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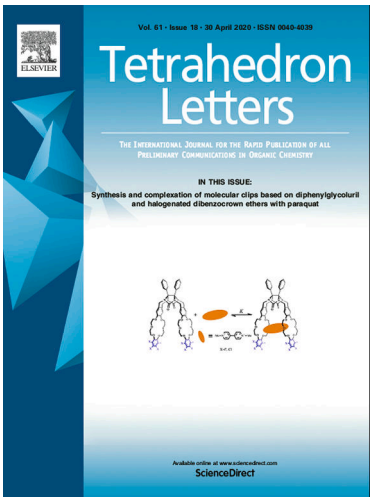

Synthesis of 6-unsubstituted 2-oxo, 2-thioxo, and 2-amino-3,4-dihydropyrimidines and their antiproliferative effect on HL-60 cells

Yoshio Nishimura, Hidetomo Kikuchi, Takanori Kubo, Yuki Gokurakuji, Yuri Nakamura, Rie Arai, Bo Yuan, Katsuyoshi Sunaga, Hidetsura Cho

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- 6-Unsubstituted 3,4-dihydropyrimidin-2(1*H*)-thiones and -ones were synthesized.
- The three-component reaction was mediated by a catalytic amount of Lewis acid.
- The reaction had broad scope for substrates and proceeded in high yields.
- Novel 6-unsubstituted 2-aminodihydropyridimidines were synthesized.
- The antiproliferative effect of the compounds on HL-60 cells was explored.

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Synthesis of 6-unsubstituted 2-oxo, 2-thioxo, and 2-amino-3,4-dihydropyrimidines and their antiproliferative effect on HL-60 cells

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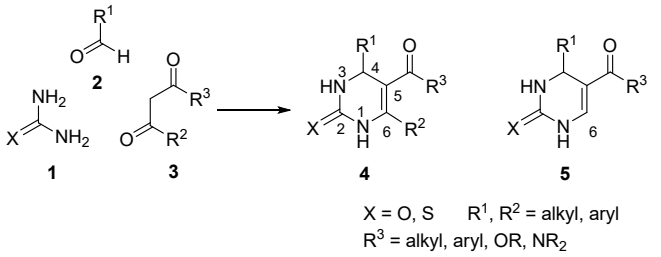
ABSTRACT

A general and efficient synthetic method for 6-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-thiones **6** and -ones **7** has been developed. In three-component reactions, the reactivity of reagents serving as the C5–C6 fragment of the dihydropyrimidine ring was compared. The reaction of thiourea or urea **12**, aldehydes **13**, and ethyl 3-dimethylaminoacrylate **9** in the presence of a catalytic amount of $AlCl_3$ by heating smoothly proceeds to give **6** and **7** in high yields. A synthetic novelty of our protocol is as follows: 1) Lewis acid-mediated reaction, 2) good to high yields, 3) broad scope as for aldehydes, and ureas. Hitherto unavailable 6-unsubstituted 2-aminodihydropyridimidine **8** has been obtained from the 2-thioxo derivative **6** by a stepwise method involving a substitution reaction with the amine at the 2-position. These 6-unsubstituted compounds **6**, **7**, and some 6-methyl derivatives **16** were assessed for their antiproliferative effect on the human promyelocytic leukemia cell line, HL-60. The 4-propyl-6-methyl derivative **16b** showed relatively strong activity with the IC_{50} value of 952 nM.

A three-component reaction called Biginelli reaction involving the condensation of urea **1**, aldehydes **2**, and β-dicarbonyl compounds **3** gives 3,4-dihydropyrimidin-2(*1H*)-ones and thiones (DHPMs) **4**. The heterocycles show a wide range of biological activities for medicinal applications (Scheme 1).[1] They display calcium channel inhibition, anticancer, antiviral, antibacterial, antifungal, antimicrobial, anti-HIV, antimalarial, anti-inflammatory, antihypertensive, and antioxidation activities. Recent additional studies on the synthesis and biological activities of DHPMs suggest their great and significant potential as leading compounds for developing medicines.[2]



Scheme 1. Synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones and -thiones **4** (DHPMs) and 6-unsubstituted DHPMs **5**

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In most Biginelli reactions, β-dicarbonyl compounds **3** such as β-ketoesters and 1,3-diketones have long been employed as the source of C5–C6 fragment, which predetermined the substituents at the 6-position (R^2 of **4** in Scheme 1). DHPMs **5** having no substituent at the 6-position were rarely accessible by the classical reaction, probably because of lack of availability of β-formylcarbonyl compounds **3** (R^2 = H) and difficulty in controling the reactivity of the compounds. Indeed, it has been reported in the literature that the classical Biginelli reactions using **3** (R^2 = H) failed.[3] Therefore, alternative methods to synthesize **5** have been developed, in which a reactant serving as an equivalent to β-formylcarbonyl compounds was used. For example, alkyl 3,3-dialkoxypropanoate was used for this purpose.[4] Namely, Kappe reported a synthetic method using a $Yb(OTf)_3$ catalyst to give **5** in moderate yields.[4a] Other reactions using methyl 3,3-dimethoxypropanoate to synthesize **5** as a synthetic intermediate either for α_{1A} receptor antagonists[4b] or marine alkaloid batzeladine D[3c] were also reported. Electron-deficient alkynes, enaminones, and enaminoates also served as the source of the C5–C6 fragment of **5**.[5] Wan carried out studies on three-component reactions using alkynes and piperazine/TsOH/TMSCl systems to give **5** with diverse substituents.[5a] Other reactions involving alkynes or enaminoates using excess acid[5b], or using enaminones to yield 5-aroyl derivatives were also reported.[5c–5d] Related three-component reactions involving two aldehydes, and urea to give 6-unsubstituted 4,5-dialkyl derivatives were also reported.[6] As a result of our studies on the synthesis of less substituted dihydropyrimidines,[7] we realized the three-component reactions

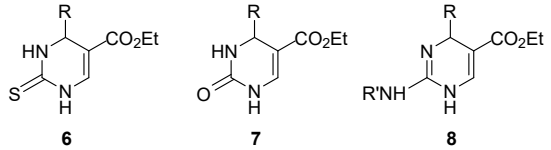
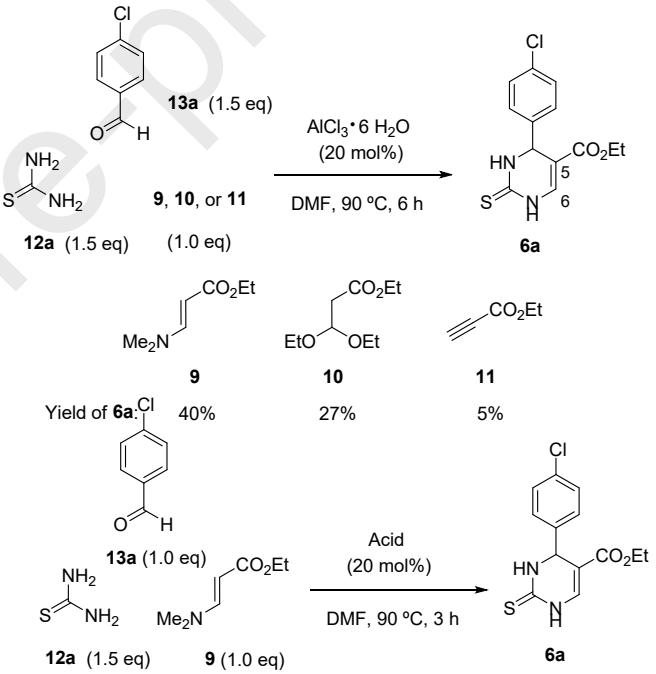


Figure 1. A series of 2-heteroatom (S, O, and N-) substituted 6-unsubstituted dihydropyrimidines **6**–**8**

using $AlCl_3$ for the synthesis of 2-thioxo derivatives **6** and 2-oxo derivatives **7**. Synthetic methods for **6** and **7** have not been reported thus far. Compared with synthetic methods for **6** and **7** mentioned above,[4,5] a synthetic novelty of our protocol is as follows: 1) Lewis acid-mediated reaction, 2) good to high yields, 3) broad scope as for aldehydes and ureas. We also transformed the 2-thioxo group of **6** to an amino group by a stepwise method involving a substitution reaction with an amine. This protocol enables the synthesis of hitherto unavailable 6-unsubstituted 2-aminodihydropyrimidines **8**. Thus, we established a synthetic method for a series of 2-heteroatom- (S, O, and N-) substituted 6-unsubstituted derivatives **6**–**8** in this study. Their *in vitro* antiproliferative effect on HL-60 (human promyelocytic leukemia) cell lines was also evaluated.

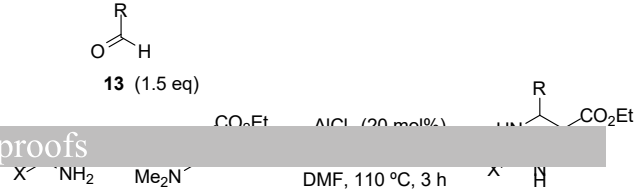
Initially, the reactivity of three reagents serving as the source of the C5–C6 fragment of the dihydropyrimidine ring was compared. Thus, ethyl 3-dimethylaminoacrylate **9**, ethyl 3,3-diethoxypropanoate **10**, and ethyl propiolate **11** were subjected to a three-component reaction involving thiourea **12a** and 4-chlorobenzaldehyde **13a** in the presence of 20 mol% $AlCl_3$ hexahydrate in DMF at 90 ºC for 6 h (Scheme 2). Among these three compounds, **9** showed relatively higher reactivity, and the corresponding 6-unsubstituted DHPM **6a** was obtained in 40% yield. Therefore, **9** was employed as a suitable C5–C6 source.



Entry	Acid (20 mol%)	Yield (%)
1	none	8
2	2 M HCl	13
3	CF_3CO_2H	38
4	MsOH	34
5	$BF_3·Et_2O$	38
6	TMSOTf	33
7	$Sc(OTf)_3$	55
8	$Y(OTf)_3$	40
9	$Yb(OTf)_3$	39
10	$La(OTf)_3$	19
11	$AlCl_3·6\ H_2O$	39
12	$InCl_3$	43
13	$CeCl_3$	38
14	$FeCl_3$	31
15	$MgCl_2$	10
16	$ZnCl_2$	23
17	$TiCl_4$	52
18	$AlCl_3$	61
19[a]	$AlCl_3$	88
20[a]	$AlCl_3·6\ H_2O$	59

a) Reaction temperature was 110 ºC, and molar ratio (**12a**:**13a**:**9**) is 1:1.5:1.5.

Sch



Next, we examined the reaction conditions, and revealed the effect of the acid. The results are summarized in Table 1. All protonic acids and Lewis acids improved the yield of **6a**. The reactions using some Lewis acids [$Sc(OTf)_3$, $TiCl_4$, $AlCl_3$] gave **6a** in good yields of >50% (entries 7, 17, and 18) at 90 ºC, and the highest yield of 61% was obtained in the reaction using anhydrous $AlCl_3$ (entry 18). Subsequently, other reaction conditions including solvents (DMA, NMP, DMSO, EtOH, THF, 1,4-dioxane, toluene, and CH_3CN), reaction temperature, catalyst loading, and molar ratio of the three reaction components were examined and optimized (see Table S1 in Supplementary Material). As a result, the optimal conditions were those for entry 19; namely, 20 mol% anhydrous $AlCl_3$ and 1:1.5:1.5 molar ratio of **12a**:**13a**:**9** at 110 ºC in DMF, which produced **6a** in a high yield of 88%. The reaction using $AlCl_3$ hexahydrate yielded **6a** in moderate yield of 59% (entry 20); use of anhydrous $AlCl_3$ promoted the reaction more effectively.

Table 1. Screening of acid catalyst, and optimization of other reaction conditions

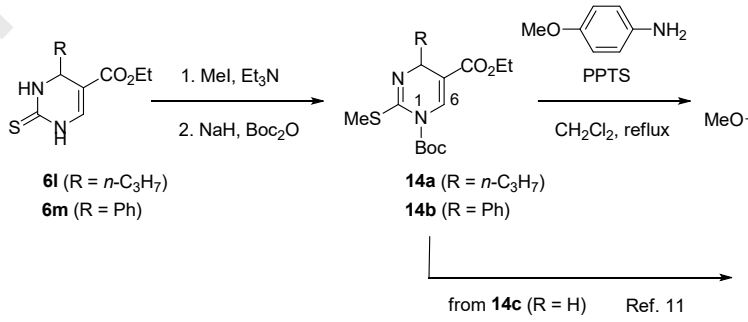
entry	X	R		Yield (%)
1	S	4-ClC_6H_4	**6a**	88
2	S	3-ClC_6H_4	**6b**	95
3	S	2-ClC_6H_4	**6c**	83
4	S	4-BrC_6H_4	**6d**	84
5	S	4-$CF_3C_6H_4$	**6e**	95
6	S	4-$NO_2C_6H_4$	**6f**	85
7	S	C_6H_5	**6g**	84
8	S	3-OHC_6H_4	**6h**	81
9	S	4-$CH_3OC_6H_4$	**6i**	58
10	S	4-$CH_3C_6H_4$	**6j**	75
11	S	*cyclo*-C_6H_{11}	**6k**	88
12	S	*n*-C_3H_7	**6l**	73
13[a]	S	H	**6m**	38
14	O	4-ClC_6H_4	**7a**	91
15	O	4-$CF_3C_6H_4$	**7b**	94
16	O	*n*-C_3H_7	**7c**	71

a) Paraformaldehyde was used, and molar ratio (**12a**:**13**:**9**) is 1.5:1.5:1.

Under the optimized reaction conditions, various aryl- and alkylaldehydes were subjected to the three-component reaction to obtain 6-unsubstituted DHPMs **6** and **7**; the results are summarized in Table 2.[8] Arylaldehydes having electron-withdrawing groups showed especially high reactivity, and the corresponding 4-aryl products **6a**–**6f** were obtained in good to high yields (entries 1–6). Although 3-hydroxybenzaldehyde, anisaldehyde, and 4-tolaldehyde showed relatively low reactivity, the reactions gave the desired products **6h**–**6j** in acceptable yields (entries 8–10). The reaction using alkylaldehydes proceeded without incident to afford the products **6k** and **6l** in good yields (entries 11 and 12). In entry 13, the reaction using paraformaldehyde in a modified 1.5:1.5:1 molar ratio of **12a**:**13**:**9** gave the simple 4,6-unsubstituted **6m** in 38% yield. The yield in the reaction using formalin solution was <20%, and paraformaldehyde showed higher reactivity. The result for entry 13 demonstrated the synthesis of **6m** from commercially available reagents in one step, whereas only multistep synthetic methods to obtain **6m** have been reported thus far.[9] The reactions using urea **12b** also proceeded smoothly to give 2-oxo products **7a**–**7c** in high yields (entries 14–16). Unfortunately, the use of a ketone, heptan-4-one, in the reaction failed to produce the desired 4,4-dialkyl product.

Table 2. Synthesis of 6-unsubstituted 3,4-dihydropyrimidin-2-thiones **6** and 2-ones **7**

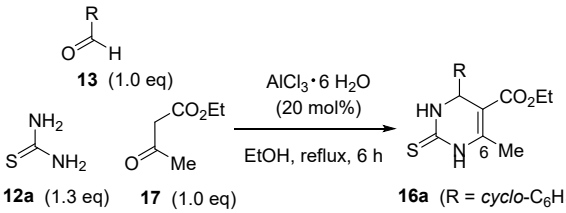
6-Unsubstituted 2-aminodihydropyrimidines, such as **8** in Scheme 3, have been hitherto unavailable; thus, we next attempted to transform the 2-thioxo group of **6** into an amino group. The 4-propyl derivative **6l** was *S*-methylated, and the corresponding 2-methylthio derivative was obtained as a mixture of tautomers (Scheme 3). In our previous report, a Boc group on the nitrogen atom of dihydropyrimidines increased the electrophilicity in the substitution reaction with amines, and the group was introduced.[10] The reaction occurred selectively at the nitrogen atom in the 1-position to give **14a** (R = *n*-C_3H_7); the structure of **14a** was determined by HSQC (heteronuclear single quantum correlation) and HMBC (heteronuclear multiple bond correlation) experiments. A significant HMBC was observed between the 6-proton and the carbonyl carbon of the Boc group at the 1-position (see Supplementary Material). Subsequently, **14a** was reacted with 4-methoxyaniline in the presence of 1.2 eq of PPTS (pyridinium *p*-toluenesulfonate), and 2-aminodihydropyrimidine **8a** (R = *n*-C_3H_7) having no Boc group was obtained in 74% yield. To our surprise, this result is in contrast to that of our previous study, in which no ring opening product **15a** (R = *n*-C_3H_7) was obtained.[11] In the reaction of **14b** (R = Ph), the major product was **8b** (R = Ph) accompanied by **15b** (R = Ph) in 67% and 25% yields, respectively. We again confirmed our previous finding that the reaction of the 4-H



Scheme 3. Attempt to synthesize 6-unsubstituted 2-aminodihydropyrimidine **8**

derivative **14c** (R = H) with 4-methoxyaniline in the presence of 0.1 eq of PPTS exclusively gave **15c** (R = H) in 76% yield with a minute amount (6%) of the 2-substituted product **8c** (R = H). These results indicate that different 4-substituents (H, *n*-C_3H_7, and Ph) have a crucial effect on the reactivity. Our research is underway to clarify the details.

In addition to **6** and **7**, 6-methyl DHPMs **16a** and **16b** were also prepared in order to clarify the 6-substituent on their biological activities (Scheme 4). To explore the antiproliferative effect of fourteen compounds of **6** and **7** (excluding **6m** and **7c**), **16a**, and **16b** in HL-60 cells, the viability of the cells was determined by XTT [2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-{(phenylamino)carbonyl}-2*H*-tetrazolium hydroxide] assay following treatment for 96 h with 1,000 nM ATRA (all-*trans* retinoic acid, a positive control reagent).[12] As shown in Figure 2, treatment with ATRA and **16b** showed relatively strong activity ($p < 0.01$).



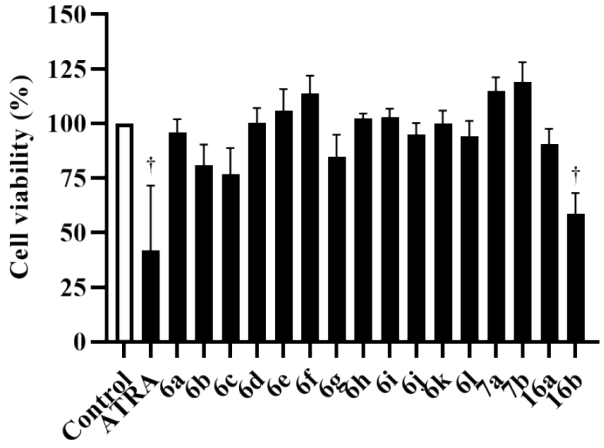


Figure 2. Antiproliferative effect of **6**, **7,** and **16** in HL-60 cells. Following treatment for 96 h with 1,000 nM ATRA, **6**, **7**, and **16**, respectively, the cell viability of HL-60 cells was determined by XTT assay as described in "Supplementary Material". Relative cell viability was calculated as the ratio of the absorbance at 450 nm of each treatment group against those of the corresponding untreated control group. Data are shown as the means and SD (standard deviation) from three independent experiments. $^{\dagger}p < 0.01$ vs. control.

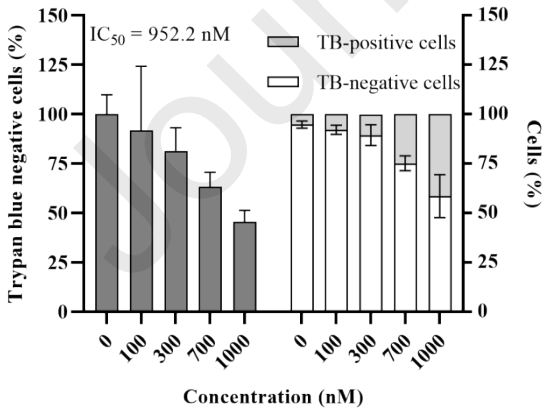


Figure 3. 16b induces cell death in a dose-dependent manner. Following treatment with various concentrations of **16b** for 96 h, the cell viability of HL-60 cells was determined by TB exclusion test as described in "Supplementary Material". (Left) Relative cell viability was calculated using counted TB-negative cells. (Right) the ratio of TB-positive cells to TB-negative cells in HL-60 cells treated with each concentration of **16b** was calculated. Data are shown as the means and SD from three independent experiments.

Furthermore, we also examined the IC_{50} (half maximal inhibitory concentration) value of **16b** by TB (trypan blue) exclusion test following treatment for 96 h with various concentrations (100, 300, dose-dependent decrease of TB-negative cells (viable cells) was observed in **16b**-treated HL-60 cells. The IC_{50} value was 952.2 nM (95% confidence interval, 658.4−2428; $R^2 = 0.6679$). Moreover, the ratio of the number of TB-positive cells (dead cells) to that of TB-negative cells in HL-60 cells at each concentration of **16b** resulted in an increase in dead cells rate in a dose-dependent manner [Figure 3 (right)]. The detail types of cell death, such as apoptosis, necrosis, autophagy, and so on, may become clear in future studies. These results suggest that the **16b**-induced antiproliferative effect was derived in large part from cell death; thus, **16b** inducing cell death at 100 nano-order concentrations might be a leading compound for the development of novel anticancer agents.

In summary, a three-component reaction involving ureas, aldehydes, and ethyl 3-dimethylaminoacrylate using anhydrous $AlCl_3$ to give **6** and **7** has been developed. General, efficient and catalytic methods for synthesis of **6** and **7** have not been reported thus far.[4,5] A synthetic novelty of our protocol is as follows: 1) Lewis acid-mediated reaction, 2) good to high yields, 3) broad scope as for aldehydes, and ureas. Hitherto unavailable 2-amino derivatives **8** have been obtained by transformation of the 2-thioxo group of **6** via the substitution reaction of **14** with amines. Although **6** and **7** showed a weak antiproliferative effect on HL-60 cells, related 6-methyl derivative **16b** showed relatively strong activity with 100 nano-order IC_{50} value.

Acknowledgments

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Supplementary Material

Supplementary Material (synthesis and characterization of compounds, spectroscopic data of IR, NMR, MS) associated with the article can be found, in the online version, at doi: ******/j.tetlet. *********.

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8. To a mixture of **12a** (23.0 mg, 0.302 mmol), **13a** (63.0 mg, 0.448 mmol), and **9** (64.0 mg, 0.447 mmol) in anhydrous DMF (0.3 mL) was added anhydrous aluminum chloride (8.0 mg, 0.0600 mmol) at room temperature, and the reaction mixture was stirred at 110 ºC for 3 h. To the mixture was added EtOAc (10 mL) and 1 M HCl aqueous solution (5 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (10 mL), and the combined organic layers were washed with water (5 mL) and brine nder umn chromatography [*n*-hexane-EtOAc (4:1 to 2:1)] to give **6a** (78.9 mg, 0.266 mmol, 88%) as pale yellow crystals.
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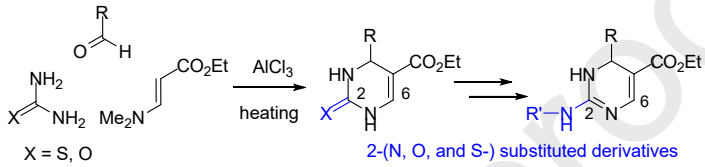
Yoshio Nishimura[a,*], Hidetomo Kikuchi[b], Takanori Kubo[a], Yuki Gokurakuji[a], Yuri Nakamura[a], Rie Arai[b], Bo Yuan[b], Katsuyoshi Sunaga[b], Hidetsura Cho[c]



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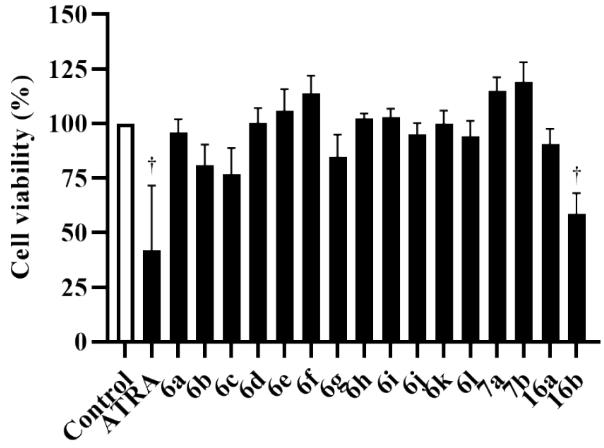
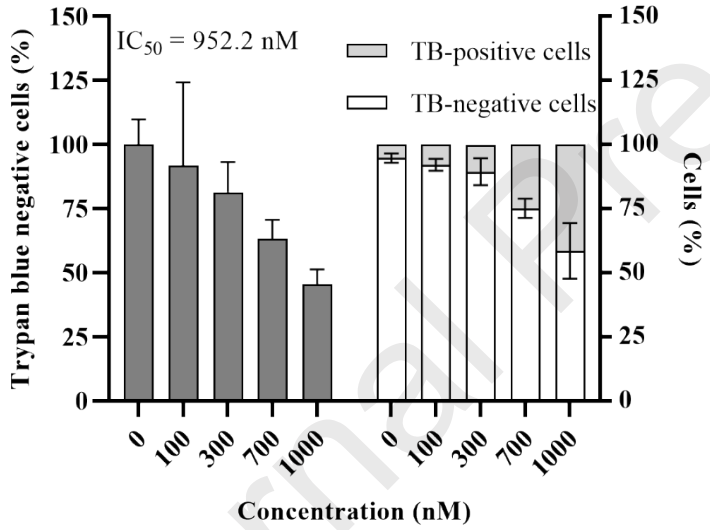
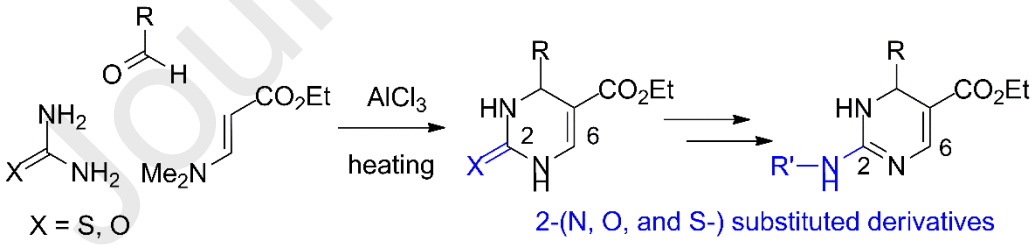
2) good to high yields
3) broad scope for aldehydes and ureas







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