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Synthesis and biological evaluation of benzo[*d*]imidazole derivatives as potential anti-cancer agents

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ABSTRACT

We herein report the synthesis, biological activity and structure–activity relationship of derivatives of 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole and benzo[*d*]imidazole. A lead compound **6o** demonstrates potent anti-proliferative activity and the ability to induce cancer cell apoptosis.

Despite more than 13 members having been identified, the cyclin-dependent kinases (CDKs) can generally be divided into two groups based on roles in cell-cycle progression and transcriptional regulation. Association of CDK1, CDK2, CDK4, and CDK6 with A-, B-, E-, and D-type cyclins ensures an orderly and controlled progression of the cell proliferation cycle. CDK7 and CDK9, on the other hand, are primarily involved in the regulation of transcription through phosphorylation of the C-terminal domain (CTD) of RNA polymerase-II (RNAP-II).[1] De-regulation of various components controlling the cell-cycle plays an essential role in tumor pathogenesis. This has promoted the development of pharmacological small-molecule CDK inhibitors that can be used for cancer therapy. However, the fact that transformed cells depleted of cyclins and CDKs continue to proliferate[2] indicates that that the specific targeting of individual cell-cycle CDKs may not be an optimal therapeutic strategy due to functional redundancy.[1]

Flavopiridol, a pioneer pan-CDK inhibitor, has demonstrated marked efficacy in refractory and relapsed chronic lymphocytic leukemia (CLL).[3] This has been attributed to flavopiridol inhibition of CDK-mediated transcriptional regulation. CLL cells are mostly accumulated mature B cells which are resistant to apoptosis. Although strongly inhibiting most CDKs, the primary mechanism of action of flavopiridol is believed to be through inhibiting CDK9 and altering the transcription of apoptosis-related proteins in CLL. Flavopiridol is the most potent CDK9 inhibitor identified, and it has been shown that this inhibition is associated with a decline in short-lived anti-apoptotic proteins Mcl-1 and X-linked inhibitor of apoptosis (XIAP), which results in reinstatement of the ability of CLL cell to undergo apoptosis.[4]

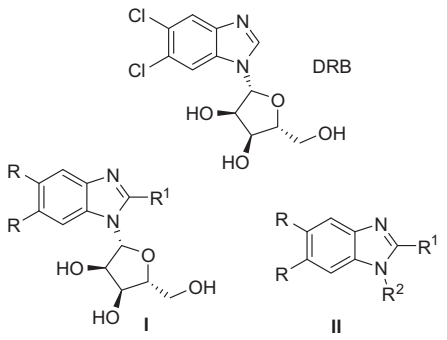

Figure 1. Structures of DRB and the designated derivatives.

5,6-Dichloro-1-β-D-ribofuranosylbenzimidazole (DRB) is an adenosine analog that has been shown to inhibit RNAPII transcription both in vitro and in vivo.[5,6] It acts by competing with ATP[7] and is believed to be the most selective CDK9 inhibitor available to date.[1] It inhibits CDK9 potently with an IC_{50} value of 600 nM by biochemical assay and shows excellent selectivity against other CDKs. However, this striking selectivity is not associated with the level of cellular potency essential for anti-cancer agents.

Our interest in developing drugs that target transcriptional CDKs has resulted in the discovery of several pre-clinical and clinical candidates for cancer therapy.[8–13] In order to identify more selective CDK9 inhibitors we selected DRB as a model for chemical

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modification and expansion aimed at defining the structure activity relationship and improving cellular potency and drug-likeness by replacing the metabolically-liable ribose of DRB with an aryl or a carbocycle. Accordingly, we prepared a class of DRB and benzo[*d*]imidazole derivatives (Type-I and Type-II, Fig. 1). In this report, we describe the synthesis and biological evaluation of these compounds. The initial structure–activity relationship analysis provided invaluable guidance in progressing our CDK9-targeted drug discovery programmes.

The synthetic chemistry employed to prepare Type-I and -II compounds is outlined in Scheme 1. Condensation reactions between benzene-1,2-diamine **1** and the appropriate carboxylic acids yielded benzo[*d*]imidazoles **2a–g**[14–16] where various substitutions, including alkyls and halides, were introduced at 2C-position of the imidazole ring system; that is, R^1 to investigate their effects on biological activity. The preparation of o-acetylated nucleosides **3** involved the formation of silylated benzimidazole by treating **2** with bis(trimethylsilyl)acetamide (BSA) in MeCN, followed by condensation with acylated sugar under Vorbrüggen's conditions[17] in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonate (TMSOTf). Subsequent hydrolysis of the latter in methanolic ammonia resulted in benzo[*d*]imidazole nucleosides **4a–d** in high yield.

Modification of the nucleoside moiety with several acyclic and cyclic systems resulted in compound class Type-II (Fig. 1). Thus treatment of benzene-1,2-diamines **1** with either 2-chlorobenzaldehyde or 2-florobenzaldehyde yielded the corresponding **5a**[18] and **5b**. Diversity of 1N-substituted benzo[*d*]imidazoles **6a–k** and **6n–r** were obtained by alkylation reactions between 1*H*-benzo[*d*]imidazoles **2a, 2d–g** and the appropriate alkyl halides. Final reduction of the nitrobenzene moieties of **6i–j** in the presence of $SnCl_4$ under acidic conditions afforded the respective anilino derivatives **6l–m**.

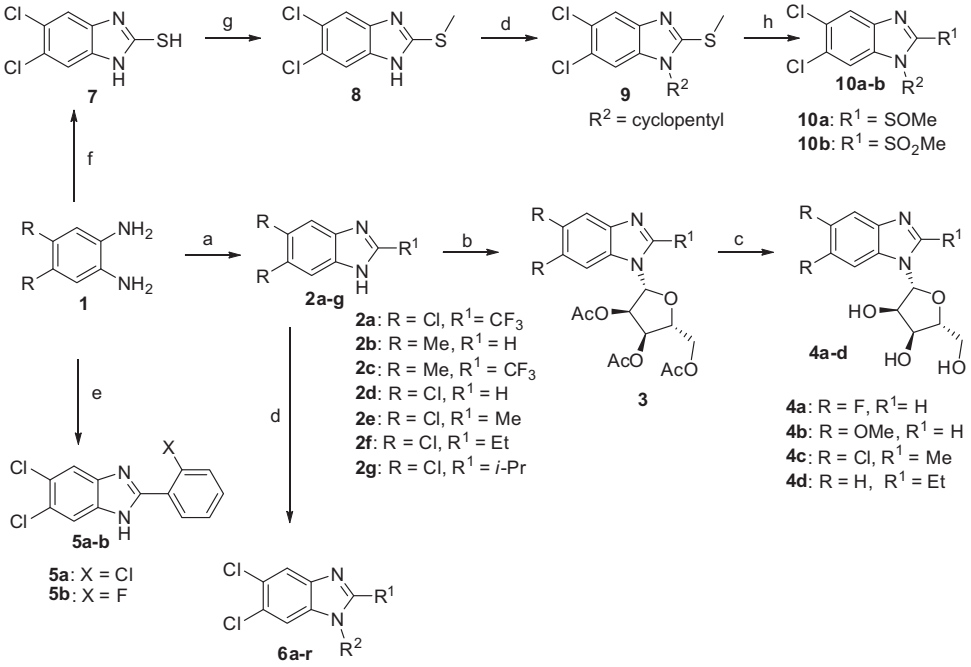
To further probe the electron donating and withdrawing effects thioether, sulfinyl and sulfonyl substituent were introduced to 2C-position of benzo[*d*]imidazole. 4,5-Dichlorobenzene-1,2-diamine **1** was heated with carbon disulfide in ethanolic potassium hydroxide, followed by methylation to give **8**,[19] which was in turn treated with chlorocyclopentane to afford 5,6-dichloro-1-cyclopentyl-2-(methylthio)-1*H*-benzo[*d*]imidazole **9**. Methylsulfinyl- (**10a**) and methylsulfonyl-1*H*-benzo[*d*]imidazole (**10b**) were obtained by oxidation in the presence of *m*-CPBA.

Anti-proliferative activity of selected compounds was assessed against HCT-116 colorectal carcinoma and MCF-7 breast carcinoma cells using a standard 48-h MTT cytotoxicity assay.[8] The results are summarized in Table 1.

Replacement of the 5,6-dichloride group of the benzimidazole nucleus with either fluoride (**4a**: R = F)[20] or methoxide (**4b**: R = OMe) in the context of 1-β-D-ribofuranosylbenzimidazole did not offer any superiority over DRB in terms of cytotoxic effects on the tumor cell lines tested. Similarly, introduction of a methyl or ethyl group at the R^1 in **4c**[21] or **4d** failed to enhance activity, irrespective of what substituent the benzene ring bears.

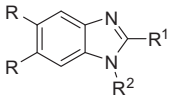
Surprisingly, compound **2a**[14] ($R^1 = CF_3$, R^2 = H, R = Cl) demonstrated good anti-proliferative activity in both HCT-116 and MCF-7 cells with GI_{50} of 7 and 6 μM respectively, being 3.5- and 6-fold more potent than DRB, suggesting that the ribose ring might be dispensable. The structural modification of **2a** by replacing 5,6-dichlorides with 5,6-dimethyl groups, that is, **2c**[14]: $R^1 = CF_3$, R = Me, or depleting trifluoromethyl (**2d**[15]: R^1 = H, R = Cl), however, dramatically reduced the activity compared with **2a**. Analogs with different substitutions at R^1, including alkyls (**2e**: R^1 = Me, **2f**: R^1 = Et, and **2g**: R^1 = *i*-Pr)[15,16] and substituted phenyls (**5a** and **5b**), in the context of 5,6-dichloro-1*H*-benzo[*d*]imidazole, had little effect on cell viability. The trifluoromethyl substitution was therefore identified as the most effective residue at the position R^1 of 5,6-dichlorid benzo[*d*]imidazole for cellular potency.

Keeping the portion of 5,6-dichloro-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole while introducing a number of acyclic or cyclic systems at 1N-position led to **6a–e**. As shown in Table 1, although **6a**–**d**, where R^1 is alkyl; that is, Me (**6a**), Et (**6b**), *i*-Pr (**6c**) or Allyl (**6d**), caused a loss in anti-proliferative activity, 5,6-dichloro-1-



Scheme 1. Reagents and conditions: (a) R^1COOH, rf; 4 h, 70–98%, or R^1COOH, Discovery Microwave, 145 °C; 20 min; (b) (i) BSA, MeCN, reflux, 1 h, (ii) (*2S,3R,4R,5R*)-5-(acetoxymethyl)tetrahydrofuran-2,3,4-triyl triacetate in MeCN, TMSOTf, reflux, 24 h, 19–50%; (c) 7 M NH_3 in MeOH, rt, 24 h, 100%; (d) 2a, 2d, 2e, 2f, 2 g, or 8; R^2X, NaOH, MeCN, 24 h, 1–70%; (e) ArCHO, $Na_2S_2O_5$, EtOH, reflux, 38–86%; (f) CS_2, KOH, EtOH, reflux, 4 hr, 87%; (g) MeI, K_2CO_3, reflux, 4 h, 80%; (h) DCM, *m*-CPBA, −40 °C–rt, 70–100%.

Table 1
Structure and growth inhibitory activity of selected compounds against human tumor cancer cells



Code	Structure			48 h MTT Cytotoxicity GI_{50} μM[a]	
	R^1	R^2	R	HCT-116	MCF-7
DRB	H	Ribose	Cl	25.0	36.0
4a	H	Ribose	F	67.0	57.9
4b	H	Ribose	OMe	>100	>100
4c	Me	Ribose	Cl	nt	nt
4d	Et	Ribose	H	70.6	71.3
2a	CF_3	H	Cl	7.0	6.0
2b	H	H	Me	51.0	20.0
2c	CF_3	H	Me	56.0	17.0
2d	H	H	Cl	66.0	73.0
2e	Me	H	Cl	51.0	28.0
2f	Et	H	Cl	46.0	48.0
2g	*i*-Pr	H	Cl	52.0	57.0
5a	*o*-Cl-phenyl	H	Cl	23.0	22.0
5b	*o*-F-phenyl	H	Cl	56.5	47.5
6a	CF_3	Me	Cl	56.0	39.0
6b	CF_3	Et	Cl	95.3	72.9
6c	CF_3	*i*-Pr	Cl	81.9	70.5
6d	CF_3	Allyl	Cl	89.2	87.0
6e	CF_3	cyclopropylmethyl	Cl	61.3	60.2
6f	CF_3	Benzyl	Cl	8.6	8.7
6g	CF_3	*m*-CF_3-benzyl	Cl	50.5	68.0
6h	CF_3	*p*-CF_3-benzyl	Cl	19.0	17.0
6i	CF_3	*o*-NO_2-benzyl	Cl	5.9	1.5
6j	CF_3	*m*-NO_2-benzyl	Cl	22.8	60.0
6k	CF_3	*p*-NO_2-benzyl	Cl	81.6	97.3
6l	CF_3	*o*-NH_2-benzyl	Cl	26.1	55.6
6m	CF_3	*m*-NH_2-benzyl	Cl	22.6	77.5
6n	H	Cyclopentyl	Cl	37.0	42.0
6o	Me	Cyclopentyl	Cl	13.0	40.0
6p	Ethyl	Cyclopentyl	Cl	38.0	52.0
6q	CF_3	Cyclopentyl	Cl	22.0	21.0
6r	*i*-Pr	Cyclopentyl	Cl	9.0	43.0
9	SMe	Cyclopentyl	Cl	2.9	3.9
10a	SOMe	Cyclopentyl	Cl	0.5	0.5
10b	SO_2Me	Cyclopentyl	Cl	0.6	0.6

[a]Values are means of at least two independent determinations; nt: not tested.

benzyl-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole **6f** (R^1 = benzyl) exhibited comparable potency to **2a**, and greater than threefold increase in anti-proliferative effect compared with DRB, indicating the tolerance of a large ring at 1N-position of the benzo[*d*]imidazole skeleton. An even more positive trend was displayed by **6i**, where an *o*-nitrobenzyl moiety at the 1N-position resulted in further enhancement of activity, with GI_{50} values of 5.9 μM and 1.5 in respective HCT-116 and MCF-7 cells. Further investigating the R^1 with different substituted benzyl functionalities giving **6g–h** and **6j–n** resulted in the loss of cellular activity.

Replacement of the ribose moiety in DRB with a cyclopentyl ring was tolerated. 5,6-Dichloro-1-cyclopentyl-1*H*-benzo[*d*]imidazole (**6n**,[22] R^1 = H) slightly reduced anti-proliferative activity compared with DRB. Keeping the 5,6-dichloro-1-cyclopentyl-1*H*-benzo[*d*]imidazole portion, but structurally modifying R^1 with a methyl or isopropyl afforded **6o** or **6r**, with ⩾2-fold increased cellular potency in HCT-116 cells (GI_{50} = 13 and 9 μM respectively). However MCF-7 cells appeared to be resistant to both compounds. **6p** or **6q**, containing a slightly bulkier group at R^1, did not offer cellular potency. The most potent anti-proliferative compounds, **10a** (GI_{50} = 0.5 μM) and **10b** (GI_{50} = 0.6 μM), were obtained when methylsulfinyl or methylsulfonyl groups respectively were introduced to R^1 position.

In light of the potent anti-proliferative activity, the CDK kinase inhibitory activities of **6o**, **6r**, **9**, and **10a–b** were evaluated by biochemical assays.[10] **6o** and **6r** inhibited CDK9T1 with K_i values of 1.51 μM and 3.33 respectively, with no activity against CDK2A. Despite their excellent cellular potency, **9**, **10a** and **10b** showed low inhibitory activity against CDK9T1, with K_i values >5 μM, suggesting that their cellular cytotoxicity might not be associated with CDK9 kinase inhibition.

In order to assess whether the lead compounds were capable of inducing apoptosis in cancer cells, caspase-3 activation assay[10] was performed on **6o**, **10a** and **10b**. As shown in Figure 2. **6o**, **10a**, **10b** and DRB activated significant caspase-3 activity at their respective GI_{50} compared with DMSO, with enhanced activity at higher concentrations.

Induction of apoptosis was further analysed by AnnexinV/PI double staining in HCT-116 cells following treatment with each compounds (Fig 3). The treatment with **6o** or DRB resulted in significant numbers of early apoptotic cells (>17% and 20% respectively), being consistent with CDK9 inhibitory mechanism.[10] **10a** and **10b** were much less effective when compared with **6o** and DRB, <7% Annexin V-positive cells were detected, indicating that their anti-proliferative property might be the major contributor to cytotoxicty in the cells.

We next examined the cell-cycle effects[10] and analysis by flow cytometry showed no effect on cell-cycle progression following treatment of HCT-116 cells with 5xGI_{50} μM of **6o**, **10a** or **10b** (Fig. 4). However DRB-treatment led to an observed accumulation

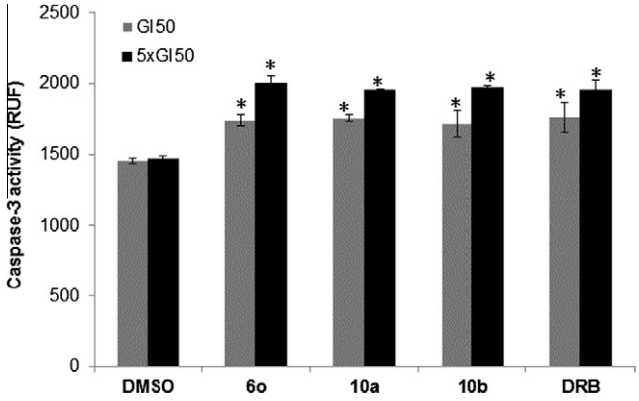


Figure 2. Induction of caspase-3 activity in HCT-116 cells after treatment with each compound at the respective GI_{50} or $5\times GI_{50}$ μM for 24 h. Vertical bars represent the mean ± s.d. of two independent experiments. Values significantly (p <0.05) different from DMSO control are marked with an asterisk (*).

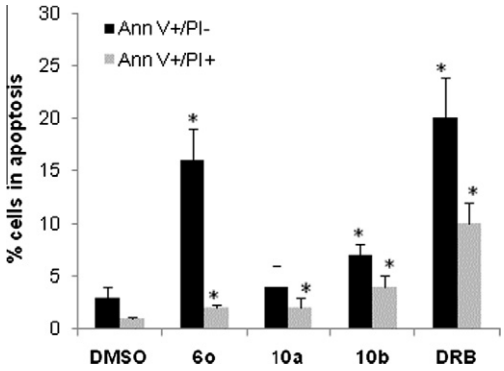


Figure 3. HCT-116 cells were exposed to $5\times GI_{50}$ μM each compounds or DMSO for 24 h and the cells were analysed by annexinV/PI strained DNA content. The percentage of cells undergoing apoptosis was defined as the sum of early apoptosis cells (AnnV+/PI−) and late apoptosis (AnnV+/PI+). Vertical bars represent the mean ± s.d. of two independent experiments. Values significantly (p <0.05) different from DMSO control are marked with an asterisk (*).

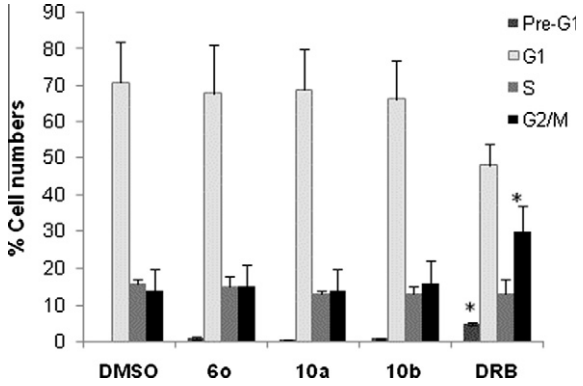


Figure 4. Cell-cycle analysis of HCT-116 cells following treatment with **6o**, **10a**, **10b** or DRB for 24 h at $5\times GI_{50}$ μM. DMSO was used as control. Vertical bars represent the mean ± s.d. of two independent experiments. Values significantly (p <0.05) different from DMSO control are marked with an asterisk (*).

of G2/M cells. Unlike other members of CDK family CDK9 has no functions outside the regulation of transcription, therefore, selectively targeting CDK9 should not exhibit any cell-cycle effect. The different responses of **6o** and DRB may lie on their different target selectivity profiles, and the G2/M cell-cycle arrest caused by DRB may be attributed to its known CK2 (Casein kinase II) inhibition.[23,24]

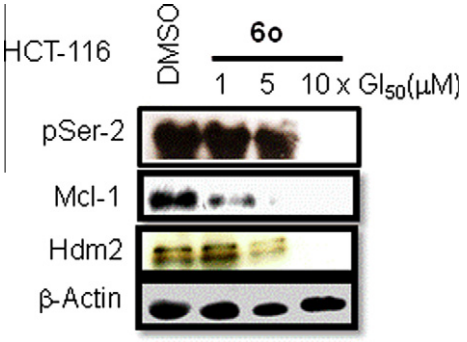


Figure 5. Cellular mode of action of **6o** by Western blotting analysis: HCT-116 cells were treated with **6o** for 24 h at the concentrations shown. The reduced levels of RNAPII CTD pSer-2 at GI_{50} μM indicated cellular CDK9 inhibition. β-Actin was used as internal control.

To confirm the cellular CDK9 inhibitory activity, HCT-116 cells were treated with **6o** for 24 h at the concentrations shown (Fig 5). Western blot analysis showed that the level of phosphorylation at Ser-2 of RNAPII CTD was reduced, starting from GI_{50} μM in a dose-dependent manner, indicating cellular CDK9 inhibition. The same treatment reduced the levels of Mcl-1 and MDM2 proteins and the cellular mechanism was consistent with the CDK9-mediated RNAPII transcriptional inhibition in cancer cells.[10]

In conclusion, a series of analogs of DRB and benzo[*d*]imidazole[25] were prepared and their SAR was studied. 5,6-Dichloro-1-cyclopentyl-1*H*-benzo[*d*]imidazoles **6o**, **10a** and **10b** possessed potent antiproliferative activity in cancer cell lines. **6o** inhibited cellular CDK9 activity and was capable of inducing apoptosis via down-regulation of anti-apoptotic proteins Mcl-1 at the concentration used to elicit its cytotoxic GI_{50} response.

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25. **6o**: ^{1}H NMR (DMSO-d_6) δ 1.71 (m, 2H, CH_2), 1.9–2.13 (m, 6H, CH_2), 2.58 (s, 3H, CH_3), 4.86 (q, J = 8.8 Hz, 1H, CH), 7.75 (s, 1H, ArH), 7.79 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6) δ 15.0, 24.8, 30.0, 56.7, 112.9, 120.1, 124.1, 133.2, 143.0, 155.4; HRMS (EI$^+$) m/z: 269.0647 [M+H]$^+$; $C_{13}H_{14}Cl_2N_2$ requires 268.0534. **10a**: ^{1}H NMR (DMSO-d_6) δ 1.73 (m, 2H, CH_2), 1.99 (m, 2H, CH_2), 2.15 (m, 6H, CH_2), 3.18 (s, 3H, CH_3), 5.35 (q, J = 8.9 Hz, 1H, CH), 8.04 (s, 1H, ArH), 8.14 (s, 1H, ArH). ^{13}C NMR (DMSO-d_6) δ 24.69, 30.91, 31.34, 38.91, 57.80, 114.60, 122.47, 127.46, 133.83, 141.70, 156.87. HRMS (EI$^+$) m/z: 318.0174 [M+H]$^+$; $C_{13}H_{14}Cl_2N_2OS$ requires 317.2341. **10b**: ^{1}H NMR (DMSO-d_6) δ 1.73 (m, 2H, CH_2), 2 (m, 2H, CH_2), 2.15 (m, 4H, 2 $\times$ CH_2), 3.69 (s, 3H, CH_3), 5.43 (q, J = 9 Hz, 1H, CH), 8.05 (s, 1H, ArH), 8.20 (s, 1H, ArH). ^{13}C NMR (DMSO-d_6) δ 24.6, 30.4, 42.9, 58.6, 115.3, 123.1, 127.2, 128.6, 133.0, 140.6, 151.6; HRMS (EI$^+$) m/z: 333.0318; $C_{13}H_{14}Cl_2N_2O_2S$ requires 333.2335.