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Asymmetric Construction of a Multi-Pharmacophore-Containing Dispirotriheterocyclic Scaffold and Identification of a Human Carboxylesterase 1 Inhibitor

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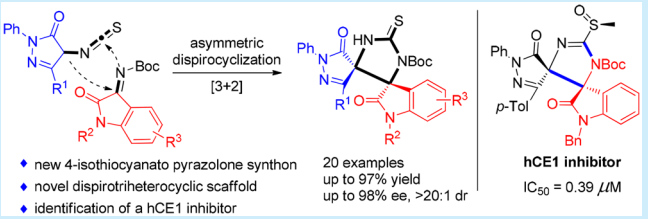
Supporting Information

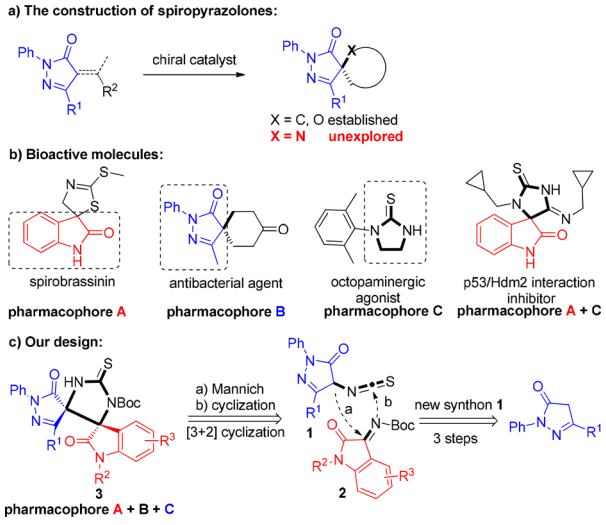
ABSTRACT: A catalytic asymmetric [3 + 2] cyclization of novel 4-isothiocyanato pyrazolones and isatin-derived ketimines was developed, delivering a wide range of intriguing dispirotriheterocyclic products in high yield with excellent diastereoselectivity and enantioselectivity. A chiral sulfoxide derivative of this dispirocyclic product was identified to be a promising hit of the human carboxylesterase 1 inhibitor, and the significant difference of the activity between two enantiomers emphasized the importance of this asymmetric process.



The efficient and asymmetric construction of spirocyclic compounds featuring rich structural diversity and complexity has been a long-standing attractive topic of intense research, because of the wide occurrence of this compound class in natural products, bioactive molecules, and pharmaceutical agents.[1] In this respect, a variety of strategies for the assembly of spirocyclic oxindoles[2] and pyrazolones[3] have emerged, driven by their prevalence in medicinal chemistry as pharmacophore structures. In sharp contrast to the remarkable progress made in accessing these diverse spirocyclic oxindoles, the construction method and structural diversity of the spirocyclic pyrazolones are rather limited. Over the past few years, despite many elegant studies toward the asymmetric synthesis of spirocyclic pyrazolones, these efforts have been predominantly restricted to products bearing all-carbon spirocenters (see Scheme 1a, X = C).[3] Very recently, an organocatalytic Michael addition/cyclization reaction and an epoxidation process of unsaturated pyrazolones were reported to construct spirocyclic pyrazolones with 4-oxygen attached to the spirocenter (X = O).[4] However, to the best of our knowledge, asymmetric access to spirocyclic pyrazolones featuring 4-nitrogen incorporated spirocenters (X = N) is still unexplored to date and, thus, potentially holds promise for the development of medicinally important compounds.

The combination of pharmacophores is a well-accepted approach used for the rational design of lead compounds.[5] Moreover, the introduction of a spiro-ring to rigidify the ligand conformation is one of the widely used strategies in drug design.[6] In this context, the fusion of oxindole and 2-thioxoimidazolidine pharmacophores through a spirocenter has shown itself as a p53/Hdm2 interaction inhibitor (Scheme 1, pharmacophore **A** + **C**).[7] Considering the priority of oxindole, pyrazolone, and 2-thioxoimidazolidine as pharmacophores, the assembly of these three structures via two vicinal

Scheme 1. Design of Dispirotriheterocyclic Scaffold from a New 4-Isothiocyanato Pyrazolone Synthon



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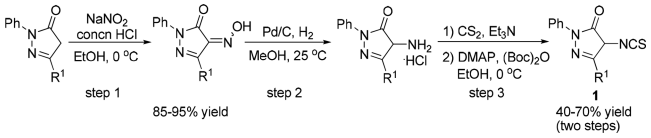
spirocenters to form a novel diaspirotriheterocyclic compound **3** attracted our intense interest, because it may possess potential biological activities (Scheme 1, moiety **A** + **B** + **C**). Inspired by our recent achievements,[8] we envisioned that this new structure might arise from 4-isothiocyanato pyrazolone **1** and isatin-derived ketimine **2** via a [3 + 2] cyclization process. Remarkably, this novel 4-isothiocyanato pyrazolone synthon **1** could be readily forged from 4-nonsubstituted pyrazolone via an oximation, reduction, and isothiocyanation sequence (see Scheme 2). Moreover, this newly designed reagent, in which

Scheme 2. Development of the 4-Isothiocyanato Pyrazolone Synthon 1



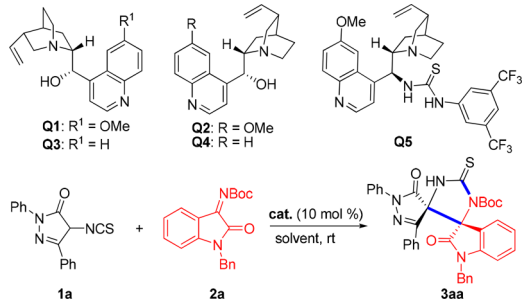
the 4-position of pyrazolone is nucleophilic and the isothiocyanato group is electrophilic, may grow up to be a powerful synthon for the construction of chiral spirocyclic pyrazolones with a nitrogen atom incorporated at the C4 position.

To test the feasibility, the [3 + 2] cyclization reaction was examined with the easily prepared 4-isothiocyanato pyrazolone **1a** and isatin-derived *N*-Boc ketimine **2a** in the presence of natural quinidine **Q1** as the catalyst in dichloromethane (DCM) at room temperature.[9] To our delight, this [3 + 2] annulation proceeded smoothly to afford the desired structurally novel dispirotriheterocyclic product **3aa** in 94% yield with excellent enantioselectivity and diastereoselectivity (90% enantiomeric excess (ee), >20:1 diastereomeric ratio (dr)) (see Table 1, entry 1). Afterward, a further trial of other natural cinchona alkaloids **Q2**−**Q4** was conducted, and all gave the product in high yield with an excellent stereochemical outcome (Table 1, entries 2−4). The well-established quinine thiourea catalyst **Q5** exhibited superior reactivity and stereocontrol, affording the dispirocyclic product within 4 h with a 96% yield, 96% ee, and >20:1 dr (Table 1, entry 5). With the distinct performance of catalyst **Q5** in hand, a quick survey of the reaction media revealed that this cyclization process worked well in various solvents (Table 1, entries 6−10). With the initially used DCM as the choice of solvent, the decrease to 5 mol % catalyst loading had almost no influence on the reaction result, furnishing the product in 96% yield, 96% ee and over 20:1 dr (entry 11). Further reducing the catalyst loading to 1 mol % only retarded the reaction to 24 h, without eroding the stereocontrol (Table 1, entry 12).

With the optimal conditions established, the substrate scope of both isatin ketimine and 4-isothiocyanato pyrazolone components was evaluated (Scheme 3). Generally, a broad spectrum of isatin *N*-Boc ketimines and 4-isothiocyanato pyrazolones were compatible to this [3 + 2] annulation process, delivering a diverse array of dispiro[pyrazolone/ethylenethiourea/oxindole] derivatives bearing two vicinal spirocenters in high yields with excellent stereocontrol.

Initially, the *N*-substituent of the oxindole moiety was investigated; besides the benzyl group, the methyl and allyl substituents were well accommodated (see Scheme 3, **3aa**−**3ad**). Moreover, a nonprotected free oxindole ring was also tolerated (**3ad**), which allows for facile variation of *N*-substitution on demand. Next, with *N*-benzyl protection, substitution on the benzene ring of the oxindole framework with either electron-withdrawing or electron-donating groups was found to be well-accommodated, affording satisfactory product yield and high levels of stereocontrol (**3ae**−**3aj**).

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	catalyst	reaction time, *t* (h)	yield[b] (%)	diastereomeric ratio, dr[c]	enantiomeric excess, ee[d] (%)
1	DCM	**Q1**	12	94	>20:1	90
2	DCM	**Q2**	12	93	>20:1	−93
3	DCM	**Q3**	12	95	20:1	93
4	DCM	**Q4**	12	95	20:1	−93
5	DCM	**Q5**	4	96	>20:1	96
6	DCE	**Q5**	4	96	>20:1	95
7	$CHCl_3$	**Q5**	4	95	>20:1	96
8	toluene	**Q5**	4	95	>20:1	94
9	Et_2O	**Q5**	4	95	>20:1	85
10	EtOAc	**Q5**	4	94	>20:1	90
11[e]	DCM	**Q5**	5	96	>20:1	96
12[f]	DCM	**Q5**	24	93	>20:1	96

[a]The reaction was conducted with **1a** (0.1 mmol), **2a** (0.11 mmol), and catalyst (0.01 mmol) in solvent (1.0 mL) at room temperature (rt). [b]Isolated yield. [c]Determined by ^{1}H NMR of the crude product. [d]Determined by chiral HPLC analysis. [e]Catalyst (5 mol %). [f]Catalyst (1 mol %).

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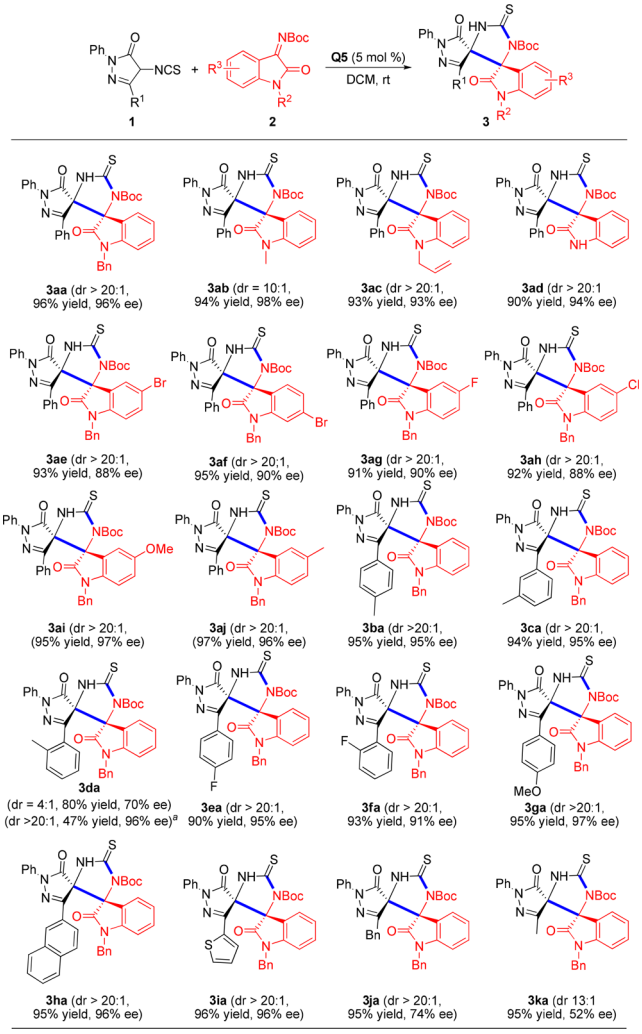
Scheme 3. Generality of the Asymmetric [3 + 2] Cyclization Reaction[a]



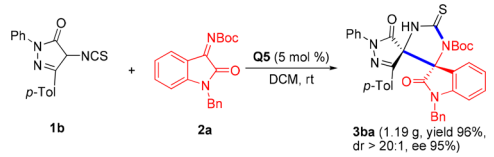
[a]After recrystallization.

Following the establishment of the broad generality of the isatin ketimine component, the substrate scope with respect to the 4-isothiocyanato pyrazolone partner was surveyed. Generally, various substituents, as exemplified by fluorine, methyl, and methoxyl groups on the aromatic ring at the C3 position of the pyrazolone, were amenable to the [3 + 2] cyclization process, affording the products in high yields with excellent stereoselectivity (**3ba**−**3ga**). Although the 2-methyl phenyl-substituted 4-isothiocyanato pyrazolone gave the corresponding product **3da** with an erosion of the yield, ee, and dr values, because of the steric hindrance, a simple recrystallization of the product elevated the enantioselectivity to 96% ee with a single diastereomer. Notably, polycyclic aromatic and heteroaromatic substituents were well-tolerated, as 2-naphthyl- and 2-thienyl-substituted pyrazolones generated the desired products **3ha** and **3ia** in high yields with excellent diastereoselectivities and enantioselectivities. In addition, the presence of alkyl groups at the C3 position of the pyrazolone moiety maintained the efficiency, but decreased the enantioselectivity, as the benzyl- and methyl-substituted pyrazolones furnished the products **3ja** and **3ka** in 74% ee and 52% ee, respectively. The absolute stereochemistry of product **3af** was unambiguously determined to be (4*S*, 3′*S*) by X-ray crystallographic analysis, and those of other products were assigned by analogy.

Following the construction of the intriguing dispiro-[pyrazolone/ethylenethiourea/oxindole] scaffold and considering our recent progress in the real-time monitoring of human carboxylesterase 1 (hCE1) activities,[10] a further investigation was carried out to evaluate whether these novel compounds featuring pharmacophore characters could inhibit hCE1. As a key target to modulate cholesterol and lipid metabolism, hCE1 has drawn much attention in recent years, both in academia and the pharmaceutical industry.[11] However, only one hCE1 inhibitor termed GR148672X has been in preclinical development for the treatment of hypertriglyceridaemia, and no hCE1 modulators have been approved as medicines to date.[12] Thus, the discovery of hCE1 inhibitors holds great potential for the development of remedies for related diseases. In this context, compounds **3aa**, **3ad**, **3ia**, and **3ba** were chosen to conduct the evaluation. As shown in Table S-1 in the Supporting Information, compound **3aa**, the *N*-nonprotected product **3ad**, and the 2-thienyl-substituted product **3ia**, together with their corresponding racemates, were all active to inhibit hCE1, although their IC_{50} values were over 100 μM (Table S-1, entries 1−6). Interestingly, the racemate of 4-methylphenyl-substituted product ***r*-3ba** has a better activity compared with **3ba** (Table S-1, entry 8 vs entry 7), with an IC_{50} of 52.62 μM. This implied that the enantiomer of **3ba** should exhibit better activity.

With these preliminary results in hand, we planned to turn our attention to the structural modification of **3ba**, instead of random screening of the compound collection of products **3**. Because of the simple operation of this [3 + 2] cyclization process, the gram-scale synthesis of compound **3ba** was facilely achieved with maintained efficiency and stereochemical outcome (Scheme 4). Next, a variety of synthetic transformations

Scheme 4. Gram-Scale Synthesis of 3ba



of **3ba** were conducted (see Figure 1). The methyl and benzyl protection of the sulfur atom was easily achieved, affording the corresponding products **4** and **5** in high yields. Moreover, **5** could be oxidized by *m*CPBA to give a chiral sulfoxide **6** in high yield with excellent diastereoselectivity, and with an excess amount of *m*CPBA, compound **5** was further oxidized to the urea derivative **7**. In addition, a cyclic guanidine **8** was obtained in the presence of ammonia and TBHP in 95% yield.[13] Interestingly, the cross coupling with phenylboronic acid afforded the amidine **9**, and the reduction of the carbonyl group of the pyrazolone moiety gave the product **10** with perfect diastereoselectivity. These useful transformations further expanded the diversity of this class of dispirocyclic compounds.

A further survey was carried out to evaluate the inhibitory activity of this new series of compounds, as shown in Table 2. The alkyl protection was detrimental, as products **4** and **5** and their racemic products lost activity to inhibit hCE1 (Table 2, entries 1−4). However, remarkably, the chiral sulfoxide **6** exhibited dramatically increased activity, of which the IC_{50} is 8.18 μM (Table 2, entry 5). Moreover, the racemic ***r*-6** displayed a better activity (Table 2, entry 6). This phenomenon

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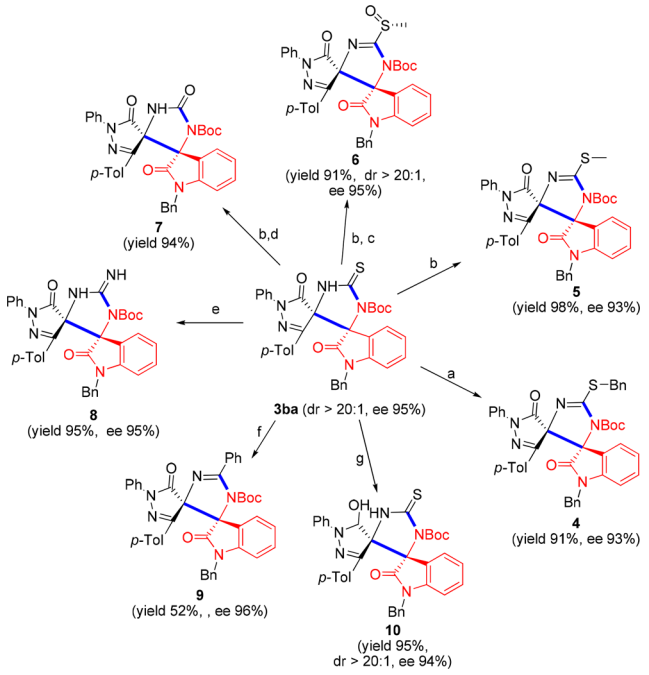

Figure 1. Synthetic transformations of **3ba**. Reaction conditions: (a) BnBr, K_2CO_3, acetone, room temperature (rt); (b) MeI, K_2CO_3, acetone, rt; (c) *m*CPBA (1.05 equiv), $CHCl_3$, 0 °C; (d) *m*CPBA (2.1 equiv), $CHCl_3$, 0 °C; (e) NH_4OH, TBHP, MeOH, rt; (f) $PhB(OH)_2$, CuTC, $Pd(PPh_3)_4$, THF, 50 °C; and (g) $NaBH_4$, THF, rt.

is identical with the observation for compound **3ba**. In addition, the urea derivative **7**, cyclic guanidine **8**, amidine **9**, the reductive product **10**, and their corresponding racemates did not give better results than the chiral sulfoxide **6** (Table 2, entries 7−14). Furthermore, the superior activities of ***r*-6** and ***r*-3ba** than **6** and **3ba**, respectively, encouraged us to synthesize the corresponding enantiomers of **6** and **3ba**.

With natural quinine **Q2**, the enantiomer of **3ba** was obtained conveniently to afford ***ent*-3ba** in 90% yield with 93% ee and >20:1 dr. Accordingly, ***ent*-6** was synthesized from ***ent*-3ba** in 93% ee. As expected, ***ent*-3ba** showed better activity than **3ba** (Table 2, entry 15 vs Table S-1, entry 7). More importantly, the IC_{50} of ***ent*-6** was only 0.39 μM, whose activity was 20-fold stronger than its enantiomer **6** (Table 2, entry 16; see Figure 2). Furthermore, the absolute stereochemistry of ***ent*-6** was determined by X-ray crystallographic analysis (see Figure 2). The significant difference of the inhibitory potency toward hCE1 between the two enantiomers of sulfoxide **6** further highlights the importance of this asymmetric [3 + 2] cyclization process.

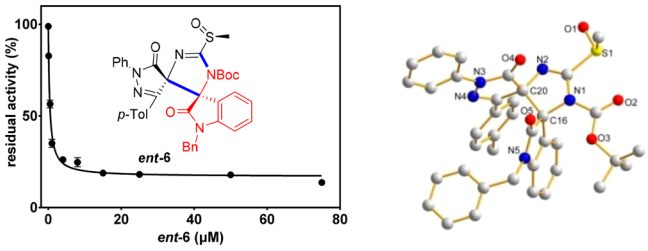

Figure 2. Inhibition curve and the X-ray structure of *ent*-6.

In conclusion, we have developed an efficient and facile catalytic asymmetric [3 + 2] cyclization of 4-isothiocyanato pyrazolones and isatin-derived ketimines. This reaction demonstrated that the readily achieved novel 4-isothiocyanato pyrazolone is a powerful synthon to construct 4-nitrogen-attached chiral spirocyclic pyrazolones by delivering a diverse array of intriguing dispirotriheterocyclic products in high yield with excellent diastereoselectivity and enantioselectivity. In addition, a novel chiral sulfoxide derivative was identified as a promising hit to inhibit human carboxylesterase 1 on the basis of diverse structural modifications, and the significant difference of the activity between two enantiomers emphasized the significance of this asymmetric process. Further studies directed toward expanding the synthetic utility of the novel 4-isothiocyanato pyrazolone reagent and elucidating the structure−activity relationship of this chiral sulfoxide inhibitor are under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01316.

Experimental details for all reactions and analytic details for all products; method for the evaluation of the activity to inhibit hCE1 (PDF)

Accession Codes

CCDC 1811799 and 1811800 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

Table 2. Inhibition Potency of Modified Products toward hCE1[a]

entry	compound	IC_{50} (μM)	entry	compound	IC_{50} (μM)
1	**4**	>100	9	**8**	59.73 ± 6.63
2	***r*-4**	>100	10	***r*-8**	47.47 ± 13.53
3	**5**	>100	11	**9**	>100
4	***r*-5**	>100	12	***r*-9**	>100
5	**6**	8.18 ± 1.32	13	**10**	28.32 ± 2.74
6	***r*-6**	3.15 ± 0.55	14	***r*-10**	>100
7	**7**	>100	15	***ent*-3ba**	27.19 ± 3.75
8	***r*-7**	>100	16	***ent*-6**	0.39 ± 0.036

[a]All data presented are averages of at least three separate experiments. The prefix ***r*** and ***ent*** represent racemate and enantiomer, respectively.

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Notes

The authors declare no competing financial interest.

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