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Letter

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The Rhodadyns, a New Class of Small Molecule Inhibitors of Dynamin GTPase Activity

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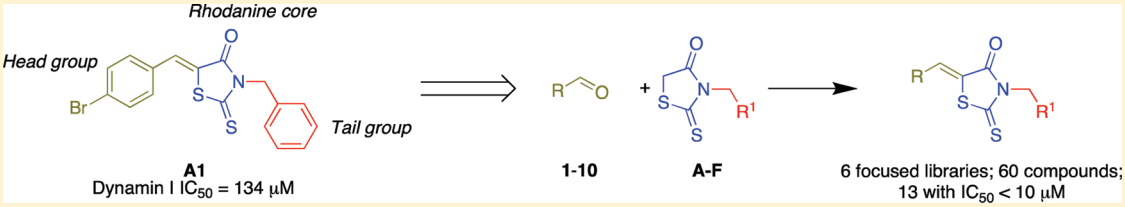
Supporting Information



ABSTRACT: Six focused rhodanine-based libraries, 60 compounds in total, were synthesized and evaluated as potential dynamin I GTPase inhibitors. Twenty-six were more potent than the lead compound with 13 returning IC_{50} values ≤10 μM, making the Rhodadyn series among the most active dynamin inhibitors reported. Two analogues were highly effective at blocking receptor-mediated endocytosis: **C10** and **D10** with $IC_{50(RME)}$ = 7.0 ± 2.2 and 5.9 ± 1.0 μM, respectively. These compounds are equipotent with the best reported in-cell dynamin inhibitors.

KEYWORDS: *dynamin inhibition, Knoevengal condensation, rhodanine*

Dynamin is a 100kD GTPase,[1] with three closely related mammalian isoforms: dynamin I (dynI),[2,3] dynamin II (dynII),[4] and dynamin III (dynIII).[5] Each isoform has a different number of spliced variants: dynI has eight, dynII has four, and dynIII has thirteen.[6] Each may have different regulatory mechanisms at distinct locations within the cell or be involved in the cellular localization of dynamin.[7,8]

The best-characterized superfamily member is dynI, exclusively expressed in brain and neuronal tissue. DynI is a key component of the synaptic vesicle (SV) recycling, which in turn is essential for the maintenance of neurotransmission, serving to retrieve empty SVs for refilling and reuse.[6,9,10] SV recycling is a specialized, rapid local endocytic recycling, considered to be a specialized form of receptor-mediated endocytosis (RME).[6−8]

Dynamin is also involved in clathrin-independent endocytosis, phagocytosis, and caveolae internalization. It has been implicated in cellular processes such as vesicle trafficking, Golgi function, organelle division, and mitochondria and chloroplast biogenesis.[7,8,11] Dynamin facilitates cell migration and invasion and potentially plays an important role in cell growth, cell spreading, and neurite outgrowth.[12]

Targeting endocytosis and trafficking defects through the dynamin inhibition represents a novel strategy for the treatment of many diseases such as neurological (e.g., epilepsy), viral, and bacterial (which enter cells via clathrin-medicated endocytosis) infections.[13−15] Disruption of the cellular transport process has been linked to over 100 diseases involving endocytosis and intracellular trafficking defects.[16,17] In humans, dynamin has been implicated in Charcot-Marie-Tooth disease,[18] centronuclear myopathy,[19] dominant optic atrophy,[20,21] and HIV entry.[22]

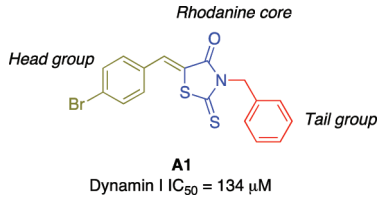
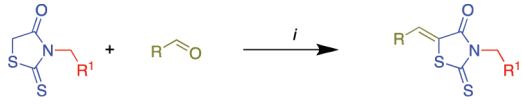


Figure 1. Chemical structure of the lead Rhodadyn **A1**.

Scheme 1[a]



[a]Reagents and conditions: (i) EtOH, MW irradiation, 120 °C, 55 min or EtOH, piperidine, reflux, 18 h.

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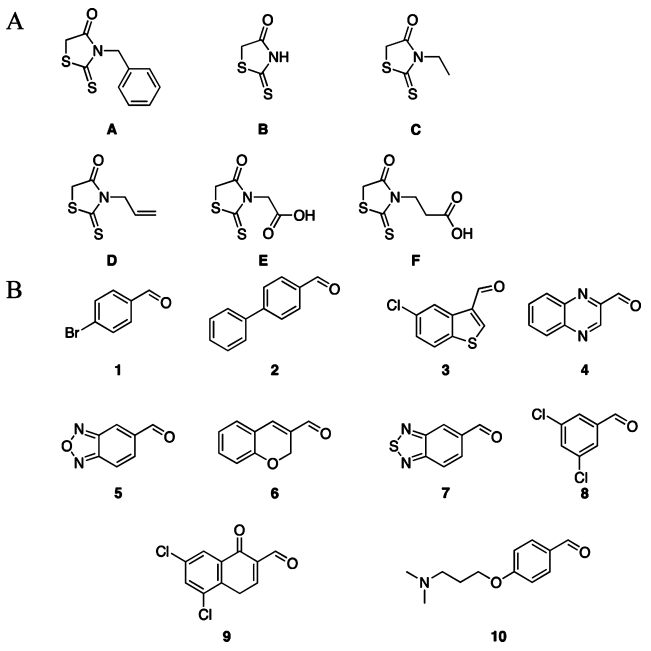


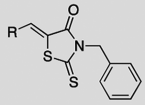
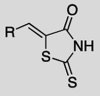
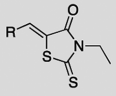
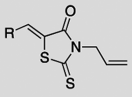
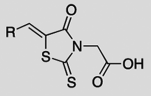
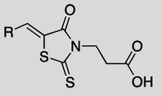
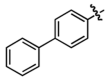
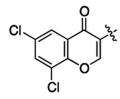
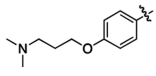
Figure 2. (a) Rhodanines (**A**–**F**) and (b) aldehydes (**1**–**10**) used in the synthesis of libraries A–F.

We have reported the MiTMAB,[23,24a] Bis-T,[25,26] RTILs,[27] Dynole,[28] Iminodyn,[29] and Pthaladyn series of compounds as novel dynamin inhibitors.[30] Each series thus far has targeted many of dynamin's four domains: the pleckstrin homology, the assembly domain, the proline-rich domain, and the GTP binding domain. Other reported dynamin inhibitors include dynasore, antipsychotics, and selective serotonin reuptake inhibitors.[31−33] As part of our ongoing studies, we identified (*Z*)-3-benzyl-5-(4-bromobenzylidene)-2-thioxothiazolidin-4-one (**A1**) (Figure 1) as a dynI inhibitor, IC_{50} = 134 μM.

While **A1** was only a moderately potent dynamin inhibitor, the primary rhodanine core is readily available or easily assessed and amenable to focused library development. Herein, we selected six commercially available rhodanines (**A**–**F**) (Figure 2a). As we were keen to explore new chemical space with the aldehyde moiety and to introduce novel isosteres with enhanced druglike character than we had previously reported,[26,29] we restricted our aldehyde library to a family of 10 aldehydes (**1**–**10**) (Figure 2b). The introduction of the aldehyde headgroup requires only a simple condensation reaction.[26,27,29,34]

The rhodanine core is a privileged scaffold in medicinal chemistry and one that has found promise among many therapeutic applications.[34,35] Using our selected rhodanines (**A**–**F**) and aldehydes (**1**–**10**), we constructed six, 10-component, focused

Table 1. Inhibition of dynI GTPase by Rhodadyn Libraries A–F

	 Library A	 Library B	 Library C	 Library D	 Library E	 Library F
	Dyn I IC_{50} (μM)					
	134±21 **A1**	- **B1**	- **C1**	- **D1**	-[a] **E1**	96±19 **F1**
	- **A2**	- **B2**	- **C2**	- **D2**	73±10 **E2**	42±13 **F2**
	- **A3**	5.5±0.5 **B3**	- **C3**	- **D3**	12.3±0.1 **E3**	48±4 **F3**
	- **A4**	43±15 **B4**	- **C4**	- **D4**	-[a] **E4**	- **F4**
	53±15 **A5**	7.4±0.5 **B5**	- **C5**	- **D5**	- **E5**	- **F5**
	- **A6**	90±0.6 **B6**	- **C6**	- **D6**	- **E6**	23.5±0.6 **F6**
	- **A7**	- **B7**	- **C7**	- **D7**	- **E7**	-[a] **F7**
	50±22 **A8**	7.5±0.6 **B8**	3.1±0.9 **C8**	31±8 **D8**	5.5±0.8 **E8**	4.4±2.6 **F8**
	7.4±0.8 **A9**	24±9 **B9**	5.1±0.8 **C9**	-[a] **D9**	3.4±0.49 **E9**	10±6 **F9**
	22±3 **A10**	- **B10**	7.1±1.0 **C10**	4.5±0.8 **D10**	- **E10**	- **F10**

[a]IC_{50} > 100 μM; −, not active up to 300 μM.

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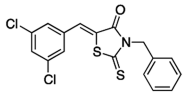
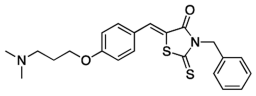
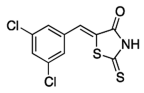
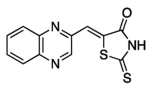
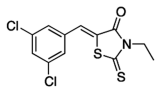
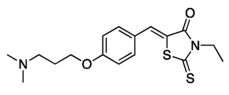
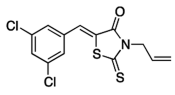
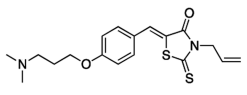
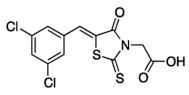
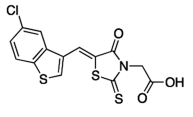
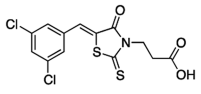
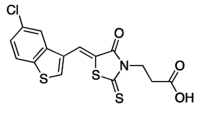
Table 2. DynI IC_{50} Values and In-Cell RME IC_{50} Values in U2OS Cells of Rhodadyn Analogues A8−F8, A10, B4, C10, D10, E3, and F3

Compound	DynI IC_{50} (μM)	RME IC_{50} (μM)	cLogP	Compound	DynI IC_{50} (μM)	RME IC_{50} (μM)	cLogP
 **A8**	5±22	-	5.66	 **A10**	22±3	-	4.48
 **B8**	7.5±0.6	18.1±7.9	4.01	 **B4**	43±15	-	2.33
 **C8**	3.1±0.9	-	4.73	 **C10**	7.1±1.0	7.0±2.2	3.55
 **D8**	31±9	-	4.90	 **D10**	4.5±0.8	5.9±1.0	3.72
 **E8**	5.5±0.8	-	3.38	 **E3**	12±0.1	-[a]	3.64
 **F8**	4.4±2.6	-	3.84	 **F3**	48±4	-	4.11

[a] IC_{50} > 100 μM; −, not active up to 300 μM.

libraries as potential dynI inhibitors. We call this the Rhodadyn class of dynamin inhibitors.

Library A examined the retention of the *N*-benzyl moiety, while library B examined removal of the *N*-benzyl moiety from the lead **A1**. All Rhodadyn libraries were synthesized as shown in Scheme 1 (see the Supporting Information) and were solids that remained stable over extended periods at room temperature.

Libraries A and B were examined for their ability to inhibit dynI, and these data are presented in Table 1.

Table 1 identified five library A analogues with noteworthy dynI inhibition. Of the actives, **A9** was the most potent, IC_{50} = 7.4 ± 0.8 μM, a 20-fold increase in potency over **A1**. Of the library A inactives, the most striking was **A7**, the sulfur isostere of **A5**, a 53 μM dynI inhibitor.

Library B contained six dynI inhibitors ranging in potency from 5.5 to 90 μM. Generally, there was a correlation between the actives in libraries A and B, with library A actives also displaying a level of activity in library B. Only **B1** and **B10** were inactive when the library A equivalents displayed inhibition. Interestingly, in both cases, the aldehydes used were relatively simple aromatic systems. The potency trend differs between libraries A and B. In library A, the most potent analogue was **A9** (7.4 μM), but in library B, **B3**, **B5**, and **B8** are equipotent (5.5−7.4 μM). There was an 8-fold increase in dynI inhibition on removal of the benzyl moiety on going from **A5** to **B5**. Analogue **B3** is marginally the most potent Rhodadyn from libraries A and B, three times more potent than dynasore,[33] but less potent than Dynole 34-2[28] or Iminodyn compounds.[36] Ten of the nineteen new analogues in libraries A and B were significantly more potent than the lead, **A1**.

From the libraries C (*N*-ethyl) and D (*N*-allyl) analogues **C1−D10** (Scheme 1 and Table 1), only **C8−C10** and **D8−D10** displayed any dynI inhibition. The *N*-ethyl analogues **C8−C10** were the most potent with IC_{50} values of 3.0, 5.1, and 6.4 μM, respectively. Within library D, **D10** was the most potent (3.6 μM), with other library D members at best modest dynI inhibitors: **D8** (31 μM) and **D9** (134 μM, equipotent with **A1**). Notwithstanding this, **C8−C10** and **D8−D10** are up to a 50-fold more active than **A1**.

Libraries E (*N*-acetic acid) and F (*N*-propionic acid) afforded high levels of dynI inhibition with **E2**, **E3**, **E8**, and **E9** returning IC_{50} values of 73, 12.3, 5.5, and 3.4 μM, respectively. Library F contained seven dynI inhibitors with **F1−F3**, **F6**, and **F8−F10** returning IC_{50} values of 9, 42, 48, 23.5, 4.3, 10, and 21.7 μM, respectively.

Interestingly, the head groups (**2** and **3**) that saw an activity loss in libraries C and D saw activity restored in libraries E and F, for example, 12.3 μM for **E3** vs inactive for **C3**/**D3**, suggesting some binding in the tail region of the molecule. Analogues derived from **8** and **9** were again the most active with IC_{50} values of 3.4 (**E9**) and 4.3 μM (**F8**). These two head groups are not only among the most active across all libraries but are the only ones retaining activity across all libraries.

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Chemically significant modifications of the tail group have limited impact on dynI inhibition, for example, the change from an ethyl (**C8**) to acetic acid (**E8**) resulted in only an IC_{50} change from 3.1 to 5.5 μM.

Given that dynamin GTPase activity is essential for endocytosis, we examined the Rhodadyns for their potential inhibition of another key endocytotic protein, clathrin. We view clathrin inhibition as an undesirable off-target action.[37,38] Gratifyingly, no clathrin inhibition was observed at 100 μM Rhodadyn concentration. Second, two compound cohorts were then examined for their ability to block in-cell endocytosis using our automated quantitative RME assay based on endocytosis of Texas Red-transferrin (TxR-Tf) into U2OS human osteosarcoma epithelial cells (see the Supporting Information).[28,36] The first cohort, **A8**−**F8**, varied only the tail group (Figure 1 and Table 2).

Surprisingly, only **B8** of the first cohort screened for RME activity was in-cell active (Table 2). This may be due to poor cell permeability or rapid compound efflux of the others. Further evaluation of RME efficacy of selected Rhodadyn analogues identified the *N*-ethyl **C10** and *N*-allyl **D10** as more potent RME blockers with IC_{50} values of 7.0 and 5.9 μM, respectively (Table 2). The *N*-benzyl **A10** was inactive. As **A10**, **C10**, and **D10** possess the same headgroup, this suggests that differences in RME activity, within this cohort, arise via the tail group with small alkyl groups better tolerated than aromatic moieties. As expected, on the basis of our observations in Table 2, analogues the carboxylate substituted **E3** and **F3** as well as the hydrophilic **B4** displayed no RME activity presumably due to poor cell permeability or rapid cellular efflux. cLog *P* calculations showed no direct correlation between compound solubility and membrane permeability (Table 2).[39]

The Rhodadyn series are highly active dynI inhibitors, and through the development of six focused compound libraries, a 50-fold increase in potency has been realized. Thirteen Rhodadyn analogues returned $IC_{50} \leq 10$ μM, and of these, **C8** (3.0 μM), **E9** (3.4 μM), and **D10** (3.6 μM) have activity better than our reported Pthaladyn series ($IC_{50} \sim 4.6$ μM), although not equal to the Iminodyn ($IC_{50} \sim 0.26$ μM) or Dynole ($IC_{50} \sim 1.30$ μM) series.[28,30]

The most active compound in each library (**A9**, **B3**, **C8**, **D10**, **E9**, and **F8**) varied significantly in regards to requisite aldehyde but varied little in actual activity ($IC_{50} \sim 7.4$, 5.5, 3.0, 3.6, 3.4, and 4.3 μM respectively). Of the 10 head groups evaluated, only one (**7**) failed to display any significant dynI inhibition. Clearly, our findings offer considerable scope to further improve on the potency of this new class of Rhodadyn compounds. The impact of the tail groups remains less clear with only 3,5-dichlorobenzaldehyde (**8**) retaining activity across all six libraries.

Examination of selected Rhodadyn analogues in our whole cell RME assay identified two, **C10** and **D10**, with best $IC_{50(RME)}$ values of 7.0 and 5.9 μM, respectively. This represents almost the same activity as compared to their measured dynI IC_{50} values and compares favorably to the decrease in activity found in the Pthaladyn (inactive), Iminodyn (24-fold decrease), and Dynole (4-fold decrease) series. **C10** and **D10** are among the most potent RME inhibitors reported, only surpassed by Dynole 34-2 ($IC_{50(RME)} \sim 5.0$ μM).[28,30,36] The development of the Rhodadyn series adds another chemical biology probe to the expanding palette of dynamin inhibitors.

■ ASSOCIATED CONTENT

Supporting Information

Details of library synthesis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s):We have entered into a commercial agreement with Abcam biochemicals (Bristol, UK) for the supply of our dynamin inhibitors. This includes the compounds listed in this paper.

■ ABBREVIATIONS

dynI, dynamin I; dynII, dynamin II; dynIII, dynamin III; SV, synaptic vesicle; RME, receptor-mediated endocytosis

■ ADDITIONAL NOTE

[a]Rhodadyn, MiTMAB, Bis-T, Dynole, Dynole 34-2, and Iminodyn are trademarks of Children's Medical Research Institute and Newcastle Innovation Ltd. Rhodadyn compounds and most other dynamin inhibitors described in this paper are available from Abcam Biochemicals Ltd. (Bristol, United Kingdom).

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