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Potent and orally active non-peptide antagonists of the human melanocortin-4 receptor based on a series of *trans*-2-disubstituted cyclohexylpiperazines

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Abstract—The melanocortin-4 receptor (MC4R) plays an important role in the regulation of energy homeostasis. Recent studies have shown that blockade of the MC4R reverses tumor-induced weight loss in mice. Herein, we describe the synthesis and identification of potent and selective non-peptide antagonists of the human MC4R from a series of 2-ethoxycarbonylcyclohexyl-piperazines. Compound **12i** was found to possess low nanomolar affinity for the MC4R, and exhibit oral bioavailability in rats. More importantly, when administered orally to mice (10 mg/kg), it led to statistically significant increases in food intake over a 24-h period.

Cachexia is a syndrome of weight loss associated with debilitating diseases such as cancer, renal failure, heart failure, and chronic infections.[1] The severity of cachexia in these illnesses is considered to be a primary determinant of the deteriorating quality of life and eventual mortality, and is characterized by a significant decrease in lean body mass.[2] Current available treatments for cachexia rely heavily on the use of high doses (>800 mg) of megestrol acetate, which leads primarily to an increase in fat mass and water content and not the desired increase in lean body mass.[3] The high doses used also may lead to undesired side-effects due to the shut down of the hypothalamic–pituitary axis (HPA).[4] Consequently, there is a need for the development of an effective therapy for the management of cachexia.

The melanotropins are small peptide-hormones, which are involved in regulating skin pigmentation, the immune system, steroid production, central sexual behavior, feeding behavior, and exocrine gland secretion.[5] They consist of melanocyte-stimulating hormones (MSH) and the adrenocorticotropic hormone (ACTH), which are derived from a large precursor peptide, proopiomelanocortin (POMC).[6] MSH appears in three different forms: α-MSH, β-MSH, and γ-MSH. In addition to these agonists, two endogenous antagonists, agouti-protein and agouti-related protein (AgRP) have been identified. All melanocortin peptides possess a His-Phe-Arg-Trp (HFRW) motif, which is crucial for activation of the melanocortin receptors.

The melanocortin peptides exert their biological effects by activating five distinct melanocortin receptors (MC1-5 R), which belong to the class A G-protein-coupled receptor superfamily.[7]

Compelling evidence suggests that the centrally expressed melanocortin-4 receptor (MC4R) plays an

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important role in the regulation of energy homeostasis associated with food intake and metabolism.[8] In animal models of feeding, it has been demonstrated that peptide antagonists of the MC4R such as AgRP and SHU9119 are effective in stimulating food intake in mice.[9] Studies have shown that icv administration of peptide MC4R antagonists leads to an increase of food intake in tumor-bearing mice, and reverses the weight loss induced by tumor growth.[10,11] A recent study has also shown that ML00253764 (**1**), a small molecule antagonist of the MC4R, effectively reduces tumor-induced weight loss in a mouse model by a peripheral route of administration.[12] Thus, a potent, selective, and orally bioavailable MC4R antagonist should have considerable potential as a novel therapy for cachexia.[13]

In addition to compound **1**, only a small number of small molecule MC4R antagonists have been recently described in the literature. A series of alkylpiperazines exemplified by **2** (IC_{50} = 52 nM) were reported to prevent AgRP binding to the MC4R. These compounds also exhibit moderate affinity (**2**, IC_{50} = 220 nM) against NDP–MSH binding.[14] MCL0129 (**3**), having a structure similar to **2**, is the only potent non-peptide antagonist reported, which possesses low nanomolar affinity on the inhibition of NDP–MSH binding (K_i = 7.9 nM). Interestingly, **3** exhibits anxiolytic-like and antidepressant-like activities in several animal models.[15] Finally, a structure–activity relationship study on a series of imidazoles related to **1**, such as **4** (K_i = 180 nM) has also been reported (Fig. 1).[16]

In our efforts to identify potent and selective antagonists of the MC4R, we have discovered a series of piperazinebenzylamines that possesses subtype selectivity and high binding affinity at the human receptor. Both agonists and antagonists have been identified from this series of compounds. For example, **5a** (K_i = 21 nM) is a potent MC4R antagonist (IC_{50} = 90 nM, on the inhibition of α-MSH-stimulated cAMP production),[17] and **5b** (K_i = 6.4 nM) is a potent MC4R agonist (EC_{50} = 3.8 nM with stimulation of cAMP levels comparable to that of α-MSH).[18] Structure–activity relationship studies in these series reveal that the basic nitrogen of the benzylamine portion plays an important role in the interactions of these compounds with the receptor, perhaps through charge–charge attraction with an acidic residue, possibly Asp-122.[19] While the presence of the benzylamine leads to highly potent antagonists and agonists such as **5a** and **5b**, respectively, the resulting compounds possess multiple highly basic centers, and as a consequence are poorly absorbed when given orally.[18] In search of potent and selective MC4R antagonists with the potential for oral administration, we screened several different substituted piperazines as replacements for the highly basic benzylamines, such as in **5a** and **5b**. During this effort, we discovered a novel series of cyclohexylpiperazines that once combined with various *N*-acylated D-2,4-dichlorophenylalanines generated several potent MC4R antagonists.[20] In this letter, we describe the synthesis and structure–activity relationships of this series of compounds, and also the pharmacokinetic profile of a selected compound as well as its oral efficacy in a murine feeding model.

In our studies, the key intermediate **11** was synthesized according to the sequence depicted in Scheme 1. Commercially available β-keto-ester **6** was subjected to reductive amination with *N*-Boc-piperazine, in the presence of sodium (triacetoxy)borohydride in dichloromethane containing 1 equiv of acetic acid, to give compound **7**. The predominantly *cis*-isomer **7** was converted to the *trans*-form **8** under basic conditions (NaOEt/EtOH).[21] The relative stereochemistry was confirmed by analyzing the coupling constant of the 1,2-protons (J = 4.1 Hz for *cis*-form, 11.6 Hz for *trans*-form) of the proton NMR spectrum.[21] Additionally, ROESY NMR experiments were performed on both compounds and the spatial relationship of the 1,2-protons was established leading to the conclusive structural assignment of **7** and **8**. Finally, treatment of *cis*-isomer **7** with $LiAlH_4$ in THF resulted in the crystalline *cis*-alcohol

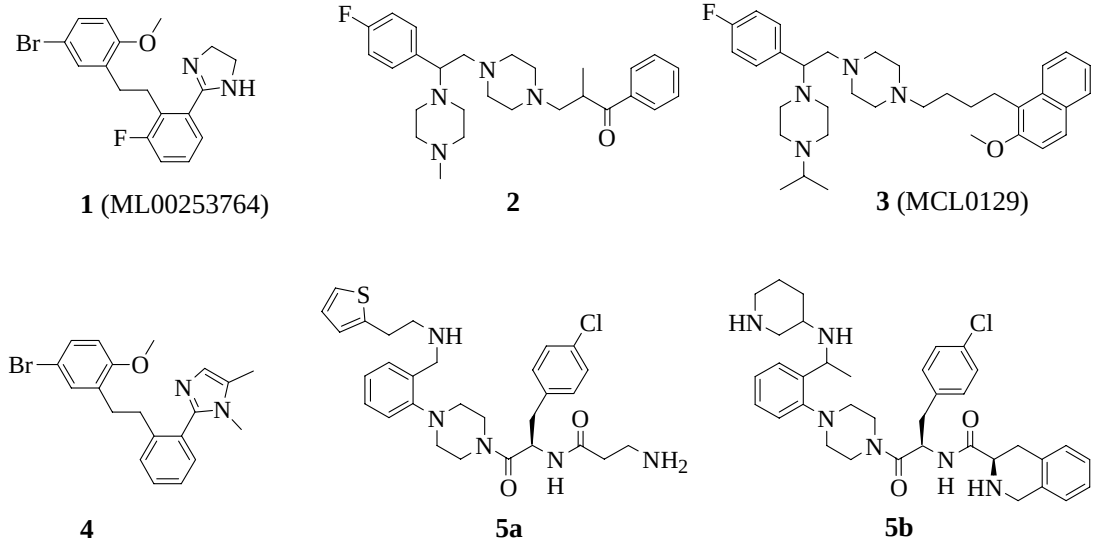
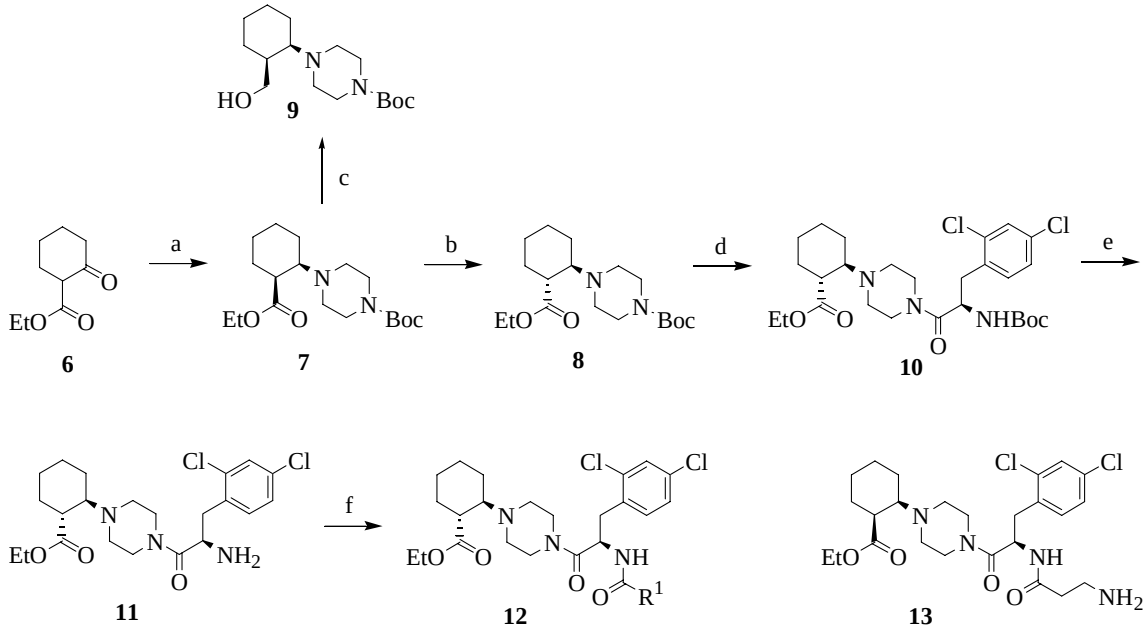


Figure 1. Small molecule ligands for the melanocortin-4 receptor.



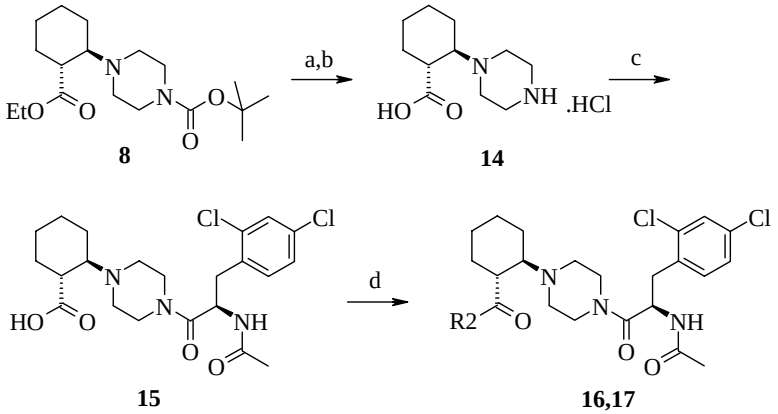
Scheme 1. Reagents: (a) *N*-Boc-piperazine/$Na(OAc)_3BH/CH_2Cl_2$/HOAc; (b) NaOEt/EtOH; (c) $LiAlH_4$, THF; (d) i—TFA/CH_2Cl_2, ii—*N*-Boc-D-(2,4-Cl)Phe-OH/HBTU/DIEA/DMF; (e) TFA/CH_2Cl_2; (f) R^1COOH/EDC/Et_3N/CH_2Cl_2; for R^1 containing BocNH, TFA/CH_2Cl_2.

9, which was subjected to X-ray diffraction studies, thus confirming the *cis*-relative stereochemistry.[22] Compound **8** was then deprotected with TFA and the resulting free amine was coupled with *N*-Boc-D-2,4-dichlorophenylalanine in the presence of HBTU to give **10**. Deprotection of **10** with TFA afforded the free amine **11**, which was coupled with various carboxylic acids to give the designed compounds **12**. When *N*-Boc-protected amino acids, such as *N*-Boc-glycine, were used in the final amide-forming step, the resulting compounds **12** were further deprotected with TFA to afford the desired products (Scheme 1).

For comparison purposes, the *cis*-cyclohexylpiperazine derivative **7** was also converted to the final compound **13** (*cis*-**12i**) by TFA deprotection in CH_2Cl_2, followed by coupling with the dipeptide *N*-(Boc-β-Ala)-D-(2,4-Cl_2)Phe-OH in the presence of HBTU. Final TFA deprotection afforded **13**.

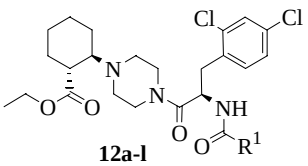
To explore the role of the ethyl ester in compound **12a**, an alternative synthetic route was devised as shown in Scheme 2. Thus, compound **8** was saponified under alkaline conditions to give the corresponding carboxylic acid, which was then deprotected in the presence of HCl in CH_2Cl_2 and diethyl ether to give hydrochloride salt **14**. *N*-acetyl-2,4-dichlorophenylalanine was preactivated by HBTU in DMF, and then treated with **14**, to afford acid **15**. This, in turn, was subjected to coupling reactions with various alcohols or amines to give the desired compounds **16** and **17**, respectively.

We first examined amides **12** in a competition-binding assay with radiolabeled [^{125}I]-NDP–MSH, using HEK293 cells stably transfected with the human MC4R as previously described.[23] Acetylation of amine **11** (K_i = 120 nM) resulted in an analog (**12a**, K_i = 11 nM) with an increase of almost 10-fold in binding affinity. These results indicate that either the NH or the carbonyl moiety of this amide

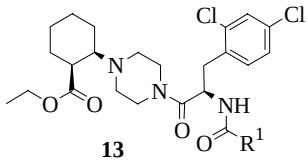


Scheme 2. Reagents: (a) KOH/EtOH/H_2O; (b) HCl/Et_2O/CH_2Cl_2; (c) *N*-Ac-(2,4-Cl)Phe-OH/HBTU/DIEA/DMF; (d) alcohol or amine/EDC/Et_3N/DMF.

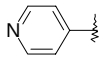
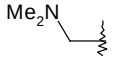
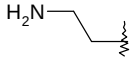
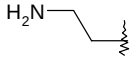
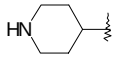
Table 1. Binding affinity of amides at the human MC4 receptor[a]



12a-l



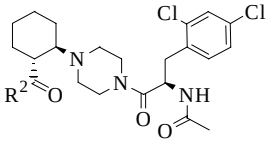
13

Compound	R^1	K_i (nM)[b]
11	—	120 ± 11
12a	–CH_3	11 ± 0.3
12b		18 ± 2
12c		10.0 ± 3
12d		19 ± 2
12e		9.8 ± 4.9
12f		11 ± 5
12g		10 ± 3
12h		17 ± 4
12i		6.3 ± 0.6
13 (*cis*-**12i**)		53 ± 21
12j		12 ± 2
12k		2.8 ± 0.6
12l		4.7 ± 1.0

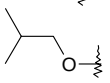
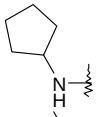
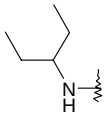
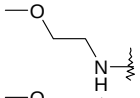
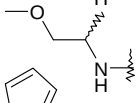
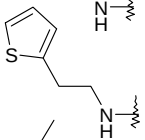
[a] Receptor stably expressed in HEK293 cells.
[b] K_i values (n = 2 or 3) ± SEM.

play a major role in binding to the receptor. Small alkyl-(**12b**), pyridinyl-(**12c**), and hydroxymethyl-(**12d**) amides had comparable K_i values to **12a**. Introduction of a basic amino group led to a slight increase in binding affinity

Table 2. Binding affinity of ethyl ester replacements at the human MC4 receptor[a]



15, 16a-c,17a-m

Compound	R^2	K_i (nM)[b]
15	–OH	580 ± 260
16a		91 ± 6
12a		11 ± 0.3
16b		46[c]
16c		48 ± 9
17a		1600 ± 30
17b		1150 ± 440
17c		850 ± 210
17d		790 ± 220
17e		700 ± 59
17f		640 ± 29
17g		640 ± 11
17h		420 ± 6
17i		92 ± 24
17j		160 ± 19
17k		160 ± 4
17l		480 ± 160
17m		1000 ± 100

[a] Receptor stably expressed in HEK293 cells.
[b] K_i values (n = 2 or 3) ± SEM.
[c] Single determination.

Table 3. Binding affinity (K_i, nM) of selected compounds at the melanocortin receptor subtypes[a]

Compound	MC1R	MC3R	MC4R	MC5R	IC_{50} (nM)[b,c]
12a	3300 ± 390	1200 ± 18	11.0 ± 0.3	840 ± 120	41[d]
12i	2800 ± 1250	460 ± 72	6.3 ± 0.6	310 ± 74	12 ± 4
12k	620 ± 40	950 ± 30	2.8 ± 0.6	190 ± 50	13[d]
12l	600 ± 54	987.0 ± 0.1	4.7 ± 1.0	290 ± 60	10[d]

[a] Melanocortin receptors stably expressed in HEK293 cells. The data are mean ± SEM (n = 2 or 3).
[b] Inhibition of α-MSH-stimulated cAMP production.
[c] No significant stimulation of cAMP production at 10 μM concentration (<5% to the level of α-MSH).
[d] Single determination.

over **12a**. Thus, **12i**, **12k**, and **12l** had K_i values of 6.3, 2.8, and 4.7 nM, respectively (Table 1). While the additional basic nitrogen played a small beneficial role in binding to the receptor, the relative configuration of the 1,2-disubstituted cyclohexane ring was much more important. Thus, the *cis*-isomer **13** (K_i = 53 nM) was almost 10-fold less potent than its corresponding *trans*-analog **12i** in MC4R binding.

A small lipophilic group at the 2-carboxylate was required for high binding affinity to the receptor. Thus, the free carboxylic acid **15** (K_i = 580 nM) lost more than 50-fold affinity when compared to its ethyl ester **12a**. The smaller methyl ester **16a** also showed a reduction in affinity when compared to **12a**. However, the slightly larger isopropyl and isobutyl esters **16b** and **16c** displayed lower potency than **12a**, suggesting that the ethyl group was optimal at this position. Amides (**17**), including tertiary ones, in general possessed higher K_i values than the ester derivatives (Table 2).

Table 4. Pharmacokinetic properties of **12i** in rats[a]

iv (5 mg/kg)	
CL (mL/min kg)	57 ± 13
$t_{1/2}$ (h)	5.8 ± 0.6
V_d (L/kg)	28.7 ± 7.4
C_{plasma} (1 h) (ng/mL)	88 ± 5
C_{brain} (1 h) (ng/g)	158 ± 73
B/*P* ratio (1 h)	1.8 ± 0.7
po (10 mg/kg)	
T_{max} (h)	2.8 ± 1.6
C_{max} (ng/mL)	117 ± 40
AUC (ng/mL h)	365.5 ± 90.3
Oral bioavailability (%)	12.2 ± 3.6

[a] Average of three animals.

All compounds were tested for their ability to stimulate cAMP production in HEK293 cells expressing the human MC4 receptor.[23] No significant stimulation was observed for any compound at 10 μM concentration (less than 10% of the maximum α-MSH stimulation, data not shown), which indicates that these compounds are not functional agonists at the human MC4R. Selected compounds were then tested for their ability to inhibit α-MSH-stimulated cAMP accumulation, to assess functional antagonism. Thus, **12a**, **12i, 12k**, and **12l** were found to dose-dependently inhibit α-MSH-stimulated cAMP production with IC_{50} values of 41, 12, 13, and 10 nM, respectively (Table 3). **12i** shifted α-MSH-stimulated cAMP dose-curve rightward and had a K_b value of 47 nM in a Schild plot. These data demonstrated that **12i** was a competitive functional antagonist at the MC4R.

The selectivity profile of **12i** at the other melanocortin receptors was also determined. Thus, it had K_i values of 2800, 460, and 310 nM, respectively, at the MC1R, MC3R, and MC5R. These data demonstrated that **12i** was very selective at the MC4R over these melanocortin subtypes, with an approximated ratio of 70 at the MC3R and 50 at the MC5R. Compounds **12a**, **12k**, and **12l** also had similar selectivity. These results are summarized in Table 3.

Compound **12i** was chosen for in vivo evaluation due to its favorable in vitro profile, as well as its desirable calculated physicochemical properties.[24] The calculated

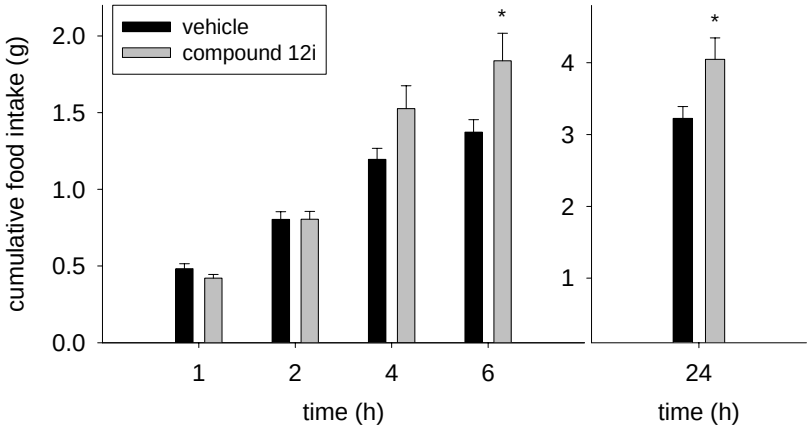


Figure 2. Effect of orally administered compound **12i** (10 mg/kg, PO, dosed in distilled water at pH 5) on night phase feeding in mice. Cumulative food intake was significantly increased at the 6- and 24-h measurement intervals (*$p < 0.05$). Values are means ± SEM.

log *D* value (2.2) agreed well with the experimental result (measured log *D* value of 1.8). After intravenous administration in Sprague–Dawley rats (5 mg/kg), **12i** had high clearance (CL = 57 ng/mL kg), and a high volume of distribution (V_d = 28.7 L/kg). This resulted in a half-life of 5.8 h in this species. The brain concentration at the 1 h time point was 158 ng/g, which was 1.8-fold of the plasma concentration at the same time point. After oral administration (10 mg/kg), the maximal concentration (C_{max} = 117 ng/mL) of **12i** was reached at the 2.8 h time point (T_{max}). The area under curve (AUC) was 365.5 ng/mL h, and this resulted in a calculated oral bioavailability of 12.2% (Table 4).

Next, we examined the effects of a single administration on normal food intake in mice over a 24 h period. Male C57BL/6 mice (7–8 weeks of age; n = 10 per group) were orally administered vehicle or 10 mg/kg of compound **12i** at the onset of the dark phase of the light/dark cycle, a time when rodents are active and normally eat. Food intake was then measured 1, 2, 4, 6, and 24 h after lights were out. Compound **12i** significantly increased cumulative food intake at the 6- and 24-h measurement intervals ($p < 0.05$; Fig. 2). This finding demonstrates that a selective MC4R antagonist with oral bioavailability has the ability to increase feeding significantly over a 24-h period and suggests that MC4R antagonists may be useful to treat diseases with an anorexia component such as cachexia. In addition, it has been described recently that **12i** reverses tumor-induced weight loss upon peripheral administration in mice.[25]

In conclusion, a series of cyclohexylpiperazines (**12**, **16**, and **17**) was synthesized. Compounds from this series were identified to be potent and selective antagonists of the human MC4R. Functionally, **12i** was found to be a competitive MC4R antagonist versus α-MSH-stimulated cAMP production. In rats, **12i** displayed reasonable plasma exposure from oral administration and penetrated into the brain. We have shown that compound **12i**, when orally administered, increases food intake in mice over a 24-h period.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bmcl.2005.06.071.

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CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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