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A-ring modifications on the triazafluorenone core structure and their mGluR1 antagonist properties

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ABSTRACT

A-ring modifications on the triazafluorenone core structure were investigated. Five membered heterocycles such as pyrazoles and isothiazoles are not tolerated. It has been found that the pyrimidine nucleus was very well tolerated on the left hand side. Amino pyrimidine compounds **24** and **27** showed acceptable PK profile with significant brain penetration. Compound **9** served as a versatile intermediate for a number of chemical transformations.

The metabotropic glutamate receptors (mGluRs) perform a variety of functions in the central and peripheral nervous systems. They are members of the G-protein coupled receptors and form a family of eight subtypes (mGlu1 to mGlu8) and are assigned to three groups. Group I mGluRs (mGluR1 and mGluR5) are widely studied and are involved in the central sensitization of pain and other neurological disorders.[1–6] There have been remarkable advances in the development of small molecules that inhibits mGluR1 activity which are useful for the treatment of neuropathic or chronic pain models in rodents. Some of the very recent examples from literature (**1**–**4**) are given below in Figure 1.[7–11]

Compound **1**, originated from the public domain, was identified as a potent mGluR1 antagonist from our high throughput screening assay. We as well as others have extensively studied the N-aromatic substitution pattern on the C-ring as well as the amino substitutions on the A-ring of triazafluorenone (Fig. 1). It has been demonstrated that a large number of amino substitutions (NR_1R_2) and a variety of aromatic rings (Ar) are tolerated in the tricyclic framework.[7,8] A thorough literature survey indicated that the A-ring modifications such as reduction/enlargement of the existing ring are unknown. Thus we decided to modify the left hand side, keeping the thienopyrimidone part as an invariable (structure **5**) as shown in Figure 2. Additionally we planned to open up the A-ring and strategically position the basic nitrogens in the molecule. Compound **4** is a close example from the literature that does not have the left hand side ring system.[11] Earlier in this program we found that a simple primary amino group is very well tol-

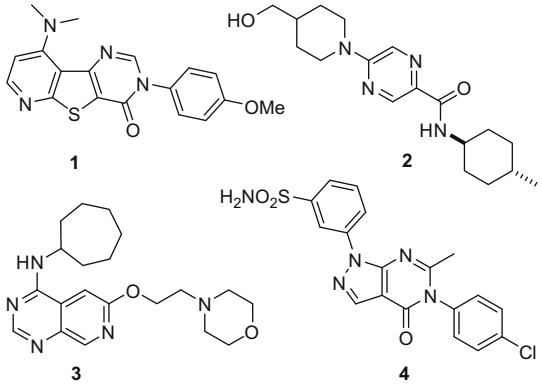

Figure 1. Representative mGluR1 antagonists.

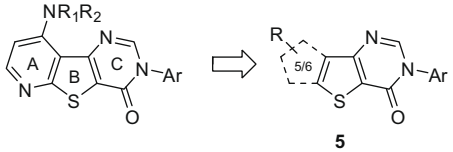

Figure 2. General SAR plans.

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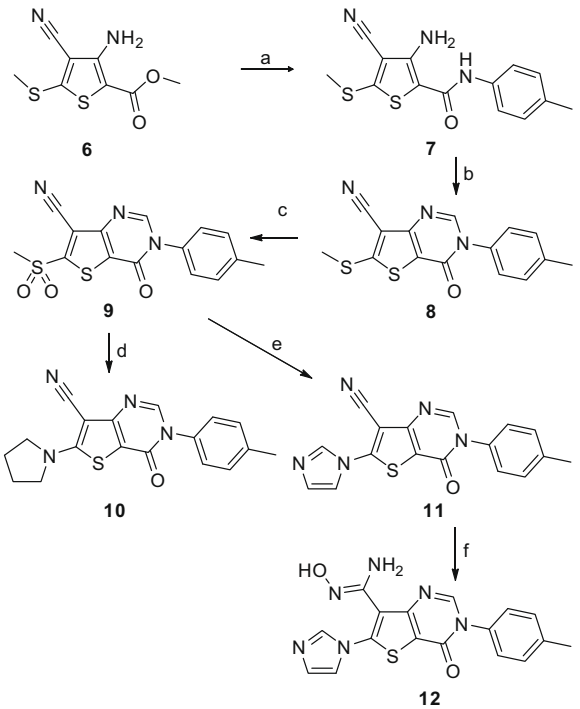
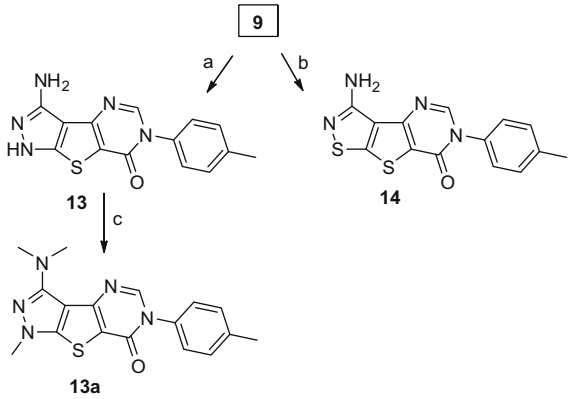
erated in the triazafluorenone core structure,[8] thus we decided to prepare compounds with free primary amino group on the left hand side of the newly designed structure. A convenient starting material (**6**) was available for this strategy. Compound **6** was converted to the amide **7** and cyclized to the thienopyrimidone **8** in good yields. The methyl sulfide moiety was oxidized to the methyl sulfone by use of hydrogen peroxide and this intermediate **9** served as a versatile intermediate for various transformations. Compound **9** was treated with amines such as pyrrolidine and imidazole to furnish compounds **10** and **11**. Compound **11** was treated with hydroxylamine to get compound **12** as shown in Scheme 1. Amidoxime **12** (mixture of *cis* and *trans*) may have all the requisite functionalities to bind to the receptor. These compounds were tested in the human mGluR1 assay[12] and found to be inactive (compounds **10**, **11** and **12**: h-mGluR1 IC_{50} >1000 nM).

Next we turned our attention to the introduction of a five membered ring in place of the pyridine nucleus as shown in Scheme 2. As can be seen from Figure 1, pyrazole moiety was well tolerated in a related system (compound **4** in which the thiophene ring is absent). Compound **9** was treated with hydrazine to afford the aminopyrrazole structure **13**. Aminoisothiazole compound **14** was prepared according to the literature procedure.[13] Methyl sulfone compound **9** was treated with NaSH and the resulting thiol derivative was cyclized with chloramine (prepared from NaOCl and NH_4OH)[14] to generate compound **14**. Unfortunately these modifications also generated compounds with only micromolar activity. One compound showed a human IC_{50} of 670 nM (permethylated compound **13a**). All attempts to prepare an amino oxathiazole A-ring analog were unsuccessful.

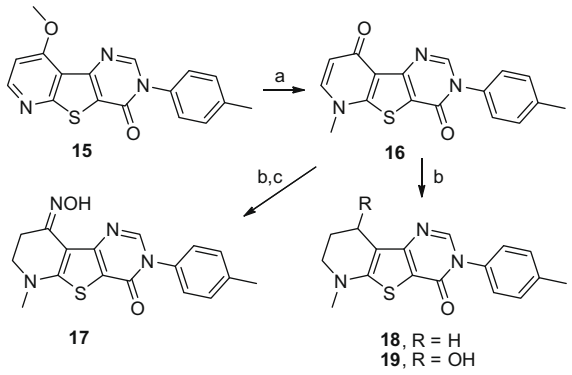
To break up the extended planar aromatic system, we next targeted the saturated A-ring of the tricyclic system. Methyl triflate activation of compound **15**[15] followed by varying equivalents of $NaBH_4$ afforded compounds **16**, **18** and **19** in good yields as illustrated in Scheme 3. Oxime analog **17** was also prepared. Any efforts to reduce the oxime functionality to amine were unsuccessful. All



Scheme 1. Reagents and conditions: (a) *p*-toluidine, Me_3Al, Tol, rt, 98%; (b) $(EtO)_3CH$, 72%; (c) H_2O_2, HOAc, 73%; (d) pyrrolidine, DMF, 60%; (e) imidazole, DMF, 100 °C, 84%; (f) $NH_2OH{\cdot}HCl$, K_2CO_3, EtOH, 80 °C, 50%.



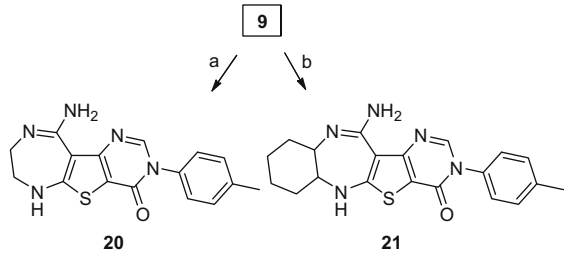
Scheme 2. Reagents and conditions: (a) $NH_2NH_2{\cdot}H_2O$, MeOH, 70 °C, 98%; (b) NaSH in DMF/H_2O, then $Cl–NH_2$, see text; (c) NaH, MeI.



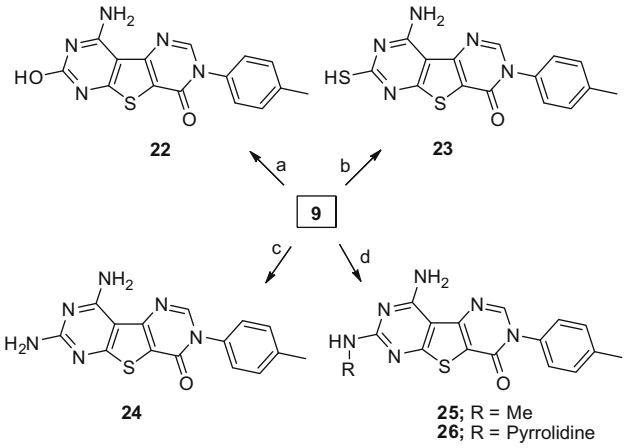
Scheme 3. Reagents and conditions: (a) MeOTf, then $NaBH_4$ (1 equiv) 60%; (b) $NaBH_4$, THF; (c) $NH_2OH{\cdot}HCl$, DMF.

compounds showed only micromolar activity in the mGluR1 assay. Similar results were obtained with compounds **20** and **21**, which were prepared from intermediate **9** by treatment with diamines as shown in Scheme 4.

Since all our attempts to introduce five or seven membered A-ring system gave only micromolar active compounds, we turned our focus to six membered ring systems. Compound **9** was treated with urea and thiourea to form compound **22** and **23**, respectively. The methyl sulfone also can be reacted with guanidine and substituted guanidines to form diamino pyrimidines as shown in Scheme 5. Compound **22** showed no activity in the mGluR1 assay, but compound **23** has shown excellent mGluR1 activity. This compound has a human IC_{50} of 3.1 nM which is more than 300-fold more potent than the hydroxyl analog **22**. Similar results were obtained for the amino compound **24** with an IC_{50} of 2.1 nM. Slightly bigger



Scheme 4. Reagents and conditions: (a) ethylene diamine, DMF, 100 °C, 58%; (b) 1,2-diaminocyclohexane, DMF, 100 °C, 60%.

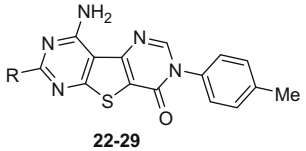


Scheme 5. Reagents and conditions: (a) urea, DMF, 80 °C, 72%; (b) thiourea, DMF, 100 °C, 49%; (c) guanidine·HCl, DMF, 100 °C, 80%; (d) R-guanidine·HCl, DMF, 100 °C.

groups such as methylamino or pyrrolidine are not tolerated as shown in Table 1.

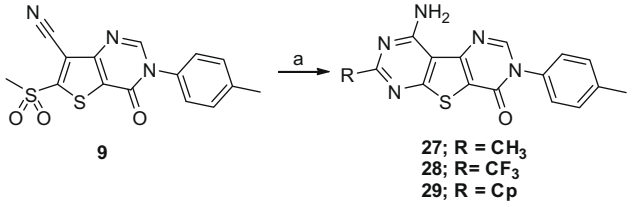
Since small functional moieties such as –SH and $–NH_2$ are very well tolerated in the A-ring, we investigated more functional groups at that position. Compounds **27–29** were synthesized by the reaction of compound **9** with different amidines under basic conditions (Scheme 6). Methyl and cyclopropyl analogs **27** (IC_{50} = 27 nM) and **29** (IC_{50} = 326 nM) were tolerated, however trifluoromethyl analog **28** did not showed any mGluR1 activity. This difference in potency might be explained by electron withdrawing effect of the trifluoromethyl group.

Table 1
mGluR1 binding properties for compounds **1**, **22–29**



Compd	R	h-mGluR1 IC_{50}[a] (nM)	h-mGluR5 IC_{50} (nM)
1		9.5	>3000
22	–OH	>1000	>3000
23	–SH	3.1	>3000
24	$–NH_2$	2.1	>3000
25	–NHMe	>1000	>3000
26	–Pyrrolyl	>1000	>3000
27	$–CH_3$	27	>3000
28	$–CF_3$	>1000	>3000
29	–Cyclopropyl	326	>3000

[a] An average of at least three measurements performed on human mGlu1/5 receptors. The standard error was 10%, and variability was less than twofold from assay to assay.

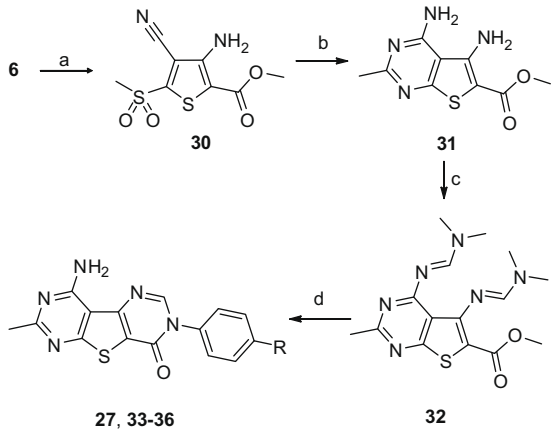


Scheme 6. Reagents and conditions: (a) alkyl imidamide, DMF, TEA, 100 °C (50–70%).

The methyl pyrimidine compound **27** showed an excellent inhibitory activity that encouraged us to study the SAR in detail, keeping the left hand side constant and varying the C-ring aromatic groups. Readily available compound **6** was treated with H_2O_2 to produce methylsulfone **30** which was then cyclized with acetamidine to form aminopyrimidine compound **31** in good yields. Compound **31** was treated with DMF–DMA to form intermediate **32** in quantitative yield. Heating a solution of compound **32** with appropriate aromatic amine in presence of acetic acid yielded the final compound in good yields (Scheme 7). As shown in Table 2, a variety of aromatic groups are tolerated at this position. For example, simple phenyl ring (**33**) showed an IC_{50} of 16 nM. Methoxy (**34**) and fluoro (**35**) derivatives showed slightly less activity (188 and 68 nM, respectively) where as the chloro derivative (**36**) showed excellent potency of 11 nM.

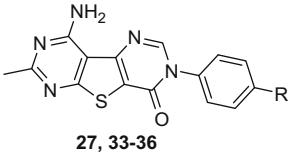
We have shown that the amino pyrimidine structures are potent in the mGluR1 assay and having achieved a desirable level of potency, we focused our attention on the pharmacokinetic properties of these molecules. The PK profile of representative examples are shown in Table 3. Compounds **24** and **27** showed reasonable rat AUC and the former compound exhibited a brain concentration of 100 ng/g @ 6 h. All mGluR1 active compounds were exquisitely selective over mGluR5.

In summary, we have tried to modify the A-ring of triazafluorenone lead structure and found that 2-alkyl or 2-amino pyrimi-



Scheme 7. Reagents and conditions: (a) H_2O_2, HOAc; (b) acetamidamide·HCl, TEA, DMSO, 100 °C, 58% (two steps); (c) DMF–DMA, DMF, 100 °C; (d) amine, HOAc, 160 °C.

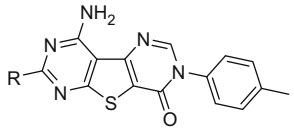
Table 2
mGluR1 binding properties for compounds **27, 33–36**



Compd	R	h-mGluR1 IC_{50}[a] (nM)	h-mGluR5 IC_{50} (nM)
27	$–CH_3$	27	>3000
33	–H	16	>3000
34	–OMe	188	>3000
35	–F	68	>3000
36	–Cl	11	>3000

[a] An average of at least three measurements performed on human mGlu1/5 receptors. The standard error was 10%, and variability was less than twofold from assay to assay.

Table 3
PK profile of selected compounds



Parameters	R = NH_2 (**24**)	R = CH_3 (**27**)
Human mGluR1 IC_{50} (nM)	2.1	27
Rat mGluR1 K_i (nM)	9.3	115.2
Human mGluR5 IC_{50} (nM)	>3000	>3000
Efflux substrate	No	No
Rat PK, (10 mg/kg), AUC (ng h/mL)[16]	965	2112
Brain concn @ 6 h (ng/g)	100	29
Brain/plasma	0.9	0.2

dines are very well tolerated. A highly versatile intermediate **9** has been used to probe the SAR of the A-ring of these tricyclics. Complementary C-ring changes have also been explored. A very comprehensive SAR study on the pyrimidine core will be published elsewhere.

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