Notes

An Efficient Synthesis of 3-Substituted Quinazolones

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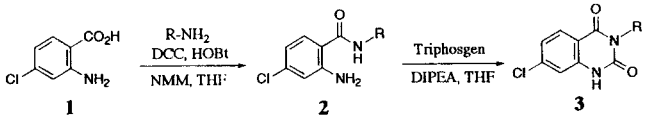
A variety of the quinazolones has appeared as key intermediates in organic syntheses as well as as therapeutically useful agents in medicinal chemistry. Particularly, 3-substituted-quinazolones have intensively been studied for their biological properties against CNS-related receptors and enzymes including serotonergic, dopaminergic, and adrenergic receptor and aldose reductase, lipoxygenase, cyclooxygenase, collagenase and carbonic anhydrase.[1] Becuse of the synthetic and clinical versatility of quinazolones, there are significant progresses in the development of synthetic methods for the construction of quinazolone ring. Among the precedent synthetic methods, the reaction of either isatonic anhydrides[2] or anthranilic isocyanate[3] with the appropriate amine, followed by subsequent treatment with a phosgen, has been frequently employed in the synthesis of quinazolones in the literature.[1a,2b] In these processes, the anthranilic acid has been used as a starting material and it was converted to the actual reacting reagents such as anhydride or isocyanate etc. Herein, we describe a convenient and effective transformation of the anthranilic acids to 3-substituted-quinazolones, which enable to avoid the tedious pre-activating processes. Our process was constisted of two steps; the selective formation of an amide bond using DCC-HOBt[4] and the subsequent ring closure using triphosgene[5] which is less hazardous than phosgene gas in large scale handling.

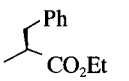
The commercially available 4-chloroanthranilic acid readily reacted with various amines, such as benzylamine, phenylhyhdrazine, *t*-butylcarbazate, and L-phenylalanine ethyl ester under DCC-HOBt mediated coupling method. N-Methylmorpholine was added to facilitate the reaction.

Under this condition, the starting 4-chloroanthranilic acid was successfully converted to the corresponding amide without any significant undesired reactions of 2-amino moiety which was one of potentially reactable sites. The resulting amide intermediates were treated with 0.36 equivalent of triphosgen in the presence of 1.0 equivalent of diisopropylethylamine at room temperature. After normal basic workup, the corresponding 3-substituted quinazolones were obtained (listed in Table 1)

Table 1. Synthesis of 3-substituted quinazoline-2,4-diones



1 2 3

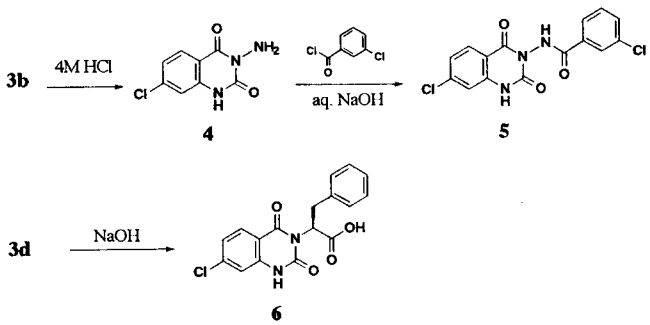
Entry	R	2 yield (%)	3 yield (%)
a	NHPh	75	95
b	$NHCO_2C(CH_3)_3$	85	98
c	CH_2Ph	88	96
d		87	97

To demonstrate the synthetic versatility and the potential pharmaceutical applications of 3-substituted-quinazolones, the quinazolones **3b** and **3d** were further modified (see Scheme 1). Deprotection of *t*-butyloxycarbonyl group of **3b** was performed by treatment with 4 M HCl to afford 3-amino quinazolone **4**. The reaction of **4** with *m*-chlorobenzoyl chloride was consequently performed to provide the benzamide **5** in 70% yield. Saponification of the quinazolone **3d** was effectively conducted by using NaOH in THF-H_2O to give the corresponding carboxylic acid **6** in 89% yield.

In conclusion, several 3-substituted quinazolones were preapred by a convenient and efficient synthetic method from anthranilic acids via two consequent steps. The prepared compounds will be subjected to a pharmacological activities against CNS-related receptors.

Experimental

All melting points were taken on a Thomas-Hoover melting point apparatus and were uncorrected. ^1H NMR spectra were obtained on Varian Gemini 200 spectrometer. Chemical shifts were reported in parts per million (δ) relative to a tetramethylsilane as an internal standard. Mass spectra were obtained using a Jeol JMS-DX 303 GC/MS and Shimadzu GCMS-QP 5000 mass spectrometer. Analytical thin layer chromatography was performed using



Scheme 1

0.25 mm silica gel glass-backed plates. E. Merck silica gel (230-400 mesh) was used for flash chromatography. Solvents and reagents were dried and purified prior to use when deemed necessary. Reactions were carried out under nitrogen or argon atmosphere unless otherwise stated.

General procedure for the preparation of amides 2. To a precooled (−12 °C) solution of 2-amino-4-chlorobenzoic acid **1** (1.72 g, 10 mmol), phenyl-hydrazine (0.98 mL, 10 mmol), and HOBt (2.7 g, 20 mmol) in dry THF (50 mL) was added N-methylmorpholine (1.1 mL, 10 mmol). After 5 min, DCC (2.06 g, 10 mmol) was added. The reaction mixture was allowed to warm to ambient temperature after 1 h and stirred an aditional 48 h. The mixture was cooled to 0 °C and filtered through Celite. The filtrate was diluted with ethylacetate and washed with saturated $NaHCO_3$ aqueous solution twice, dried over $MgSO_4$, and concentrated. The product was recrystalized from a mixture of ethyl acetate and hexane to give **2a** (1.96 g, 75%) as a white powder.

***N*-1-Phenyl-2-amino-4-chlorobenzamide (2a).** mp 166-168 °C; ^{1}H NMR ($CDCl_3$) δ 5.66 (br s, 2H, N*H*$_2$), 6.28 (d, *J*=3.4 Hz, 1H, N*H*), 6.67-6.74 (m, 2H, Ar*H*), 6.93-6.99 (m, 3H, Ar*H*), 7.29-7.33 (m, 2H, Ar*H*), 7.43 (d, *J*=8.4 Hz, 1H, Ar*H*), 7.78 (d, *J*=2.6 Hz, 1H, N*H*); MS (EI) m/z 263 (M^++2), 261 (M^+), 154, 99.

***tert*-Butyl-2-(2-amino-4-chlorobenzoyl)-1-hydrazine carboxylate (2b).** yield 85%, a white powder; mp 200-202 °C; ^{1}H NMR (DMSO-d_6) δ 1.42 (s, 9H, C(C*H*$_3$)$_3$), 6.53 (dd, *J*=2.1, 8.6 Hz, 1H, Ar*H*), 6.67 (br s, 2H, N*H*$_2$), 6.79 (d, *J*=2.1 Hz, 1H, Ar*H*), 7.51 (d, *J*=8.6 Hz, 1H, Ar*H*), 8.79 (s, 1H, N*H*), 9.95 (s, 1H, N*H*); MS (EI) m/z 285 (M^+), 154, 99, 84, 57.

***N*-1-Benzyl-2-amino-4-chlorobenzamide (2c).** yield 88%, a white solid; mp 108-109 °C; ^{1}H NMR ($CDCl_3$) δ 4.57 (d, *J*=5.6 Hz, 2H, C*H*$_2$), 5.66 (br s, 2H, N*H*$_2$), 6.27 (br s, 1H, N*H*), 6.56 (dd, *J*=2.0, 8.4 Hz, 1H, Ar*H*), 6.66 (d, *J*=2.0 Hz, 1H, Ar*H*), 7.19-7.36 (m, 6H, Ar*H*); MS (EI) m/z 263 (M^++2), 261 (M^+), 154, 106, 91.

Ethyl 2(*S*)-2-[(2-amino-4-chlorobenzoyl)amino]-3-phenylpropanoate (2d). yield 87%, a gray solid; mp 138-140 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, C*H*$_3$), 3.21 (m, *J*=2.6 Hz, 2H, C*H*$_2$), 4.19 (q, 2H, C*H*$_2$), 4.92-5.02 (m, 1H, C*H*), 5.60 (br s, 2H, N*H*$_2$), 6.44 (br s, 1H, N*H*), 6.53-6.64 (m, 2H, Ar*H*), 7.05-7.32 (m, 6H, Ar*H*); MS (EI) m/z 348 (M^++2), 346 (M^+), 255, 154.

General procedure for the preparation of 3-Substituted quinazoline 2,4-diones 3

To a 0 °C solution of triphosgen (0.39 g, 1.3 mmol) in THF (7 mL) were dropwise added the **2a** (0.94 g, 3.6 mmol) and diisopropylethylamine (0.62 mL, 3.6 mmol) in THF (12 mL) *via* cannula. After for 2 h, the reaction mixture was diluted with ethyl acetate and washed with 5% $NaHCO_3$ aqueous solution, dried over $MgSO_4$, and concentrated. The product was recrystalized from a mixture of ethyl acetate and hexane to give **3a** (0.98 g, 95%) as a white solid.

3-Anilino-7-Chloro-1,2,3,4-tetrahydro-2,4-quinazolinedione (3a). mp 265-266 °C; ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ 6.74-6.89 (m, 3H, Ar*H*), 7.13-7.23 (m, 3H, Ar*H*), 7.28 (d, *J*=1.8 Hz, 1H, Ar*H*), 7.80 (s, 1H, N*H*), 8.00 (d, *J*=8.4 Hz, 1H, Ar*H*), 11.59 (s, 1H, N*H*); MS (EI) m/z 289 (M^++2), 287 (M^+), 180, 154, 84.

***tert*-Butyl *N*-(7-chloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl) carbamate (3b).** yield 98%, a white solid; mp 303-305 °C; ^{1}H NMR (DMSO-d_6) δ 1.45 (s, 9H, C(C*H*$_3$)$_3$), 7.25-7.34 (m, 2H, Ar*H*), 7.96 (d, *J*=8.4 Hz, 1H, Ar*H*), 9.69 (s, 1H, N*H*), 11.78 (s, 1H, N*H*); MS (EI) m/z 238 (M^+-OC(C*H*$_3$)$_3$), 210 (M^+-C*O*$_2$C(C*H*$_3$)$_3$), 180, 57.

3-Benzyl-7-chloro-1,2,3,4-tetrahydro-2,4-quinazolinedione (3c). yield 96%, a white solid; mp 266-268 °C; ^{1}H NMR (DMSO-d_6) δ 5.08 (s, 2H, C*H*$_2$), 7.22-7.33 (m, 7H, Ar*H*), 7.95 (d, *J*=8.4 Hz, 1H, Ar*H*), 11.70 (br s, 1H, N*H*); MS (EI) m/z 288 (M^++2), 286 (M^+), 181, 154, 91.

Ethyl 2(*S*)-2-(7-chloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)-3-phenylpropanoate (3d). yield 97%, a white solid; mp 126-128 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, C*H*$_3$), 3.45 (dd, *J*=10.2, 14.2 Hz, 1H, C*H*$_2$), 3.65 (dd, *J*=5.4, 14.2 Hz, 1H, C*H*$_2$), 4.27 (q, 2H, C*H*$_2$), 5.81 (dd, *J*=5.4, 10.2 Hz, 1H, C*H*), 6.98 (d, *J*=1.8 Hz, 1H, Ar*H*), 7.10-7.27 (m, 6H, Ar*H*), 7.97 (d, *J*=8.4 Hz, 1H, Ar*H*), 10.14 (s, 1H, N*H*); MS (EI) m/z 374 (M^++2), 372 (M^+), 299, 176, 131.

***N*-1-(7-Chloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)-3-chlorobenzamide (5).** The compound **3b** (1.55 g, 5 mmol) was dissolved in 4 M HCl in dioxane (30 mL) and stirred for 6h. The solution was evaporated under reduced pressure and followed by normal workup to provide a crude 3-amino-7-chloro-1,2,3,4-tetrahydro-2,4-quinazolinedione **4**: mp 298-300 °C; ^{1}H NMR (DMSO-d_6) δ 5.49 (br s, 2H, N*H*$_2$), 7.22-7.30 (m, 2H, Ar*H*), 7.95 (d, *J*=8.4 Hz, 1H, Ar*H*), 11.78 (br s, 1H, N*H*); MS (EI) m/z 211 (M^+), 180, 84. The above crude **4** was dissolved in THF and was adjusted to pH >10 with 2 N NaOH. The resulting solution was added 3-chlorobenzoyl chloride (1.75 mL, 10 mmol). After for 10 h, the reaction mixture was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. The product was recrystalized from a mixture of ethyl acetate and hexane to give **5** (1.23 g, 70%) as a white solid. mp 282-283 °C; ^{1}H NMR (DMSO-d_6) δ 7.28-7.36 (m, 2H, Ar*H*), 7.58-7.77 (m, 2H, Ar*H*), 7.90-8.00 (m, 3H, Ar*H*), 11.40 (br s, 1H, N*H*), 11.90 (br s, 1H, N*H*); MS (EI) m/z 350 (M^+), 180, 139, 11.

2(*S*)-2-(7-Chloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)-3-phenylpropionic acid (6). The ester **3d** (0.16 g, 0.4 mmol) was dissolved in THF (3 mL), 2 N NaOH (1 mL) and stirred for 40 h. The mixture was diluted with water and evaporated. The aqueous phase was washed with diethyl ether and acidified with 1 N HCl to pH 3. The mixture was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. The product was recrystalized from THF, ethyl acetate and hexane to give the acid **36** (0.12 g, 89%) as a white solid. mp 277-279 °C; ^{1}H NMR (acetone-d_6) δ 3.38-3.61 (m, 2H, C*H*$_2$), 5.82 (dd, *J*=6.2, 9.8 Hz, 1H, C*H*), 7.06-7.24 (m, 7H, Ar*H*), 7.90 (d, *J*=8.4 Hz, 1H, Ar*H*), 10.38 (br s, 1H, N*H*); MS (EI) m/z 299 (M^+-C*O*$_2$H), 147, 91.

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A Peptide-Binding Receptor with the Extended Binding Site

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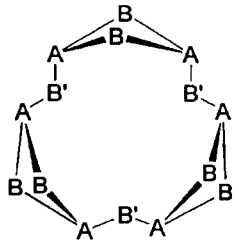
The last decade has witnessed an explosion in the field of molecular recognition. Since the pioneering work of Pederson, Cram and Lehn to define a new area of organic chemistry almost twenty years ago,[1] many molecular receptors capable of interacting selectively with other molecules have been described. For example, many crown ethers were developed for the selective recognition of metal ions and amine salts. Also, many molecular receptors including calixarenes, cyclodextrins, cyclophanes and cleft-shaped molecules for organic substrates such as nucleic acids, aromatics, peptidic molecules and carboxylic acids were described in recent literatures.[2] Among those are cyclooligomeric receptors derived from trimesic acid (**A**) and chiral 1,2-diamines (**B**).[3] From standpoint of the creation of synthetic receptors that have properties similar to those of such remarkable biological receptors as antibodies and enzymes, this class of receptors are attractive because of the following reasons. First, there are many ways in which **A** and **B** are combined. Thus many receptors having well-defined binding sites, with different sizes and arrays of functional groups, can be readily prepared by various combinations of **A** and **B** using macrolactamization reaction. Second, cyclooligomeric receptors derived from **A** and **B** have found to be capable of interacting with polypeptides sequence-selectively. Furthermore, peptide-binding selectivities of these receptors are sensitive to the way which **A** and **B** are combined. Therefore, careful design of cyclooligomers from **A** and **B** might lead to the development of synthetic receptors with the desired binding properties to a given substrate.

Here, as the continuing efforts to develop the selective peptide-binding synthetic receptors, a readily accessible cyclooligomeric receptor **1** is described. Receptor **1** has conformationally well-defined hydrophobic binding cavity composed of trisubstituted benzene rings and periphery of hydrogen bond donors/acceptors. Furthermore, CPK modeling studies on **1** ($A_6B_6B'_3$) and the known receptor **2** ($A_4B_4B'_2$)[4] receptor indicated that **1** have the extended



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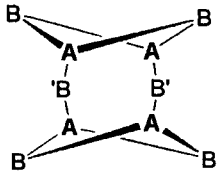

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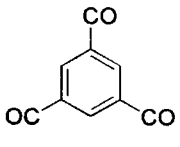
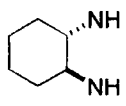
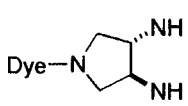


A



B



B'