理學碩士 學位論文

I. Studies on the Synthesis of Pyrazolo[1,5-α][1,3,5]triazine Class CRHR1 Antagonists

II. Synthetic Studies Toward CRHR1 Antagonists Through C-H Activation of 2,7-Dimethylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one

I. 피라졸로[1,5-α][1,3,5]트라이아진류 CRHR1 길항제 합성에 관한 연구

II. 2,7-디메틸피라졸로[1,5-α][1,3,5]트라이아진-4(*3H*)-온의 탄소-수소 활성화반응을 통해 CRHR1 길항제 합성에 관한 연구

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Abstract

Part I. Studies on the Synthesis of Pyrazolo[1,5-α][1,3,5]triazine class CRHR1 antagonists

The study of corticotrophin-releasing hormone is of great interest in mental health. Compounds that have a pyrazolo[1,5-α][1,3,5]triazine skeleton such as BMK-I-152 and MJL1-109-2 have been revealed as high-affinity potential CRHR1 Positron Emission Tomography (PET) ligands. It has become obvious that fluorinated compounds have an extraordinary property in medicinal chemistry and will play an important role in therapeutic applications. Since BMK-I-152 had shown extremely high binding affinities but less desirable in vivo PK behavior, we were curious about the outcome on the change of the methoxy group of BMK-I-152 to a trifluoromethyl group. Part I describes the study on the synthesis of such trifluoromethyl-containing pyrazolo[1,5-α][1,3,5]triazine class CRHR1 antagonists.

Key words: CRHR1 antagonists, fluoro compound, pyrazolo[1,5-α]-1,3,5-triazine

Part II. Synthetic Studies Toward CRHR1 Antagonists Through C-H Activation of 2,7-Dimethylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one

Synthesis of CRHR1 antagonists in a linear fashion requires lengthy steps. Therefore, a convergent synthesis using an intermolecular coupling reaction as a key step will be a very attractive alternative. Herein, we report an efficient intermolecular reaction of two fragments based on the C-H activation of 2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one using palladium catalyst. This protocol can be utilized as a novel approach for the efficient synthesis of pyrazolo[1,5-α][1,3,5]triazine class CRHR1 antagonists.

Key words: C-H activation, pyrazole, CRHR1 antagonists, palladium catalysis

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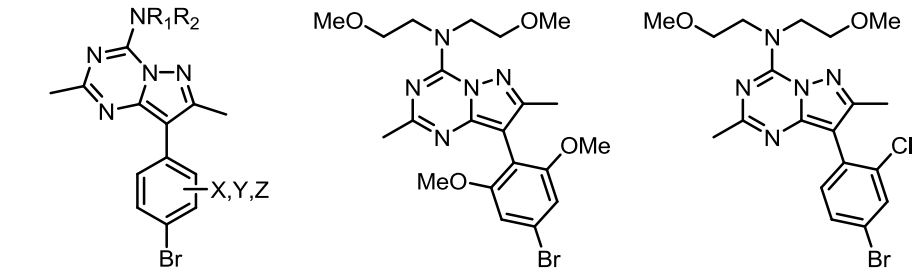
Part I.

Studies on the Synthesis of Pyrazolo[1,5-α][1,3,5]triazine class CRHR1 antagonists

I. Introduction

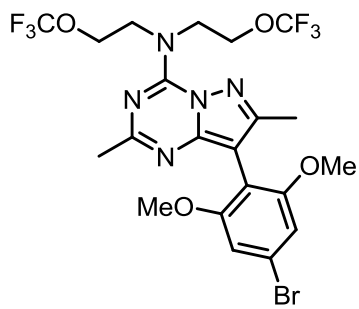
Corticotropin-releasing hormone (CRH), which was first isolated from ovine hypothalamus by Vale and coworkers[1] in 1981, is a 41-amino-acid neuropeptide. By regulating the hypothalamus-pituitary-adrenal axis (HPA),[2] CRH plays an extremely important role in the body's response to stress.[3] It was reported that hypersecretion of CRH triggers chronic stress, which leads to mental syndromes such as anxiety and depression.[4] Through binding to two classes of G-protein-coupled receptors, namely corticotropin-releasing hormone type 1 receptor (CRHR1) and corticotropin-releasing hormone type 2 receptor (CRHR2), CRH exhibits various biological functions.[5] In particular, CRHR1 densities in the prefrontal cortex have a close relation with disorders like Alzheimer's disease.[6] Therefore, CRH receptor antagonists may be employed as possible anxiolytic or antidepressant drugs and numerous non-peptide CRHR1 antagonists[7] have been disclosed as possible treatments for stress-related sicknesses over the past two decades. Compounds that have pyrazolo[1,5-α][1,3,5]triazine skeleton such as MJL1-109-2[7b] and BMK-I-152[7c] have been revealed as high-affinity potential CRHR1 Positron Emission Tomography (PET) ligands (**Figure 1**) as well as drug candidates.

It has become obvious that fluorinated compounds have an extraordinary record in medicinal chemistry and will play an ongoing role in therapeutic applications.[8] As we have seen extremely high binding affinity of BMK-I-152 in the CRHR1 receptor but with an undesirable pharmacokinetic profile, we have been curious about the outcome on the exchange of the methoxy group to trifluoromethoxy group at the amine chain (**Figure 2**, **I**). Then we designed the synthetic route for this compound and started our research.



pyrazolo[1,5-*a*][1,3,5]triazine skeleton BMK-I-152 MJL1-109-2

Figure 1. Pyrazolo[1,5-α][1,3,5]triazine skeleton and CRHR1 antagonists that contain this structure

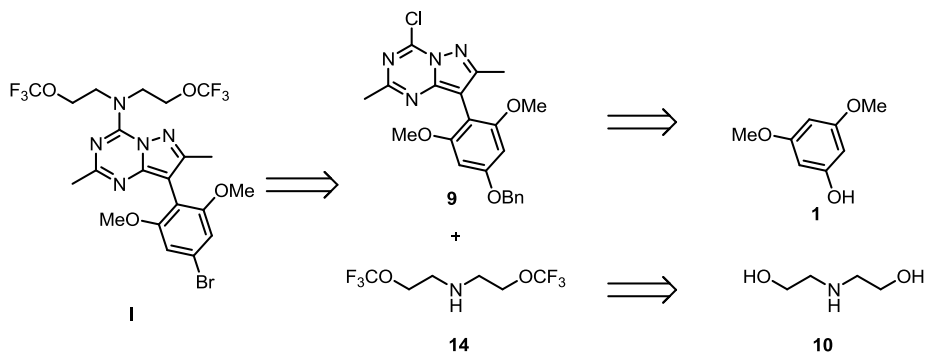


I

Figure 2. Target molecule **I**

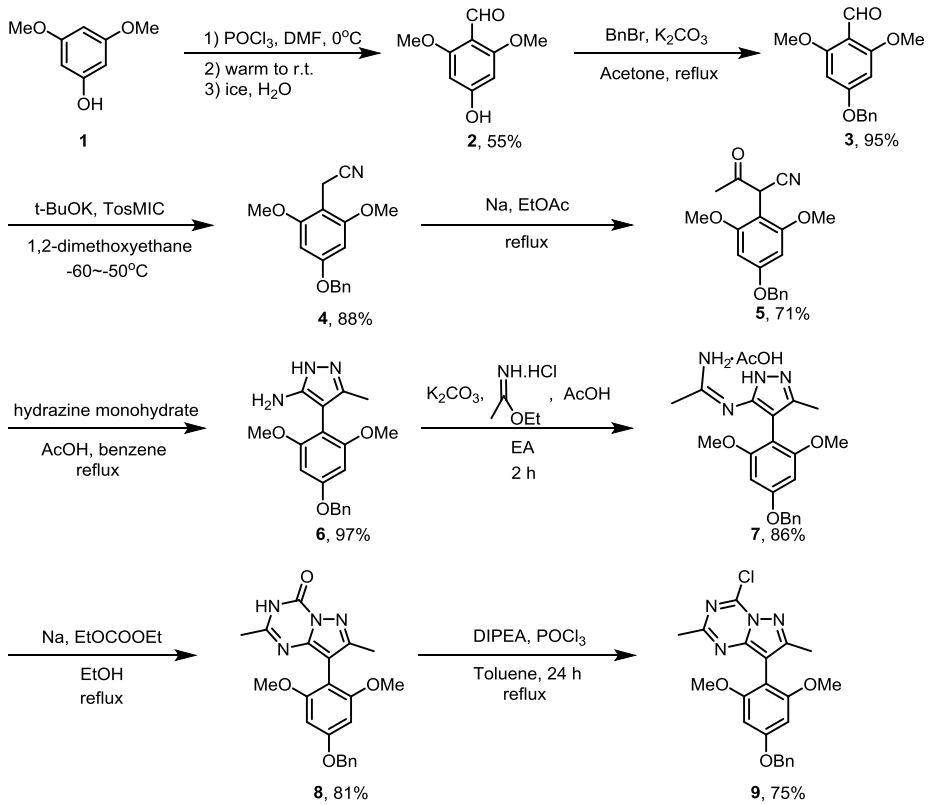
II. Results and Discussion

A retrosynthetic analysis of the target compound (**I**) is outlined in **Scheme 1**. We planned to construct the C-N bond of the triazine core by coupling of the chloro derivative **9** and the second amine **14**. Compound **9** was prepared from 3,5-dimethoxyphenol **1** and compound **14** was thought to be synthesized from diethanolamine **10**.

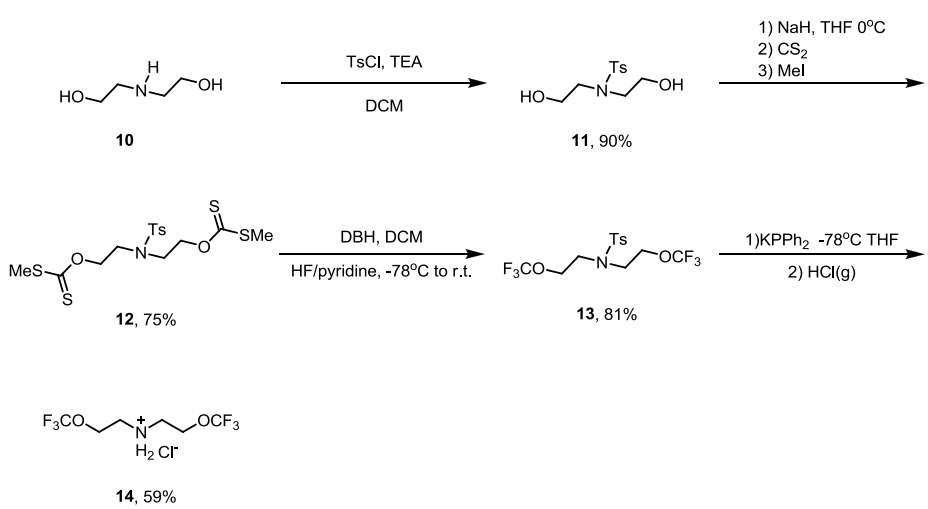


Scheme 1. Retrosynthesis

The synthesis of compound **9** was accomplished mostly according to a known procedure (**Scheme 2**).[7a] Vilsmeier-Haack reaction of 3,5-dimethoxyphenol **1** gave the desired aldehyde derivative **2** in 55% yield and then the hydroxyl group was protected through the use of benzyl bromide to form the corresponding benzyl ether **3**. The benzyl ether **3** was treated with toluenesulfonylmethyl isocyanide (TosMIC)[9] to provide the arylacetonitrile derivative **4**. Synthesis from the cyanide **4** to compound **9** was done basically following the reported procedure.[7a] It should be noted that the chlorination reaction of **8** to make **9** needed extremely anhydrous conditions; otherwise compound **9** could turn back to **8** by hydrolysis.



Scheme 2. Synthesis of the chloro derivative **9**

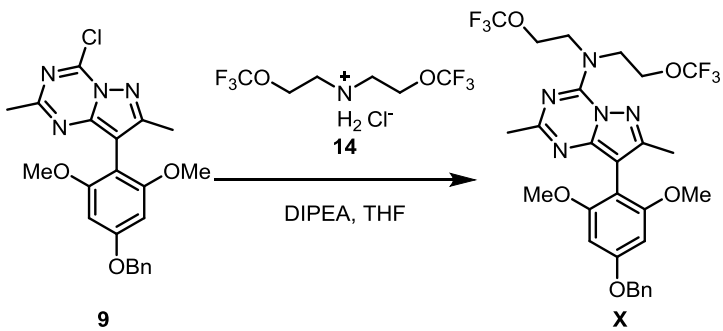


Scheme 3. Synthesis of the amine derivative **14**

Synthesis of the amine derivative **14** was initiated from diethanolamine **10**

(**Scheme 3**). First of all, the free amine **10** was protected with a tosyl group. Secondly, preparation of the xanthate **12** followed by fluorination to make compound **13** utilized the process reported by Blazejewski and coworkers.[10] After that, we tried to remove the tosyl protecting group. As is well-known, it needs a rather harsh reaction condition to take off the tosyl group to reveal the amine. We attempted various methods such as Na-naphthalenide system[11] and Birch reduction conditions,[12] but all attempts have been unsuccessful. Finally, through the use of $KPPh_2$, a protocol reported by Tomooka *et al.*,[13] we obtained the desired amine compound **14** as a hydrochloric acid salt form.

With the desired chloro compound **9** and the amine derivative **14**, we tried to do the simple coupling reaction (**Scheme 4**). However, during the reaction, some side products were formed presumably due to an intramolecular alkylation onto the heterocyclic ring nitrogen and the desired product could not be successfully obtained. Similar results were reported by Zuev and coworkers.[14]

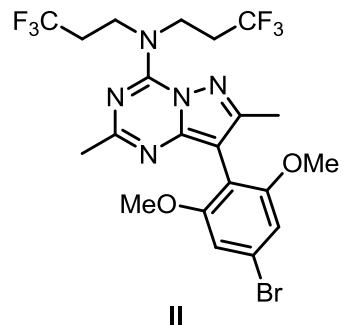


Scheme 4. Coupling of **9** and **14**

Thus we changed our target molecule to the one that has trifluoromethyl group at the amine chain rather than trifluoromethoxy group (**Figure 3**, **II**).

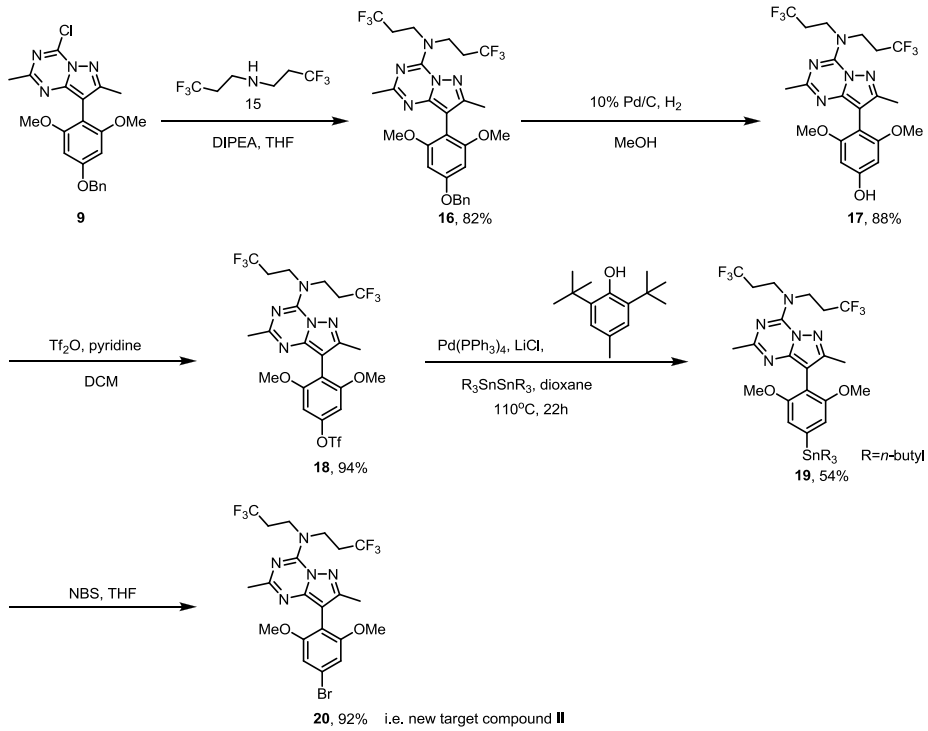
We used commercially available bis(3,3,3-trifluoropropyl)amine **15** for the coupling reaction with **9** (**Scheme 5**). The desired product was acquired in 82% yield. Deprotection of the benzyl group (H_2, Pd/C) followed by conversion to triflate yielded compound **18**, which was converted to the trialkyltin precursor **19**.

Compound **19** was treated with *N*-bromosuccinimide (NBS) in THF to prepare the final bromo-substituted compound.



II

Figure 3. New target molecule **II**



Scheme 5. Synthesis of the new target compound **II**

III. Conclusion

In summary, we have synthesized 8-(4-bromo-2,6-dimethoxyphenyl)-2,7-dimethyl-*N*,*N*-bis(3,3,3-trifluoropropyl)pyrazolo[1,5-α][1,3,5]triazin-4-amine **20** as the final compound which was structurally based on BMK-I-152. Although it was unsuccessful to obtain a molecule with trifluoromethoxy group at the amine chain, we did the deprotection of the tosyl group which was linked at the nitrogen atom and successfully obtained the bis[2-(trifluoromethoxy)ethyl]amine as its hydrochloric acid salt form. We sent the final compound **20** to carry out a binding assay to assess the CRF_1 antagonist effect. The IC_{50} of **20** was 120 nM (performed by CEREP SA-Le Bois l'Eveque), whereas the former BMK-I-152 had a K_i of 0.35±0.05 nM. Further studies to develop better CRHR1 antagonists are in progress in our laboratory.

IV. Experimental procedure

4-Hydroxy-2,6-dimethoxybenzaldehyde (2)

25.00 g (162.17 mmol) of 3,5-dimethoxyphenol was placed in a 500 mL round bottom flask. It was dissolved with 30.2 mL (324.0 mmol) $POCl_3$. The solution was cooled at 0 ^oC and 18.6 mL (241.23 mmol) DMF was added with syringe pump for 4 hours. Then, the reaction mixture was warmed to room temperature and stirred for 16 h. When the starting material disappeared on TLC, 200 g of ice was added to the reaction flask in an ice bath. This aqueous solution was basified by NaOH (aq) to pH 6. Then the generated solids were filtered and dried in vacuum oven (40 ^oC) overnight. The dried solids were washed with chloroform and dried in vacuum oven (16.24 g, 55% yield). ^1H NMR (DMSO-d_6, δ=2.50 ppm, 400 MHz): 10.15 (s, 1H), 6.08 (s, 2H), 3.75 (s, 6H). HRMS calcd. for $C_9H_{10}O_4$ 183.0579, obsd. 183.0652.

4-Benzyloxy-2,6-dimethoxybenzaldehyde (3)

4-Hydroxy-2,6-dimethoxybenzaldehyde (**2**) (815.4 mg, 4.48 mmol) was dissolved in acetone (45 mL) and then K_2CO_3 (1.86 g, 13.46 mmol) and benzyl bromide (0.59 mL, 4.96 mmol) were added. The mixture was heated to reflux overnight. When TLC showed no starting material, the mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was washed with a large amount of n-hexane then dried without further purification (1.16 g, 95% yield). ^1H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): 10.36 (s, 1H), 7.43 (m, 5H), 6.16 (s, 2H), 5.12 (s, 2H), 3.86 (s, 6H). HRMS calcd. for $C_{16}H_{16}O_4$ 273.1049, obsd. 273.1107.

(4-Benzyloxy-2,6-dimethoxyphenyl)acetonitrile (4)

A solution of TosMIC (4.89 g, 25.05 mmol) in 21 mL 1,2-dimethoxyethane was added dropwise to a stirred suspension of *tert*-BuOK (5.11 g, 45.54 mmol) in 21 mL of 1,2-dimethoxyethane in a round bottom flask while maintaining the reaction temperature at -40 ^oC to -30 ^oC. A solution of 4-benzyloxy-2,6-dimethoxybenzaldehyde (**3**) (6.20 g, 22.77 mmol) in 1,2-dimethoxyethane (63 mL, if not dissolved completely, more solvent

can be added) was added to the reaction mixture dropwise while keeping the reaction temperature at -60 °C to -50 °C. Stirring was continued at -60 °C to -50 °C until TLC (hexane-EtOAc 3:1, v/v) showed no trace of the starting material (about 2.5 h needed). Methanol (50 mL) was added at once and the mixture was heated to reflux for 15 min. The mixture was cooled to room temperature, concentrated under reduced pressure, and partitioned between 0.5 M citric acid (42 mL) and dichloromethane (21 mL), and the aqueous layer was extracted with more dichloromethane (21 mL×2). Combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (21 mL), the organic layer dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified on a silica gel chromatographic column to give pale yellow plate solids (5.66 g, 88% yield). ^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): 7.40 (m, 5H), 6.21 (s, 2H), 5.06 (s, 2H), 3.82 (s, 6H), 3.60 (s, 2H). HRMS calcd. for $C_{17}H_{17}NO_3$ 284.1208, obsd. 284.1279.

2-(4-Benzyloxy-2,6-dimethoxyphenyl)-3-oxobutanenitrile (5)

To a solution of (4-benzyloxy-2,6-dimethoxyphenyl)acetonitrile (**4**) (5.98 g, 21.11 mmol) in ethyl acetate (25 mL) were added sodium pellets (0.97 g, 42.19 mmol) portionwise at room temperature. Upon completion of Na addition, the reaction mixture was heated to reflux. After ca. 50 min, a turbid white precipitate started to appear. The reaction mixture was allowed to stir at the reflux temperature for another hour. After cooling to room temperature, more ethyl acetate (50 mL) was added to the white suspension to facilitate stirring, and the resultant mixture was stirred at room temperature overnight. The mixture was filtered and the white solid collected was washed with copious amounts of ethyl ether. The solid was collected and suspended in water (60 mL) and the solution was acidified to pH ≈ 5 using 0.1 N aqueous HCl solution. It was extracted with ethyl acetate (30 mL×3) and combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After pumping at high vacuum, the oily residue converted to a white solid (4.91 g, 71% yield). ^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): 7.41 (m, 5H), 6.23 (s, 2H), 5.08 (s, 1H), 5.07 (s, 2H), 3.82 (s, 6H), 2.16 (s, 3H). HRMS calcd. for $C_{19}H_{19}NO_4$ 326.1314, obsd. 326.1384.

4-(4-Benzyloxy-2,6-dimethoxyphenyl)-5-methyl-*2H*-pyrazol-3-yl-amine (6)

A mixture of 2-(4-benzyloxy-2,6-dimethoxyphenyl)-3-oxobutyronitrile (**5**) (4.80 g, 14.75 mmol), hydrazine monohydrate (1.07 mL, 22.06 mmol), and acetic acid (1.41 mL, 24.63 mmol) in toluene (40 mL) was heated to reflux while removing water using a Dean-Stark trap for 5 hours. The reaction mixture was cooled to room temperature, washed by saturated aqueous $NaHCO_3$ solution and water. Then dried over anhydrous $MgSO_4$ and concentrated using rotary evaporation. The residue was dried to give a pale yellow foam without further purification (4.88 g, 97% yield). ^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): 7.41 (m, 5H), 6.30 (s, 2H), 5.10 (s, 1H), 3.74 (s, 6H), 2.07 (s, 3H). HRMS calcd. for $C_{19}H_{21}N_3O_3$ 340.1583, obsd. 340.1651.

N-[4-(4-Benzyloxy-2,6-dimethoxyphenyl)-5-methyl-*2H*-pyrazol-3-yl]acetamidine acetic acid salt (7)

K_2CO_3 (4.15 g, 30.03 mmol) was dissolved in water (10 mL) and then ethyl acetimidate hydrochloride (3.10 g, 25.08 mmol) was added. To the suspension, ethyl acetate (15 mL) was added and the two-phase system was stirred forcefully for about 5 minutes. The aqueous phase (and some undissolved salts) was removed by a separatory funnel. The organic phase was dried (anhydrous $MgSO_4$), filtered and added to the round bottom flask with 4-(4-benzyloxy-2,6-dimethoxyphenyl)-5-methyl-*2H*-pyrazol-3-ylamine (**6**) (3.40 g, 10.02 mmol) and a stirring bar. After 1 hour, when TLC showed no starting material, acetic acid (0.86 mL, 15.02 mmol) was added to the reaction mixture. Solids began to show up 15 minutes later. Finally, the solids were filtered, washed by ethyl acetate and dried in vacuum oven (3.80 g, 86% yield). ^{1}H NMR (CD_3OD-d_4, δ=3.31 ppm, 400 MHz): 7.39 (m, 5H), 6.40 (s, 2H), 5.17 (s, 2H), 3.73 (s, 6H), 2.32 (s, 3H), 2.07 (s, 3H), 1.89 (s, 3H). HRMS calcd. for $C_{21}H_{24}N_4O_3$ 381.1848, obsd. 381.1913.

8-(4-Benzyloxy-2,6-dimethoxyphenyl)-2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one (8)

Sodium pellets (10.12 g, 0.44 mol) were added portionwise to dry ethanol (400 mL) in a two-necked round bottom flask equipped with a condenser. After all sodium pellets disappeared, the solution was cooled to room temperature. Then *N*-[4-(4-benzyloxy-2,6-dimethoxyphenyl)-5-methyl-*2H*-pyrazol-3-yl]acetamidine acetic acid salt (**7**) (14.71 g,

33.39 mmol) and diethyl carbonate (42.4 mL, 0.35 mol) was added in sequence. The mixture was heated to reflux overnight. After cooling to room temperature, the reaction mixture was evaporated. The solid was dissolved in water and acidified by 0.1 N aqueous HCl solution and extracted with ethyl acetate (100 mL×3). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was recrystallized with hot ethyl acetate, and 11.00 g (15.3 mmol, 81% yield) of white solids formed. ^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): 11.80 (br, s, 1H) 7.37 (m, 5H), 6.28 (s, 2H), 5.04 (s, 2H), 3.69 (s, 6H), 2.38 (s, 3H), 2.24 (s, 3H). HRMS calcd. for $C_{22}H_{22}N_4O_4$ 407.1641, obsd. 407.1695.

8-(4-Benzyloxy-2,6-dimethoxyphenyl)-4-chloro-2,7-dimethylpyrazolo[1,5-α][1,3,5]triazine (9)

To a two-neck round bottom flask equipped with a reflux condenser, 8-(4-Benzyloxy-2,6-dimethoxyphenyl)-2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one (**8**) (0.50 g, 1.23 mmol) was added. The flask was evacuated and backfilled with inert gas three times. Dry toluene (12.3 mL), dry *N*,*N*-diisopropylethylamine (0.64 mL, 3.67 mmol), and distilled $POCl_3$ (0.23 mL, 2.47 mmol) were added via a syringe in sequence. The reaction mixture was heated to reflux for 24 hours under inert gas. Then the mixture was cooled to room temperature and partitioned between ethyl acetate (7 mL) and ice water (7 mL) quickly. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified on a short silica gel chromatographic column (hexane-EtOAc 4:1, v/v) quickly. Yellow solids were collected finally (0.39 g, 75% yield). ^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): 7.42 (m, 5H) 6.33 (s, 2H), 5.11 (s, 2H), 3.71 (s, 6H), 2.61 (s, 3H), 2.36 (s, 3H). HRMS calcd. for $C_{22}H_{21}ClN_4O_3$ 425.1302, obsd. 425.1365.

N,*N*-Bis(2-hydroxyethyl)-4-methylbenzenesulfonamide (11)

p-Toluenesulfonyl chloride (45.4 g, 0.238 mol) was dissolved in DCM (100 mL). Then the solution was added dropwise to diethanolamine (**10**) (30.0 g, 0.285 mol) and triethylamine (72.7 g, 0.718 mol) in a flask equipped with ice water bath. After being

stirred at room temperature for 4 h, the reaction mixture became viscous. The solvent was removed using a rotary evaporator, and the residue was extracted with water and DCM. The organic layer was concentrated and recrystallized from a mixed solvent of water and ethanol. White crystals were collected by filtration, washed with water, and dried in vacuo. 55.6 g (90%) white solids were obtained. ^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): 7.70 (d, 2H), 7.33 (d, 2H), 3.87 (t, 4H), 3.43 (s, 2H), 3.27 (t, 4H), 2.43 (s, 3H). HRMS calcd. for $C_{11}H_{17}NO_4S$ 260.0878, obsd. 260.0939.

S,S'-Dimethyl *O,O'*-2,2'-(tosylazanediyl)bis(ethane-2,1-diyl) dicarbono dithioate (12)

N,N-Bis(2-hydroxyethyl)-4-methylbenzenesulfonamide (**11**) (2.75 g, 10.62 mmol) and sodium hydride (60 % dispersion in mineral oil, Sigma-Aldrich, 2.12 g, 53.10 mmol) were added to a round-bottomed flask. Then the flask was equipped with an ice bath and 53 mL THF was added in it. After the mixture was stirred for 10 minutes, CS_2 (3.20 mL, 53.10 mmol) was added dropwise, followed by 3.34 mL (53.10 mmol) iodomethane. The mixture was stirred for about 4 hours at room temperature. The extra NaH was quenched by water and it was extracted with DCM. Combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified on a silica gel chromatographic column to give the desired compound (3.48 g, 75%). ^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 500 MHz): 7.72 (d, 2H), 7.32 (d, 2H), 4.77 (t, 4H), 3.61 (t, 4H), 2.55 (s, 6H), 2.43 (s, 3H). HRMS calcd. for $C_{15}H_{21}NO_4S_5$ 440.0074, obsd. 440.0136.

4-Methyl-*N,N*-bis[2-(trifluoromethoxy)ethyl]benzenesulfonamide (13)

A Teflon round-bottomed flask equipped with a magnetic stirring bar was charged with 1,3-dibromo-5,5-dimethylhydantoin (DBH, 31.57 g, 110.40 mmol) and DCM (92 mL). The flask was immersed in a dry ice/acetone cooling bath and the HF/pyridine complex (27 mL) was added via a plastic syringe. The *S,S'*-dimethyl *O,O'*-2,2'-(tosylazanediyl) bis(ethane-2,1-diyl) dicarbonodithioate (**12**) (8.09 g, 18.40 mmol) was solved in 92 mL DCM and then added to the mixture above. The cooling bath was removed and the reaction mixture was allowed to reach room temperature over 2 hours. The mixture was bascified with NaOH solution under ice bath. The organic layer was removed and the

aqueous phase was extracted with DCM. Combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified on a silica gel chromatographic column to give the desired compound (5.86 g, 81%). ^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 500 MHz): 7.70 (d, 2H), 7.34 (d, 2H), 4.13 (t, 4H), 3.48 (t, 4H), 2.44 (s, 3H). HRMS calcd. for $C_{13}H_{15}F_6NO_4S$ 396.0626, obsd. 396.0686.

Bis[2-(trifluoromethoxy)ethyl]amine hydrochloric salt (14)

To a solution of 4-methyl-*N*,*N*-bis[2-(trifluoromethoxy)ethyl]benzenesulfonamide (**13**) (2.17 g, 5.49 mmol) in THF (23 mL) equipped with acetone/dry ice bath was added potassium diphenylphosphide (0.50 M THF solution, 16.5 mL, 8.24 mmol). The reaction mixture was stirred for 2 h at the same temperature (-78^{o}C). After that, the cooling bath was removed and dilute hydrochloric acid (6 N, 3 mL) was added. Then the mixture was allowed to warm to room temperature and stirred for 30 min. NaOH solution (3 N, 11 mL) was added and the mixture was extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. To the solution, HCl (g) was added until no more solids showed up. The white solids were filtered, wash with a large amount of ether and dried in vacuum oven (0.89 g, 59%). ^{1}H NMR (DMSO-d_6, δ=2.50 ppm, 400 MHz): 9.75 (s, 2H), 4.44 (t, 4H), 3.37 (t, 4H). HRMS calcd. for the free amine $C_6H_9F_6NO_2$ 242.0537, obsd. 242.0603.

8-(4-Benzyloxy-2,6-dimethoxyphenyl)-2,7-dimethyl-*N*,*N*-bis(3,3,3-trifluoro propyl)pyrazolo[1,5-α][1,3,5]triazin-4-amine (16)

8-(4-Benzyloxy-2,6-dimethoxyphenyl)-4-chloro-2,7-dimethylpyrazolo[1,5-α][1,3,5] triazine (**9**) (531.1 mg, 1.25 mmol) was dissolved in dry THF (25 mL). Bis(3,3,3-trifluoropropyl)amine (313.7 mg, 1.50 mmol) and dry *N*,*N*-diisopropylethylamine (0.44 mL, 2.53 mmol) were added via a syringe. When the starting material disappeared on TLC, the solvent was removed and the residue was purified by chromatographic column. White solids were obtained finally (0.61 g, 82%). ^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): 7.42 (m, 5H), 6.32 (s, 2H), 5.10 (s, 2H), 4.15 (m, 4H), 3.73 (s, 6H), 2.74 (m, 4H), 2.41 (s, 3H), 2.22 (s, 3H). HRMS calcd. for $C_{28}H_{29}F_6N_5O_3$ 598.2175, obsd. 598.2236.

4-{4-[Bis(3,3,3-trifluoropropyl)amino]-2,7-dimethylpyrazolo[1,5-α][1,3,5] triazin-8-yl}-3,5-dimethoxyphenol (17)

To a solution of 8-(4-Benzyloxy-2,6-dimethoxyphenyl)-2,7-dimethyl-*N*,*N*-bis(3,3,3-trifluoropropyl)pyrazolo[1,5-α][1,3,5]triazin-4-amine (**16**) (2.09 g, 3.50 mmol) in methanol (56 mL) was added 10% Pd/C (de Gussa type, Aldrich) and the mixture was stirred under hydrogen atmosphere at room temperature. When TLC showed no starting material, the mixture was diluted with ethyl acetate and filtered through a bed of Celite. The filtrate was concentrated under reduced pressure to give a white solid (1.57 g, 88% yield). ^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): 10.15 (br, s, 1H), 5.84 (s, 2H), 4.21 (br, s, 4H), 3.60 (s, 6H), 2.77 (m, 4H), 2.52 (s, 3H), 2.19 (s, 3H). HRMS calcd. for $C_{21}H_{23}F_6N_5O_3$ 508.1705, obsd. 508.1773.

4-{4-[Bis(3,3,3-trifluoropropyl)amino]-2,7-dimethylpyrazolo[1,5-α][1,3,5] triazin-8-yl}-3,5-dimethoxyphenyl trifluoromethanesulfonate (18)

4-{4-[Bis(3,3,3-trifluoropropyl)amino]-2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-8-yl} -3,5-dimethoxyphenol (**17**) (1.57 g, 3.09 mmol) was dissolved in dry DCM (62 mL). The solution was cooled to 0 ^{o}C, then dry pyridine (0.50 mL, 6.21 mmol) and trifluoromethanesulfonic anhydride (0.62 mL, 3.69 mmol) were added via a syringe slowly at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 30 minutes and then at room temperature overnight. The mixture was quenched by water and extracted with DCM. Combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified on a silica gel chromatographic column (elution with hexane-EtOAc 4:1, v/v) to give white solids (1.85 g, 94% yield). ^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): 6.55 (s, 2H), 4.18 (br, s, 4H), 3.77 (s, 6H), 2.74 (m, 4H), 2.42 (s, 3H), 2.20 (s, 3H). HRMS calcd. for $C_{22}H_{22}F_9N_5O_5S$ 640.1198, obsd. 640.1262.

8-[2,6-Dimethoxy-4-(tributylstannyl)phenyl]-2,7-dimethyl-*N*,*N*-bis(3,3,3-trifluoro propyl)pyrazolo[1,5-α][1,3,5]triazin-4-amine (19)

To a solution of 4-{4-[bis(3,3,3-trifluoropropyl)amino]-2,7-dimethylpyrazolo[1,5-α] [1,3,5]triazin-8-yl}-3,5-dimethoxyphenyl trifluoromethanesulfonate (**18**) (64.0 mg, 0.10

mmol) in dioxane (1 mL) were added lithium chloride (12.7 mg, 0.30 mmol), tetrakis(triphenylphosphine)palladium (5.78 mg, 0.0050 mmol), one crystal of 2,6-di-*tert*-butyl-4-methylphenol, and hexabutylditin (0.10 mL, 0.20 mmol) under argon. The mixture was heated to 110 ^{o}C for 22 h and then cooled to room temperature. It was diluted with ethyl acetate and washed with 10% aqueous ammonium hydroxide solution. The organic layer was filtered through a bed of Celite. The filtrate was dried over anhydrous $MgSO_4$, and the concentrated crude product was purified on silica gel chromatographic column, which provided 42.2 mg (54% yield) of white solids. ^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): 6.73 (s, 2H), 4.17 (br, s, 4H), 3.77 (s, 6H), 2.74 (m, 4H), 2.41 (s, 3H), 2.23 (s, 3H), 1.58 (m, 6H), 1.38 (m, 6H), 1.08 (m, 6H), 0.94 (m, 9H). HRMS calcd. for $C_{33}H_{49}F_6N_5O_2Sn$ 782.2812, obsd. 782.2873.

8-(4-Bromo-2,6-dimethoxyphenyl)-2,7-dimethyl-*N*,*N*-bis(3,3,3-trifluoropropyl) pyrazolo[1,5-α][1,3,5]triazin-4-amine (20)

8-[2,6-dimethoxy-4-(tributylstannyl)phenyl]-2,7-dimethyl-*N*,*N*-bis(3,3,3-trifluoropropyl) pyrazolo[1,5-α][1,3,5]triazin-4-amine (**19**) (30.0 mg, 0.0384 mmol) was dissolved in dry THF (0.4 mL). NBS (7.5 mg, 0.0421 mmol) was added to the solution. When TLC showed no starting material, the solvent was removed in vacuo. Then residue was purified on silica gel chromatographic column to give white solids (20.2 mg, 92% yield). ^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): 6.80 (s, 2H), 4.17 (br, s, 4H), 3.75 (s, 6H), 2.74 (m, 4H), 2.41 (s, 3H), 2.20 (s, 3H). HRMS calcd. for $C_{21}H_{22}BrF_6N_5O_2$ 570.0861, obsd. 570.0927.

V. References

(1) Vale, W.; Spiess, J.; Rivier, C.; Rivier, J. *Science* **1981**, *213*, 1394.

(2) (a) Owens, M. J.; Nemeroff, C. B. *Pharmacol. Rev.* **1991**, *43*, 425. (b) Chrousos, G. P. *N. Engl. J. Med.* **1995**, *332*, 1351.

(3) (a) Chrousos, G. P.; Schulte, H. M.; Oldfield, E. H.; Loriaux, D. L.; Cutler, G. B.; Kellner, C. H.; Gold, P. W. *Psychopharmacol. Bull.* **1983**, *19*, 416. (b) Dunn, A. J.; Berridge, C. W. *Brain Res. Rev.* **1990**, *15*, 71. (c) Smagin, G. N.; Heinrichs, S. C.; Dunn, A. J. *Peptides.* **2001**, *22*, 713. (d) Swiergiel, A. H.; Leskov, I. L.; Dunn, A. J. *Behav. Brain. Res.* **2008**, *186*, 32.

(4) Dunn, A. J.; File, S. E. *Horm. Behav.* **1987**, *21*, 193.

(5) (a) Yang, X. M.; Gorman, A. L.; Dunn, A. J. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 1064. (b) Chen, R.; Lewis, K. A.; Perrin, M. H.; Vale, W. W. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 8967. (c) Perrin, M.; Donaldson, C.; Chen, R.; Blount, A.; Berggren, T.; Bilezikjian, L.; Sawchenko, P.; Vale, W. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 2969. (d) Liaw, C. W.; Lovenberg, T. W.; Barry, G.; Oltersdorf, T.; Grigoriadis, D. E.; de Souza, E. B. *Endocrinology* **1996**, *137*, 72. (e) Smagin, G. N.; Dunn, A. J. *Eur. J. Pharmacol.* **2000**, *405*, 199. (f) Nazarloo, H. P.; Buttrick, P. M.; Saadat, H.; Dunn, A. J. *Curr. Protein Pept. Sci.* **2006**, *7*, 229.

(6) Grigoriadis, D. E.; Struble, B. G.; Prica, D. L.; De Sauza, B. B. *Neuropharmacol.* **1989**, *28*, 761.

(7) (a) He, L.; Gilligan, P. J.; Zaczek, R.; Fitzgerald, L. W.; McElroy, J.; Shen, H. S. L.; Saye, J. A.; Kalin, N. H.; Shelton, S.; Christ, D.; Trainor, G.; Hartig, P. *J. Med. Chem.* **2000**, *43*, 449. (b) Jagoda, E.; Contoreggi, C.; Lee, M. J.; Kao, C. H.; Szajek, L. P.; Listwak, S.; Gold, P.; Chrousos, G.; Greiner, E.; Kim, B. M.; Jacobson, A. E.; Rice, K. C.; Eckelman, W. *J. Med. Chem.* **2003**, *46*, 3559. (c) Lang, L.; Ma, Y.; Kim, B. M.; Jagoda, E. M.; Rice, K. C.; Szajek, L. P.; Contoreggi, C.; Gold, P. W.; Chrousos, G. P.; Eckelman, W. C.; Kiesewetter, D. O. *J. Labelled Comp. Radiopharm.* **2009**, *52*, 394.

(8) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.*

2008, *37*, 320. (b) Filler, R.; Saha, R. *Future Med. Chem.* **2009**, *1*, 777.

(9) van Leusen, A. M.; Oomkes, P. G. *Synthetic. Commun.* **1980**, *10*, 399.

(10) Blazejewski, J.-C.; Anselmi, E.; Wakselman, C. *J. Org. Chem.* **2001**, *66*, 1061.

(11) Suzuki, H.; Unemoto, M.; Hagiwara, M.; Ohyama, T.; Yokoyama, Y.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1717.

(12) Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493.

(13) Yoshida, S.; Igawa, K.; Tomooka, K. *J. Am. Chem. Soc.* **2012**, *134*, 19358.

(14) Zuev, D.; Mattson, R. J.; Huang, H.; Mattson, G. K.; Zueva, L.; Nielsen, J. M.; Kozlowski, E. S.; Huang, X. S.; Wu, D.; Gao, Q.; Lodge, N. J.; Bronson, J. J.; Macor, J. E. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2484.

Part II.

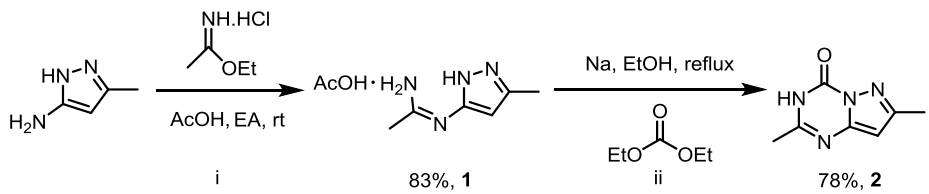
Synthetic Studies Toward CRHR1 Antagonists Through C-H Activation of 2,7-Dimethylpyrazolo[1,5-α][1,3,5]triazine-4(*3H*)-one

I. Introduction

Due to the structural complexity of the CRH1 antagonists containing the 8-aryl-substituted 2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one unit, the synthesis of these antagonists in a linear fashion usually requires cumbersome and lengthy synthetic steps. Therefore, many research groups concentrated on the development of efficient and convergent synthetic routes for the pyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one class CRHR1 antagonists.[1] In 2011, Zuev *et al.*[2] have successfully accomplished the same class antagonist molecule synthesis by utilizing microwave-assisted Suzuki coupling to combine a brominated *N*-heterocyclic compound and an arylboronic acid. General Pd-catalyzed cross-coupling reactions require pre-functionalized reactants such as ArMgX,[3] $ArB(OR)_2$,[4] or $ArSnR_3$,[5] from which stoichiometric amounts of halogenated and organometallic wastes are produced. A direct C-H activation has been developed as an attractive, atom-economical alternative to avoid unwanted side products.[6] We previously reported on the development of an environmentally friendly C-H arylation of indole moieties using magnetically recyclable and heterogeneous Pd-Fe_3O_4 nanocrystal catalysts.[7] We envisioned the use of coupling reactions through C-H activation by utilizing the Pd catalyst to successfully synthesize the pyrazolotriazine class CRHR1 antagonists. Since Sames and coworkers[8] reported the first intermolecular C-H arylation of pyrazoles in 2009, research has concentrated on developing novel ways to synthesize substituted pyrazole derivatives.[9] In this section, we reveal the first palladium catalyzed intermolecular C-H activation for 2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one as a key step to efficiently synthesize major intermediates for pyrazolo[1,5-α][1,3,5]triazine classes CRHR1 antagonists.

II. Results and Discussion

The coupling through C-H activation reaction requires 2,7-dimethyl pyrazolo [1,5-α][1,3,5]triazin-4(*3H*)-one (**2**) to be a substrate and it was synthesized in 2 steps for 65% overall yield, as reported earlier[10] (**Scheme 1**). From the commercially available staring materials, 3-methyl-1*H*-pyrazol-5-amine and ethyl acetimidate hydrochloride, an acetic acid salt of an amidine **1** was obtained at 83% yield. Compound **1** with diethyl carbonate in a basic ethanolic solution furnished the urea **2** in 78% yield.

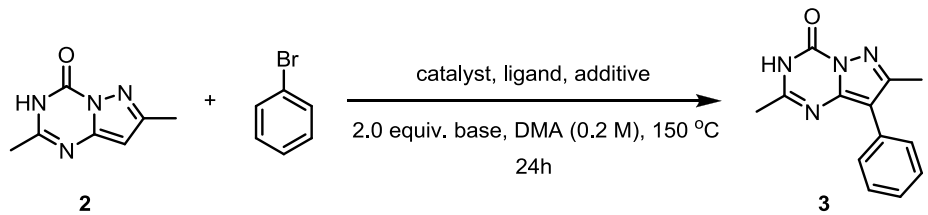


Scheme 1. Synthesis of 2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one

With the desired pyrazolotriazinone **2**, we carried out an intermolecular coupling reaction with aryl halides through C-H activation. This intermolecular coupling approach through direct C-H arylation of pyrazoles was previously developed by Kumpulainen *et al.*[9f] in 2014. We chose bromobenzene as a model substrate for coupling with the urea **2** for optimal reaction conditions. Because of the poor solubility of **2** in xylenes (the solvent of choice by Kumpulainen *et al.*), a polar aprotic solvent *N*,*N*-dimethylacetamide (DMA) was used instead. To our delight, the reaction of **2** (0.20 mmol) with bromobenzene (0.80 mmol, 4 equiv.) in the presence of $Pd(OAc)_2$ (0.01 mmol, 5 mol%) and K_2CO_3 in DMA (1.0 mL) produced the desired product **3**, albeit in 24% yield (**Table 1**, entry 1). Since the basic amine and carbonyl functionalities of compound **2** can act as a ligand for the Pd catalyst, we carried out the reaction in the presence of an extra ligand and/or an additive. When 30 mol% pivalic acid was added as an additive,[9f] a noticeable

increase in the yield (47%) was observed (**Table 1**, entry 2). Adding 30 mol% PPh_3 also dramatically enhanced the reactivity to result in 56% yield (**Table 1**, entry 3).[9f] A synergistic effect was observed from the addition of both the PPh_3 (0.06 mmol, 30 mol%) and the PivOH (0.06 mmol, 30 mol%) in the presence of

Table 1. Optimization of reaction conditions[a]



Entry	Catalyst	PPh_3	PivOH	Base	Isolated Yield(%)
1	5% $Pd(OAc)_2$	0%	0%	K_2CO_3	24
2	5% $Pd(OAc)_2$	0%	30%	K_2CO_3	47
3	5% $Pd(OAc)_2$	30%	0%	K_2CO_3	56
4	**5% $Pd(OAc)_2$**	**30%**	**30%**	**K_2CO_3**	**88**
5	5% $Pd(PPh_3)_2Cl_2$	30%	30%	K_2CO_3	65
6	5% $(PhCN)_2PdCl_2$	30%	30%	K_2CO_3	50
7	5% $PdCl_2$	30%	30%	K_2CO_3	59
8	5% $Pd(OAc)_2$	30%	30%	Cs_2CO_3	75
9	5% $Pd(OAc)_2$	30%	30%	Na_2CO_3	10
10	5% $Pd(OAc)_2$	30%	30%	KOAc	18

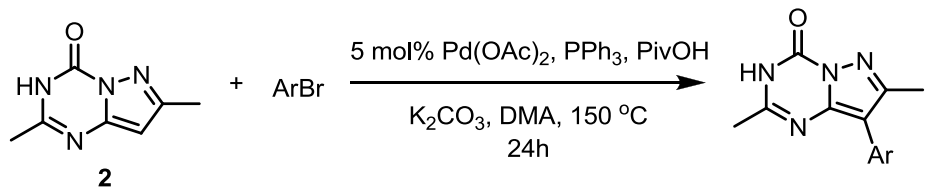
[a]Reaction conditions: starting material (**2**) (0.20 mmol), bromobenzene (0.80 mmol), PPh_3 (0.06 mmol), PivOH (0.06 mmol), palladium complex (0.01 mmol) and DMA (1.0 mL), 150 °C, 24 h.

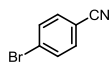
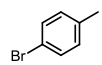
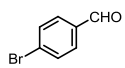
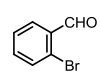
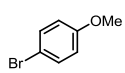
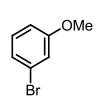
K_2CO_3 (0.40mmol, 2 equiv.) that led to 88% yield of the desired coupling product (**Table 1**, entry 4). These results revealed that both the phosphine ligand and pivalic acid played crucial roles in the reaction thus we thought it may act as a

concerted metalation deprotonation (CMD) pathway.[11] We examined other palladium sources, such as $Pd(PPh_3)_2Cl_2$, $(PhCN)_2PdCl_2$ and $PdCl_2$, but no yield improvement was observed (**Table 1**, entries 5-7, respectively). Finally, the reactions were tested against a series of different inorganic bases. With a strong base, Cs_2CO_3, there was a slightly low yield, while reactions in the presence of Na_2CO_3 or KOAc gave very poor yields (**Table 1**, entries 8-10, respectively).

This protocol was examined through the use of a variety of aryl bromides in optimized reaction conditions (**Table 2**). From **Table 2**, it was evident that both the electronic and steric substrate environments influenced the reaction yields. When there was a nitrile (electron-withdrawing) substitution at the *para*-position of the aryl bromide, the reaction led to an excellent yield (90%, **Table 2**, entry 1). However, the reaction with *m*-cyanobromobenzene produced a moderate yield (44%, **Table 2**, entry 2). In the reaction of a *para*-formyl substrate, some unknown side products were detected along with the desired product and led to a moderate yield (**Table 2**, entry 3). A similar result was observed when the formyl group was at the *meta*-position (**Table 2**, entry 4). Electron-donating methoxy and methyl groups in *p*- or *m*- substituted bromobenzene derivatives produced moderate yields (**Table 2**, entries 5-8). When there was a substituent at the *ortho*-position, only trace amounts of desired products were observed regardless of the electronic nature of the substituent (**Table 2**, entries 9-12). However, by increasing the Pd-catalyst amount to 10 mol%, the reaction yields noticeably improved to 53% and 33% for electron-withdrawing *ortho*-cyano- and formyl-substitutions (**Table 2**, entries 9 and 10, respectively). Additionally, there was an improvement for *m*-substituted bromobenzene derivatives by using 10 mol% $Pd(OAc)_2$ (**Table 2**, entries 2 and 8). However, no enhancements were observed even with increased amount of Pd catalyst when an electron-donating methoxy- or methyl group was positioned at the *ortho*-position (**Table 2**, entries 11 and 12, respectively). Overall, the reaction was quite sensitive to steric and electronic factors.

Table 2. Substrate scope



Entry	Substrate	Product	Isolated Yield (%)	Entry	Substrate	Product	Isolated Yield (%)
1		**4**	90	7		**10**	42
2		**5**	44 (79)[a]	8		**11**	40 (58)[a]
3		**6**	51	9		**12**	trace (53)[a]
4		**7**	47	10		**13**	trace (33)[a]
5		**8**	45	11			trace[a]
6		**9**	44	12			trace[a]
[a] using 10 mol% $Pd(OAc)_2$							

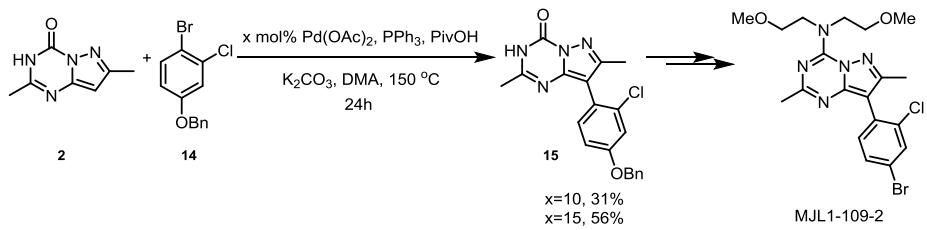
Employment of aryl iodides instead of aryl bromides did not improve the reaction yields as indicated in **Table 3**. Except for the case of 2-cyanophenyl iodide, where 60% yield was achieved with 10 mol% catalyst (**Table 3**, entry 4), all the other cases examined showed a small amount or trace of the desired product. Instead, large amounts of aryl-aryl coupling products and reduced (C-I to

C-H) aryl compounds were observed. This indicates that the rate determining step of the reaction resides in the activation of the C-H bond of the pyrazolotriazinone **2**.

Table 3. Results on the reaction with aryl iodides

Entry	Substrate	Product	Isolated Yield (%)	Entry	Substrate	Product	Isolated Yield (%)
1		**7**	trace[a]	2		**9**	13[a]
3		**11**	17[a]	4		**12**	60[a]
5		**13**	trace[a]				
[a] The same reaction conditions as in **Table 2**, except for 10 mol% $Pd(OAc)_2$.							

With the optimized reaction conditions for the C-H activation-mediated coupling, we carried out the coupling reaction of **2** and *O*-benzyl 4-bromo-3-chlorophenol (**14**) to yield compound **15**. Compound **15** is an intermediate in the construction of MJL1-109-2, a known CRHR1 antagonist (**Scheme 2**). Considering the steric effects of compound **14**, we employed 10 mol% $Pd(OAc)_2$ as a catalyst, which resulted in product **15** at 31% yield. By increasing the catalyst loading to 15 mol%, the yield was raised to 56%. The chlorine substituent next to the Br remained intact after the reaction. Therefore, we developed a simple synthetic method for compound **15**, a synthetic precursor for the MJL1-109-2. This process provides a convergent pathway for the desired antagonist.



Scheme 2. Synthesis of an intermediate toward MJL1-109-2

III. Conclusion

In summary, we developed a novel synthetic protocol for 8-aryl substituted pyrazolo[1,5-α][1,3,5]triazine class CRHR1 antagonists that employ palladium-catalyzed intermolecular direct C-H arylation. The coupling reaction yield was directly dependent upon a phosphine ligand, pivalic acid additive and base selection. By using 5~10 mol% catalyst, we were successful in achieving coupling reactions of compound **2** with both electron-rich and electron-poor aryl bromides that have substituents at *para*- or *meta*-positions in moderate to excellent yields. *Ortho*-substituted aryl bromides, using 10~15 mol% $Pd(OAc)_2$, produced desired products in moderate yields. Using this method, we were able to prepare a synthetic precursor for MJL1-109-2, a known non-peptide CRHR1 antagonist. Variations in the aryl bromide can provide convenient ways to synthesize potential pyrazolo[1,5-α][1,3,5]triazine class CRHR1 antagonists. Efforts are underway to explore new applications of C-H activation reaction of heteroaromatic compounds in our laboratory.

IV. Experimental procedure

General

All the reactions were carried out using oven-dried glassware. Commercial reagents were used without further purification unless otherwise noted. Thin layer chromatography (TLC) plates were used to check the reaction and the spots were visualized under UV light. Flash column chromatography was used to isolate eluted products with a mixture of dichloromethane and methanol. ^{1}H and ^{13}C NMR spectra were acquired through the Agilent MR DD2 (400 MHz) spectrophotometer.

Synthesis of 2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one (2)

(i) Ethyl acetimidate hydrochloride (5.86 g, 47.4 mmol) was added to a 200 mL round bottom flask containing K_2CO_3 (10.57 g, 76.5 mmol) dissolved in water (25 mL). Ethyl acetate (38 mL) was added to the suspension and the two-phase system was stirred forcefully for about 5 minutes. The aqueous phase (and some undissolved salts) was removed by a separatory funnel. The organic phase was dried over anhydrous $MgSO_4$, filtered, and then transferred to the round bottom flask containing commercially available 3-amino-5-methylpyrazole (2.48 g, 25.5 mmol) and a stirring bar. The mixture was stirred for 1 h until TLC did not show any more starting material. Acetic acid (2.2 mL, 38.3 mmol) was then added to the reaction mixture and solids began to appear 15 minutes later. After 30 minutes, the solids were filtered and washed with ethyl acetate before being dried in a vacuum oven (4.19 g, 83% yield). ^{1}H NMR (CD_3OD-d_4, δ=3.31 ppm, 400 MHz): δ 5.90 (s, 1H), 2.38 (s, 3H), 2.31 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (CD_3OD-d_4, δ=49.00 ppm, 100 MHz) δ 180.0, 163.6, 149.0, 142.1, 95.9, 24.1, 19.0, 10.6.

(ii) Sodium pellets (0.47 g, 20.4 mmol) were added portionwise to dry ethanol (18 mL) in a two-necked 50 mL round bottom flask equipped with a condenser. After all sodium pellets dissolved, the solution was cooled to room temperature. Acetic acid salt **1** (0.30 g, 1.51 mmol) and diethyl carbonate (1.9 mL, 15.7 mmol) were added in sequence and the mixture was heated to reflux overnight. After cooling to room temperature, the solvent was evaporated. This remaining solid was dissolved in water and acidified by 6 N aq HCl

solution. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using 95:5 (v/v) dichloromethane/methanol as eluent (194.3 mg, 78% yield). ^{1}H NMR (DMSO-d_6, δ=2.50 ppm, 400 MHz): δ 12.30 (s, 1H), 6.18 (s, 1H), 2.28 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (DMSO-d_6, δ=39.5 ppm, 100 MHz) δ 154.7, 154.0, 149.4, 143.8, 97.6, 20.7, 14.2. HRMS calcd. for $C_7H_8N_4O$ 164.0698, obsd. 165.0772 (MH^+).

General procedure for coupling through C-H activation.

Synthesis of 2,7-dimethyl-8-phenylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one (3)

2,7-Dimethylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one **2** (32.8 mg, 0.20 mmol), potassium carbonate (55.3 mg, 0.40 mmol), pivalic acid (6.1 mg, 0.06 mmol), palladium acetate (2.2 mg, 0.01 mmol, 5 mol%), and triphenylphosphine (15.7 mg, 0.06 mmol) were added to a 25 mL oven dried vial equipped with a stirring bar and rubber septum. The flask was evacuated and backfilled with argon for three times before DMA (1.0 mL) and bromobenzene (84 μL, 0.80 mmol) were added via a syringe. The reaction mixture was stirred at room temperature for about 5 minutes, and then heated to 150 ^{o}C for 24 h. The reaction was cooled to room temperature and solvent was removed under reduced pressure. The crude product was purified on a chromatographic column with DCM/MeOH as eluent. ^{1}H NMR (DMSO-d_6, δ=2.50 ppm, 400 MHz): δ 12.42 (s, 1H), 7.61 (d, 2H), 7.45 (t, 2H), 7.31 (t, 1H), 2.43 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (DMSO-d_6, δ=39.5 ppm, 100 MHz) δ 154.5, 152.6, 145.7, 143.8, 131.3, 128.6, 128.4, 126.5, 110.2, 20.9, 14.2. HRMS calcd. for $C_{13}H_{12}N_4O$ 240.1011, obsd. 241.1083 (MH^+).

4-(2,7-Dimethyl-4-oxo-3,4-dihydropyrazolo[1,5-α][1,3,5]triazin-8-yl) benzonitrile (4)

^{1}H NMR (DMSO-d_6, δ=2.50 ppm, 400 MHz): δ 12.59 (s, 1H), 7.90 (s, 2H), 7.89 (s, 2H), 2.48 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (DMSO-d_6, δ=39.52 ppm, 100 MHz) δ 155.8, 152.5, 146.6, 143.7, 136.6, 132.3, 128.7, 119.1, 108.5, 108.2, 21.1, 14.6. HRMS calcd. for $C_{14}H_{11}N_5O$ 265.0964, obsd. 266.1038 (MH^+).

3-(2,7-Dimethyl-4-oxo-3,4-dihydropyrazolo[1,5-α][1,3,5]triazin-8-yl) benzonitrile (5)

^{1}H NMR (DMSO-d_6, δ=2.50 ppm, 400 MHz): δ 12.55 (s, 1H), 8.06 (dd, 1H), 8.01-7.96 (m, 1H), 7.77 (ddd, 1H), 7.67 (t, 1H), 2.47 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (DMSO-d_6, δ=39.52 ppm, 100 MHz) δ 155.5, 152.5, 146.3, 143.7, 133.0, 132.8, 131.4, 130.1, 129.8, 118.9, 111.6, 108.0, 21.0, 14.2. HRMS calcd. for $C_{14}H_{11}N_5O$ 265.0964, obsd. 266.1038 (MH^+).

4-(2,7-Dimethyl-4-oxo-3,4-dihydropyrazolo[1,5-α][1,3,5]triazin-8-yl) benzaldehyde (6)

^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): δ 10.60 (s, 1H), 10.06 (s, 1H), 7.98 (d, 2H), 7.84 (d, 2H), 2.62 (s, 3H), 2.57 (s, 3H). ^{13}C NMR ($CDCl_3$-*d*, δ=77.16 ppm, 100 MHz) δ 192.0, 155.4, 153.5, 146.2, 145.5, 137.4, 135.0, 130.2, 129.3, 111.9, 21.9, 14.9. HRMS calcd. for $C_{14}H_{12}N_4O_2$ 268.0960, obsd. 269.1034 (MH^+).

3-(2,7-Dimethyl-4-oxo-3,4-dihydropyrazolo[1,5-α][1,3,5]triazin-8-yl) benzaldehyde (7)

^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): δ 11.00 (s, 1H), 10.09 (s, 1H), 8.13 (t, 1H), 7.92-7.84 (m, 2H), 7.65 (t, 1H), 2.59 (s, 3H), 2.57 (s, 3H). ^{13}C NMR ($CDCl_3$-*d*, δ=77.16 ppm, 100 MHz) δ 192.4, 155.4, 153.7, 146.0, 145.8, 136.9, 134.9, 132.1, 130.1, 129.5, 128.6, 111.6, 21.7, 14.6. HRMS calcd. for $C_{14}H_{12}N_4O_2$ 268.0960, obsd. 269.1036 (MH^+).

8-(4-Methoxyphenyl)-2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one (8)

^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): δ 10.74 (s, 1H), 7.53 (d, 2H), 7.01 (d, 2H), 3.86 (s, 3H), 2.54 (s, 3H), 2.53 (s, 3H). ^{13}C NMR ($CDCl_3$-*d*, δ=77.16 ppm, 100 MHz) δ 159.0, 155.7, 152.2, 148.6, 130.3, 129.1, 128.8, 123.1, 114.4, 55.5, 21.8, 14.5. HRMS calcd. for $C_{14}H_{14}N_4O_2$ 270.1117, obsd. 271.1190 (MH^+).

8-(3-Methoxyphenyl)-2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one (9)

^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): δ 11.34 (s, 1H), 7.38 (t, 1H), 7.21-7.15 (m,

2H), 6.90 (dd, 1H), 3.86 (s, 3H), 2.57 (s, 3H), 2.55 (s, 3H). ^{13}C NMR ($CDCl_3$-*d*, δ=77.16 ppm, 100 MHz) δ 159.8, 155.8, 152.9, 146.1, 132.1, 129.8, 129.1, 128.8, 121.5, 115.1, 112.8, 55.4, 21.8, 14.6. HRMS calcd. for $C_{14}H_{14}N_4O_2$ 270.1117, obsd. 271.1189 (MH^+).

2,7-Dimethyl-8-*p*-tolylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one (10)

^{1}H NMR (DMSO-d_6, δ=2.50 ppm, 400 MHz): δ 12.39 (s, 1H), 7.49 (d, 2H), 7.25 (d, 2H), 2.40 (s, 3H), 2.33 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (DMSO-d_6, δ=39.52 ppm, 100 MHz) δ 154.2, 152.6, 145.5, 143.8, 135.7, 129.0, 128.5, 128.3, 110.2, 20.9, 20.8, 14.2. HRMS calcd. for $C_{14}H_{14}N_4O$ 254.1168, obsd. 255.1241 (MH^+).

2,7-Dimethyl-8-*m*-tolylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one (11)

^{1}H NMR (DMSO-d_6, δ=2.50 ppm, 400 MHz): δ 12.40 (s, 1H), 7.38 (d, 2H), 7.32 (t, 1H), 7.12 (d, 1H), 2.41 (s, 3H), 2.35 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (DMSO-d_6, δ=39.52 ppm, 100 MHz) δ 154.4, 152.6, 145.6, 143.8, 137.4, 131.2, 129.2, 128.3, 127.2, 125.8, 110.3, 21.2, 21.0, 14.2. HRMS calcd. for $C_{14}H_{14}N_4O$ 254.1168, obsd. 255.1241 (MH^+).

2-(2,7-Dimethyl-4-oxo-3,4-dihydropyrazolo[1,5-α][1,3,5]triazin-8-yl) benzonitrile (12)

^{1}H NMR (DMSO-d_6, δ=2.50 ppm, 400 MHz): δ 12.59 (s, 1H), 7.98-7.94 (m, 1H), 7.79 (td, 1H), 7.60 (dd, 1H), 7.58-7.54 (m, 1H), 2.30 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (DMSO-d_6, δ=39.52 ppm, 100 MHz) δ 155.5, 152.9, 146.9, 143.7, 134.7, 133.3, 133.2, 131.9, 128.3, 118.2, 112.7, 108.2, 20.9, 13.2. HRMS calcd. for $C_{14}H_{11}N_5O$ 265.0964, obsd. 266.1037 (MH^+).

2-(2,7-Dimethyl-4-oxo-3,4-dihydropyrazolo[1,5-α][1,3,5]triazin-8-yl) benzaldehyde (13)

^{1}H NMR ($CDCl_3$-*d*, δ=7.26 ppm, 400 MHz): δ 11.23 (s, 1H), 9.88 (s, 1H), 8.08 (d, 1H), 7.73-7.64 (m, 1H), 7.55 (t, 1H), 7.41 (d, 1H), 2.49 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$-*d*, δ=77.16 ppm, 100 MHz) δ 191.8, 156.2, 154.2, 146.8, 145.6, 134.5, 134.1, 133.5, 131.9, 128.7, 128.6, 109.5, 21.7, 13.7. HRMS calcd. for $C_{14}H_{12}N_4O_2$ 268.0960,

obsd. 269.1035 (MH^+).

8-[4-(Benzyloxy)-2-chlorophenyl]-2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(*3H*)-one (15)

^{1}H NMR ($CDCl_3$-d, δ=7.26 ppm, 400 MHz): δ 7.47-7.33 (m, 5H), 7.23 (d, 1H), 7.15 (d, 1H), 6.97 (dd, 1H), 5.09 (s, 2H), 2.51 (s, 3H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$-*d*, δ=77.16 ppm, 100 MHz) δ 159.5, 157.0, 153.0, 146.3, 146.0, 136.4, 135.5, 133.3, 128.9, 128.4, 127.7, 121.8, 116.3, 114.0, 111.4, 70.5, 21.7, 13.8. HRMS calcd. for $C_{20}H_{17}ClN_4O_2$ 380.1040, obsd. 381.1115 (MH^+).

V. References

(1) (a) Chen, Y. L.; Mansbach, R. S.; Winter, S. M.; Brooks, E.; Collins, J.; Corman, M. L.; Dunaiskis, A. R.; Faraci, W. S.; Gallaschun, R. J.; Schmidt, A.; Schulz, D. W. *J. Med. Chem.* **1997**, *40*, 1749. (b) Luthin, D. R.; Rabinovich, A. K.; Bhumralkar, D. R.; Youngblood, K. L.; Bychowski, R. A.; Dhanoa, D. S.; May, J. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 765. (c) Hsin, L.-W.; Webster, E. L.; Chrousos, G. P.; Gold, P. W.; Eckelman, W. C.; Contoreggi, C.; Rice, K. C. *J. Labelled Comp. Radiopharm.* **2000**, *43*, 899. (d) Tian, X.; Hsin, L.-W.; Webster, E. L.; Contoreggi, C.; Chrousos, G. P.; Gold, P. W.; Habib, K.; Ayala, A.; Eckelman, W. C.; Jacobson, A. E.; Rice, K. C. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 331. (e) Di Fabio, R.; Arban, R.; Bernasconi, G.; Braggio, S.; Blaney, F. E.; Capelli, A. M.; Castiglioni, E.; Donati, D.; Fazzolari, E.; Ratti, E.; Feriani, A.; Contini, S.; Gentile, G.; Ghirlanda, D.; Sabbatini, F. M.; Andreotti, D.; Spada, S.; Marchioro, C.; Worby, A.; St-Denis, Y. *J. Med. Chem.* **2008**, *51*, 7273. (f) Hartz, R. A.; Ahuja, V. T.; Arvanitis, A. G.; Rafalski, M.; Yue, E. W.; Denhart, D. J.; Schmitz, W. D.; Ditta, J. L.; Deskus, J. A.; Brenner, A. B.; Hobbs, F. W.; Payne, J.; Lelas, S.; Li, Y. W.; Molski, T. F.; Mattson, G. K.; Peng, Y.; Wong, H.; Grace, J. E.; Lentz, K. A.; Qian-Cutrone, J.; Zhuo, X.; Shu, Y. Z.; Lodge, N. J.; Zaczek, R.; Combs, A. P.; Olson, R. E.; Bronson, J. J.; Mattson, R. J.; Macor, J. E. *J. Med. Chem.* **2009**, *52*, 4173. (g) Leahy, D. K.; Li, J.; Sausker, J. B.; Zhu, J.; Fitzgerald, M. A.; Lai, C.; Buono, F. G.; Braem, A.; de Mas, N.; Manaloto, Z.; Lo, E.; Merkl, W.; Su, B.-N.; Gao, Q.; Ng, A. T.; Hartz, R. A. *Org. Process. Res. Dev.* **2010**, *14*, 1221. (h) Saito, T.; Obitsu, T.; Minamoto, C.; Sugiura, T.; Matsumura, N.; Ueno, S.; Kishi, A.; Katsumata, S.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2011**, *19*, 5955. (i) Takahashi, Y.; Hashizume, M.; Shin, K.; Terauchi, T.; Takeda, K.; Hibi, S.; Murata-Tai, K.; Fujisawa, M.; Shikata, K.; Taguchi, R.; Ino, M.; Shibata, H.; Yonaga, M. *J. Med. Chem.* **2012**, *55*, 8450.

(2) Zuev, D.; Mattson, R. J.; Huang, H.; Mattson, G. K.; Zueva, L.; Nielsen, J. M.; Kozlowski, E. S.; Huang, X. S.; Wu, D.; Gao, Q.; Lodge, N. J.; Bronson, J. J.; Macor, J. E. *Bioorg. Med. Chem. Lett* **2011**, *21*, 2484.

(3) Ichikawa, H.; Ohno, Y.; Usami, Y.; Arimoto, M. *Heterocycles* **2006**, *68*, 2247.

(4) Brad Nolt, M.; Zhao, Z.; Wolkenberg, S. E. *Tetrahedron Lett.* **2008**, *49*, 3137.

(5) Jeon, S. L.; Choi, J. H.; Kim, B. T.; Jeong, I. H. *J. Fluorine. Chem.* **2007**, *128*, 1191.

(6) (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (b) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Rev.* **2011**, *111*, 1293. (c) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem.*

Soc. Rev. **2011**, *40*, 4740. (d) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236. (e) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960. (f) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281.

(7) Chung, J.; Kim, J.; Jang, Y.; Byun, S.; Hyeon, T.; Kim, B. M. *Tetrahedron Lett.* **2013**, *54*, 5192.

(8) Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042.

(9) (a) Kumar, S.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2009**, *74*, 7046. (b) Santelli, M.; Doucet, H.; Fall, Y. *Synthesis* **2009**, *2010*, 127. (c) Doucet, H.; Ammar, H.; Beladhria, A.; Beydoun, K.; Salem, R. *Synthesis* **2011**, *2011*, 2553. (d) Yan, T.; Chen, L.; Bruneau, C.; Dixneuf, P. H.; Doucet, H. *J. Org. Chem.* **2012**, *77*, 7659. (e) Iaroshenko, V. O.; Gevorgyan, A.; Davydova, O.; Villinger, A.; Langer, P. *J. Org. Chem.* **2014**, *79*, 2906. (f) Kumpulainen, E. T. T.; Pohjakallio, A. *Adv. Synth. Catal.* **2014**, *356*, 1555.

(10) (a) Brandt, T. A.; Caron, S.; Damon, D. B.; DiBrino, J.; Ghosh, A.; Griffith, D. A.; Kedia, S.; Ragan, J. A.; Rose, P. R.; Vanderplas, B. C.; Wei, L. *Tetrahedron* **2009**, *65*, 3292. (b) Lang, L.; Ma, Y.; Kim, B. M.; Jagoda, E. M.; Rice, K. C.; Szajek, L. P.; Contoreggi, C.; Gold, P. W.; Chrousos, G. P.; Eckelman, W. C.; Kiesewetter, D. O. *J. Labelled Comp. Radiopharm.* **2009**, *52*, 394.

(11) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

국문초록

I. 피라졸로[1,5-α][1,3,5]트라이아진류 CRHR1 길항제 합성에 관한 연구

부신피질자극호르몬 유리호르몬에 대한 연구는 정신 건강에 있어서 매우 흥미로운 주제이다. 피라졸로[1,5-α][1,3,5]트라이아진 구조를 가진 화합물들, 예를 들면, BMK-I-152 그리고 MJL1-109-2 등은 높은 친화성을 가진 CRHR1 양전자방출단층촬영술 리간드로 알려져 있다. 불소 원자가 들어가는 화합물들은 의약화학적인 면에서 놀랍고 특이한 성질이 있고 앞으로도 치료상의 응용이 많을 것으로 보인다. 따라서 우리는 아민 사슬에 메톡시 작용기가 있는 BMK-I-152로부터 트라이플루오로메틸 작용기로 변화시켰을 때의 결과가 궁금하였다. 본 연구에서는 피라졸로[1,5-α][1,3,5]트라이아진류 CRHR1 길항제를 합성하였다.

II. 2,7-디메틸피라졸로[1,5-α][1,3,5]트라이아진-4(*3H*)-온의 탄소-수소 활성화반응을 통해 CRHR1 길항제 합성에 관한 연구

일반적으로 CRHR1 길항제를 합성할 때 긴 합성단계가 필요하므로 합성의 효율이 낮아진다. 그렇기 때문에 탄소-수소 활성화반응을 통한 합성법은 매우 효과적인 대안책일 것이다. 본 연구에서는 팔라듐 촉매와 2,7-디메틸피라졸로[1,5-α][1,3,5]트라이아진-4(*3H*)-온의 탄소-수소 활성화반응을 기반으로 분자간 짝지움 반응을 하였다. 이 방법은 피라졸로[1,5-α][1,3,5]트라이아진류 CRHR1 길항제를 합성하는 데에 있어 새로운 접근방식으로 쓰일 수 있다.