



Clomiphene Analogs with Activity *In Vitro* and *In Vivo* against Human Breast Cancer Cells

R. Jeffrey Baumann,*† Tammy L. Bush,* Doreen E. Cross-Doersen,*
Elizabeth A. Cashman,* Paul S. Wright,* John H. Zwolshen,* Gregory F. Davis,*
Donald P. Matthews,‡ David M. Bender§ and Alan J. Bitonti*

*ONCOLOGY, HOECHST MARION ROUSSEL, BRIDGEWATER, NJ 08807; ‡ENDOCRINE DEPARTMENT, ELI LILLY & CO., INDIANAPOLIS, IN 46285; AND §DEPARTMENT OF CHEMISTRY, COLORADO STATE UNIVERSITY, FT. COLLINS, CO 80523, U.S.A.

ABSTRACT. Six hundred triphenylethylenes were assayed for antiproliferative activity against MCF-7, LY2, and MDA-MB-231 breast cancer cells using sulforhodamine B dye to measure proliferation. Here we report on just 63 of the compounds, mostly clomiphene analogs, with substitutions on the α' or β ring, at the vinyl position or in the side chain, of which 23 were active, as defined by antiproliferation IC_{50} values $\leq 1 \mu M$. Activity profiles showed that 23 and 11 analogs were active toward MCF-7 and LY2, respectively, but none were active against MDA-MB-231. The IC_{50} values of tamoxifen were $2.0 \mu M$ against MCF-7 and $7.5 \mu M$ against LY2 and MDA-MB-231. Estradiol reversed antiproliferative activities of several E isomers but not their Z isomer counterparts. Clomiphene side chain analogs **46** [(E)-1-butanamine, 4-[4-(2-chloro-1,2-diphenylethenyl)phenoxy]-N,N-diethyl-dihydrogen citrate (MDL 103,323)] and **57** [(E)-N-[p-(2-chloro-1,2-diphenylvinyl)phenyl]-N,N-diethylethylenediamine dihydrogen citrate (MDL 101,986)] were 4- to 5-fold more effective than tamoxifen. Methylene additions up to $(-CH_2-)_{12}$ in the clomiphene side chain showed that analog **46** $(-CH_2-)_{4}$ side chain] had maximal antiproliferative activity, binding affinity, and inhibition of transcription of an estrogen response element luciferase construct in transfected MCF-7 cells. Intraperitoneal administration of **46** or **57** inhibited progression of MCF-7 breast tumor xenografts in nude mice with ED_{50} values of <0.02 mg/mouse/day. Both analogs may hold promise for treating ER positive breast cancer and are of interest for further development. *BIOCHEM PHARMACOL* 55;6:841–851, 1998. © 1998 Elsevier Science Inc.

KEY WORDS. clomiphene analogs; antiestrogens; breast cancer; MCF-7; LY2; tamoxifen resistance; estrogen receptor

The number of new cases of breast cancer diagnosed every year is approximately 180,000, making this disease the most prevalent cancer in women [1]. Breast cancer is a hormone-dependent cancer, and an estimated 70% of tumors are positive for the ER^h [2]. Two classes of antiestrogen drugs known to antagonize the growth of hormone-dependent breast cancer cells are steroidal antiestrogens such as ICI 164,384 [3] and nonsteroidal antiestrogens such as the TPEs clomiphene [4], toremifene [5], and tamoxifen [6, 7]. Tamoxifen is used worldwide by over a million women for the treatment of ER positive breast cancer. Its continued use has reduced both the annual rate of death and disease

recurrence among breast cancer patients [8], and it has a low incidence of short- and long-term side-effects. However, tamoxifen resistance eventually develops, resulting in the failure of tamoxifen therapy, thus creating the need for additional nontoxic therapeutic modalities.

Prior to the development of tamoxifen, the first reported active nonsteroidal antiestrogen, ethamoxypiphetol (MER-25), was synthesized at the Wm. S. Merrell Co. [9] and subsequently shown to have antifertility activity [10] and antitumor activity [11]. These findings were the incentive for more intensive efforts leading to the synthesis of clomiphene [12], Upjohn's nafoxidine [13], and later tamoxifen at Imperial Chemical Industries [14]. For a review of antiestrogens, see Ref. 15. Clomiphene is marketed by Hoechst Marion Roussel as a fertility agent, but it has been used in clinical trials for the treatment of breast cancer [16]. Cumulative results were published from various clinical trials, and objective responses were noted in 28% of late stage breast cancer patients given clomiphene, which compared favorably with responses to tamoxifen (27%) in unselected patients [17]. Because of our earlier efforts in antiestrogen research, approximately 600 TPEs were avail-

† Corresponding author: Dr. R. Jeffrey Baumann (c/o Dr. Paul S. Wright) Oncology, Hoechst Marion Roussel Route 202-206N, Bridgewater, NJ 08807. Tel. (908) 231-4000, FAX: (908) 231-2727.

^hAbbreviations: CSCS, charcoal stripped calf serum; ER, estrogen receptor; FBS, fetal bovine serum; HBSS, Hanks' Balanced Salt Solution; IMEM, Improved Minimum Essential Medium, Eagle's; MTCG, monothio-glycerol; MTT, 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NSB, nonspecific binding; RBA, relative binding affinity; SRB, sulforhodamine B dye; tam, tamoxifen citrate; and TPE, triphenylethylene.

Received 21 January 1997; accepted 12 September 1997.

able in the Hoechst Marion Roussel chemical inventory. Having set goals to seek compounds significantly more potent than tamoxifen, and with efficacy against tamoxifen-resistant breast cancer cells, we screened the TPEs for antiproliferative activity against three human breast cancer cell lines: MCF-7 (ER positive, tamoxifen-susceptible), LY2 (ER positive, tamoxifen-resistant), and MDA-MB-231 (ER negative, tamoxifen-resistant).

In this paper, we present results on 63 TPEs with substitutions in the α ring side chain, or on the α' or β ring, or at the vinyl Cl of clomiphene. Of the 63 analogs, 23 were found to have antiproliferative IC_{50} values $\leq 1 \mu M$, and many had IC_{50} values lower than that of tamoxifen toward MCF-7 and LY2. Furthermore, several of the 23 analogs were separated into pure *E* and *Z* isomers to define isomer specificities in terms of biological and biochemical activities including antiproliferative assays, antitumor activity in nude mice, and ER relative binding activities.

MDL 103,323 [(*E*)-1-butanamine, 4-[4-(2-chloro-1,2-diphenylethenyl)phenoxy]-*N,N*-diethyl-dihydrogen citrate] and MDL 101,986 [(*E*)-*N*-[*p*-(2-chloro-1,2-diphenylvinyl)phenyl]-*N,N*-diethylethylenediamine dihydrogen citrate] are *E* isomers of the clomiphene analogs 46 and 57, respectively. Both showed significant antitumor activity against MCF-7 human tumor xenografts in nude mice with ED_{50} values < 0.02 mg/mouse/day, administered orally for 6 weeks. In addition, the antiproliferative activities of both isomers were several-fold better than tamoxifen toward MCF-7 and LY2 cell lines. The biological activities of these analogs suggest potential utility for the treatment of estrogen-dependent breast cancer.

MATERIALS AND METHODS

Cell Lines

MCF-7 (ATCC HTB 22) and MDA-MB-231 (ATCC HTB 26) were obtained from the American Type Culture Collection. LY2 cells were provided by Dr. Marc Lippman [18]. Cells were maintained in Costar T75 flasks containing IMEM without phenol red (Biofluids, Inc.) supplemented with 4 mM glutamine and 5% FBS (Gibco BRL).

TPEs

All compounds were analyzed for structural integrity and spectral purity by NMR prior to their use in assays. The majority of TPEs had been synthesized as mixtures of isomers, and were screened without further modifications. However, several of the isomer mixtures that showed interesting biological activity were resolved into pure isomers and retested. To obtain pure *E* and *Z* isomers, isomeric mixtures were made basic with 2 N NaOH, extracted with chloroform, and analyzed by HPLC on a Porasil column (Waters) monitored by UV at 270 nm. The mobile solvent was hexane:chloroform:triethylamine (20:80:0.02). For preparative HPLC, a 19 \times 300 mm semipreparative column was used with a flow of 15 mL/min and an injection volume

of 50 μL containing 25 mg of compound. The individual isomer peaks were collected and identified by NMR and mass spectrometry. The *E* isomer of 22 (4-hydroxyclophenone) isomerized to an approximately equal mixture of *E* and *Z* isomers within 2 weeks in hexane/ $CHCl_3$, but not in DMSO. Binding assays with the *E* isomer were performed within 3 days of its dissolution in DMSO. Tamoxifen citrate (tam) and 4-hydroxytamoxifen citrate were obtained from ICI America, Inc.

Antiproliferation Assay

SRB stains protein and is used to measure cell growth. Because the SRB assay is suitable for large-scale screening with several practical advantages over the MTT assay, the National Cancer Institute adopted this assay for use in routine antiproliferative screening.

Antiproliferative assays were performed using SRB (Sigma) as described [19] with modifications. Cells were harvested when nearly confluent from IMEM/FBS using trypsin/EDTA, washed once with serum-free IMEM, and resuspended in IMEM/FBS. Stock drug solutions (10 mM) were prepared in DMSO and diluted with serum-free IMEM. Drug dilutions and all additions of drugs, cells, and medium to microtiter wells were made with a Perkin Elmer Cetus PRO/PETTE. Aliquots (100 μL) of 1×10^4 MCF-7 cells or 3×10^3 LY2 or MDA-MB-231 cells were dispensed in duplicate into 96-well microtiter plates and incubated at 37° in 5% CO_2 for 20–24 hr, and the medium was replaced with 100 μL of IMEM/FBS containing drug concentrations from 0.078 to 10 μM in duplicate. After 4 days of incubation, the medium and drugs were replaced. After a total of 8 days of incubation, the medium was removed and the cell monolayers were fixed for 60 min at 4° with 100 μL of 10% trichloroacetic acid, rinsed five times with water, and dried. The fixed cells were stained for 30 min at room temperature with 100 μL of 0.4% SRB in 1% acetic acid, rinsed four times with 1% acetic acid, and dried, and the SRB was extracted for 5 min with 100 μL of 10 mM Tris base, pH 10.5. Absorbances were determined at 492 nm with a Titertek Multiscan MCC/340 plate reader. Concentration–response curves were constructed to estimate IC_{50} values, defined as the micromolar concentration of drug inhibiting 50% of proliferation. To determine the effect of estradiol on IC_{50} values, compounds were assayed in medium supplemented with 0.1 μM estradiol (Sigma).

The following guidelines were used for making comparisons on various compound activities. Active compounds had antiproliferative IC_{50} values $\leq 1 \mu M$ toward any cell line, compounds were selective for MCF-7 or LY2 if antiproliferative IC_{50} values against the cell lines differed by ≥ 5 -fold, and estradiol reversal of growth antagonism was positive if the IC_{50} in estradiol-supplemented medium was ≥ 3 -fold the IC_{50} determined in unsupplemented medium.

Extraction of ER

MCF-7 or LY2 cells were cultured for 15–30 passages in IMEM supplemented with 5% CSCS (Cocalico Biologicals) and 4 $\mu\text{g}/\text{mL}$ bovine insulin (Gibco BRL), since preliminary assays indicated the ER yield was 2- to 3-fold greater if CSCS was substituted for FBS. The monolayers were rinsed with HBSS (Gibco BRL), scraped into HBSS containing 0.1% (v/v) MTG, and centrifuged for 10 min at 800 *g*. To extract total ER (cytosolic + nuclear), cells were resuspended in 2 packed cell volumes of high salt extraction buffer [10% (v/v) glycerol, 500 mM KCl, 25 mM HEPES buffer, pH 7.8] [18, 20, 21], frozen and thawed three times, mixed for 30 min at 4°, and centrifuged at 4° for 30 min at 12,000 *g*. Supernatants were retained as the source of ER and stored at –80°.

Relative Binding Affinities

RBAs were determined in 96-well microtiter plates with conical wells [22]. Drugs were prepared as 10 mM stock solutions in DMSO, and further dilutions were made with Tris/EDTA buffer (TE buffer) containing the following supplements and final concentrations of 8 mM Tris, pH 7.4, 1 mM EDTA, 0.4% BSA [23], 12.5% (v/v) dimethylformamide, 0.1% (v/v) MTG and 2 nM [2,4,6,7-³H]estradiol, 114 Ci/mmol (Amersham). Cell extracts (15 μL) were added to begin the assay in final volumes of 100 μL , in triplicate, and incubated at 4° for 16–18 hr. Receptor bound [³H]estradiol was separated from unbound [³H]estradiol with 100 μL of TE buffer, pH 7.4, containing 0.1% (v/v) MTG, 0.5% BSA, 0.05% dextran T70, and 0.5% Norit A at 4° for 15 min and centrifuged at 4° for 20 min at 1200 *g*. The mean net disintegrations per minute were determined in 160 μL of supernatant by subtracting the mean of the NSB (NSB = dpm bound in the presence of 1 μM nonradioactive estradiol). The IC_{50} values were estimated from percent control versus concentration curves, and RBAs were calculated from the expression:

$$\text{RBA} = \frac{\text{IC}_{50} \text{ estradiol}}{\text{IC}_{50} \text{ TPE}} \times 100, \text{ according to Korenman [24].}$$

Concentration–response curves of several E isomers were analyzed for parallelism using Graph Pad software (Prism Version 2.01).

Transfection

To determine whether isomers of side chain analogs inhibited expression of an estrogen responsive gene, the pGL2-basic vector (Promega) was digested with *Sma*I and *Xho*I, and a DNA fragment containing two copies of the vitellogenin estrogen response element [25], adjacent to a 180 bp fragment encoding the thymidine kinase promoter [26], was inserted upstream to the luciferase gene. This plasmid, pVETLUC, was provided by Drs. Steven Busch and Gary

Martin. MCF-7 cells were transfected with the pVETLUC plasmid by electroporation. Cells (2×10^6) were combined with 50 μg of plasmid DNA in 1 mL of OPTI-MEM 1 medium in an electroporation chamber (Gibco BRL). The suspension was subjected to a charge of 500 V/cm, 800 microfarads, at 0° and low resistance. Following a 1-min recovery period, the cells were resuspended in growth medium, viability was assessed by trypan blue exclusion, and cells were dispensed into 96-well microtiter plates at approximately 1×10^4 cells/well. The culture medium was replaced with fresh medium after 4 hr of incubation at 37°, and after 24 hr with fresh medium containing 1 nM estradiol and side chain-extended analogs and incubated for 18–22 hr. The cells were rinsed once with HBSS and, after freezing at –70° for 15 min, 150 μL of lysis buffer (Promega) was added and the plates were agitated for 20 min at ambient temperature. The lysates were analyzed for luciferase (Promega assay system) in a luminometer. The IC_{50} values were determined from log-log curve fits using Biolinks software from Dynatech.

Antitumor Effects of TPEs

Nude mice were housed in microisolator cages under positive air pressure, and all surgical manipulations and drug treatments were performed in a laminar flow cabinet. MCF-7 cells (2×10^6) were inoculated s.c. into the flanks of female *nu/nu* mice, and tumors were allowed to develop. Tumors of 400–500 mm^3 were taken from maintenance mice, cut into 2- mm^3 pieces, and transplanted into the flanks of naive mice using a 13-Ga trocar. These xenografts were allowed to grow to volumes of 50–100 mm^3 , at which time mice ($N = 6$) were assigned randomly to control or drug treatment groups. To assess tumor growth and the effects of TPEs, tumors were measured weekly with Vernier calipers in two dimensions as described previously [27]. TPEs were administered daily, 5 days/week, as a solution in 6% ethanol, 4% Tween 80, 0.8% NaCl, and 0.68 mM citric acid (0.2 mL/dose) [28].

RESULTS

Substitutions on the α' and β Rings of 1 and 15, and at the Vinyl Cl of 15

The compounds in Table 1 consist of two groups, analogs of 1, $R = \text{H}$ (2–14) and analogs of 15, $R = \text{Cl}$ (clomiphene) (16–25). The necessity of Cl for activity ($\text{IC}_{50} \leq 1 \mu\text{M}$, see Materials and Methods) is clearly shown, since compound 15 was ten and five times more active than compound 1 toward MCF-7 and LY2, respectively. Further comparisons show that just 2 analogs of 1 (7 and 9) and 6 analogs of 15 (16, 19, and 22–25) were active. Compound 26 was also active, but it is the HCl salt of clomiphene, not a clomiphene analog. Very little improvement in the activity of 15 against MCF-7 was generated by various substitutions at R_1 or R_2 except for the hydroxy analog (22) which was 10 times more active than 15 and 100 times more active than

TABLE 1. Antiproliferative activities of analogs substituted on the α' and β rings of 1 and 15

Compound	R	R ₁	R ₂	IC ₅₀ * (μM)		
				MCF-7	LY2	MDA-MB-231
1†	H‡	H	H	8.0	8.0	ND§
2	H	CH ₃	H	4.0	4.0	ND
3	H	OCH ₃	H	2.0	3.0	4.5
4	H	Cl	H	5.8	6.2	ND
5	H	F	H	1.4	3.3	ND
6	H	C(CH ₃) ₃	H	1.3	4.5	ND
7	H	Biphenyl	H	0.85	3.0	ND
8	H	H	CH ₃	3.4	2.5	ND
9	H	OCH ₃	CH ₃	1.0	2.7	6.0
10	H	Cl	CH ₃	4.1	6.2	6.2
11	H	H	Cl	3.2	3.2	ND
12	H	OCH ₃	Cl	3.0	3.5	ND
13	H	Cl	Cl	3.0	4.7	ND
14	H	H	O-DEAE	2.7	5.4	ND
15	Cl	H	H	0.8	1.5	7.2
16	Cl	OH	H	3.0	1.0	> 10
17	Cl	OCH ₃	H	1.3	2.3	6.6
18	Cl	Cl	H	1.5	3.0	4.0
19	Cl	Cl	CH ₃	0.5	1.9	3.6
20	Cl	C(CH ₃) ₃	H	1.2	3.3	ND
21	Cl		H	1.1	3.0	ND
22	Cl	H	OH	0.07	1.6	> 10
23	Cl	H	CH ₃	0.8	1.0	ND
24	Cl	H	OCH ₃	0.6	0.8	6.5
25	Cl	OCH ₃	Cl	0.8	0.9	3.1
26	Cl	H	H	0.6	1.4	7.2

* Most IC₅₀ values ≤ 1 μM are means of at least two experiments.

† Compounds are citrate salts except for 1, 2, 4, 7, 13, 19, 25, and 26 which are hydrochloride salts and 6 which is a free base.

‡ Isomer configuration: isomeric mixtures except for 1, 4, 6, 13, and 14 are one isomer of unknown configuration; 7 is *E* configuration; 10 and 11, isomer status unknown.

§ ND = not determined.

|| O(CH₂)₂N(C₂H₅)₂.

1. Furthermore, compound 22 was about 40 times more active than compound 16 against MCF-7, demonstrating the superior antiproliferative activity of the β -4-OH over the α' -4-OH.

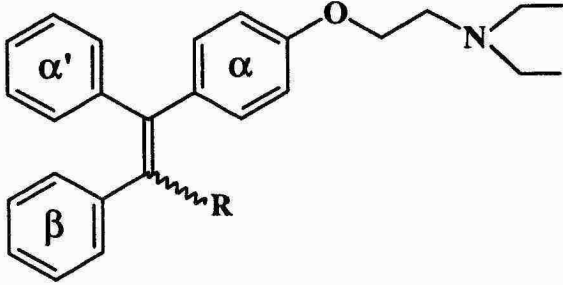
Several analogs of 15 with various substitutions for the vinyl Cl are shown in Table 2. The only improvements in antiproliferative activity seen with these analogs were with compounds 27, 33, and 34, which were at best 2-fold more active than 15 against LY2 cells.

Variations on the Alkyl Ether Side Chain

A number of substitutions were made on the alkyl ether side chain of clomiphene, as shown in Table 3. Compounds 38 and 40 are included for comparison to show that

without side chains the structures were devoid of activity against MCF-7 or LY2. The unsubstituted vinyl compound (39) is shown for comparison to 51 to emphasize the potency differential between 39 and 51, that is, 51 was more active than 39 by a factor of 21. In reference to the 17 analogs (41–57), 11 showed either the same activity as 15, or were more active than 15, against MCF-7. Among those were clomiphene side chain analogs that markedly affected antiproliferative activity. For example, variations on the alkylamino groups showed the monoethyl analog of clomiphene (43), as well as clomiphene, to be approximately 8-fold more active than the dipropyl analog of clomiphene (41). In addition, compound 46, which differs from 15 by an extension of 2 methylene groups in the side chain producing a butyl chain, was more active than 15

TABLE 2. Antiproliferative activity of vinyl substituted clomiphene analogs against breast cancer cells



Compound*	R†	IC ₅₀ ‡ (μM)		
		MCF-7	LY2	MDA-MB-231
1§	H	8.0	8.0	ND
15§	Cl	0.8	1.5	7.2
27	Br	0.8	0.7	6.4
28	F	2.7	2.3	ND
29	NO ₂	2.0	2.0	ND
30	CN	6.0	5.0	ND
31	CONH ₂	2.5	2.5	ND
32	CH ₃	2.4	2.4	ND
33	CH ₂ CH ₃	0.7	0.7	5.4
34	(CH ₂) ₂ CH ₃	1.0	1.0	5.2
35	(CH ₂) ₃ CH ₃	2.5	2.5	ND
36	O(CH ₂) ₂ N(C ₂ H ₅) ₂	6.0	6.0	ND
37	C ₆ H ₅	3.0	3.5	ND

* Compounds are citrate salts except for 33 which is an HCl salt, 36 which is an oxalate salt, and 31 and 37 which are free bases.

† Isomer configurations: isomer mixtures except for 30 and 35 are one isomer of unknown configuration, and the isomer status is unknown for 36.

‡ IC₅₀ values ≤1 μM are means of at least two determinations.

§ Compounds from Table 1 included here for comparison.

^{||} ND = not determined.

against both MCF-7 and LY2. Therefore, to investigate the biological effects of longer side chains, additional analogs with side chains extending from 5 to 12 methylene groups were synthesized. *E* and *Z* isomers of the analogs were purified and assayed for antagonism of MCF-7 growth, estradiol-enhanced expression of luciferase in transiently transfected MCF-7 cells and estradiol binding to MCF-7 ER, as shown in Table 4. Maximal activity against cell growth, luciferase expression, and in the competitive binding assay correlated with the *E* isomer of the 4 carbon side chain analog (46). Side chain extensions longer than the butyl side chain did not improve activity, and regardless of side chain length the *Z* isomers were uniformly less active.

Further observations from Table 3 show that the activity of clomiphene against MCF-7, but not LY2, was either maintained or improved upon by a number of analogs with heterocyclic groups such as pyrrolidyl (47), piperidyl (48, 51) and 4-methylpiperazinyl (50). Therefore, we synthesized analogs with pyrrolidyl (52), piperidyl (53) or 4-methylpiperazinyl (54) groups and butyl side chains in anticipation that the butyl side chain would enhance antiproliferative activity. However, activities were not improved upon, since the IC₅₀ values of the butyl side chain analogs were substantially greater than those of the respective ethyl side chain counterparts. Additional side chain analogs substituting O with C (55), S (56), or N (57)

produced activities the same as or 2–3 times greater than that of clomiphene against MCF-7. However, the activities of these analogs against LY2 were the same as or not as potent as clomiphene.

Estradiol Reversal of Activities of Pure Isomers and of 22

Pure *E* and *Z* isomers of several analogs were assayed for cell growth antagonism and reversal by estradiol, as shown in Table 5. While both isomers of each analog elicited some degree of growth antagonism, estradiol reversal was positive if estradiol supplementation increased the IC₅₀ by ≥3-fold over the IC₅₀ in unsupplemented medium. Thus, growth antagonism by *E* isomers 15, 23, 24, and 27 was reversed in LY2 cells but not in MCF-7 cells. However, growth antagonism by *E* isomers 46, 48, 55, 56, and 57 was reversed in both cell lines. None of the *Z* isomer-induced growth antagonism was reversed by estradiol.

As mentioned above, compound 22 (4-hydroxyclo-miphene) had the lowest IC₅₀ of all clomiphene analogs tested against MCF-7. The data in Fig. 1 show a biphasic concentration–response curve of compound 22 mediated growth antagonism and a monophasic concentration response showing reversal by estradiol. Reversal of antagonism was complete at concentrations of 22 up to 2.5 μM, partial at 5 μM, but no reversal was seen at 10 μM. Several *E* isomers

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.