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Letter

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

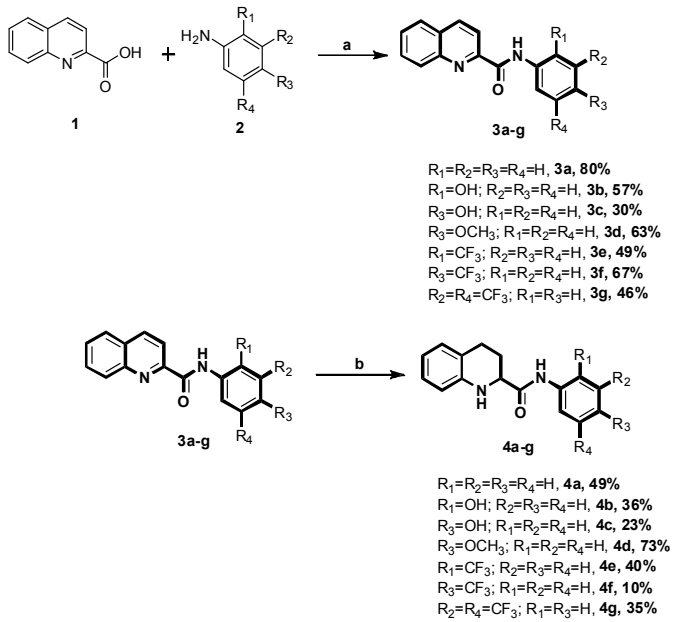
ABSTRACT: 1,2,3,4-Tetrahydroquinolines have been identified as the most potent inhibitors of LPS-induced NF-κB transcriptional activity. To discover new molecules of this class with excellent activities, we designed and synthesized a series of novel derivatives of 1,2,3,4-tetrahydroquinolines (**4a-g**, **5a-h**, **6a-h**, and **7a-h**) and bio-evaluated 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.

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 signalling 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 and anti Parkinson's diseases etc. María José Abad *et al*.[18] were 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 (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**)

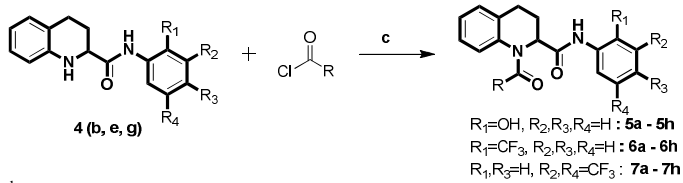
Scheme 1. Synthesis of **3a-g** and **4a-g** series of scaffolds[a]



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

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]

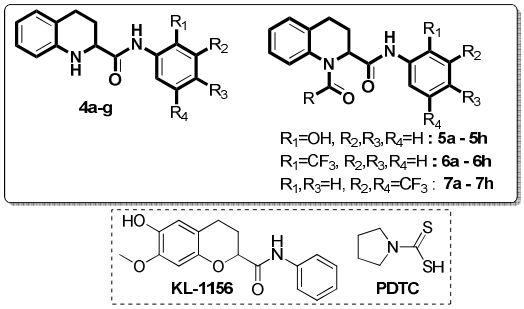
Scheme 2. Synthesis of **5a-h**, **6a-h** and **7a-h** series of scaffolds[b]



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

Initially, we screened the **4a-g** derivatives; they exhibited marginal inhibitory effects on NF-κB transcriptional activity (Table 1). After having 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 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 (-CF3) and electron-rich groups (-OCH3 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 2nd and 3rd 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.

Table 1. Inhibitory effect on LPS-induced NF-κB transcriptional activity for 1,2,3,4-tetrahydroquinolines.



No.	Substituents (R group)				% inhibition at 100 μM	IC_{50}[c] (μM)
	R_1	R_2	R_3	R_4		
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
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.

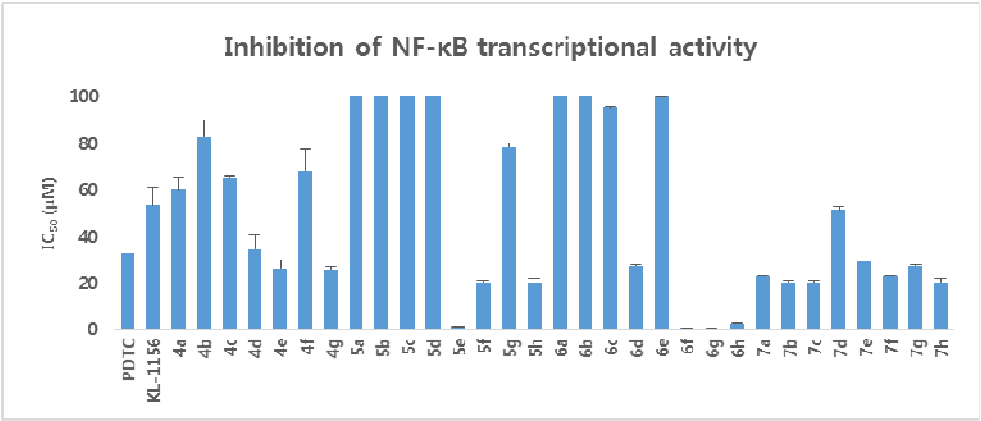


Figure 1. Efficacy of **4a-g**, **5a-h**, **6a-h** and **7a-h** analogues in Inhibition of NF-κB transcriptional activities

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 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) (Figure 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 (Figure 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 (Figure 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 –CF3 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.

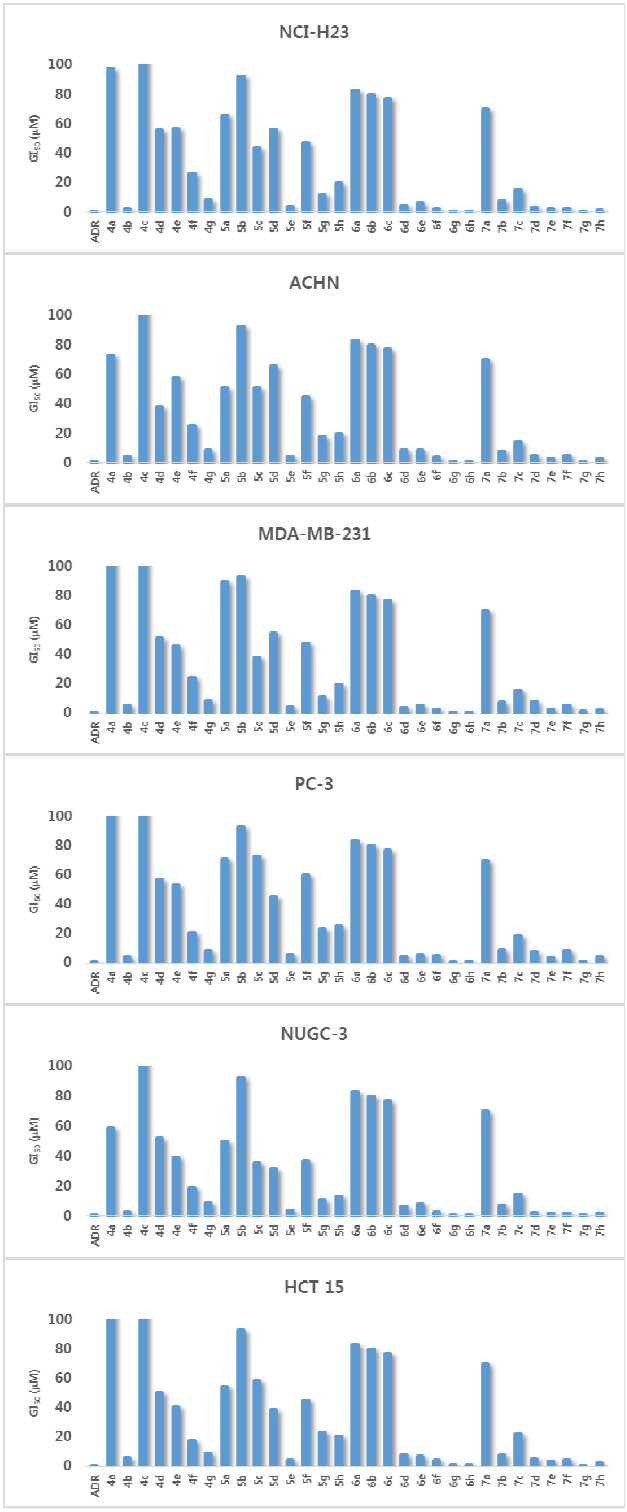
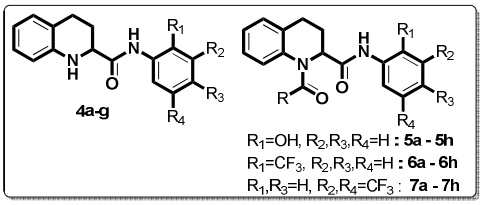


Figure 2. In *vitro* efficacy of **4a-g**, **5a-h**, **6a-h** and **7a-h** analogues in inhibiting growth of human cancer cell lines.

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



						GI$_{50}$ (μM)[d]					
No.	R	R$_1$	R$_2$	R$_3$	R$_4$	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

						GI$_{50}$ (μM)[d]					
No.	R	R$_1$	R$_2$	R$_3$	R$_4$	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

						GI$_{50}$ (μM)[d]					
No.	R	R$_1$	R$_2$	R$_3$	R$_4$	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

						GI$_{50}$ (μM)[d]					
No.	R	R$_1$	R$_2$	R$_3$	R$_4$	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

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

ASSOCIATED CONTENT

Supporting Information. Synthetic Procedures, characterization of final products, biological assay protocols and data and pharmacology profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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ABBREVIATIONS

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

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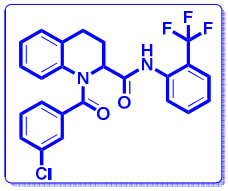
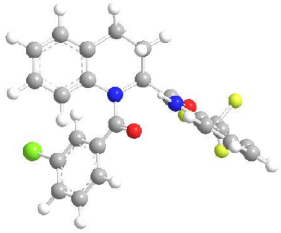
TOC Graphics





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