	25	67	11
48	32			15	22	13

[a] The relative potency of curcumin mimics obtained by dividing the IC_{50} value of curcumin by that of each curcumin mimic.

[b] Human androgen-insensitive prostate cancer cell line.

[c] Human androgen-insensitive prostate cancer cell line.

[d] Human androgen-sensitive prostate cancer cell line.

[e] Human aggressive cervical cancer cell line.

Table 5

24 h Mouse-Plasma Concentrations of Curcumin, 14, and 24

	concentration in mouse plasma (ng/mL)		
time	**curcumin**	**14**	**24**
30 min	0.04	0.41	2.46
1 h	0.33	0.71	6.73
2 h	0.57	0.38	15.94
4 h	0.13	0.28	61.92
1 day	0.03	0.05	18.09

		curcumin	**14**	**24**
t_{max} (h)		2	1	4
C_{max} (ng/mL)		0.57	0.71	61.90
area under curve (AUC)	(ng mL^{-1} h^{-1})	2.43	5.04	892.77