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Development of Novel 1,2,3,4-Tetrahydroquinoline Scaffolds as Potent NF-κB Inhibitors and Cytotoxic Agents

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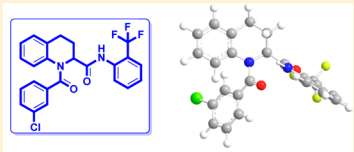
Supporting Information

ABSTRACT: 1,2,3,4-Tetrahydroquinolines have been identified as the most potent inhibitors of LPS-induced NF-κB transcriptional activity. To discover new molecules of this class with excellent activities, we designed and synthesized a series of novel derivatives of 1,2,3,4-tetrahydroquinolines (**4a−g**, **5a−h**, **6a−h**, and **7a−h**) and bioevaluated their *in vitro* activity against human cancer cell lines (NCI-H23, ACHN, MDA-MB-231, PC-3, NUGC-3, and HCT 15). Among all synthesized scaffolds, **6g** exhibited the most potent inhibition (53 times that of a reference compound) of LPS-induced NF-κB transcriptional activity and the most potent cytotoxicity against all evaluated human cancer cell lines.



Inhibition of NF-κB activity	IC_{50} (μM)
	0.70±0.071
Human Cancer Cell lines	**GI_{50} (μM)**
NCI-H23	0.292±0.0111
ACHN	0.526±0.178
MDA-MB-231	0.288±0.0992
PC-3	0.729±0.131
NUGC-3	0.754±0.129
HCT 15	0.797±0.173

KEYWORDS: *1,2,3,4-Tetrahydroquinolines, NF-κB inactivation, in vitro cytotoxicity, human cancer cell lines*

NF-κB is a lymphoid-specific protein that binds to the enhancer of kappa light chain in the nucleus of B cells; NF-κB was discovered by Sen and Baltimore.[1] NF-κB is involved in the regulation of many immune and inflammatory responses, cellular growth, and apoptosis.[2,3] At present, NF-κB and its signaling is one of the most exciting and extensively studied research fields since NF-κB dysregulation is associated with many diseases such as cancer, AIDS, asthma, arthritis, diabetes, and inflammatory bowel disease.[4−6] Several natural and synthetic compounds, including some drugs, have been tested for their potential to inhibit NF-κB, but very few of them are suitable for anticancer therapy.[7,8] Therefore, it has been suggested that the development of novel NF-κB inhibitors with antitumor and anti-inflammatory activities is most important. Our group has been involved in the development of novel potent NF-κB inhibitors[9−11] with anticancer activity.

Besides, quinolines and tetrahydroquinolines are important ubiquitous structural motifs in biologically active natural products and pharmacologically relevant therapeutic agents.[12−16] However, Khan et al.[17] demonstrated that tetrahydroquinolines can be used as NF-κB inhibitors as well as anti-HIV agents, anti-Parkinson's diseases, etc. María José Abad et al.[18] also tested quinoline-based compounds as modulators of HIV transcription through NF-κB and Sp1 inhibition. These distinct inhibitory activities have encouraged us to prepare such core motifs to test our hypothesis that their derivatives would act as most potent NF-κB inhibitors and have anticancer activity. We designed and synthesized different novel derivatives of 1,2,3,4-tetrahydroquinoline-2-carboxylic acid *N*-(substituted)phenyl amide and tested them as potential NF-κB inhibitors and also evaluated their cytotoxicities against six human cancer cell lines (NCI-H23, ACHN, MDA-MB-231, PC-3, NUGC-3, and HCT-15). Based on our previous reports,[9−11] we wish to maintain amide functionality to the core motifs, and the effect of the synthesized molecules on NF-κB transcriptional activity was measured by using a reported procedure.[19] *In vitro* cytotoxicity assay was performed using the number of cells measured indirectly by the sulforhodamine B method according to the National Cancer Institute (USA) protocol.[20]

We commenced our synthesis from commercially available quinoline-2-carboxylic acid, which underwent amidation reaction with various substituted aromatic amines in the presence of the coupling reagent 1,1′-carbonyldiimidazole

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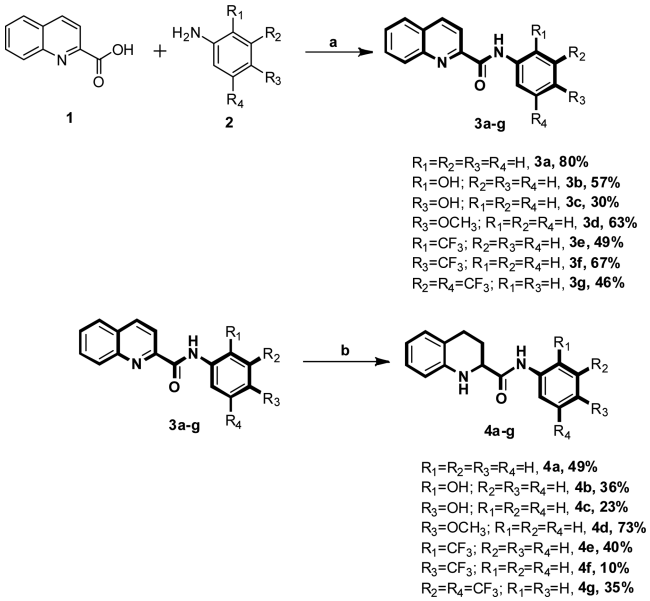
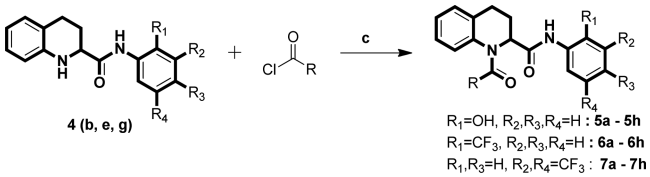
Scheme 1. Synthesis of 3a−g and 4a−g Series of Scaffolds[a]



[a]Reagents and conditions: (a) CDI, anhydrous THF, RT, 1 h. (b) Pd/C, H_2 balloon, EtOH, RT, 24 h.

Scheme 2. Synthesis of 5a−h, 6a−h, and 7a−h Series of Scaffolds[b]

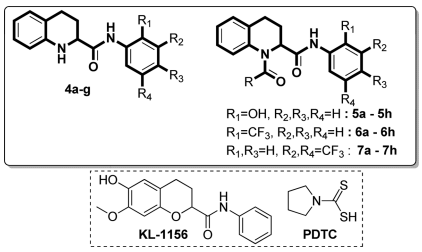


[b]Reagents and conditions: (c) triethylamine, anhydrous THF, 0 °C, 5−10 min, RT, 30−60 min.

(CDI) in tetrahydrofuran at room temperature. This reaction afforded the **3a−g** series of *N*-(substituted)quinoline-2-carboxamides in good yields (Scheme 1). The **3a−g** derivatives were also converted to **4a−g** by Pd/C hydrogenation reaction (H_2 balloon) in ethanol solvent at room temperature. To obtain the **5a−h**, **6a−h**, and **7a−h** series, we performed acylation reaction in the presence of triethylamine in anhydrous tetrahydrofuran (Scheme 2). All newly synthesized derivatives (**3a−g**, **4a−g**, **5a−h**, **6a−h**, and **7a−h**) were confirmed by ^{1}H and ^{13}C NMR and mass spectra. In evaluation studies of inhibition of LPS-induced NF-κB transcriptional activity, we compared all synthesized derivatives (**4a−g**, **5a−h**, **6a−h**, and **7a−h**) with the reference compound pyrrolidine dithiocarbamate (PDTC), which acts as an antioxidant and is a potent inhibitor of NF-κB activation,[21−25] and also with the lead compound KL-1156, which is an inhibitor of NF-κB translocation to the nucleus in LPS-stimulated RAW 264.7 macrophages.[26]

Initially, we screened the **4a−g** derivatives; they exhibited marginal inhibitory effects on NF-κB transcriptional activity (Table 1). After finding that the tetrahydroquinoline core motif was less potent, we next turned our attention mainly to the substitutions of R, R_1, R_2, R_3, and R_4, which resulted in 24 derivatives (**5a−h**, **6a−h**, and **7a−h**; Table 1). Among them, **5e** (IC_{50}: 1.4 ± 0.71 μM), **6f** (IC_{50}: 0.90 ± 0.071 μM), **6g** (IC_{50}: 0.70 ± 0.071 μM), and **6h** (IC_{50}: 2.7 ± 0.42 μM) exhibited outstanding inhibitory effects (Figure 1) on LPS-induced NF-κB transcriptional activity in comparison with remaining derivatives (Table 1). After having the initial experimental results, structure−activity relationship development was initiated for the tetrahydroquinoline scaffold. The 1,2,3,4-tetrahydroquinoline-2-carboxamide motif was modified at two key positions interpreted as R, and substitutions were performed at the aromatic system (R_1, R_2, R_3, and R_4). In the first set of compounds, we performed different substitutions at R_1, R_2, R_3, and R_4, which resulted in **4a−g** analogues. Subsequently $R_1 = R_2 = R_3 = R_4 = H$ (**4a**, IC_{50} 60 μM) was

Table 1. Inhibitory Effect on LPS-Induced NF-κB Transcriptional Activity for 1,2,3,4-Tetrahydroquinolines



No.	substituents (R group) R_1	R_2	R_3	R_4	% inhibition at 100 μM	IC_{50}[c] (μM)
PDTC						37.2
KL-1156					72	53 ± 15
4a	H	H	H	H	85	60 ± 10
4b	OH	H	H	H	57	83 ± 9.9
4c	H	H	OH	H	64	65 ± 0.71
4d	H	H	OCH_3	H	>100	34 ± 12
4e	CF_3	H	H	H	>100	26 ± 5.0
4f	H	H	CF_3	H	79	68 ± 16
4g	H	CF_3	H	CF_3	>100	26 ± 1.4

No.	substituents (R group)	% inhibition at 100 μM	IC_{50}[c] (μM)	No.	% inhibition at 100 μM	IC_{50}[c] (μM)	No.	% inhibition at 100 μM	IC_{50}[c] (μM)
5a	methyl	19		**6a**	32		**7a**	85	23 ± 0.0
5b	ethyl	31		**6b**	43		**7b**	91	20 ± 0.71
5c	propyl	41		**6c**	51	95 ± 0.71	**7c**	88	20 ± 0.71

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Table 1. continued

No.	substituents (R group)	% inhibition at 100 μM	IC_{50}[c] (μM)	No.	% inhibition at 100 μM	IC_{50}[c] (μM)	No.	% inhibition at 100 μM	IC_{50}[c] (μM)
5d	octyl	22		**6d**	63	27 ± 0.71	**7d**	58	51 ± 21
5e	phenyl	>100	1.4 ± 0.071	**6e**	44		**7e**	66	29 ± 0.71
5f	2-chlorophenyl	78	20 ± 0.71	**6f**	82	0.90 ± 0.071	**7f**	90	23 ± 0.0
5g	3-chlorophenyl	58	78 ± 2.1	**6g**	90	0.70 ± 0.071	**7g**	68	27 ± 0.71
5h	4-chlorophenyl	82	20 ± 2.8	**6h**	92	2.7 ± 0.42	**7h**	92	20 ± 2.1

[c]IC_{50} values are means of the concentration (μM) exhibiting 50% inhibition of LPS-induced NF-κB transcriptional activity.

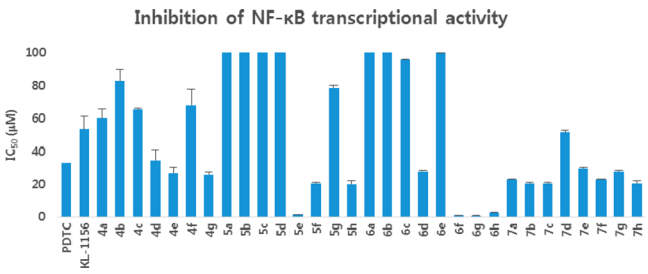

Figure 1. Efficacy of **4a−g**, **5a−h**, **6a−h**, and **7a−h** analogues in inhibition of NF-κB transcriptional activities.

prepared to study the effect of the core 1,2,3,4-tetrahydroquinoline-2-carboxamide motif. We also examined the electronic influence of different groups at R_1, R_2, R_3, and R_4, including electron-deficient ($-CF_3$) and electron-rich groups ($-OCH_3$ and $-OH$). Next, we introduced various acyl and aroyl groups at the 1-position of tetrahydroquinoline-2-carboxamides, which resulted in **5a−h**, **6a−h**, and **7a−h** analogues. Sizes of different aliphatic chains (−R) and substituents at the aromatic ring were then examined. The inhibitory effects of these compounds (**4a−g**, **5a−h**, **6a−h**, and **7a−h**) depended on the nature of the substitution at the R-position and the substituents (R_1, R_2, R_3, and R_4) on the *N*-phenyl ring of tetrahydroquinoline-2-carboxamides. For instance, with R = an alkyl group (methyl, ethyl, propyl, or octyl), we did not notice any significant inhibitory effects, but with R = phenyl. The following compounds exhibited excellent inhibitory effects on LPS-induced NF-κB transcriptional activity (Figure 2): **5e** (IC_{50}: 1.4 ± 0.071 μM, about 26 and 37 times more potent than PDTC and KL-1156, respectively), **6f** (IC_{50}: 0.90 ± 0.071 μM, about 41 and 58 times more potent), **6g** (IC_{50}: 0.70 ± 0.071 μM, about 53 and 75 times), and **6h** (IC_{50}: 2.7 ± 0.42 μM, about 13 and 19 times). We also tested other substitutions at the R-position and different substituents at the R_1, R_2, R_3, and R_4 positions of the 1,2,3,4-tetrahydroquinoline core motif (Table 1). To explain the trend toward NF-κB inhibition interestingly, the electron-withdrawing group $-CF_3$ at the R_1 position resulted in outstanding inhibitory effects on LPS-induced NF-κB transcriptional activity in comparison with any electron-releasing group (for example, −OH). We also noticed that −I and +M effect groups (such as −Cl) at the second and third positions of the aryl group of R in combination with $-CF_3$ at the R_1 position also showed excellent inhibition of NF-κB transcriptional activity (**6g**, IC_{50}: 0.70 ± 0.071 μM; **6f**, IC_{50}: 0.90 ± 0.071 μM). Overall, most of the synthesized compounds (**4d**, **4e**, **4g**, **5f**, **5h**, **6d**, **7a−c**, and **7e−h**) were more potent inhibitors of NF-κB transcriptional activity than PDTC and KL-1156 (Figure 2). We next studied the *in vitro* cytotoxicity of the synthesized compounds and initially evaluated quinoline-2-carboxamide derivatives (**3a−g**) with the human lung cancer cell line (NCI-H23) and doxorubicin (ADR) as a reference compound.

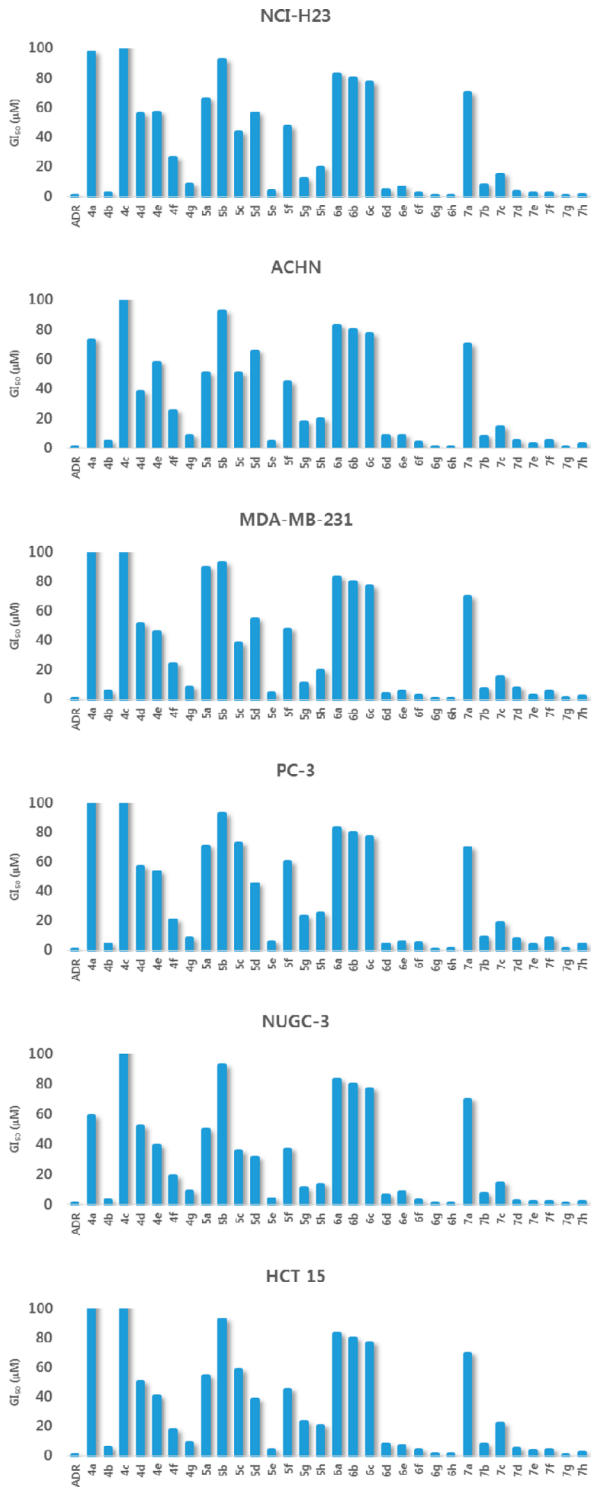

Figure 2. *In vitro* efficacy of **4a−g**, **5a−h**, **6a−h**, and **7a−h** analogues in inhibiting growth of human cancer cell lines.

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Table 2. Cytotoxicity of 3a–g Series against Lung Cancer (NCI-H23) Cell Lines

No.	R_1	R_2	R_3	R_4	GI_{50} (μM)[d]
ADR					0.101 ± 0.00602
3a	H	H	H	H	108 ± 8.74
3b	OH	H	H	H	87.5 ± 9.77
3c	H	H	OH	H	102 ± 11.4
3d	H	H	OCH_3	H	7.65 ± 1.93
3e	CF_3	H	H	H	>90
3f	H	H	CF_3	H	>90
3g	H	CF_3	H	CF_3	1.44 ± 0.463

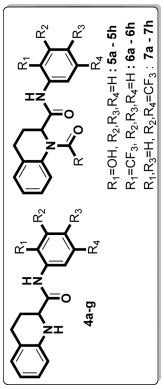
[d] GI_{50} values are taken as a mean from three experiments and correspond to the agent's concentration causing a 50% decrease in net cell growth.

As shown in Table 2, electron-withdrawing substituents such as $-CF_3$ at the R_2 and R_4 positions of the phenyl ring (**3g**, GI_{50} 1.44 ± 0.463 μM) resulted in the most potent cytotoxicity. The series **4a–g**, **5a–h**, **6a–h**, and **7a–h** were also evaluated for *in vitro* cytotoxicity against six human cancer cells: NCI-H23, ACHN (renal), MDA-MB-231 (breast), PC-3 (prostate), NUGC-3 (gastric), and HCT15 (colon) (Table 3). Any substitution on the phenyl ring was not beneficial, and only **4b** (GI_{50} 2.23 ± 0.455 μM) exhibited better cytotoxic activities against all tested cell lines than other analogues of the **4a–g** series (Table 3). To further confirm that the tetrahydroquinoline motif is beneficial for cytotoxicity, we executed acylation reaction with triethyl amine in tetrahydrofuran with **4b**, **4e**, and **4g**; introduction of electron-rich or electron-withdrawing substituents at the R_1 position afforded **5a–h**, **6a–h**, and **7a–h** analogues. As expected, these analogues had improved cytotoxicity against all tested cell lines (Figure 2), suggesting that substitutions at the R_1 position and the first position of the tetrahydroquinoline motif are most important (Table 3). Compound **5e** exhibited the highest cytotoxicity (Table 3) against all evaluated cell lines (NCI-H23, GI_{50} 3.49 ± 0.999 μM; NUGC-3, GI_{50} 3.78 ± 0.618 μM; HCT 15, GI_{50} 3.83 ± 0.994 μM). The importance of an electron-withdrawing group was also confirmed by **6g** and **6h** derivatives, which have $-CF_3$ and $-Cl$ on both phenyl rings and exhibited outstanding cytotoxicity (**6g**, GI_{50} 0.292 ± 0.111–0.797 ± 0.173 μM; **6h**, GI_{50} 0.307 ± 0.0.0941–0.839 ± 0.0610 μM) against all tested cell lines (Figure 2, Table 3). The $-CF_3$ group at the R_2 and R_4 positions of the phenyl ring in **7g** also resulted in potent cytotoxicity against all tested cell lines (0.420–1.19 μM; Table 3). Compound **7h** also exhibited potent cytotoxicity against lung (NCI-H23 (GI_{50} 0.889 ± 0.102 μM) and gastric (NUGC-3, GI_{50} 1.66 ± 0.406 μM) cancer cell lines and moderate cytotoxicity against the other four cell lines (Table 3).

In summary, we identified a new class of 1,2,3,4-tetrahydroquinolines as the most potent NF-κB inhibitors and potent cytotoxic agents against human cancer cell lines.

The first round of screening starting from the initial lead scaffold **4a** led to the discovery of **6f**, **6g**, and **6h** analogues. These new lead analogues inhibited LPS-induced NF-κB transcriptional activity 41, 53, and 13 times more potently, respectively, than the reference compound PDTC. Analogues **6f**, **6g**, and **6h** have also shown the most potent *in vitro* cytotoxicity against all evaluated human cancer cell lines. Thus, **6f**, **6g**, **6h**, and related analogues provide new chemical tools for development of pathway-selective NF-κB inhibitors with

Table 3. Cytotoxicity against NCI-H23, ACHN, MDA-MB-231, PC-3 NUGC-3, and HCT-15 Cancer Cell Lines



No.	R	R_1	R_2	R_3	R_4	GI_{50} (μM)[d] NCI-H23	ACHN	MDA-MB-231	PC-3	NUGC-3	HCT 15
ADR		ref				0.0726 ± 0.00940	0.0995 ± 0.00848	0.112 ± 0.0132	0.0923 ± 0.0103	0.125 ± 0.0104	0.0854 ± 0.00329
4a		H	H	H	H	97.1 ± 15.3	72.9 ± 11.4	108 ± 17.8	110 ± 15.6	59.0 ± 9.88	109 ± 15.0
4b		OH	H	H	H	2.23 ± 0.455	3.99 ± 1.33	5.26 ± 1.77	4.31 ± 1.34	2.68 ± 0.824	5.61 ± 1.31
4c		H	H	OH	H	>100	>100	>100	>100	>100	>100
4d		H	H	OCH_3	H	55.7 ± 9.80	38.0 ± 11.7	51.4 ± 11.2	56.9 ± 17.6	51.9 ± 11.0	50.2 ± 8.10
4e		CF_3	H	H	H	56.8 ± 11.4	57.6 ± 11.7	45.5 ± 13.1	53.3 ± 9.65	39.3 ± 8.58	40.4 ± 4.68
4f		H	H	CF_3	H	25.8 ± 4.12	25.0 ± 8.17	24.2 ± 5.10	20.3 ± 7.35	18.6 ± 5.76	17.6 ± 3.45
4g		H	CF_3	H	CF_3	8.41 ± 1.01	8.19 ± 3.78	8.27 ± 2.74	8.12 ± 5.09	8.76 ± 1.36	8.70 ± 3.02

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Table 3. continued

No.	R	R_1	R_2	R_3	R_4	GI_{50} (μM)[d]					
						NCI-H23	ACHN	MDA-MB-231	PC-3	NUGC-3	HCT 15
5a	methyl	OH	H	H	H	65.7 ± 8.84	50.7 ± 6.32	89.6 ± 9.29	70.7 ± 14.6	49.7 ± 10.9	54.5 ± 7.60
5b	ethyl	OH	H	H	H	>90	>90	>90	>90	>90	>90
5c	propyl	OH	H	H	H	43.1 ± 6.24	50.6 ± 11.2	38.0 ± 3.55	72.5 ± 9.36	35.4 ± 7.10	58.3 ± 9.89
5d	octyl	OH	H	H	H	55.8 ± 8.08	65.0 ± 6.13	54.3 ± 10.0	45.2 ± 7.03	31.1 ± 5.10	38.4 ± 6.27
5e	phenyl	OH	H	H	H	3.49 ± 0.999	4.26 ± 1.21	4.21 ± 0.892	5.69 ± 1.21	3.78 ± 0.618	3.83 ± 0.994
5f	2-chlorophenyl	OH	H	H	H	46.9 ± 2.99	44.2 ± 9.55	47.4 ± 5.04	60.0 ± 14.3	36.8 ± 6.41	44.9 ± 8.04
5g	3-chlorophenyl	OH	H	H	H	11.6 ± 2.75	17.2 ± 3.54	10.6 ± 1.60	23.3 ± 4.39	11.0 ± 2.34	23.1 ± 5.28
5h	4-chlorophenyl	OH	H	H	H	19.2 ± 3.77	19.6 ± 5.06	19.6 ± 3.54	25.1 ± 4.62	13.4 ± 2.20	20.2 ± 2.97

No.	R	R_1	R_2	R_3	R_4	GI_{50} (μM)[d]					
						NCI-H23	ACHN	MDA-MB-231	PC-3	NUGC-3	HCT 15
6a	methyl	CF_3	H	H	H	>80	>80	>80	>80	>80	>80
6b	ethyl	CF_3	H	H	H	>80	>80	>80	>80	>80	>80
6c	propyl	CF_3	H	H	H	>70	>70	>70	>70	>70	>70
6d	octyl	CF_3	H	H	H	4.22 ± 1.26	8.33 ± 3.09	3.35 ± 0.482	4.32 ± 1.04	6.18 ± 1.30	7.70 ± 1.11
6e	phenyl	CF_3	H	H	H	6.34 ± 2.52	8.09 ± 1.68	5.29 ± 0.846	5.56 ± 0.990	8.12 ± 1.44	6.50 ± 1.14
6f	2-chlorophenyl	CF_3	H	H	H	2.15 ± 0.680	3.90 ± 0.946	2.53 ± 0.625	5.14 ± 1.02	2.73 ± 0.554	4.22 ± 0.303
6g	3-chlorophenyl	CF_3	H	H	H	0.292 ± 0.111	0.526 ± 0.178	0.288 ± 0.0992	0.729 ± 0.131	0.754 ± 0.129	0.797 ± 0.173
6h	4-chlorophenyl	CF_3	H	H	H	0.307 ± 0.0941	0.824 ± 0.0708	0.533 ± 0.0824	0.786 ± 0.0996	0.551 ± 0.126	0.839 ± 0.0610

No.	R	R_1	R_2	R_3	R_4	GI_{50} (μM)[d]					
						NCI-H23	ACHN	MDA-MB-231	PC-3	NUGC-3	HCT 15
7a	methyl	H	CF_3	H	CF_3	>70	>70	>70	>70	>70	>70
7b	ethyl	H	CF_3	H	CF_3	7.82 ± 1.62	7.72 ± 2.40	7.28 ± 0.965	8.54 ± 1.99	7.22 ± 1.35	7.62 ± 0.902
7c	propyl	H	CF_3	H	CF_3	15.0 ± 2.67	13.9 ± 4.03	15.2 ± 2.44	18.6 ± 2.87	14.4 ± 3.49	21.9 ± 3.11
7d	octyl	H	CF_3	H	CF_3	3.23 ± 0.397	4.52 ± 1.13	7.53 ± 1.69	7.43 ± 1.89	2.23 ± 0.579	4.97 ± 1.09
7e	phenyl	H	CF_3	H	CF_3	2.13 ± 0.638	2.92 ± 0.640	2.43 ± 0.632	3.50 ± 0.630	1.68 ± 0.238	3.54 ± 1.20
7f	2-chlorophenyl	H	CF_3	H	CF_3	2.08 ± 0.482	4.70 ± 0.733	5.25 ± 1.08	8.04 ± 2.55	1.93 ± 0.404	4.05 ± 0.820
7g	3-chlorophenyl	H	CF_3	H	CF_3	0.420 ± 0.0607	0.813 ± 0.271	1.19 ± 0.313	1.05 ± 0.254	0.560 ± 0.189	0.625 ± 0.0674
7h	4-chlorophenyl	H	CF_3	H	CF_3	0.889 ± 0.102	2.57 ± 0.981	2.00 ± 0.683	4.23 ± 1.67	1.66 ± 0.406	2.22 ± 0.216

[d] GI_{50} values are taken as a mean from three experiments and correspond to the agent's concentration causing a 50% decrease in net cell growth.

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anticancer activity. Work on the enhancement of potency and pharmacological profiles of these probe molecules are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.6b00004.

Synthetic procedures, characterization of final products, biological assay protocols, and data and pharmacology profiles (PDF)

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Notes

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■ ABBREVIATIONS

LPS, lipopolysaccharide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells

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