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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.

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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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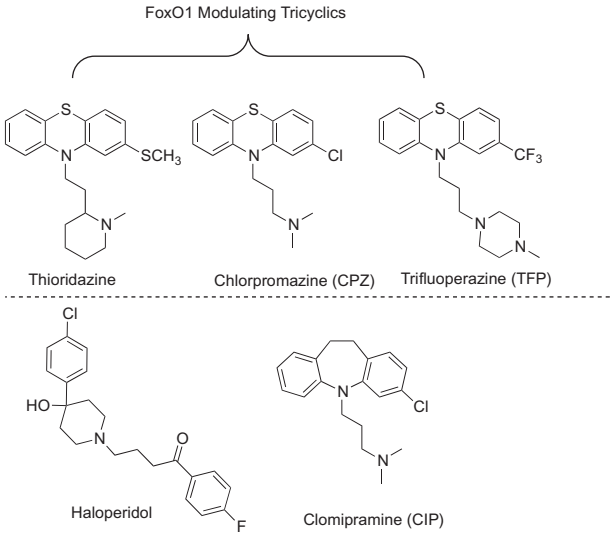

Figure 1. FDA approved neuroleptic medications.

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

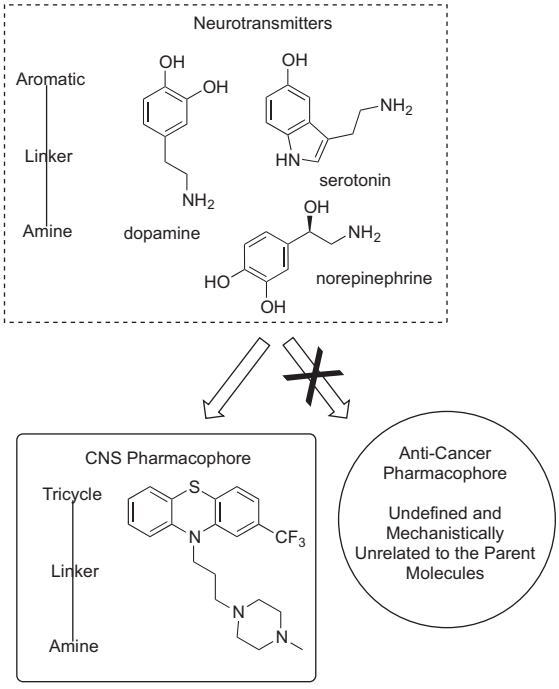

Figure 2. Pharmacophore of the tricyclics: CNS vs anti-cancer.

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[*bf*]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-chloroproprionyl 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

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