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Reengineered tricyclic anti-cancer agents

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ABSTRACT

The phenothiazine and dibenzazepine tricyclics are potent neurotropic drugs with a documented but underutilized anti-cancer side effect. Reengineering these agents (TFP, CPZ, CIP) by replacing the basic amine with a neutral polar functional group (e.g., RTC-1, RTC-2) abrogated their CNS effects as demonstrated by in vitro pharmacological assays and in vivo behavioral models. Further optimization generated several phenothiazines and dibenzazepines with improved anti-cancer potency, exemplified by RTC-5. This new lead demonstrated efficacy against a xenograft model of an EGFR driven cancer without the neurotropic effects exhibited by the parent molecules. Its effects were attributed to concomitant negative regulation of PI3K-AKT and RAS-ERK signaling.

1. Introduction

The genesis and progression of cancers requires the coordinated activation of oncogenes via activating mutations or amplifications and the simultaneous loss of function in a tumor suppressor. A prominent oncogene, the Epidermal Growth Factor Receptor (EGFR) is a receptor tyrosine kinase (RTK) that responds to mitogenic signals by inducing multiple intracellular kinase networks. Many of these are aberrantly activated in lung adenocarcinomas including PI3K-AKT and RAS-RAF-MEK-ERK which are induced by activated EGFR to stimulate cell growth and replication, respectively. The inhibition of kinases represented a promising strategy for the treatment of some forms of cancer demonstrated by the clinical success of drugs targeting BCR-ABL (gleevec, Chronic Myeloid Leukemia),[1] EGFR (erlotinib, gefitinib, Non-Small Cell Lung Carcinoma (NSCLC)),[2,3] and B-Raf (vemurafenib, B-Raf V600E mutant melanoma).[4] However, as a generalized treatment strategy, the inhibition of a single pathway does not provide a dramatic increase over the standard of care, cytotoxic chemotherapy. Compensatory activation mechanisms in transformed cells, pathway crosstalk, and the emergence of resistant mutants limits efficacy. Furthermore, for cancer cells to sustain the pro-survival and growth promoting output of these networks, activated kinase signaling typically pairs with a concomitant loss of phosphatase activity. Thus, while kinase inhibitors turn off the 'on switch,' there is a corresponding requirement to restore the 'off switch' engendered by tumor suppressors.[5,6]

Generating leads for a specific disease indication without a priori screens or target information is an insurmountable task. An encouraging strategy, using existing drug molecules as leads offers several advantages.[7] These starting points exhibit drug like properties and information about sites of metabolism and tissue distribution is available. This approach also emphasizes the segregable nature of the chemical fragments used to build such molecules. It piqued our interest that a chemical genetic screen selected several tricyclic neuroleptics (thioridazine, chlorpromazine (CPZ), and trifluoperazine (TFP), Fig. 1) as modulators of FoxO1 localization.[8] FoxO1 is a transcription factor and tumor suppressor that is active when unphosphorylated and localized to the nucleus. FoxO1 is inactivated by cytoplasmic sequestration when it is phosphorylated at multiple sites by activated kinases including AKT and ERK.[9–12] Therefore, FoxO1 cellular localization provides a surrogate marker for the activation status of oncogenic signaling. This anticancer effect of the tricyclics, restoring FoxO1 nuclear localization in transformed, PTEN deficient cells, was attributed to negative regulation of PI3K-AKT signaling. The hits from this screen possessed an advantageous property as whole pathway modulators distinct from individual kinase inhibitors.

The tricyclics selected in this screen are members of a large class of drugs, first developed in the 1950s as antagonists of monoamine receptors and transporters.[13] Their uses are myriad for

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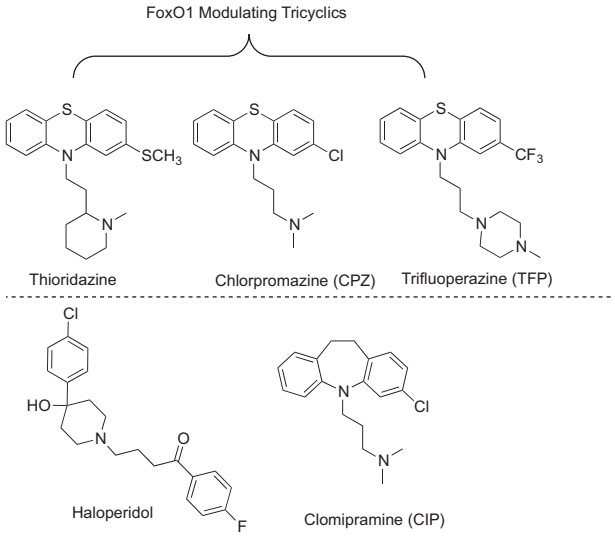


Figure 1. FDA approved neuroleptic medications.

diseases of the peripheral and central nervous systems (CNS) including numerous psychiatric conditions. They are notably unselective with a strong side effect profile due to binding to multiple receptor classes and subtypes in different tissues. This potent, primary activity, both on and off target, would interfere with studying their anti-cancer properties and precludes their use in animal models. It is conceivable that an appropriately selected agent could be used clinically for treating specific cancers.[14] However, the pronounced sedative, extrapyramidal, and anti-cholinergic effects are severely dose limiting.

We proposed to reengineer the tricyclic antipsychotics to optimize their anti-cancer side effect.[15,16] This effect has been documented in a number of basic research studies[17–24] and clinical epidemiological studies.[25] Phenothiazines are frequently observed in high throughput screens of FDA approved compounds and interact with numerous biological targets.[26] The CNS pharmacophore of these drugs is a consequence of their structural similarity to the monoamine neurotransmitters whose binding they obstruct (dopamine, serotonin, norepinephrine).[27] From both the tricyclics and the natural substrates of these receptors and transporters it is clear that the heterocycle, a 2–3 carbon linker, and an amine are essential for the CNS effects (Fig. 2). In the screen discussed earlier,[8] the antipsychotic haloperidol was examined to rule out the possibility that dopamine receptor antagonism played a role in FoxO1 modulation. Haloperidol is a powerful antagonist and inverse-agonist to a number of neurotransmitter receptors.[28] It is structurally unrelated to the tricyclics but it contains an amine, a key component for binding dopamine receptors. Haloperidol did not affect FoxO1 localization and thus does not perturb oncogenic signaling. This led us to speculate that the chemical fragments in the tricyclics that were responsible for the CNS versus the anti-cancer properties were not identical. Here, we systematically probe the tricyclics' structure to determine the anti-cancer pharmacophore. Our first efforts examined alternative functionalization of the dimethylamine portion. Deleting this functional group would conceivably eliminate the CNS activity of these molecules, facilitating their development for a specific anti-cancer purpose.

2. Chemistry

In synthesizing reengineered tricyclics (RTCs) we resolved to accomplish two disparate goals. The first was to eliminate the CNS pharmacology. Since CPZ is less potent at its target CNS

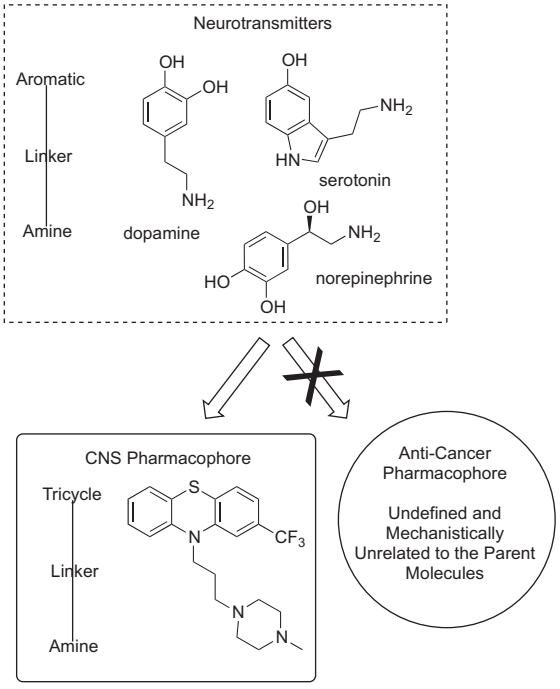


Figure 2. Pharmacophore of the tricyclics: CNS vs anti-cancer.

receptors than TFP,[29] we utilized the 2-chlorophenothiazine tricycle (I, Fig. 3). We also included the 3-chloro-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (IIa, Fig. 3) tricycle exemplified in the anti-depressant Clomipramine (CIP, Fig. 1). Its two carbon bridge is an isostere of the phenothiazine sulfur.[30] Simple derivatives of CPZ and CIP were prepared with one key modification: exchange of the dimethylamine base for a neutral polar substituent (sulfonamide, carbamate, amide, urea: e.g., RTCs (1–4): Tables 1 and S2–S3).

Our first series included two (A), three (B), and four (C) carbon linker variants. In the phenothiazine series, the B and C-linker amines were accessed by direct alkylation with a bromoalkyl phthalimide followed by phthaloyl deprotection. The A-linker required an alternative approach of acylation with chloroacetyl chloride, followed by azide substitution and combined reduction to the saturated amine. This acylation approach[31] was adapted to the dibenzazepine series which resisted most attempts at direct alkylation. Here the B-linker and C-linker analogues were prepared by acylation with chloroacetyl chloride and 3-chloropropionyl chloride, respectively, followed by conversion to the nitrile, and combined reduction to the amine precursors. These precursors were derivatized with substituted sulfonyl chlorides, chloroformates, and acyl chlorides (Schemes 1 and 2).[32]

The second objective was to optimize these resulting compounds to improve their anti-cancer potency and physiochemical properties. Systematic, iterative rounds of optimization introduced alterations to the tricycle, linker, and to the pendant N-linked side chain (Fig. 3).

Due to their unrivaled biological activity, subsequent efforts converged mainly on sulfonamides. The 4-trifluoromethoxybenzenesulfonamide of the 3-linker variant proved especially potent (RTC-5). Aiming to improve its properties, we introduced variations to the tricyclic moiety (Fig. 3). These include the thioxanthene (III) and dibenzocycloheptene (IV) heterocyclic tricycles present in thioxithene and amitriptyline, respectively. Their syntheses rely on modifications to published routes (Scheme S1).[33,34]

The next set of analogues defined the minimally potent pharmacophore. These included removing the bridging atom(s) in the tricyclic moiety (acyclic, V), and one of the fused benzene rings

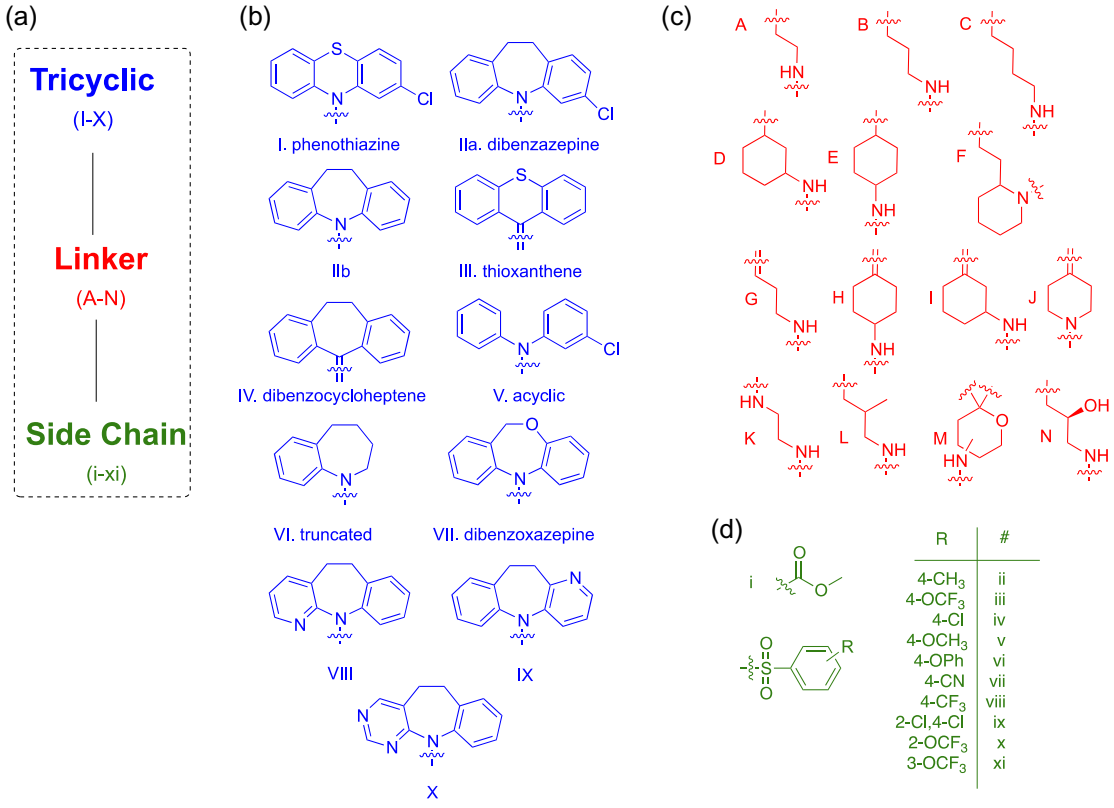


Figure 3. Tricyclic, linker, and side chain variants.

Table 1
Cell viability screen of reengineered tricyclics

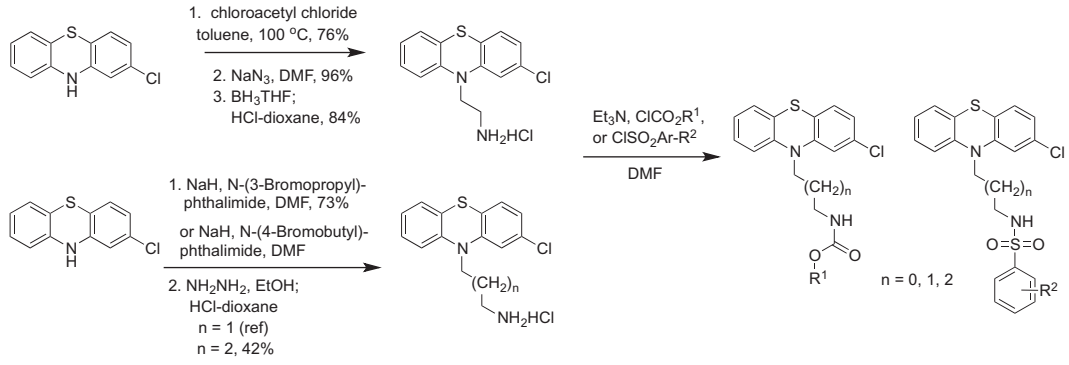
RTC	Tricyclic	Linker	Side chain	GI_{50} (μM)
1	I	B	ii	>40
2	I	B	i	>40
3	IIa	B	ii	>40
4	IIa	B	i	>40
5	IIa	B	iii	12.6
6	IIa	B	iv	20.0
7	I	A	ii	24.4
8	I	A	i	Inactive
9	I	A	iii	25.0
10	I	A	iv	20.0
11	IIa	A	iii	22.0
12	IIa	A	iv	19.1
13	I	C	ii	>40
14	I	C	i	>40
15	IIa	C	iii	Inactive
16	IIa	C	iv	Inactive
17	I	B	v	>40
18	I	B	vi	>40
19	I	B	vii	>40
20	I	B	iii	>40
21	IIa	B	viii	12.6
22	IIa	B	vii	20.0
23	IIa	B	v	24.4
24	IIa	B	ix	Inactive
25	IIa	B	x	25.0
26	IIa	B	xi	20.0
27	IIb	B	iii	22.0
28	VII	B	iii	19.1
29	VII	B	iv	>40
30	IIb	N	iii	15.0
Ent-30	IIb	N	iii	18.0

(truncated, VI) (Scheme S2). Once established, our next efforts focused on improving the potency and pharmacokinetic properties of RTC-5. We introduced heteroatoms: dibenzoxazepine (VII, Scheme S3)[35–37] and a nitrogen substituted dibenzazepine series (VIII–X, Scheme S4).[38,39] Several analogues included constrained cyclic linkers intended to increase drug likeness by limiting rotatable bonds.[40] These utilized the dibenzazepine (IIb) and dibenzocycloheptene (IV) tricycles and were prepared via reductive amination,[41] McMurry coupling,[42] and alkylation sequences, respectively (Schemes S5–S7). Three additional series included: modified linkers (K, L) and a spirocyclic ether (M) series (Schemes S8 and S9).

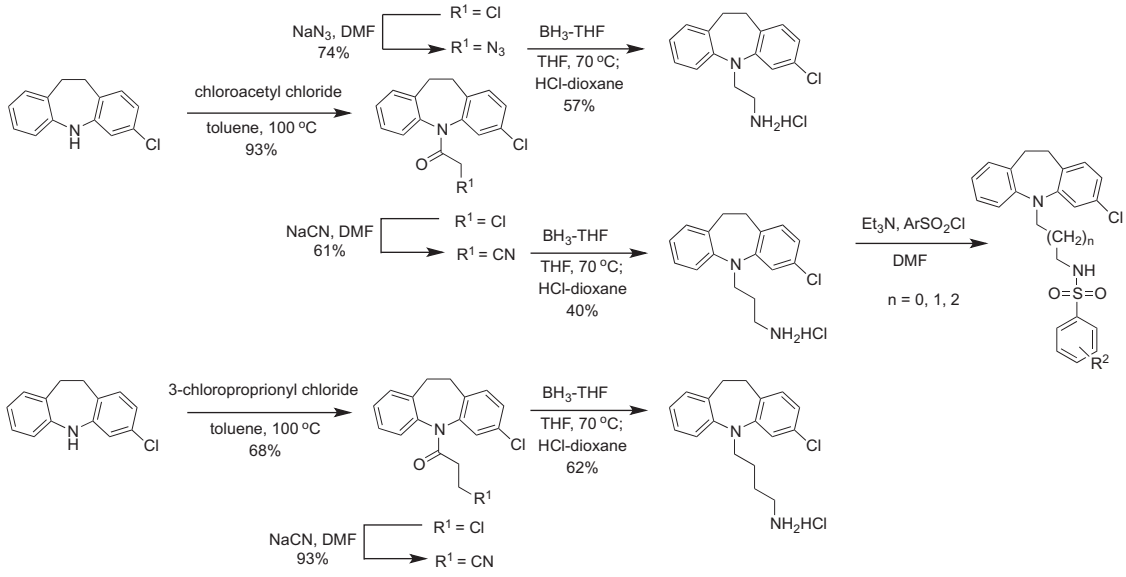
A special case unto itself, RTC-30 contains a hydroxylated linker (N) that confers increased oral bioavailability. Its synthesis began with the alkylation of iminodibenzyl with *S*-epichlorohydrin.[43] Epoxide opening with sodium azide followed by reduction provides the amine precursor. Quantitative sulfonylation of the amine provided RTC-30. Installation of this hydrophilic linker adds a degree of complexity because it introduces a chiral center. However, both enantiomers were accessed from the commercially available and optically pure forms of epichlorohydrin (Scheme 3).

3. Results and discussion

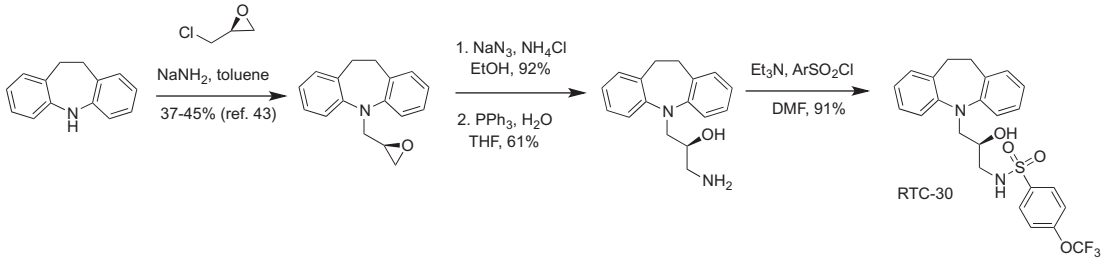
All compounds were subjected to an MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) cell viability screen[44] using H1650 lung adenocarcinoma cells. This cell line harbors an activating mutation in EGFR and inactivated PTEN, and thus is characterized by constitutively activated AKT and ERK signaling. These lesions confer resistance to single pathway RTK inhibitors such as erlotinib.[45] As a guide, the cells were treated with compound at five concentration points bracketing 1–40 μM in increments of 10 μM. Cells were exposed to drug for 48 h. Growth Inhibition (GI_{50}) potencies are reported only in ranges where the data exhibit a sigmoidal dose response. If the data did not converge on a sigmoidal response curve but still showed a response, they are



Scheme 1. Synthesis of phenothiazine derivatives with varied linker lengths and N-modifications.



Scheme 2. Synthesis of dibenzazepine analogues with varied linker lengths and N-modifications.



Scheme 3. Synthesis of RTC-30.

presumed >40 μM. If the response was negligible with residual absorbance >80% at 40 μM, the compound is deemed 'inactive' (Fig. 4).

A panel of tricyclic drugs was surveyed and most exhibited weak reductions on cell viability (Table S1). TFP was the most active and provided a benchmark (12.2 μM) while CIP was weakly potent (>40 μM). The first set of compounds including RTCs (1–4), were weakly potent (>40 μM, Table 1). Cell cycle analysis of RTC-1 and RTC-2 on H1650 cells revealed a dose dependent sub-G1 accumulation indicative of apoptosis at 20 and 40 μM (Fig. S1). Clonogenic assays verified some loss of cell viability, which became evident at 20 and 40 μM after seven days of treatment (Fig. S2). Despite this lackluster potency, we believed this set to be a significant departure and conducted a series of in vitro and in vivo pharmacological assays. Emphatically, this set did not possess the neurotropic properties of the parent molecules (vide infra). With this required departure confirmed, we pursued a more diverse series of analogues.

Next, we evaluated the A and C-linker variations (Table 1). All of the C-linker analogues decidedly lost potency (13–16), while some of the A-linker analogues (7, 9–12) were comparable or slightly inferior to the B-linker versions. Attempts to optimize the potencies of carbamate derivates akin to RTC-2 did not prove fruitful in either phenothiazine or dibenzazepine series, and aliphatic

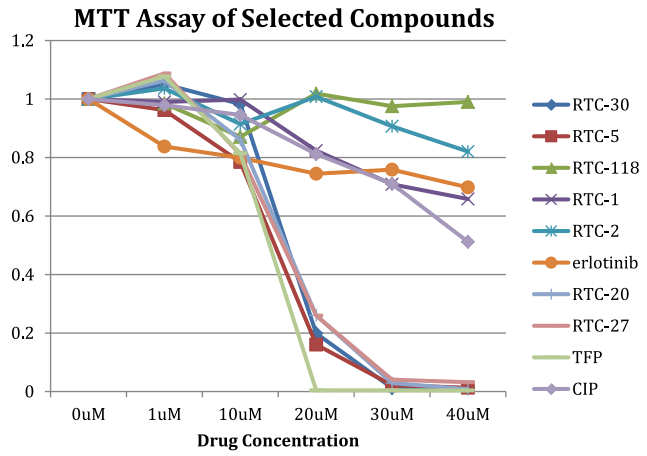


Figure 4. MTT assay of selected compounds, H1650 cells.

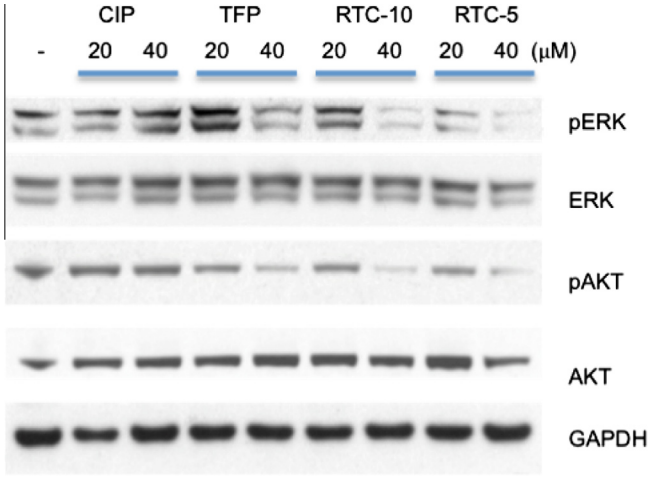


Figure 5. Western blot analysis of AKT and ERK levels.

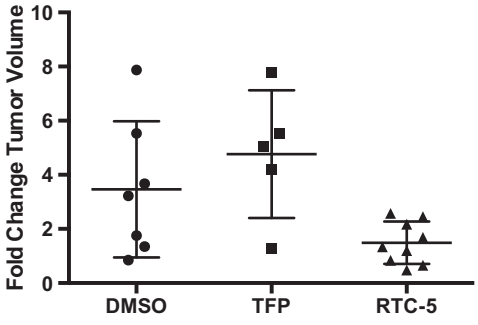


Figure 6. H1650 xenograft study in mice.

and aryl amides were similarly inactive. Several sulfonamides, however, exhibited potencies comparable with TFP.

The search for an optimal sulfonamide yielded reproducible trends. Aliphatic sulfonamides were inactive (Tables S2 and S3). In the aryl series, electron donating groups at the 4 position (17, OCH_3), (18, OPh) and substituents at the 2 position (24, 25) reliably generated weakly active or inactive compounds (Table 1). The most potent phenothiazines and dibenzazepines possess electron withdrawing substituents: halogen, trifluoromethyl, or trifluoromethoxy substituents at 3 and 4 positions of a benzenesulfonamide core. A number of analogues emerged from the dibenzazepine B-linker aryl sulfonamides series: RTC-21 (4-CF_3), 22 (4-CN), 6 (4-Cl), 24 (3,4-dichloro), and 5 (4-OCF_3). RTC-5 represented a significant breakthrough and was subjected to a much more comprehensive biological and pharmacological evaluation.

In concordance with the results obtained for RTC-1 and RTC-2, RTC-5 induced a sub-G1 accumulation and cell cycle arrest, similar to but more pronounced than TFP and CIP (Fig. S3). A further confirmation of its apoptotic mechanism, treatment of cells with RTC-5 resulted in an increase in Annexin V staining. Additional treatment with the pan caspase inhibitor Z-VAD reversed Annexin V staining (Fig. S4), indicating that apoptosis was caspase-mediated. Seeking its molecular target, the effects of RTC-5 treatment on intracellular kinases were evaluated by Western blot. Both PI3K-AKT and RAS-ERK pathways are simultaneously, negatively regulated by RTC-5 as indicated by decreases in phospho-AKT and phospho-ERK levels (Fig. 5). RTC-10, a potent phenothiazine analogue, and TFP exhibit similar effects. A DiscoveRx kinome screen confirmed that RTC-5 was not inhibiting any target relevant kinase in an ATP competitive manner (unpublished results). Recent literature reports implicate the activation of the tumor suppressor Protein Phosphatase 2A (PP2A) as the source of the anti-cancer effects demonstrated by the tricyclics.[23] PP2A is a ubiquitously expressed tumor suppressor that negatively regulates multiple oncogenic signaling pathways including AKT and ERK.[46–48] Unpublished experiments have confirmed this mechanism for our RTCs and these results will be presented shortly.

Probing its in vivo effects, we performed a xenograft study using the H1650 lung cancer cell line. Treatment with 100 mg/kg RTC-5 caused a statistically significant decrease in mean fold change in tumor volume (1.49 ± 0.26, $n = 9$) compared to vehicle control (3.46 ± 0.95, $n = 7$) ($p < 0.004$, student's t test). In this same study, TFP could not be dosed higher than 10 mg/kg due to marked CNS effects (Fig. 6).

Inspired by these results, we continued synthesizing molecules with conservative variations. Introducing an oxygen to the central ring of the tricycle (dibenzoxazepines, 28–29, Table 1) afforded less potent compounds. Eliminating the bridging atoms or removing one of the fused benzene rings provided inactive analogues illustrating that the intact tricycle is required for activity (68–71, Table S6).

The tricyclics contain a charged amine that confers aqueous solubility and oral bioavailability. As a necessary consequence, its removal diminishes these desirable qualities. The resulting compounds are lipophilic, less water soluble, and less orally bioavailable. Fortunately, the development of RTC-30 imparted a major solution to this problem (vide infra).

This concern was addressed in other ways by incorporating polar modifications and restricting rotatable bonds. Two series containing modified linkers (Table S7) and three series containing nitrogen substituted tricyclic systems (62–67, Table S5) proved less potent than RTC-5. In another series, several commercially available heterocyclic arylsulfonyl chlorides were obtained and introduced. Of these, some thiophene analogues (76, 77) provided potent compounds, not surprisingly since thiophenes are benzene ring isosteres. However, most of these heterocyclic analogues were weakly potent, inactive, or unlikely to exhibit improved pharmacokinetic properties (Table S8).

A dibenzocycloheptene (IV) series in which the tricyclic nitrogen is replaced with a double bond provided several active compounds (56–59, Table S5). In a similar vein, several series of analogues with cyclic linkers were investigated. Those in which the sulfonamide nitrogen is endocyclic (F, J), were decidedly inactive (94–99). Those in which the nitrogen is exocyclic (D, E, H, I)

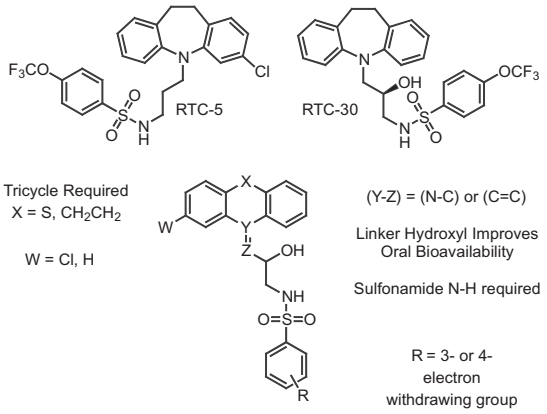


Figure 7. Consensus structure.

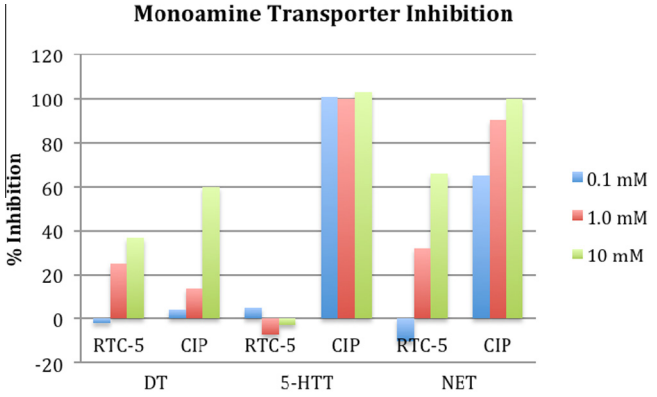


Figure 8. Monoamine transporter inhibition (CIP vs RTC-5). Antagonist radioligand assays: DT: [^{3}H]BTCP; 5-HTT: [^{3}H]imipramine; NET: [^{3}H]nisoxetine; each bar represents the average of two independent determinations.

proved comparable in potency to RTC-5 (100–107), as did several members of a genus containing a spirocyclic ether (M, 108-114) (Table S9).

Sulfone, urea, and sulfonyl urea analogues were deemed inactive confirming a general preference for the sulfonamide moiety (115–117, Table S10). Moreover, making *N*-Me versions of five of the most potent compounds (118–122, Table S11) rendered them inactive demonstrating an absolute requirement for the sulfonamide *N–H*. A consensus structure activity relationship picture emerged at the end of these studies (Fig. 7).

It deserves final mention that the compounds prepared in this study exhibit relatively modest, micromolar potencies. To address this issue, we highlight that the MTT assay uses a transformed, metastatic NSCLC cell line with multiple, activated tumor promoting pathways. The RTCs possess a different mechanism of action from cytotoxics and even from kinase inhibitors, and their advantages have only become apparent in vivo. For comparison, some FDA approved kinase inhibitors including vemurafenib[49] and sorafenib[50] require micromolar serum concentrations for efficacious dosing. Using the MTT assay as a guide, RTC-5, RTC-30 and numerous analogues strikingly display activity in a model of metastatic NSCLC for which there are no treatments.[51] Comparable to RTC-5, the GI_{50} of RTC-30 in the MTT assay was 15 μM, slightly better than its enantiomer. However, its improved pharmacokinetic properties are what prompted and enabled its subsequent in vivo evaluation.

4. Pharmacology

RTCs 1–3 were evaluated for binding to a panel of dopamine receptors (D_1–D_5). TFP, CPZ, and CIP bind this panel indiscriminately. D_2 is the most clinically relevant subtype and its antagonism is attributed to the antipsychotic effects associated with these drugs. At 0.1 mM ligand concentration, none of our compounds displayed significant binding to D_2 or any of the dopamine receptor subtypes (D_1–D_4 <5%, D_5 <10%) (Fig. S5). At 1.0 mM and of less physiological relevance, RTC-2 displayed minimal binding to D_1–D_3 (14%, 21%, 22%) as did RTC-1 for D_1 and D_2 (12%, 14%). TFP, in contrast exhibits >95% binding at 1.0 mM to all five subtypes, and at 0.1 mM, >95% towards D_1–D_3 with predominant binding to D_4 (73%) and D_5 (81%) (Fig. S6). Clearly, this single modification, conversion of an amine to a neutral polar functional group diminished the neurotropic properties of these molecules.

We also examined the neurotropic effects of compound administration in vivo using a scoring test for lethargy.[52] The effects on mouse behavior, notably sedation, were rather striking with TFP. RTC-1 and RTC-2 do not induce lethargy in this system and are comparable to control (Fig. S7).

In pharmacokinetic studies in mice, RTC-1 exhibits significant absorption by intra-peritoneal (IP) route (50%), orally (17%) and low clearance (11.1 ml/min/kg, $t_{1/2}$ = 0.61 h). RTC-2 exhibits significant absorption IP (47%), and orally (16%), and moderate clearance (52.5 ml/min/kg $t_{1/2}$ = 0.61 h). In both cases, the reduced oral exposure is likely due to poor solubility in the aqueous vehicle (10% DMSO, 30% Cremophor EL, 60% water). The poor exposure is likely exacerbated for RTC-2 due to its increased rate of clearance. This lack of oral bioavailability was a concern addressed in subsequent synthetic efforts (Tables S12 and S13).

Because of its increased potency, RTC-5 was compared to CIP against a much more comprehensive panel of amine transporters, GPCRs, other receptors, and ion channels. Tested at three concentrations, 0.1 mM, 1.0 mM, and 10 mM, CIP completely inhibits the serotonin transporter (5-HT, K_i = 0.28 nM,[53]) the source of its on-target biological effects, as well as the dopamine (DT, 14% (1.0 mM), 60% (10 mM), and norepinephrine (NET, 5%, (0.1 mM) 90% (1.0 mM), 100% (10 mM)) transporters. In contrast, RTC-5 does not bind the serotonin (5-HTT, <5%) and binds the dopamine (DT) and norepinephrine (NET) transporters weakly and only at the elevated concentrations (Fig. 8).

CIP binds several dopamine and serotonin subtypes. RTC-5 does not bind most dopamine or serotonin receptor subtypes except for some residual binding at 5-HT_{5A} (24% (1.0 mM), 68% (10 mM)) (Figs. S8 and S9). Several tricyclics have been associated with QT interval prolongation.[54] These cardiovascular liabilities of CIP are attributed to ion channel inhibition. RTC-5 does not bind a panel of calcium and potassium channels (Figs. S10 and S11). RTC-5 exhibits negligible effects on a voltage gated sodium channel ($Na_{v1.5}$) compared to CIP in a patch clamp assay (Fig. S12). It also does not bind a panel of receptors (M_2, H_1, H_2, hERG) localized to heart tissues and linked to QT interval prolongation (Fig. S13).

The pharmacokinetic properties in mice of RTC-5 were reasonable with significant absorption by IP (34–38%), orally (15–18%) and moderate clearance (42 ml/min/kg $t_{1/2}$ = 0.61 h) (Table S14). The properties of RTC-30 were dramatically improved with IP absorption (62–94%) and oral absorption (36–50%) nearly doubled with similar clearance (44 ml/min/kg $t_{1/2}$ = 0.81 h) (Table S15).

5. Conclusion

The identification of molecular drivers involved in oncogenesis played an instrumental role in redefining the study and treatment of cancer. This information permits the precise targeting of diseases with a defined molecular mechanism and resulted in the successful development of pharmaceuticals for a small but increasing number of aggressive, untreatable cancers. While much of this

early work focused on RTKs like EGFR and its immediate downstream signaling partners, there are many more targets to be addressed. Capitalizing on and evolving with this trend, the utilization of chemical genetic screens enables the dissection of complicated signaling pathways involved in these diseases. Small molecule hits from these screens possess a mode of action not discernible from classical phenotypic assays. Translation of these discoveries will provide new tools for modulating these undefined and previously deemed undruggable pathways.

Prior to this work, numerous reports indicated the anti-cancer properties of the tricyclics. On the surface, this was a finding of dubious importance. The tricyclics are an ancient class and not an active area of development. Achieving appreciable serum concentrations to observe the anti-cancer effects would cause dose-limiting effects on the CNS of experimental animals. Although the tricyclics are FDA approved drugs, we recognized that these compounds were not optimized for this anti-cancer purpose. Towards this end, we introduced an important modification: changing the amine to a sulfonamide. This eliminated the CNS associated pharmacology and enabled further optimization of the anti-cancer effect. We also recognized the importance of their novel mechanism of action: dual pathway inhibition of PI3K-AKT and RAS-ERK signaling via putative activation of the tumor suppressor PP2A.

Efforts to reengineer the tricyclics produced a series of potent compounds exemplified by RTC-5 and RTC-30. Their effects on cells and animal models have been documented and here we delineate the structural features important for their activity. RTC-5 and RTC-30 will continue to be studied in selected models of cancers susceptible to dual pathway inhibition. The results of these studies will be presented in due course.

Competing interests statement

The Icahn School of Medicine at Mount Sinai on behalf of the authors G.N., M.O., N.S.D., D.B.K. have filed patents covering composition of matter on the small molecules disclosed herein for the treatment of human cancer and other diseases. Dual Therapeutics LLC has licensed this intellectual property. The authors G.N., M.O., N.S.D., D.B.K. have an ownership interest in Dual Therapeutics LLC. G.N. and M.O. are consultants for Dual Therapeutics LLC.

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Supplementary data

Supplementary data (experimental data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2015.07.007.

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