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Design and synthesis of guanidine-containing novel retinoids

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ABSTRACT

Guanidine-containing new retinoids **1**–**4** were synthesized through the addition of guanidine to the activated carboxylic acids (retinoids) promoted by carbonyldiimidazole (CDI). A set of structurally and functionally diverse guanidine derivatives of retinoids were obtained in high yields (78–82%). We are in the process of studying the biological effect of these molecules on retinoic acid signaling pathways.

In the context of our ongoing chemical biology project, studying the role of retinoic acid signaling pathways during zebra fish embryogenesis, we synthesized novel retinoid libraries. Retinoids (retinol [vitamin A] and its biologically active metabolites) are essential signaling molecules that control various developmental pathways and influence the proliferation and differentiation of a variety of cell types in the adult.[1,2] A number of synthetic retinoids have been synthesized that interact selectively with their receptors.[3] Understanding the importance of the retinoids we were interested in synthesizing a small library of new retinoids. We first tried to synthesize compounds **5** and **6** as new retinoic acid analogues by introducing constrained phenyl ring system in the place of conjugated alkene backbone (spacers in ATRA) to avoid the ATRA (all-trans retinoic acid) metabolism into its isomers, 9-*cis*-RA and 13-*cis*-RA (Fig. 1). Then we hypothesized that, acid group could be further derivatized to different bioactive retinoids to increase efficacy and potency and this may open new avenue of retinoic acid signaling pathways during zebra fish embryogenesis. For this purpose we synthesized novel guanidine-containing retinoids.

We transformed the carboxylic acid group to the corresponding acyl guanidine derivative because, guanidines are strongly basic and are fully protonated under physiological conditions which is crucial for specific ligand-receptor interactions and possess a wide range of interesting and important biochemical and pharmaceutical properties.[4–7] Guanidino-containing drugs such as MIBG and MGBG were shown several decades ago to have antitumor properties and have been subjected to intense preclinical and clinical evaluation.[8] So we undertook the projects to synthesize novel guanidine-containing retinoids for studying the retinoic acid signaling pathways. To our surprise, a search of the literature failed to

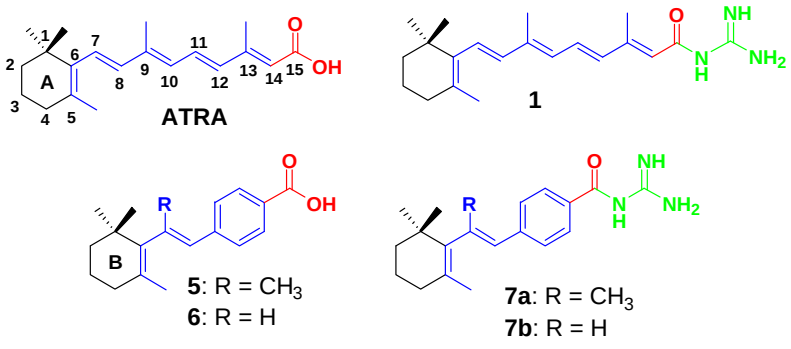

Figure 1.

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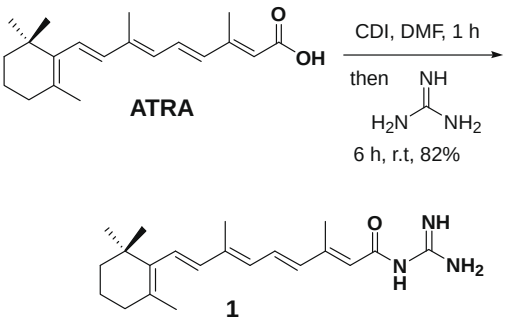
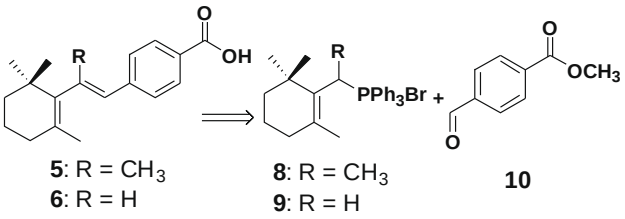


Scheme 1.



Scheme 2. Retrosynthetic analysis.

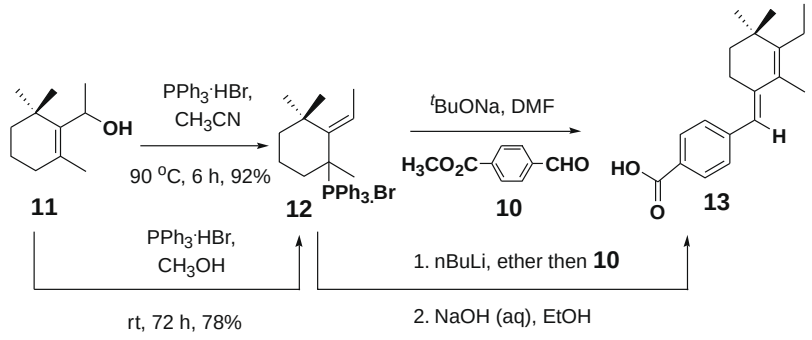
uncover any examples of guanidine-containing retinoic acid derivatives (Fig. 1). Herein we first report the synthesis of guanidine-containing retinoids by simple addition of guanidine to the activated carboxylic acids (retinoids) promoted by CDI.

The guanidino retinoid **1** was synthesized from the all-trans retinoic acid (ATRA) using CDI as a carboxylic acid activating agent in DMF. The activated ATRA was treated with guanidine in DMF at room temperature and generated the guanidino retinoid **1** with an 82% yield (Scheme 1). A signal at 160.4 ppm in ^{13}C NMR spectrum confirms the presence of guanidine group.

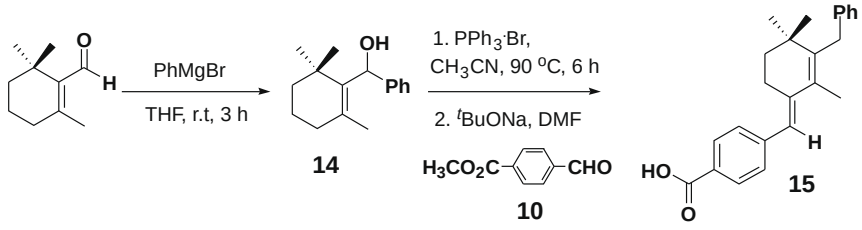
Retrosynthetic analysis suggests that our constrained retinoids **5** and **6** could be synthesized by the Wittig reaction of the ylides **8** and **9** with the aldehyde **10** (Scheme 2), and by subsequent hydrolysis.

In the process of synthesizing **5**, starting from the allylic alcohol **11**, we encountered the unusual Wittig salt **12** which led to the formation of the unusual compound **13** when the ylide **12** was treated with aldehyde **10** (Scheme 3).[9]

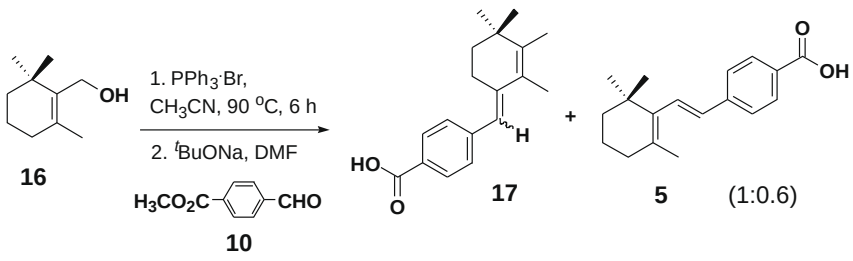
To explore the mechanism of the unusual Wittig salt **12** formation, we first tried to understand the substitution effect at α-position of the allylic alcohol **11**. For this purpose we synthesized the allylic alcohol **14** from Grignard reaction of β-cyclocitral with phenyl magnesium bromide in THF. The allylic alcohol **14** was converted into the corresponding ylide using PPh_3Br followed by the



Scheme 3.



Scheme 4.

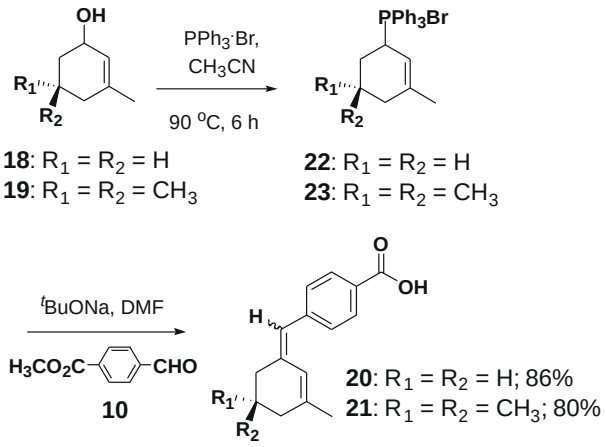


Scheme 5.

Wittig reaction with aldehyde **10** furnishing the unusual product **15** with 83% yield (Scheme 4).

In case of the alpha position of the allylic alcohol was substituted with hydrogen **16** (1° alcohol) gave both unusual **17** and usual **5** Wittig products with 1:0.6 ratio (Scheme 5). From these experiments we found that when alpha position was substituted with methyl, phenyl gave exclusively the unusual Wittig salt, whereas the alpha position substituted with hydrogen gives both usual and unusual products.

Further we explored to figure out whether this unusual Wittig salt formation occurs when alcohol group is outside or it is common in case alcohol group is inside the ring system. For this we have chosen the allylic alcohols **18** and **19** which were treated with triphenylphosphonium bromide in acetonitrile at 90 °C. Without further purification the ylides were subjected to the Wittig reaction with aldehyde **10**. To our surprise reactions utilizing allylic alcohols inside the ring system **18** and **19** generated the more normal Wittig products **20** and **21** with 86% and 80% yields, respectively, via the usual Wittig ylides **22** and **23** (Scheme 6). This clearly proves that the unusual reaction occurs when the allylic alcohol is outside the ring system.



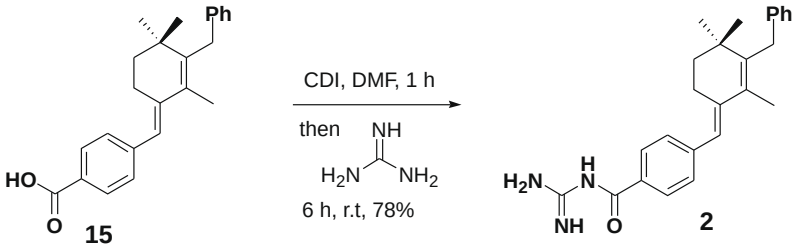
Scheme 6.

These new derivatives **20** and **21**, which also have the hydrophobic cyclohexene ring and constrained phenyl ring system in the place of conjugated alkene backbone in ATRA, and the carboxylic acid group remain intact. Comparing the structural relation of our original target-constrained retinoids **5** and **6** with the new unusual products **13** and **15**, these new compounds having the extension of the double bond conjugation via the 4th position of the cyclohexene ring unit may block to avoid the retinoic acid metabolism caused by Cytochrome P450 enzymes (CYPs) which will be the extra complement in this new finding as novel retinoids. It is believed that the physiologically most prominent pathway starts with the rate-limiting hydroxylation at C-4 position of the cyclohexenyl ring leading to the formation of 4-hydroxy-ATRA, then by a reductase enzyme into 4-oxo-ATRA that is then further transformed by CYP(s) into more polar metabolites.[10] So, this finding clearly demonstrates the utility of this methodology in synthesizing retinoic acid analogues where newly synthesized retinoids are more resistant to be metabolized by enzymes.

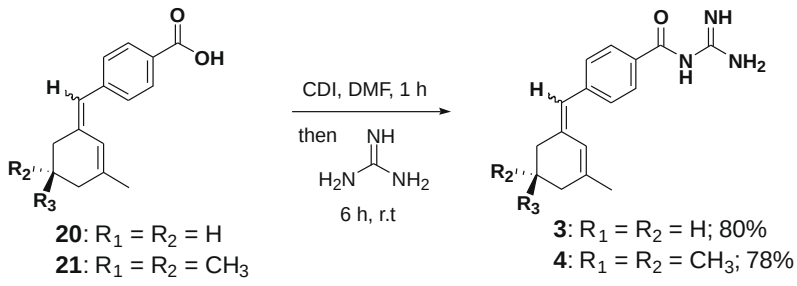
Encouraged by these remarkable results and having established a new strategy for synthesizing the new retinoid derivatives and for increasing the biological activity of this compound, we have designed and synthesized the guanidino retinoid **2**. The guanidino retinoid **2** was synthesized from the acid **15** using CDI as a carboxylic acid activating agent in DMF. The activated carboxylic acid was treated with guanidine in DMF at room temperature and generated the guanidino retinoid **2** with 78% yield (Scheme 7). A signal at 163.6 ppm in ^{13}C NMR spectrum confirms the presence of guanidine group.

Spurred by this result, we next tried to expand this guanidation to the retinoic acid analogues **20** and **21**.[11] As expected, we obtained the guanidino retinoids **3** (80%) and **4** (78%) with good yields (Scheme 8).

In all cases, the product was isolated as an air stable solid without column chromatography. After completion of the reaction, the reaction mixture was poured into water and the final products **1–4** were filtered and washed with water and were readily adaptable to synthesis for the construction of combinatorial libraries also to scale-up.[12] Biological evaluation of these novel retinoids is currently underway in our laboratory. It is worth mentioning that,



Scheme 7.



Scheme 8.

this is the first report where guanidine-containing novel retinoids are synthesized and could potentially be useful to study the retinoic acid biology and may be used as therapeutic candidates for diseases induced by RA signaling.

In conclusion, we have synthesized novel retinoids (**13**, **15**, **20**, and **21**) and found that when alcohols are outside the ring they produce unusual Wittig salts, whereas when alcohols are inside the ring they produce usual Wittig salts. These acids are further transformed to synthesize guanidine derivatives of new retinoids through 1,1′-carbonyldiimidazole (CDI), which is based on the addition of guanidine to the activated carboxylic acids promoted by CDI. Structurally and functionally diverse guanidine-containing new retinoids were obtained in high yields with high purity. Biological evaluation of these novel retinoids is currently underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data (copies of ^{1}H, ^{13}C NMR and Mass spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.008.

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11. *General procedure for preparation of retinoids* **20** and **21**: A flask equipped with a magnetic stirring bar, a septum inlet was charged with ylide **22/23** (1 mmol), dry DMF (5 mL), and ^{t}BuONa (3 mmol) under nitrogen. The mixture was stirred at room temperature for 5–10 min. To this solution was added aldehyde **10** (1 mmol) and the resulting mixture was then stirred at room temperature for 12 h. the reaction mixture was treated with water (20 mL) and neutralized with 1 M HCl and the product was extracted with ethyl acetate (3×10 mL) washed with brine, and dried over Na_2SO_4. The product was isolated by chromatography over silica gel.
Data for compounds **20** and **21**: *Compound* **20**: Mixture of two isomers (*E*:*Z* = 1:0.38) 4-(3-methyl-cyclohex-2-enylidenemethyl)-benzoic acid mp = 176–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70–1.80 (m), 1.80–1.91 (m), 2.10–2.22 (m), 2.38–2.48 (m), 2.58–2.70 (m), 6.04 (s), 6.15 (s), 6.23 (s), 6.45 (s), 7.36–7.39 (m), 7.46–7.61 (m), 7.65–7.78 (m), 8.04–8.07 (m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 24.6, 26.8, 30.9, 31.7, 32.8, 121.1, 121.8, 124.3, 125.8, 127.8, 129.0, 129.2, 129.4, 130.4, 132.5, 132.6, 141.1, 141.8, 143.7, 144.2, 171.8. HR-MS: ($C_{15}H_{16}O_2$) calcd ($[M-H]^+$) 227.1078; found 227.1086.
Compound **21**: Mixture of two isomers (*E*:*Z* = 1:0.17) 4-(3,5,5-trimethyl-cyclohex-2-enylidenemethyl)-benzoic acid mp = 150–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$ and few drops of CD_3OD): δ 0.89 (s, 6H), 0.94 (s, 1H), 1.78 (s, 4H), 1.91 (3, 3H), 2.10 (s, 0.4H), 2.33 (s, 2H), 5.97 (s, 1H), 6.13 (s, .17H), 6.26 (s, 1H), 6.38 (s, 0.17H), 7.28–7.31 (m, 3.21 H), 7.94–7.97 (m, 2.50H); ^{13}C NMR (75 MHz, $CDCl_3$ and few drops of CD_3OD): δ 24.5, 28.7, 31.3, 40.2, 45.2, 124.9, 126.4, 129.1, 130.0, 139.1, 140.5, 143.8, 169.7. HR-MS: ($C_{17}H_{20}O_2$) calcd ($[M-H]^+$) 255.1391; found 255.1399].
12. *General procedure for preparation of guanidino retinoids* **1**–**4**: A solution of guanidine hydrochloride (2 mmol) in DMF:dioxane (1:1; 5 mL) was added sodium *tert*-butoxide (2 mmol) and the reaction mixture was heated under nitrogen at 50–55 °C for 30 min. The mixture was cooled to room temperature, the solid sodium chloride was filtered and the filtrate was added to the 1-h stirred solution of retinoid and CDI in DMF at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, water (10 mL) was added, the solid product was collected by filtration and the solid was washed with cold water to remove excess guanidine.
Data for compounds **1**–**4**: Compound **1**: *N*-[3,7-dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoyl]-guanidine. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 6H), 1.40–1.50 (m, 2H), 1.52–1.60 (m, 2H), 1.69 (s, 3H), 1.95–2.08 (m, 5H), 2.28 (s, 3H), 2.50–2.51 (m, 3H), 5.73–5.85 (m, 1H), 6.17–6.28 (m, 3H), 6.30–6.40 (m, 1H), 6.83–6.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.1, 13.8, 13.9, 19.2, 22.0, 29.3, 33.1, 34.3, 127.8, 127.9, 129.8, 130.2, 130.4, 130.5, 130.6, 136.5, 136.9, 137.5, 137.7, 138.6, 138.7, 149.4, 160.4, 170.0; HR-MS: ($C_{21}H_{32}N_3O$) calcd ($[M+H]^+$) 342.2545; found 342.2556.
Compound **2**: *N*-[4-(3-benzyl-2,4,4-trimethyl-cyclohex-2-enylidenemethyl)-benzoyl]-guanidine. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (s, 6H), 1.51–1.55 (m, 2H), 1.79 (s, 3H), 2.50–2.51 (m, 2H), 2.66–2.68 (m, 2H), 2.73 (s, 1H), 3.66 (s, 2H), 6.56 (m, 1H), 7.14–7.17 (m, 3H), 7.26–7.36 (m, 3H), 7.43–7.46 (d, J = 9 Hz, 1H), 7.90–7.92 (d, J = 6 Hz, 1H), 8.03–8.05 (d, J = 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.8, 24.8, 28.3, 35.7, 36.4, 122.8, 126.3, 128.6, 129.1, 129.4, 129.9, 137.3, 140.5, 141.5, 143.9, 144.7, 163.6, 176.3. HR-MS: ($C_{25}H_{29}N_3O$) calcd ($[M+H]^+$) 388.2391; found 388.2390.
Compound **3**: *N*-[4-(3-methyl-cyclohex-2-enylidenemethyl)-benzoyl]-guanidine. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57–1.1.70 (m, 2H), 1.80 (s, 3H), 2.03–2.13 (m, 2H), 2.48–2.60 (m, 6H), 6.01 (s, 1H), 6.20 (s, 1H), 7.23–7.27 (d, J = 12 Hz, 2H), 7.98–7.02 (d, J = 12 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 24.7, 26.8, 30.7, 124.5, 127.9, 128.8, 129.3, 137.4, 139.3, 140.2, 140.7, 142.7, 163.8, 176.4; HR-MS: ($C_{16}H_{20}N_3O$) calcd ($[M+H]^+$) 270.1606; found 270.1614.
Compound **4**: *N*-[4-(3,5,5-trimethyl-cyclohex-2-enylidenemethyl)-benzoyl]-guanidine. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (s, 6H), 1.78 (s, 3H), 1.91 (s, 2H), 2.33 (s, 2H), 2.48–2.53 (m, 4H), 2.74 (s, 1H), 2.90 (s, 1H), 3.52 (s, 1H), 6.01 (s, 1H), 6.32 (s, 1H), 7.24–7.28 (d, J = 12 Hz, 2H), 8.01–8.05 (d, J = 12 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.0, 29.1, 31.2, 45.1, 126.0, 127.3, 128.8, 129.5, 137.6, 137.9, 138.0, 140.6, 163.2, 176.5; HR-MS: ($C_{18}H_{24}N_3O$) calcd ($[M+H]^+$) 298.1921; found 298.1928.