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Exploring hydroamination-cycloaddition-fragmentation sequences to access polycyclicguanidines and vinyl-2-aminoimidazoles

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ABSTRACT

The intramolecular hydroamination of a guanidine on an eneyne unit affords a guanidine-substituted diene capable of reacting with dienophiles. These substrates undergo [4+2]-cycloaddition reactions to generate a series of complex cyclic- and spirocyclic-guanidines. Select substrates can further undergo a ring opening-elimination cascade that ultimately reveals a vinyl-2-aminoimidazole. As such this cascade reaction may find application in the synthesis of oroidin-type natural products and their analogues.

1. Introduction

Marine sponges have been a prolific source of pyrrole-2-aminoimidazole alkaloids (PAIs).[1,2] Members of this family have been prized for their biological activities, especially as anti-tumors agents, anti-microbial or anti-biofilm agents.[3] Besides their potential utility as therapeutics leads, the community has been fascinated with the genesis of the more structurally complex members of this family from the simple building blocks e.g. oroidin and hymenedin (Fig. 1). Initial hypotheses suggested that these dimeric products were forged by electrocyclic reactions ([2+2] or [4+2] cycloadditions) of the vinyl-2-aminoimidazole fragment or from stepwise addition/isomerization sequences of the rapidly interconverting iminium ion tautomers of the 2-aminoimidazole core.[4]

However, Molinksi and Romo have recently shown that these cyclized and/or dimerized homologues arise from an enzymatic process. More specifically through the generation of a radical cation, via SET to an oxido-reductase.

We have previously demonstrated that propargylguanidines can be regiodivergently cyclized to the 5-*exo* product with Ag(I) or to the 6-*endo* product with Rh(II) catalysis (Scheme 1A).[5] We became interested in extending the utility of this propargylguanidine hydroamination sequence to rapidly construct complex polycyclic guanidine scaffolds via the intermediacy of a guanidine-substituted diene, akin to the oroidin biosynthetic manifold. We envisioned that extension of the alkyne to an enyne would generate substrates at the same oxidation state as the vinyl-2-aminoimidazoles, albeit transposed (Scheme 1B). While the reactivity of many heteroatom substituted dienes have been studied, this represents an unknown class of guanidine-substituted dienes.

Herein we explore the reactivity of these dienes to generate polycyclic guanidinium ion containing compounds and compounds that are structurally aligned with the PAIs. These complex structures arise from simple linear precursors via a cascade hydroamination-[4+2]-cycloaddition sequence.

2. Results and discussion

2.1. 6-Endo-selective hydroamination/[4+2] cycloaddition

We began by examining the hydraomination-[4+2]-cycloaddition cascade reaction with guanidine **1a** (Scheme 2). Exposure of **1a** to Rh(II) cleanly gave the *6-endo* product **2a** in 70% yield. This guanidine-substituted diene cleanly reacted with 4-phenyl-1,2,4-triazole-3,5-dione at room temperature to give **3a** in 94% yield. Exploratory reactions showed that the diene **2a** does not spontaneously react with electron poor dieneophiles (e.g. acrylates,

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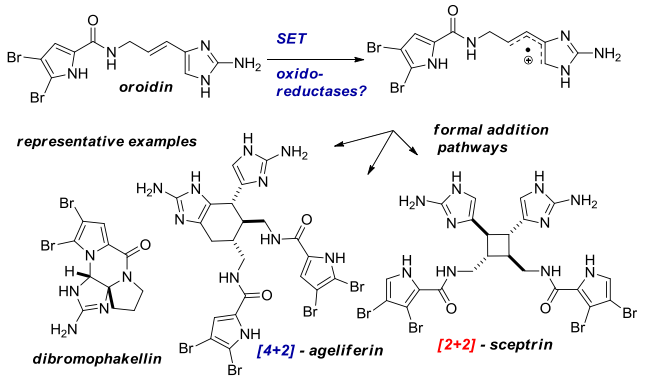
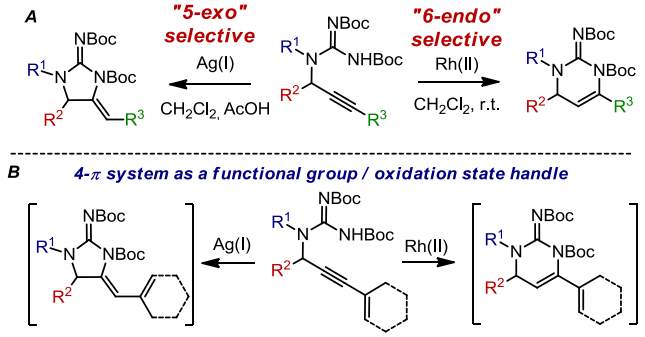


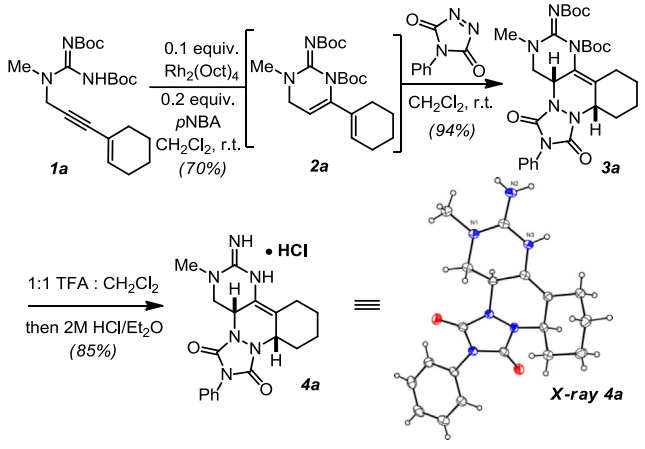
Fig. 1. Biogenesis of complex pyrrole-2-aminoimidazole alkaloids from simple precursors.



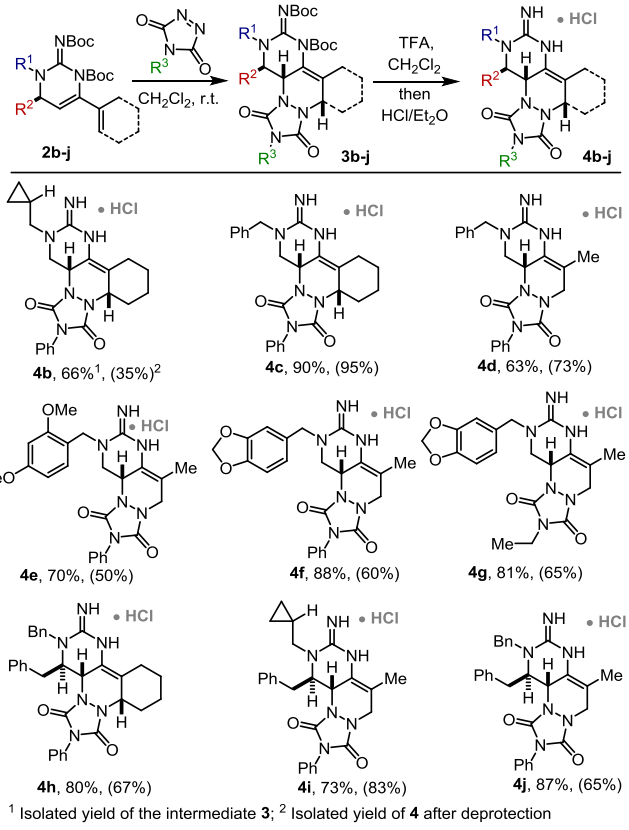
Scheme 1. Applications of ene-ynes in the guanidine hydroamination sequence.

quinones or fumarates) suggesting that the di-acylated guanidine renders the diene relatively electron poor. The hydroamination-cycloaddition cascade can be carried out in a one-pot sequence to afford **3a** in 74% isolated yield. Deprotection of the guanidine with trifluoroacetic acid followed by salt exchange gave **4a** as a crystalline hydrochloride, the structure of which was confirmed by X-ray crystallography.

This reaction development permitted the synthesis of a focused library of these polycyclic guanidines (Scheme 3). Substitutions on the guanidine nitrogen (N1) are universally tolerated. As demonstrated, both cyclic and acyclic ene-ynes participate to give tetra- or



Scheme 2. 6-*endo*-selective hydroamination/[4+2]-cycloaddition sequence to access polyclicguanidines.

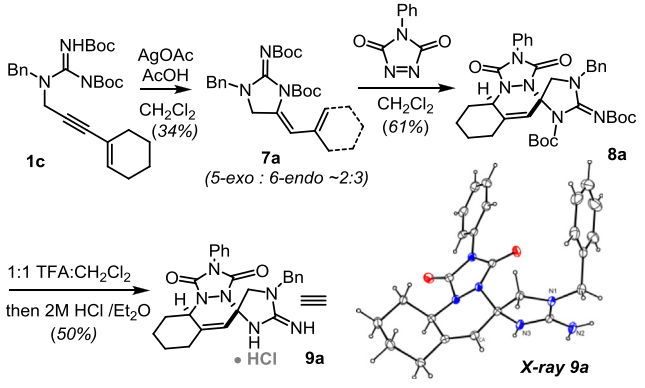


Scheme 3. Scope of the 6-*endo*-selective hydroamination/[4+2]-cycloaddition sequence.

tri-cyclic guanidines respectively (e.g. **4b**-**4g**). Other triazolinediones can be employed (**4g**). Substituents on the dihydroaminopyrimidine effectively control the approach of the dienophile to give the adducts **4h-i** as single diastereomers.

2.2. 5-Exo-selective hydroamination/[4+2] cycloaddition

We then investigated the [4+2]-cycloaddition reaction on the 5-*exo*-dig derived dienes (Scheme 4). Interestingly hydroamination of **1c** under Ag(I) conditions gave **7a** in poor yield as the minor regiosiomer All other substrates in this series cyclize with >10:1 selectivity favoring the expected 5-*exo*-dig product. Reaction of **7a** with 4-phenyl-1,2,4-triazole-3,5-dione proceeded cleanly to give



Scheme 4. 5-*exo*-selective hydroamination/[4+2]-cycloaddition sequence.

the protected spirocyclic guanidine **8a**. Deprotection of **8a** with TFA for 30 min followed by salt exchange gave **9a** in good yield, the structure of which was ultimately confirmed by X-ray crystallography. On working with this compound we ultimately observed that it decomposed when stored in solution, to give a compound that appeared to be an isomer of **9a** as suggested by an identical mass (ultimately proven to be compound **10a** in Scheme 6).

Insight into this decomposition was gained when studying the same reaction on substrate **1h** (Scheme 5). Cyclization of **1h** in the presence of Ag(I) gave **7b** in good yield as a single regioisomer. Substitution at the alpha-position of the propargylguanidine favors the kinetically preferred 5-*exo*-dig product. Cycloaddition of the resultant diene gives **8b** as a single diastereomer. Deprotection of **8b** with TFA does not lead to the deprotected spirocycle but instead the allylic aminal fragments to reveal the vinyl-2-aminoimidazole **10b**.

The structure of **10b** was confirmed by X-ray crystallography and the spectral data were consistent with those of the isomer obtained from the decomposition of **9a**. Presumably the more substituted 2-aminoimidazole ring in **8b** fragments faster via stabilization of the intermediate N-acyliminium ion.

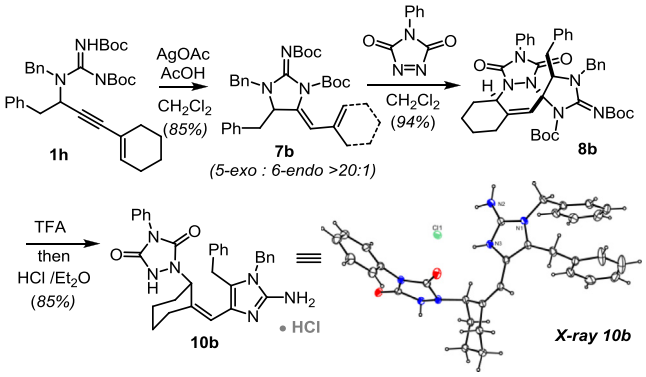
It was subsequently found that deprotection of the cycloadducts with 1:1 TFA:CH_2Cl_2 for >2 h universally provides the ring-opened vinyl-2-aminoimidazoles **10a-i** in good yield (Scheme 6).[6]

Having noted that the di-Boc-guanidine substituted dienes react with very reactive dienophiles, we also examined their participation in the acylnitroso Diels-Alder reaction (Scheme 7). Using Read de Alaniz's conditions, we were able to generate the acylnitroso intermediate *in-situ* by oxidation of the *N*-hydroxycarbamate **11**.[7] This smoothly underwent cycloaddition with the dienes **2a,f,g** to give the adducts **12a-c** in moderate to good yield. These cycloadditions afford a single regio-isomer, confirmed in **12a** by HMBC correlation of the C12 methine proton to the carbonyl of the benzylcarbamate. This is consistent with the more electron rich end of the diene reacting with the nitrogen of the acylnitroso system as previously demonstrated.[7b] These intermediates can be deprotected without reduction of the internal alkene to give **13a-c**.

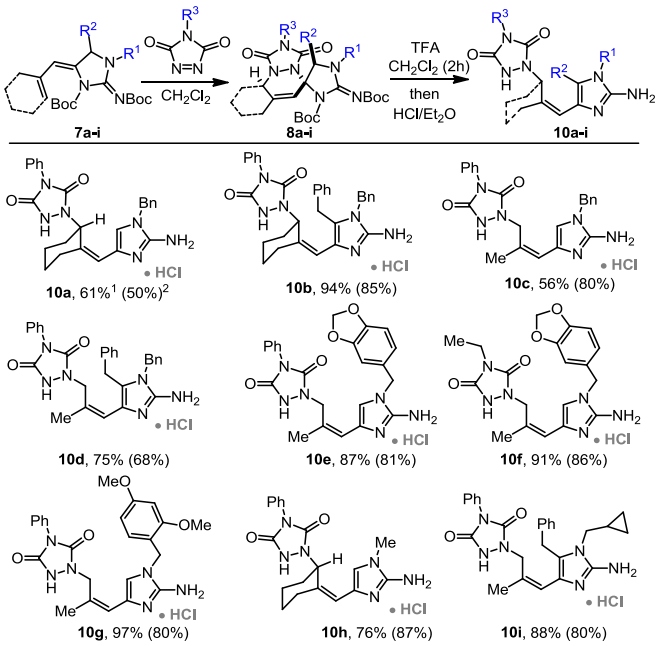
We also examined a hydroamination-Michael addition-[4+2]-cycloaddition sequence (Scheme 8). Reaction of the guanidine **14** with Ag(I) delivers the bicyclic guanidine substituted diene **15** in good yield. Reaction with 4-phenyl-1,2,4-triazole-3,5-dione gave the spirocycle **16**. This example further serves to illustrate that guanidine substituted dienes that are only mono-acylated are competent dienes as well.

3. Conclusion

In conclusion, we have demonstrated that ene-yne containing di-

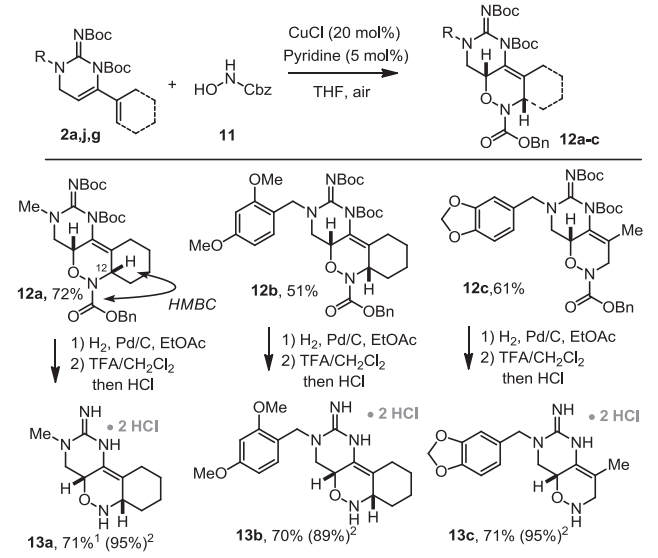


Scheme 5. 5-*exo*-selective hydroamination/[4+2]-cycloaddition-fragmentation sequence.



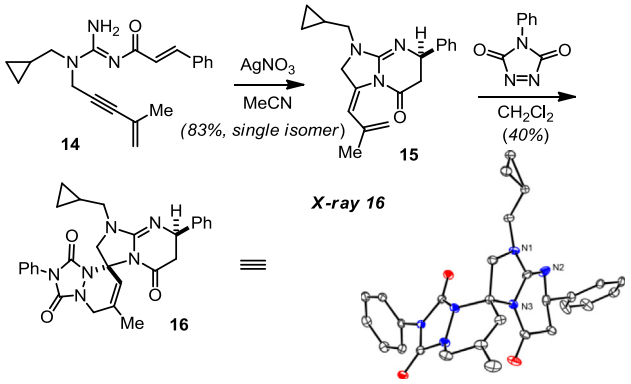
Scheme 6. Scope of the [4+2]-Cycloaddition-fragmentation sequence to access vinyl-2-aminoimidazoles.

Boc-guanidines generally undergo selective Rh(II)-mediated 6-*endo*-dig or Ag(I)-mediated 5-*exo*-dig hydroamination. The hydroamination products behave as electron poor dienes but can participate in [4+2]-cycloadditions with activated dienophiles. Cycloaddition of the 5-*exo*-dig products with a triazolinediones generates a spirocyclic allylic aminal which is prone to elimination to reveal a vinyl-2-aminoimidazole. As such, this sequence may find use in the preparation of PAI natural products or analogues. Given the successful reaction of mono-acylsubstituted dienes, we are currently examining the ability of these more electron-rich systems to engage a wider variety of dieneophiles to access other complex and interesting structures.



[1] Yield after hydrogenolysis of Cbz group. [2] Yield after deprotection / salt exchange.

Scheme 7. [4+2]-Cycloaddition sequence with an acylnitroso-dienophile.



Scheme 8. Hydroamination-Michael addition -[4+2]-cycloaddition sequence.

4. Experimental section

4.1. General experimental considerations

Unless otherwise noted all starting materials were either known compounds or were obtained from commercial sources and used without purification. All reactions requiring anhydrous conditions were performed under a positive pressure of nitrogen using flame-dried glassware. Rhodium (II) octanoate, Silver nitrate, and Silver acetate were purchased from Sigma-Aldrich. Dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN), toluene ($C_6H_5CH_3$), tetrahydrofuran (THF) and diethyl ether (Et_2O) were degassed with argon and passed through a solvent purification system (J.C. Meyer of Glass Contour) containing either alumina or molecular sieves. Flash chromatography was performed by CombiFlash R_f (TELEDYNE ISCO) or on Merk silica gel Kieselgel 60 (230–400 mesh) from EM science with the indicated solvent.

^{1}H NMR spectra were recorded on Varian Unity-300, Inova-400, or VXR-500 MHz spectrometers as indicated. The chemical shifts (δ) of proton resonances are reported relative to $CDCl_3$, DMSO-d_5, or CD_3OD using the following format: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent), coupling constant(s) (J in Hz), integral].[1,2] ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz. The chemical shifts of carbon resonances are reported relative to the deuterated solvent peak.

Infrared spectra were recorded on a Nicolet 380-FT IR spectrometer fitted with a SmartOrbit sample system. All absorptions are reported in cm-1 relative to polystyrene (1601 cm-1).

Mass spectra were obtained at the University of Utah CIF on a Micromass Quattro II (ESI/APCI) for LRMS or an LCT XE premier (ESI/APCI-TOF) for HRMS.

4.2. Synthetic procedures and characterization data

4.2.1. General procedure 1 for the guanylation of propargyl amines ***S-2a-i*** *to form* ***1a-i***

To a stirring solution of *S*-methyl-*N*,*N*′-diBocpseudothiourea (1.1 equiv), HgO (1.1 equiv), and triethylamine (3.0 equiv) in CH_2Cl_2 was added the appropriate propargyl amine (1.0 equiv). The reaction was stirred at room temperature until complete as judged by TLC. The reaction mixture was filtered through a short plug of Celite, concentrated, and purified by column chromatography to yield the propargylguanidine.

*4.2.1.1. 1-(3-(cyclohex-1-en-1-yl)prop-2-yn-1-yl)-1-methyl-di-Boc-guanidine (**1a**).* The general procedure 1 was used to yield the propargylguanidine as a pale yellow solid (0.549 g, 71% yield). R_f = 0.45 (20% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (s. 1H), 6.09 (s, 1H), 4.39 (s, 2H), 3.09 (s, 3H), 2.09 (m, 4H), 1.61 (m, 2H), 1.57 (m, 2H), 1.49 (s, 18H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.3, 153.6, 150.2, 137.4, 120.5, 87.5, 82.7, 79.3, 77.6, 36.4, 32.2, 28.9, 28.4, 28.3, 26.5, 22.5, 21.8 ppm; LRMS (ESI) Calculated for $C_{21}H_{34}N_3O_4$ *m/z* (M+H): 392.3, Obsd 392.4.

*4.2.1.2. 1-(3-(cyclohex-1-en-1-yl)prop-2-yn-1-yl)-1-(cyclopropylmethyl)-di-Boc-guanidine (**1b**).* Prepared according to the general procedure 1, to give the propargylguanidine as white solid in 67% yield (0.573 g). R_f = 0.68 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 6.06 (s, 1H), 4.51 (s, 2H), 3.46 (s, 2H), 2.00 (m, 4H), 1.61 (m, 2H), 1.57 (m, 2H), 1.49 (s, 18H), 1.07 (m, 1H), 0.56 (m, 2H), 0.31 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.3, 154.6, 150.5, 135.1, 120.1, 86.8, 81.7, 80.6, 79.2, 52.1, 38.2, 29.0, 28.1, 28.0, 25.5, 22.1, 21.4, 8.9, 3.7 ppm; LRMS (ESI) Calculated for $C_{24}H_{38}N_3O_4$ *m/z* (M+H): 432.3, Obsd. 432.4.

*4.2.1.3. 1-Benzyl-1-(3-(cyclohex-1-en-1-yl)prop-2-yn-1-yl)-di-Boc-guanidine (**1c**).* Prepared according to the general procedure 1, to give the propargylguanidine as white solid in 71% yield (0.657 g). R_f = 0.55 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.33–7.26 (m, 5H), 6.07 (s, 1H), 4.83 (s, 2H), 4.21 (s, 2H), 2.08 (m, 4H), 1.62 (m, 2H), 1.57 (m, 2H), 1.50 (s, 18H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.4, 153.8, 150.7, 136.1, 135.6, 128.7, 128.5, 127.8, 120.3, 87.5, 82.3, 80.3, 79.8, 51.4, 38.7, 29.2, 28.3, 25.7, 22.4, 21.6 ppm; LRMS (ESI) Calculated for $C_{27}H_{38}N_3O_4$ *m/z* (M+H): 468.3, Obsd. 468.4.

*4.2.1.4. 1-(3-(cyclohex-1-en-1-yl)prop-2-yn-1-yl)-1-(2,4-dimethoxybenzyl)-di-Boc-guanidine (**1d**).* Prepared according to the general procedure 1, to give the propargylguanidine as white solid in 83% yield (0.703 g). R_f = 0.71 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.33–7.27 (m, 5H), 5.27 (s, 1H), 5.22 (s, 1H), 4.83 (s, 2H), 4.24 (s, 2H), 1.86 (s, 3H), 1.51 (s, 9H), 1.49 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.4, 155.3, 150.6, 135.8, 128.6, 128.2, 127.7, 126.2, 122.4, 86.6, 82.4, 82.1, 79.6, 51.3, 38.4, 28.4, 28.3, 23.3 ppm; LRMS (ESI) Calculated for $C_{24}H_{34}N_3O_4$ *m/z* (M+H): 428.3, Obsd. 428.3.

*4.2.1.5. 1-(3-(cyclohex-1-en-1-yl)prop-2-yn-1-yl)-1-(2,4-dimethoxybenzyl)-di-Boc-guanidine (**1e**).* Prepared according to the general procedure 1, to give the propargylguanidine as white solid in 68% yield (0.700 g). R_f = 0.56 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.22 (m, 1H), 6.46 (m, 2H), 6.07 (s, 1H), 4.59 (br, 2H), 4.25 (s, 2H), 3.83 (s, 3H), 3.78 (s, 3H), 2.08 (m, 4H), 1.62 (m, 2H), 1.57 (m, 2H), 1.51 (s, 9H), 1.50 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.3, 160.8, 158.1, 152.5, 150.2, 134.6, 131.4, 120.0, 115.4, 103.9, 98.2, 86.3, 81.1, 80.6, 78.4, 77.5, 59.8, 55.0, 54.9, 46.2, 28.8, 27.9, 27.8, 25.2, 21.9, 21.2 ppm; LRMS (ESI) Calculated for $C_{29}H_{42}N_3O_6$ *m/z* (M+H): 528.3, Obsd. 528.3.

*4.2.1.6. 1-(benzo[d][1,3]dioxol-5-ylmethyl)-1-(4-methylpent-4-en-2-yn-1-yl)-di-Boc-guanidine (**1f**).* Prepared according to the general procedure 1, to give the propargylguanidine as white solid in 81% yield (0.756 g). R_f = 0.48 (20% ethyl acetate/n-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.0 (s, 1H), 6.83–6.74 (m, 3H), 5.93 (s, 2H), 5.28 (s, 1H), 5.23 (s, 1H), 4.72 (s, 2H), 4.23 (s, 2H), 1.87 (s, 9H), 1.50 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.3, 155.1, 150.5, 147.9, 147.2, 129.3, 126.1, 122.3, 121.8, 108.1, 101.0, 86.5, 82.2, 82.0, 79.5, 51.0, 38.1, 28.1, 28.0, 23.2 ppm; LRMS (ESI) Calculated for $C_{25}H_{34}N_3O_6$ *m/z* (M+H): 472.2, Obsd. 472.4.

*4.2.1.7. 1-(2,4-dimethoxybenzyl)-1-(4-methylpent-4-en-2-yn-1-yl)-di-Boc-guanidine (**1g**).* Prepared according to the general procedure 1, to give the propargylguanidine as white solid in 50% yield (0.483 g). R_f = 0.63 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.20 (m, 1H), 6.45 (m, 2H), 5.27 (s, 1H), 5.21 (s, 1H), 4.59 (s, 2H), 4.26 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 1.87 (s, 3H), 1.51 (s, 18H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4, 160.9, 158.2, 150.4, 131.5, 126.2, 121.8, 115.4, 104.1, 98.4, 85.8, 82.7, 81.3, 78.7, 55.1, 46.5, 36.4, 28.0, 27.9, 23.2 ppm; LRMS (ESI) Calculated for $C_{26}H_{38}N_3O_6$ *m/z* (M+H): 488.3, Obsd. 488.5.

*4.2.1.8. 1-(cyclopropylmethyl)-1-(5-methyl-1-phenylhex-5-en-3-yn-2-yl)-di-Boc-guanidine (**1h**).* Prepared according to the general procedure 1, to give the propargylguanidine as white solid in 22% yield (0.210 g). R_f = 0.50 (20% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.35–7.21 (m, 5H), 5.20 (s, 1H), 5.18 (s, 1H), 3.52 (m, 1H), 3.34 (dd, J = 14.7, 6.9 Hz, 1H), 3.27 (dd, J = 12.7, 4.9 Hz, 1H), 2.98 (dd, J = 12.7, 9.8 Hz, 1H), 1.80 (s, 3H), 1.51 (s, 9H), 1.49 (s, 9H), 1.24 (m, 1H), 0.59 (m, 2H), 0.35 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.9, 153.2, 150.8, 137.3, 129.9, 128.3, 126.9, 126.2, 122.1, 88.0, 85.7, 81.9, 79.3, 53.5, 51.5, 41.4, 28.3, 28.2, 23.3, 10.8, 5.7, 4.3 ppm; LRMS (ESI) Calculated for $C_{28}H_{40}N_3O_4$ *m/z* (M+H): 482.3, Obsd. 482.5.

*4.2.1.9. 1-Benzyl-1-(4-(cyclohex-1-en-1-yl)-1-phenylbut-3-yn-2-yl)-di-Boc-guanidine (**1i**).* Prepared according to the general procedure 1, to give the propargylguanidine as pale yellow solid in 78% yield (0.861 g). R_f = 0.51 (40% ethyl acetate/n-hexanes). ^{1}H NMR (500 MHz, CDCl3) δ 8.85 (s, 1H), 7.36–7.18 (m, 10H), 5.94 (s, 1H), 4.97 (br, 1H), 4.62 (d, J = 16.7 Hz, 1H), 3.15 (dd, J = 12.7, 4.4 Hz, 1H), 2.76 (dd, J = 12.2, 9.8 Hz, 1H), 2.02 (m, 2H), 1.95 (m, 2H), 1.53 (m, 4H), 1.48 (s, 9H), 1.47 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.5, 154.3, 150.3, 138.4, 137.2, 128.6, 127.3, 127.1, 126.5, 126.3, 125.8, 122.3, 88.7, 84.8, 82.6, 78.9, 49.8, 46.3, 28.5, 28.3, 27.4, 24.7, 22.8, 21.7 ppm; LRMS (ESI) Calculated for $C_{34}H_{44}N_3O_4$ *m/z* (M+H): 558.3, Obsd. 558.5.

*4.2.2. General procedure 2 for the 6-endo cyclization of the propargyl guanidines **1a-g***

To a stirring solution of the appropriate propargylguanidine (1.0 mmol) in CH_2Cl_2 (0.07 M) was added rhodium(II) octanoate dimer (10 mol%) and 4-nitrobenzoic acid (0.2 equiv). The reaction was stirred at room temperature until the reaction was complete by TLC. After completion, the reaction mixture was concentrated by rotary evaporation, and purified by column chromatography to yield 6-*endo-dig* cyclized guanidine.

*4.2.2.1. tert-butyl (E)-2-((tert-butoxycarbonyl)imino)-6-(cyclohex-1-en-1-yl)-3-methyl-3,4-dihydropyrimidine-1(2H)-carboxylate (**2a**).* The general procedure 2 was used to yield 6-*endo-dig* cyclized guanidine as a white solid (6-*endo-dig*:5-*exo-dig* = >20:1), (0.274 g, total 70% yield). R_f = 0. 28 (60% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (s. 1H), 5.61 (t, J = 5.2 Hz, 1H), 3.70 (d, J = 4.3 Hz, 2H), 3.05 (s, 3H), 2.16 (m, 4H), 1.69 (m, 2H), 1.60 (m, 2H), 1.54 (s, 9H), 1.41 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 150.5, 149.6, 143.2, 132.4, 126.5, 110.0, 82.3, 78.7, 47.3, 37.7, 28.3, 28.1, 25.7, 25.6, 22.7, 22.3 ppm; LRMS (ESI) Calculated for $C_{21}H_{34}N_3O_4$ *m/z* (M+H): 392.3, Obsd. 392.3.

*4.2.2.2. tert-butyl (E)-2-((tert-butoxycarbonyl)imino)-6-(cyclohex-1-en-1-yl)-3-(cyclopropylmethyl)-3,4-dihydropyrimidine-1(2H)-carboxylate (**2b**).* Prepared according to the general procedure 2, to give 6-*endo-dig* cyclized guanidine as a white solid in 31% yield (6-*endo-dig*:5-*exo-dig* = >20:1), (0.134 g). R_f = 0.74 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (s, 1H), 5.64 (t, J = 5.1 Hz, 1H), 3.78 (d, J = 4.9 Hz, 1H), 3.33 (d, J = 6.8 Hz, 1H), 2.17 (m, 4H), 1.70 (m, 2H), 1.60 (m, 2H), 1.54 (s, 9H), 1.41 (s, 9H), 1.06 (m, 1H), 0.50 (m, 2H), 0.20 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.5, 150.4, 149.5, 143.2, 132.2, 126.3, 110.3, 82.0, 78.4, 53.4, 44.4, 28.2, 27.9, 25.6, 25.5, 22.6, 22.1, 9.0, 3.4 ppm; LRMS (ESI) Calculated for $C_{24}H_{38}N_3O_4$ *m/z* (M+H): 432.3, Obsd. 432.4.

*4.2.2.3. tert-butyl (E)-3-benzyl-2-((tert-butoxycarbonyl)imino)-6-(cyclohex-1-en-1-yl)-3,4-dihydropyrimidine-1(2H)-carboxylate (**2c**).* Prepared according to the general procedure 2, to give 6-*endo-dig* cyclized guanidine as a white solid in 76% yield (6-*endo-dig*:5-*exo-dig* = >20:1), (0.327 g). R_f = 0.25 (20% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.21 (m, 5H), 6.41 (s, 1H), 5.51 (t, J = 5.1 Hz, 1H), 4.70 (s, 2H), 3.55 (d, J = 4.1 Hz, 2H), 2.19 (m, 2H), 2.15 (m, 2H), 1.69 (m, 2H), 1.61 (m, 2H), 1.55 (s, 9H), 1.43 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.5, 151.0, 149.6, 143.3, 136.2, 132.2, 128.6, 127.9, 127.5, 126.5, 110.5, 82.3, 78.7, 52.1, 43.6, 28.2, 28.0, 25.6, 25.5, 22.6, 22.1 ppm; LRMS (ESI) Calculated for $C_{27}H_{38}N_3O_4$ *m/z* (M+H): 468.3, Obsd. 468.4.

*4.2.2.4. tert-butyl (E)-3-benzyl-2-((tert-butoxycarbonyl)imino)-6-(prop-1-en-2-yl)-3,4-dihydropyrimidine-1(2H)-carboxylate (**2d**).* Prepared according to the general procedure 2, to give 6-*endo-dig* cyclized guanidine as a white solid in 79% yield (6-*endo-dig*:5-*exo-dig* = >20:1), (0.338 g). R_f = 0.57 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.21 (m, 5H), 5.72 (s, 1H), 5.65 (t, J = 4.3 Hz, 1H), 5.07 (s, 1H), 4.71 (s, 2H), 3.58 (d, J = 3.4 Hz, 2H), 1.93 (s, 3H), 1.55 (s, 9H), 1.43 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 150.9, 149.4, 142.9, 138.3, 136.1, 128.6, 127.8, 127.5, 115.1, 112.9, 82.9, 78.7, 52.1, 43.6, 28.2, 27.8, 20.0 ppm; LRMS (ESI) Calculated for $C_{24}H_{34}N_3O_4$ *m/z* (M+H): 428.3, Obsd. 428.3.

*4.2.2.5. tert-butyl (E)-2-((tert-butoxycarbonyl)imino)-3-(2,4-dimethoxybenzyl)-6-(prop-1-en-2-yl)-3,4-dihydropyrimidine-1(2H)-carboxylate (**2e**).* Prepared according to the general procedure 2, to give 6-*endo-dig* cyclized guanidine as a pale yellow solid in 70% yield (6-*endo-dig*:5-*exo-dig* = >20:1), (0.341 g). R_f = 0.41 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (m, 1H), 6.41 (m, 2H), 5.71 (s, 1H), 5.71 (s, 1H), 5.62 (t, J = 5.5 Hz, 1H), 5.05 (s, 1H), 4.64 (s, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 3.60 (d, J = 5.0 Hz, 2H), 1.91 (s, 3H), 1.54 (s, 9H), 1.43 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.5, 160.4, 158.6, 150.9, 149.5, 142.9, 138.4, 130.6, 116.6, 114.9, 113.3, 104.3, 98.3, 82.6, 78.4, 55.3, 55.2, 46.7, 43.4, 28.3, 27.9, 20.0 ppm; LRMS (ESI) Calculated for $C_{26}H_{38}N_3O_6$ *m/z* (M+H): 488.3, Obsd. 488.3.

*4.2.2.6. tert-butyl (E)-3-(benzo[d][1,3]dioxol-5-ylmethyl)-2-((tert-butoxycarbonyl)imino)-6-(prop-1-en-2-yl)-3,4-dihydropyrimidine-1(2H)-carboxylate (**2f**).* Prepared according to the general procedure 2, to give 6-*endo-dig* cyclized guanidine as a pale yellow solid in 76% yield (6-*endo-dig*:5-*exo-dig* = 10:1), (0.358 g). R_f = 0.50 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74–6.70 (m, 3H), 5.92 (s, 2H), 5.71 (s, 1H), 5.67 (t, J = 5.0 Hz, 1H), 5.06 (s, 1H), 4.60 (s, 2H), 3.58 (d, J = 3.9 Hz, 2H), 1.93 (s, 3H), 1.55 (s, 9H), 1.43 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.3, 150.8, 149.3, 147.9, 147.1, 142.8, 138.3, 129.8, 121.4, 115.0, 112.9, 108.4, 108.2, 101.0, 82.8, 78.6, 51.8, 28.2, 27.8, 19.9 ppm; LRMS (ESI) Calculated for $C_{25}H_{34}N_3O_6$ *m/z* (M+H): 472.2, Obsd. 472.3.

*4.2.2.7. tert-butyl (E)-3,4-dibenzyl-2-((tert-butoxycarbonyl)imino)-6-(cyclohex-1-en-1-yl)-3,4-dihydropyrimidine-1(2H)-carboxylate (**2g**).* Prepared according to the general procedure 2, to give 6-*endo-dig* cyclized guanidine as a white solid in 96% yield (6-*endo-dig*:5-*exo-dig* = >20:1), (0.535 g). R_f = 0.56 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.07 (m, 10H), 6.44 (s,

1H), 5.32 (d, J = 6.9 Hz, 1H), 5.15 (d, J = 15.2 Hz, 1H), 4.12 (d, J = 15.2 Hz, 1H), 3.68 (m, 1H), 2.67 (m, 2H), 2.20 (m, 3H), 2.01 (m, 1H), 1.69 (m, 2H), 1.61 (m, 2H), 1.58 (s, 9H), 1.50 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.6, 150.8, 149.9, 142.1, 137.2, 136.3, 132.4, 129.4, 128.7, 128.5, 128.3, 127.7, 126.8, 126.7, 113.7, 82.3, 78.8, 56.3, 51.3, 39.5, 28.3, 28.1, 25.6, 25.5, 22.6, 22.2 ppm; LRMS (ESI) Calculated for $C_{34}H_{44}N_3O_4$ m/z (M+H): 558.3, Obsd 558.2.

*4.2.2.8. tert-butyl (E)-4-benzyl-2-((tert-butoxycarbonyl)imino)-3-(cyclopropylmethyl)-6-(prop-1-en-2-yl)-3,4-dihydropyrimidine-1(2H)-carboxylate (**2h**).* Prepared according to the general procedure 2, to give 6-*endo-dig* cyclized guanidine as a white solid in 54% yield (6-*endo-dig*:5-*exo-dig* = 3:2), (0.260 g). R_f = 0.26 (20% ethyl acetate/*n*-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.15 (m, 5H), 5.70 (s, 1H), 5.58 (d, J = 6.9 Hz, 1H), 5.07 (t, J = 1.5 Hz, 1H), 4.01 (m, 1H), 3.47 (dd, J = 14.3, 7.1 Hz, 1H), 3.19 (dd, J = 14.3, 6.5 Hz, 1H), 3.00 (dd, J = 12.6, 5.4 Hz, 1H), 2.71 (dd, J = 12.6, 10.5 Hz, 1H), 1.89 (s, 3H), 1.56 (s, 9H), 1.49 (s, 9H), 1.05 (m, 1H), 0.55 (m, 2H), 0.23 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.8, 150.5, 149.9, 141.8, 138.7, 137.4, 129.5, 128.7, 127.0, 116.8, 115.3, 82.9, 78.9, 57.5, 53.5, 40.1, 28.4, 28.2, 20.1, 9.6, 4.2, 3.8 ppm; LRMS (ESI) Calculated for $C_{28}H_{40}N_3O_4$ m/z (M+H): 482.3, Obsd. 482.4.

*4.2.2.9. tert-butyl (E)-3,4-dibenzyl-2-((tert-butoxycarbonyl)imino)-6-(prop-1-en-2-yl)-3,4-dihydropyrimidine-1(2H)-carboxylate (**2i**).* Prepared according to the general procedure 2, to give 6-*endo-dig* cyclized guanidine as a white solid in 70% yield (6-*endo-dig*:5-*exo-dig* = >20:1), (0.362 g). R_f = 0.60 (40% ethyl acetate/*n*-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.05 (m, 10H), 5.77 (s, 1H), 5.50 (d, J = 7.0 Hz, 1H), 5.18 (d, J = 15.1 Hz, 1H), 5.12 (s, 1H), 4.09 (d, J = 15.1 Hz, 1H), 3.74 (m, 1H), 2.71 (m, 2H), 1.91 (s, 3H), 1.60 (s, 9H), 1.53 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.6, 150.9, 149.8, 141.9, 138.6, 137.1, 136.3, 129.4, 128.6, 128.3, 127.8, 127.0, 116.7, 115.3, 83.0, 79.0, 56.4, 51.8, 39.5, 28.3, 28.1, 20.0 ppm; LRMS (ESI) Calculated for $C_{31}H_{40}N_3O_4$ m/z (M+H): 518.3, Obsd. 518.2.

*4.2.3. General procedure 3 for the cycloaddition of the guanidine dienes **2a-i***

To a stirring solution of the desired 6-*endo-dig* cyclic guanidine (diene, 1 equiv) in CH_2Cl_2 (0.07 M) was added the appropriate triazoledione (dienophile, 1.2 equiv). The reaction was stirred at room temperature until judged complete by TLC. After completion, the reaction mixture was concentrated by rotary evaporation, and purified by column chromatography to yield polycyclic guanidine.

*4.2.3.1. tert-butyl (4aR,9aS,E)-2-((tert-butoxycarbonyl)imino)-3-methyl-6,8-dioxo-7-phenyl-3,4,4a,7,8,9a,10,11,12,13-decahydro-6H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]cinnoline-1(2H)-carboxylate (**3a**).* Prepared using the general procedure 3 to yield the polycyclic guanidine as a pale yellow solid, (0.160 g, 94% yield). R_f = 0.46 (40% ethyl acetate/*n*-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.51–7.36 (m. 5H), 4.57 (m, 1H), 4.44 (m, 1H), 3.99 (dd, J = 14.0, 3.0 Hz, 1H), 3.84 (dd, J = 14.0, 7.5 Hz, 1H), 3.39 (m, 1H), 3.02 (s, 3H), 2.49 (m, 1H), 1.92 (m, 2H), 1.78 (m, 1H), 1.57 (m, 2H), 1.53 (s, 9H), 1.45 (s, 9H), 1.38 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 154.5, 151.1, 149.5, 149.0, 134.3, 130.7, 129.1, 128.2, 125.3, 118.7, 82.9, 78.9, 55.2, 54.8, 50.1, 37.3, 30.8, 28.5, 28.2, 28.0, 26.6, 24.1 ppm; LRMS (ESI) Calculated for $C_{29}H_{39}N_6O_6$ m/z (M+H): 567.3, Obsd. 567.4.

*4.2.3.2. tert-butyl (4aR,9aS,E)-2-((tert-butoxycarbonyl)imino)-3-(cyclopropylmethyl)-6,8-dioxo-7-phenyl-3,4,4a,7,8,9a,10,11,12,13-decahydro-6H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]cinnoline-1(2H)-carboxylate (**3b**).* Prepared according to the general procedure 3, to give the polycyclic guanidine as white solid in 35% yield (0.064 g). R_f = 0.45 (40% ethyl acetate/*n*-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.49–7.34 (m, 5H), 4.60 (m, 1H), 4.43 (m, 1H), 4.35 (dd, J = 14.3, 1.5 Hz, 1H), 3.77 (dd, J = 14.3, 7.2 Hz, 1H), 3.46 (m, 1H), 3.42 (dd, J = 14.3, 7.8 Hz, 1H), 3.19 (dd, J = 14.3, 6.0 Hz, 1H), 2.45 (m, 1H), 1.89 (m, 2H), 1.72 (m, 1H), 1.54 (m, 1H), 1.49 (s, 9H), 1.45 (m, 1H), 1.42 (s, 9H), 1.33 (m, 1H), 1.05 (m, 1H), 0.52 (m, 1H), 0.45 (m, 1H), 0.21 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.6, 155.1, 151.6, 149.7, 149.3, 134.7, 130.9, 129.2, 128.4, 125.4, 119.4, 82.9, 79.0, 57.4, 54.8, 52.8, 47.1, 31.1, 28.6, 28.3, 28.1,27.0, 24.3, 9.2, 3.9, 3.2 ppm; LRMS (ESI) Calculated for $C_{32}H_{43}N_6O_6$ m/z (M+H): 607.3, Obsd. 607.3.

*4.2.3.3. tert-butyl (4aR,9aS,E)-3-benzyl-2-((tert-butoxycarbonyl)imino)-6,8-dioxo-7-phenyl-3,4,4a,7,8,9a,10,11,12,13-decahydro-6H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]cinnoline-1(2H)-carboxylate (**3c**).* Prepared according to the general procedure 3, to give the polycyclic guanidine as white solid in 95% yield (0.183 g). R_f = 0.43 (40% ethyl acetate/*n*-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.23 (m, 10H), 5.30 (d, J = 15.2 Hz, 1H), 4.55 (m, 1H), 4.40 (m, 1H), 4.06 (dd, J = 14.3, 1.6 Hz, 1H), 4.01 (d, J = 15.2 Hz, 1H), 3.75 (dd, J = 14.3, 7.3 Hz, 1H), 3.53 (m, 1H), 2.41 (m, 1H), 1.97 (m, 1H), 1.90 (m, 1H), 1.77 (m, 1H), 1.58 (m, 1H), 1.54 (s, 9H), 1.47 (s, 9H), 1.37 (m, 1H), 1.29 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.4, 154.3, 151.7, 149.6, 149.2, 136.5, 135.0, 130.8, 129.1, 128.5, 128.2, 128.1, 127.7, 125.2, 119.2, 83.0, 79.1, 56.4, 54.7, 51.6, 47.0, 30.9, 28.5, 28.3, 28.1, 27.0, 24.3 ppm; LRMS (ESI) Calculated for $C_{35}H_{43}N_6O_6$ m/z (M+H): 643.3, Obsd. 643.3.

*4.2.3.4. tert-butyl (R,E)-2-benzyl-3-((tert-butoxycarbonyl)imino)-5-methyl-8,10-dioxo-9-phenyl-2,3,6,9,10,11a-hexahydro-8H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]pyridazine-4(1H)-carboxylate (**3d**).* Prepared according to general procedure 3, to the give polycyclic guanidine as white solid in 73% yield (0.132 g). R_f = 0.39 (40% ethyl acetate/*n*-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.25 (m, 10H), 4.86 (d, J = 15.2 Hz, 1H), 4.60 (m, 1H), 4.46 (d, J = 15.2 Hz, 1H), 4.27 (d, J = 16.3 Hz, 1H), 3.99 (d, J = 16.3 Hz, 1H), 3.74 (m, 2H), 2.10 (s, 3H), 1.55 (s, 9H), 1.49 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 153.3, 151.3, 149.2, 136.1, 130.8, 129.4, 128.9, 128.6, 128.5, 127.9, 127.5, 125.5, 122.3, 114.6, 83.6, 79.5, 54.6, 52.4, 47.3, 46.1, 28.4, 28.3, 15.7 ppm; LRMS (ESI) Calculated for $C_{32}H_{39}N_6O_6$ m/z (M+H): 603.3, Obsd. 603.4.

*4.2.3.5. tert-butyl (R,E)-3-((tert-butoxycarbonyl)imino)-2-(2,4-dimethoxybenzyl)-5-methyl-8,10-dioxo-9-phenyl-2,3,6,9,10,11a-hexahydro-8H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]pyridazine-4(1H)-carboxylate (**3e**).* Prepared according to the general procedure 3, to give the polycyclic guanidine as pale yellow solid in 50% yield (0.099 g). R_f = 0.47 (40% ethyl acetate/*n*-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.33 (m, 5H), 7.15 (m, 1H), 6.38 (m, 2H), 4.94 (d, J = 14.7 Hz, 1H), 4.55 (m, 1H), 4.22 (d, J = 16.5 Hz, 1H), 4.20 (d, J = 14.7 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.69 (m, 1H), 2.05 (s, 3H), 1.53 (s, 9H), 1.46 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.7, 159.8, 158.9, 153.0, 151.1, 151.0, 149.1, 131.2, 130.8, 129.2, 128.4, 127.0, 125.3, 122.2, 116.4, 104.2, 98.3, 83.0, 78.9, 55.3, 55.2, 54.9, 46.6, 46.5, 45.9, 28.3, 28.1, 15.5 ppm; LRMS (ESI) Calculated for $C_{34}H_{43}N_6O_8$ m/z (M+H): 663.3, Obsd. 663.4.

*4.2.3.6. tert-butyl (R,E)-2-(benzo[d][1,3]dioxol-5-ylmethyl)-3-((tert-butoxycarbonyl)imino)-5-methyl-8,10-dioxo-9-phenyl-2,3,6,9,10,11a-hexahydro-8H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]pyridazine-4(1H)-carboxylate (**3f**).* Prepared according to the general procedure 3, to give the polycyclic guanidine as pale yellow solid in 60% yield (0.116 g). R_f = 0.35 (40% ethyl acetate/*n*-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.36 (m, 5H), 6.76 (s, 1H), 6.72 (m, 2H), 5.90 (m, 2H), 4.76 (d, J = 15.1 Hz, 1H), 4.60 (m, 1H), 4.60 (m, 1H), 4.34 (d, J = 15.1 Hz, 1H), 4.28 (d, J = 16.1 Hz, 1H), 4.02 (d, J = 16.1 Hz, 1H), 3.77 (dd, J = 13.7, 4.0 Hz, 1H), 3.69 (dd, J = 13.7, 7.4 Hz, 1H), 2.09

(s, 3H), 1.55 (s, 9H), 1.48 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.9, 153.3, 151.3, 151.2, 149.2, 148.1, 147.4, 130.8, 129.8, 129.4, 128.6, 127.5, 125.4, 122.2, 122.1, 108.9, 108.4, 101.2, 83.5, 79.4, 54.6, 52.2, 46.9, 46.1, 28.4, 28.2, 15.7 ppm; LRMS (ESI) Calculated for $C_{33}H_{39}N_6O_8$ *m/z* (M+H): 647.3, Obsd. 647.3.

*4.2.3.7. tert-butyl (R,E)-2-(benzo[d][1,3]dioxol-5-ylmethyl)-3-((tert-butoxycarbonyl)imino)-5-methyl-8,10-dioxo-9-phenyl-2,3,6,9,10,11a-hexahydro-8H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]pyridazine-4(1H)-carboxylate (**3g**).* Prepared according to the general procedure 3, to give the polycyclic guanidine as pale yellow solid in 61% yield (0.110 g). R_f = 0.29 (40% ethyl acetate/*n*-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 6.74–6.71 (m, 3H), 5.92 (s, 2H), 4.74 (d, *J* = 15.1 Hz, 1H), 4.48 (m, 1H), 4.34 (d, *J* = 15.1 Hz, 1H), 4.18 (dd, *J* = 16.1, 2.0 Hz, 1H), 3.92 (dd, *J* = 16.1, 2.0 Hz, 1H), 3.68 (qd, *J* = 7.3, 5.4 Hz, 2H), 2.05 (d, *J* = 1.5 Hz, 3H), 1.54 (s, 9H), 1.47 (s, 9H), 1.23 (t, *J* = 7.3 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.8, 154.5, 152.3, 151.2, 149.2, 148.0, 147.3, 129.7, 127.5, 122.3, 122.0, 108.8, 108.3, 101.1, 83.3, 79.3, 54.4, 52.1, 46.9, 45.8, 34.5, 28.3, 28.2, 15.6, 13.4 ppm; LRMS (ESI) Calculated for $C_{29}H_{39}N_6O_8$ *m/z* (M+H): 599.3, Obsd. 599.4.

*4.2.3.8. tert-butyl (4aR,9aS,E)-3,4-dibenzyl-2-((tert-butoxycarbonyl)imino)-6,8-dioxo-7-phenyl-3,4,4a,7,8,9a,10,11,12,13-decahydro-6H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]cinnoline-1(2H)-carboxylate (**3h**).* Prepared according to the general procedure 3, to give the polycyclic guanidine as white solid in 67% yield (0.147 g). R_f = 0.67 (40% ethyl acetate/*n*-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.19 (m, 13H), 7.03 (m, 2H), 5.12 (d, *J* = 15.0 Hz, 1H), 4.66 (dd, *J* = 11.0, 2.3 Hz, 1H), 4.38 (s, 1H), 4.36 (m, 1H), 3.61 (m, 1H), 3.27 (dd, *J* = 13.2, 2.8 Hz, 1H), 2.90 (dd, *J* = 12.3, 12.3 Hz, 1H), 2.84 (d, *J* = 15.0 Hz, 1H), 2.33 (m, 1H), 1.89 (m, 1H), 1.83 (m, 1H), 1.73 (m, 1H), 1.56 (s, 9H), 1.51 (s, 9H), 1.49 (m, 1H), 1.27 (m, 1H), 1.16 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 154.7, 151.9, 149.6, 149.3, 137.1, 136.7, 134.8, 130.7, 129.7, 129.1, 128.9, 128.5, 128.2, 128.1, 127.5, 127.1, 125.3, 119.5, 82.9, 79.0, 63.0, 59.3, 54.4, 52.1, 43.3, 30.6, 28.3, 28.2, 28.1, 26.8, 24.2 ppm; LRMS (ESI) Calculated for $C_{42}H_{49}N_6O_6$ *m/z* (M+H): 733.4, Obsd. 733.4.

*4.2.3.9. tert-butyl (11aR,E)-1-benzyl-3-((tert-butoxycarbonyl)imino)-2-(cyclopropylmethyl)-5-methyl-8,10-dioxo-9-phenyl-2,3,6,9,10,11a-hexahydro-8H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]pyridazine-4(1H)-carboxylate (**3i**).* Prepared according to general procedure 3, to give the polycyclic guanidine as white solid in 83% yield (0.164 g). R_f = 0.10 (20% ethyl acetate/*n*-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.56–7.24 (m, 10H), 5.06 (dd, *J* = 10.4, 4.9 Hz, 1H), 4.55 (s, 1H), 4.40 (d, *J* = 16.6 Hz, 1H), 3.98 (d, *J* = 16.6 Hz, 1H), 3.68 (dd, *J* = 14.2, 6.3 Hz, 1H), 3.20 (dd, *J* = 13.2, 4.9 Hz, 1H), 2.99 (dd, *J* = 13.2, 10.3 Hz, 1H), 2.13 (s, 3H), 2.09 (dd, *J* = 14.2, 7.3 Hz, 1H), 1.60 (s, 9H), 1.56 (s, 9H), 0.78 (m, 1H), 0.50 (m, 1H), 0.36 (m, 1H), 0.05 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 154.7, 151.9, 151.0, 149.6, 136.9, 130.8, 130.4, 129.5, 129.0, 128.7, 127.2, 125.7, 123.0, 83.2, 79.5, 63.1, 58.3, 53.2, 46.0, 43.7, 28.4, 28.3, 15.3, 9.5, 5.0, 2.1 ppm; LRMS (ESI) Calculated for $C_{36}H_{45}N_6O_6$ *m/z* (M+H): 657.3, Obsd. 657.3.

*4.2.3.10. tert-butyl (11aR,E)-1,2-dibenzyl-3-((tert-butoxycarbonyl)imino)-5-methyl-8,10-dioxo-9-phenyl-2,3,6,9,10,11a-hexahydro-8H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]pyridazine-4(1H)-carboxylate (**3j**).* Prepared according to general procedure 3, to give the polycyclic guanidine as white solid in 65% yield (0.135 g). R_f = 0.53 (40% ethyl acetate/*n*-hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.20 (m, 13H), 6.89 (m, 2H), 5.06 (d, *J* = 14.7 Hz, 1H), 4.42 (s, 1H), 4.41 (dd, *J* = 10.7, 3.9 Hz, 1H), 4.27 (d, *J* = 16.6 Hz, 1H), 3.83 (d, *J* = 16.6 Hz, 1H), 3.23 (dd, *J* = 13.7, 3.9 Hz, 1H), 3.00 (d, *J* = 14.7 Hz, 1H), 2.89 (dd, *J* = 13.7, 10.7 Hz, 1H), 2.13 (s, 3H), 1.58 (s, 9H), 1.52 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.8, 153.4, 151.9, 151.0, 149.6, 137.0, 136.4, 130.7, 129.9, 129.4, 129.0, 128.6, 128.5, 128.4, 127.8, 127.5, 127.3, 125.5, 123.0, 83.3, 79.6, 62.3, 58.6, 52.6, 45.9, 43.2, 28.4, 28.3, 15.3 ppm; LRMS (ESI) Calculated for $C_{39}H_{45}N_6O_6$ *m/z* (M+H): 693.3, Obsd. 693.4.

*4.2.4. General procedure 4 for the deprotection and salt exchange of guanidines **3a-j***

A 50 mL round-bottom flask was charged with the appropriate polycyclic guanidine (0.2 mmol). The CH_2Cl_2/TFA mixture (1:1, 4.0 mL) was added. The reaction mixture was stirred at room temperature for 2 h. The crude mixture was taken up in MeOH and 2 M HCl in ethyl ether was added. The mixture was again concentrated and the resulting solid triturated with ethyl ether. The solid was then collected to give the title compound.

*4.2.4.1. (4aR,9aS)-2-imino-3-methyl-7-phenyl-1,2,3,4,4a,9a,10,11,12,13-decahydro-6H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]cinnoline-6,8(7H)-dione (**4a**).* Prepared according to the general procedure 4 to afford the HCl salt as a white powder (69 mg, 85%). ^1H NMR (500 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.20 (s, 2H), 7.50–7.42 (m. 5H), 4.67 (s, 1H), 4.39 (d, *J* = 8.8 Hz, 1H), 4.29 (d, *J* = 7.3 Hz, 1H), 3.63 (t, *J* = 8.6 Hz, 1H), 3.07 (s, 4H), 2.17 (m, 1H), 1.81 (m, 1H), 1.78 (m, 2H), 1.54 (m, 1H), 1.34 (m, 1H), 1.20 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 153.9, 151.5, 149.1, 130.8, 128.8, 128.1, 126.0, 117.6, 114.2, 53.2, 49.1, 49.0, 37.3, 30.2, 26.8, 26.3, 23.5 ppm; HRMS (ESI) Calculated for $C_{19}H_{23}N_6O_2$ *m/z* (M+H): 367.1882, Obsd. 367.1890.

*4.2.4.2. (4aR,9aS)-3-(cyclopropylmethyl)-2-imino-7-phenyl-1,2,3,4,4a,9a,10,11,12,13-decahydro-6H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]cinnoline-6,8(7H)-dione (**4b**).* Prepared according to the general procedure 4, to give the polycyclic guanidine as white solid in 66% yield (59 mg). ^1H NMR (500 MHz, DMSO-d_6) δ 10.41 (s, 1H), 7.98 (s, 2H), 7.53–7.41 (m, 5H), 4.64 (m, 1H), 4.51 (dd, *J* = 12.4, 5.7 Hz, 1H), 4.42 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.63 (t, *J* = 12.4 Hz, 1H), 3.39 (m, 2H), 2.94 (m, 1H), 2.17 (m, 1H), 1.91 (m, 1H), 1.80 (m, 2H), 1.55 (m, 1H), 1.37 (m, 1H), 1.24 (m, 1H), 1.04 (m, 1H), 0.54 (m, 1H), 0.31 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 156.1, 152.6, 151.3, 132.3, 130.2, 129.7, 127.5, 119.4, 117.0, 55.8, 55.5, 51.6, 49.7, 31.9, 28.3, 28.1, 25.3, 9.8, 4.2, 4.1 ppm; HRMS (ESI) Calculated for $C_{22}H_{28}N_6O_2$ *m/z* (M+H): 408.2274, Obsd. 408.2285.

*4.2.4.3. (4aR,9aS)-3-benzyl-2-imino-7-phenyl-1,2,3,4,4a,9a,10,11,12,13-decahydro-6H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]cinnoline-6,8(7H)-dione (**4c**).* Prepared according to the general procedure 4, to give the polycyclic guanidine as white solid in 90% yield (79 mg). ^1H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.53 (s, 2H), 7.49–7.34 (m, 10H), 4.82 (d, *J* = 16.2 Hz, 1H), 4.66 (d, *J* = 16.2 Hz, 1H), 4.63 (s, 1H), 4.40 (d, *J* = 10.4 Hz, 1H), 4.30 (dd, *J* = 12.2, 5.2 Hz, 1H), 3.56 (t, *J* = 11.9 Hz, 1H), 3.12 (m, 1H), 2.15 (m, 1H), 1.89 (m, 1H), 1.78 (m, 2H), 1.54 (m, 1H), 1.34 (m, 1H), 1.24 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 154.0, 151.5, 149.2, 134.5, 130.9, 128.9, 128.8, 128.2, 128.0, 127.4, 126.1, 117.7, 114.7, 53.3, 52.0, 49.2, 46.8, 30.2, 26.9, 26.4, 23.6 ppm; HRMS (ESI) Calculated for $C_{25}H_{27}N_6O_2$ *m/z* (M+H): 443.2195, Obsd. 443.2205.

*4.2.4.4. (R)-2-benzyl-3-imino-5-methyl-9-phenyl-1,2,3,4,6,11a-hexahydro-8H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]pyridazine-8,10(9H)-dione (**4d**).* Prepared according to the general procedure 4, to give the polycyclic guanidine as white solid in 63% yield (55 mg). ^1H NMR (500 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.38 (s, 2H), 7.49–7.32 (m, 10H), 4.70 (d, *J* = 15.9 Hz, 1H), 4.63 (m, 1H), 4.54 (d, *J* = 15.9 Hz, 1H), 4.22 (m, 2H), 3.94 (d, *J* = 15.3 Hz, 1H), 3.44 (t, *J* = 11.5 Hz, 1H), 1.88 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 152.9, 151.2, 150.6, 134.2, 130.7, 128.6, 127.9, 127.8, 127.1, 125.8, 119.9, 106.9, 51.8, 48.6, 46.4, 44.8, 13.8 ppm; HRMS (ESI) Calculated for $C_{22}H_{24}N_6O_2$ *m/*

z (M+H): 404.1961, Obsd. 404.1971.

*4.2.4.5. (R)-2-(2,4-dimethoxybenzyl)-3-imino-5-methyl-9-phenyl-1,2,3,4,6,11a-hexahydro-8H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]pyridazine-8,10(9H)-dione (**4e**).* Prepared according to the general procedure 4, to give the polycyclic guanidine as white solid in 70% yield (70 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.34 (s, 2H), 7.48–7.42 (m, 5H), 7.24 (m, 1H), 6.60 (s, 1H), 6.51 (m, 1H), 4.60 (d, J = 15.2 Hz, 1H), 4.54 (m, 1H), 4.47 (d, J = 15.2 Hz, 1H), 4.32 (d, J = 7.8 Hz, 1H), 4.20 (d, J = 14.7 Hz, 1H), 3.92 (d, J = 14.7 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.36 (m, 1H), 1.88 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.7, 159.8, 158.9, 153.0, 151.1, 151.0, 149.1, 131.2, 130.8, 129.2, 128.4, 127.0, 125.3, 122.2, 116.4, 104.2, 98.3, 83.0, 78.9, 55.3, 55.2, 54.9, 46.6, 46.5, 45.9, 28.3, 28.1, 15.5 ppm; HRMS (ESI) Calculated for $C_{24}H_{27}N_6O_4$ *m/z* (M+H): 463.2094, Obsd. 463.2099.

*4.2.4.6. (R)-2-(benzo[d][1,3]dioxol-5-ylmethyl)-3-imino-5-methyl-9-phenyl-1,2,3,4,6,11a-hexahydro-8H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]pyridazine-8,10(9H)-dione (**4f**).* Prepared according to the general procedure 4, to give the polycyclic guanidine as white solid in 88% yield (85 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.93 (s, 1H), 8.51 (s, 2H), 7.48–7.40 (m, 5H), 6.94–6.82 (m, 3H), 6.01 (s, 1H), 6.72 (m, 2H), 5.90 (m, 2H), 4.76 (d, J = 15.1 Hz, 1H), 4.60 (m, 1H), 4.60 (m, 1H), 4.34 (d, J = 15.1 Hz, 1H), 4.28 (d, J = 16.1 Hz, 1H), 4.02 (d, J = 16.1 Hz, 1H), 3.77 (dd, J = 13.7, 4.0 Hz, 1H), 3.69 (dd, J = 13.7, 7.4 Hz, 1H), 2.09 (s, 3H), 1.55 (s, 9H), 1.48 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 153.2, 151.1, 150.9, 147.7, 147.1, 131.0, 128.9, 128.2, 128.0, 126.1, 121.3, 120.1, 108.5, 108.1, 107.0, 101.2, 51.7, 48.8, 46.2, 45.0, 13.9 ppm; HRMS (ESI) Calculated for $C_{23}H_{23}N_6O_4$ *m/z* (M+H): 447.1781, Obsd. 447.1782.

*4.2.4.7. (R)-2-(benzo[d][1,3]dioxol-5-ylmethyl)-9-ethyl-3-imino-5-methyl-1,2,3,4,6,11a-hexahydro-8H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]pyridazine-8,10(9H)-dione (**4g**).* Prepared according to the general procedure 4, to give the polycyclic guanidine as white solid in 81% yield (70 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.46 (s, 2H), 6.93–6.82 (m, 3H), 6.02 (s, 2H), 4.68 (d, J = 16.1 Hz, 1H), 4.55 (d, J = 16.1 Hz, 1H), 4.51 (m, 1H), 4.20 (dd, J = 11.7, 4.9 Hz, 1H), 4.12 (d, J = 15.7 Hz, 1H), 3.81 (d, J = 15.7 Hz, 1H), 3.39 (m, 3H), 1.85 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 154.3, 151.9, 151.2, 147.7, 147.1, 128.0, 121.3, 120.3, 108.4, 108.1, 107.1, 101.2, 51.7, 48.6, 46.3, 44.8, 33.7, 13.9, 12.9 ppm; HRMS (ESI) Calculated for $C_{19}H_{23}N_6O_4$ *m/z* (M+H): 399.1781, Obsd. 399.1783.

*4.2.4.8. (4aR,9aS)-3,4-dibenzyl-2-imino-7-phenyl-1,2,3,4,4a,9a,10,11,12,13-decahydro-6H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]cinnoline-6,8(7H)-dione (**4h**).* Prepared according to the general procedure 4, to give the polycyclic guanidine as white solid in 80% yield (91 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.54 (s, 2H), 7.51–7.14 (m, 15H), 5.00 (d, J = 16.6 Hz, 1H), 4.97 (s, 1H), 4.48 (s, 2H), 4.09 (d, J = 16.6 Hz, 1H), 3.44 (d, J = 12.7 Hz, 1H), 3.23 (d, J = 12.7 Hz, 1H), 2.94 (m, 1H), 2.27 (m, 1H), 1.83 (m, 2H), 1.78 (m, 1H), 1.55 (m, 1H), 1.32 (m, 1H), 1.02 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 165.7, 154.5, 149.7, 135.8, 135.4, 131.0, 130.3, 128.8, 128.6, 128.5, 128.2, 127.9, 127.1, 126.6, 126.2, 123.8, 117.1, 60.0, 59.5, 53.3, 50.7, 39.0, 31.0, 27.2, 26.7, 23.4 ppm; HRMS (ESI) Calculated for $C_{32}H_{33}N_6O_2$ *m/z* (M+H): 533.2665, Obsd. 533.2671.

*4.2.4.9. (11aR)-1-benzyl-2-(cyclopropylmethyl)-3-imino-5-methyl-9-phenyl-1,2,3,4,6,11a-hexahydro-8H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]pyridazine-8,10(9H)-dione (**4i**).* Prepared according to the general procedure 4, to give the polycyclic guanidine as white solid in 72% yield (71 mg). ^{1}H NMR (500 MHz, CD_3OD) δ 7.57–7.29 (m, 10H), 4.97 (s, 2H), 4.30 (d, J = 15.9 Hz, 1H), 4.06 (d, J = 15.9 Hz, 1H), 3.55 (dd, J = 14.6, 6.2 Hz, 1H), 3.39 (d, J = 14.6, 3.8 Hz, 1H), 3.32 (d, J = 14.6, 3.8 Hz, 1H), 2.87 (dd, J = 14.6, 7.5 Hz, 1H), 1.82 (s, 3H), 1.03 (m, 1H), 0.64 (m, 1H), 0.56 (m, 1H), 0.31 (m, 1H), 0.21 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 157.8, 155.9, 153.6, 137.1, 132.7, 131.6, 130.3, 130.1, 129.8, 128.7, 127.5, 121.2, 118.9, 61.2, 60.0, 54.2, 47.0, 40.2, 14.4, 10.1, 5.2, 3.3 ppm; HRMS (ESI) Calculated for $C_{26}H_{30}N_6O_2$ *m/z* (M+H): 458.2430, Obsd. 458.2436.

*4.2.4.10. (11aR)-1,2-dibenzyl-3-imino-5-methyl-9-phenyl-1,2,3,4,6,11a-hexahydro-8H-pyrimido[5,4-c][1,2,4]triazolo[1,2-a]pyridazine-8,10(9H)-dione (**4j**).* Prepared according to general procedure 4, to give the polycyclic guanidine as white solid in 87% yield (92 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.39 (s, 2H), 7.53–7.13 (m, 15H), 5.03 (d, J = 16.5 Hz, 1H), 4.91 (s, 1H), 4.44 (q, J = 4.3 Hz, 1H), 4.37 (d, J = 16.5 Hz, 1H), 4.23 (d, J = 15.3 Hz, 1H), 4.04 (d, J = 15.3 Hz, 1H), 3.44 (dd, J = 14.3, 4.0 Hz, 1H), 3.28 (dd, J = 14.3, 4.6 Hz, 1H), 1.79 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 155.7, 153.1, 151.9, 135.3, 135.2, 131.1, 130.5, 128.9, 128.5, 128.2, 127.9, 127.2, 126.8, 126.3, 119.2, 116.1, 59.1, 57.0, 50.1, 45.8, 37.4, 14.3 ppm; HRMS (ESI) Calculated for $C_{29}H_{29}N_6O_2$ *m/z* (M+H): 493.2352, Obsd. 493.2355.

4.2.5. General procedure 5 for the cyclization of propargylguanidines using silver (I)

To a stirring solution of the preferred propargylguanidine (1.0 mmol) in CH_2Cl_2 (0.07 M) was added silver acetate (10 mol%) and acetic acid (3.0 equiv). After completion, the reaction mixture was concentrated by rotary evaporation, and purified by column chromatography to give 5-*exo-dig* cyclized guanidine.

*4.2.5.1. tert-butyl (2E,5Z)-3-benzyl-2-((tert-butoxycarbonyl)imino)-5-(cyclohex-1-en-1-ylmethylene)imidazolidine-1-carboxylate (**7a**).* The general procedure 5 was used to give 5-*exo-dig* cyclized guanidine as a white solid in 85% yield (5-*exo-dig*:6-*endo-dig* = 2:3), (0.398 g). R_f = 0.50 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 5.75 (s, 1H), 5.49 (s, 1H), 4.58 (s, 2H), 3.70 (s, 2H), 2.22 (m, 2H), 2.13 (m, 2H), 1.63 (m, 4H), 1.54 (s, 9H), 1.47 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.2, 151.9, 149.3, 135.6, 134.1, 129.3, 128.8, 128.4, 127.9, 126.0, 120.3, 83.5, 79.2, 49.7, 48.4, 28.3, 28.1, 27.0, 25.8, 22.7, 22.2 ppm; LRMS (ESI) Calculated for $C_{27}H_{38}N_3O_4$ *m/z* (M+H): 468.3, Obsd. 468.3.

*4.2.5.2. tert-butyl (2E,5Z)-3,4-dibenzyl-2-((tert-butoxycarbonyl)imino)-5-(cyclohex-1-en-1-ylmethylene)imidazolidine-1-carboxylate (**7b**).* Prepared according to the general procedure 5, to give the 5-*exo-dig* cyclized guanidine as a white solid in 85% yield (5-*exo-dig*:6-*endo-dig* = >20:1), (0.474 g). R_f = 0.50 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.01 (m, 10H), 5.52 (s, 1H), 5.07 (d, J = 15.1 Hz, 1H), 4.72 (s, 1H), 4.13 (d, J = 15.1 Hz, 1H), 3.63 (dd, J = 9.4, 4.2 Hz, 1H), 2.86 (dd, J = 13.0, 9.4 Hz, 1H), 2.41 (dd, J = 13.0, 9.4 Hz, 1H), 2.20 (m, 1H), 2.07 (m, 3H), 1.72 (m, 2H), 1.64 (m, 1H), 1.55 (s, 9H), 1.52 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.6, 152.1, 149.8, 136.2, 136.1, 134.1, 130.0, 129.7, 129.0, 128.5, 128.4, 128.1, 127.1, 122.3, 83.4, 79.4, 61.7, 46.9, 38.8, 28.4, 28.3, 26.9, 25.9, 22.9, 22.4 ppm; LRMS (ESI) Calculated for $C_{34}H_{44}N_3O_4$ *m/z* (M+H): 558.3, Obsd. 558.3.

*4.2.5.3. tert-butyl (2E,5Z)-3-benzyl-2-((tert-butoxycarbonyl)imino)-5-(2-methylallylidene)imidazolidine-1-carboxylate (**7c**).* Prepared according to the general procedure 5, to give the 5-*exo-dig* cyclized guanidine as a white solid in 54% yield (5-*exo-dig*:6-*endo-dig* = 10:1), (0.231 g). R_f = 0.49 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5H), 5.60 (s, 1H), 5.00 (s, 2H), 4.60 (s, 2H), 3.72 (d, J = 1.0 Hz, 2H), 1.94 (s, 3H), 1.54 (s, 9H), 1.46 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.5, 152.1, 149.2, 140.3, 135.5, 128.9, 128.6, 128.5, 128.0, 119.1, 117.5, 84.2, 79.4, 49.6, 48.5,

28.4, 28.1, 21.2 ppm; LRMS (ESI) Calculated for $C_{24}H_{34}N_3O_4$ *m/z* (M+H): 428.3, Obsd. 428.3.

*4.2.5.4. tert-butyl (2E,5Z)-3,4-dibenzyl-2-((tert-butoxycarbonyl) imino)-5-(2-methylallylidene)imidazolidine-1-carboxylate (**7d**).* Prepared according to the general procedure 5, to give the 5-*exo-dig* cyclized guanidine as a white solid in 90% yield (5-*exo-dig*:6-*endo-dig* = >20:1), (0.466 g). R_f = 0.47 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.00 (m, 10H), 5.07 (d, *J* = 15.1 Hz, 1H), 4.92 (s, 1H), 4.83 (s, 1H), 4.78 (s, 1H), 4.16 (d, *J* = 15.1 Hz, 1H), 3.66 (dd, *J* = 9.7, 4.6 Hz, 1H), 2.86 (dd, *J* = 13.1, 4.6 Hz, 1H), 2.46 (dd, *J* = 13.1, 9.7 Hz, 1H), 1.56 (s, 3H), 1.56 (s, 9H), 1.51 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.7, 152.0, 149.4, 140.0, 135.9, 135.8, 130.6, 129.9, 129.0, 128.5, 128.4, 128.1, 127.1, 83.8, 79.4, 61.5, 46.9, 38.8, 28.3, 28.2, 20.9 ppm; LRMS (ESI) Calculated for $C_{31}H_{40}N_3O_4$ *m/z* (M+H): 518.3, Obsd. 518.4.

*4.2.5.5. tert-butyl (2E,5Z)-3-(benzo[d][1,3]dioxol-5-ylmethyl)-2-((tert-butoxycarbonyl)imino)-5-(2-methylallylidene)imidazolidine-1-carboxylate (**7e**).* Prepared according to general procedure 5, to give the 5-*exo-dig* cyclized guanidine as a white solid in 80% yield (5-*exo-dig*:6-*endo-dig* = 10:1), (0.377 g). R_f = 0.45 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79–6.74 (m, 3H), 5.94 (s, 2H), 5.61 (s, 1H), 5.01 (s, 2H), 4.49 (s, 2H), 3.74 (s, 2H), 1.94 (s, 3H), 1.54 (s, 9H), 1.46 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.3, 151.8, 149.0, 148.0, 147.4, 140.0, 129.0, 128.3, 121.9, 118.9, 117.3, 108.9, 108.3, 101.1, 84.0, 79.2, 49.3, 48.1, 28.2, 28.0, 21.0 ppm; LRMS (ESI) Calculated for $C_{25}H_{34}N_3O_6$ *m/z* (M+H): 472.2, Obsd. 472.3.

*4.2.5.6. tert-butyl (2E,5Z)-2-((tert-butoxycarbonyl)imino)-3-(2,4-dimethoxybenzyl)-5-(2-methylallylidene)imidazolidine-1-carboxylate (**7f**).* Prepared according to general procedure 5, to give the 5-*exo-dig* cyclized guanidine as a white solid in 60% yield (5-*exo-dig*:6-*endo-dig* = 9:1), (0.377 g). R_f = 0.39 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (m, 1H), 6.44 (m, 2H), 5.59 (s, 1H), 4.99 (s, 1H), 4.98 (s, 1H), 4.54 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.75 (s, 2H), 1.93 (s, 3H), 1.54 (s, 9H), 1.46 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.7, 159.2, 158.6, 151.7, 148.9, 140.0, 131.4, 128.8, 118.3, 116.8, 115.6, 104.3, 98.2, 83.5, 78.7, 55.1, 49.4, 42.4, 28.1, 28.0, 20.8 ppm; LRMS (ESI) Calculated for $C_{26}H_{38}N_3O_6$ *m/z* (M+H): 488.3, Obsd. 488.4.

*4.2.5.7. tert-butyl (2E,5Z)-2-((tert-butoxycarbonyl)imino)-5-(cyclohex-1-en-1-ylmethylene)-3-methylimidazolidine-1-carboxylate (**7g**).* Prepared according to the general procedure 5, to give the 5-*exo-dig* cyclized guanidine as a white solid, (5-*exo-dig*:6-*endo-dig* = 1:1), (0.211 g, total 54% yield). R_f = 0.21 (60% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (s. 1H), 5.58 (s, 1H), 3.90 (s, 2H), 2.97 (s, 3H), 2.20 (m, 2H), 2.14 (m, 2H), 1.63 (m, 4H), 1.51 (s, 9H), 1.46 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.9, 151.8, 149.2, 134.0, 129.1, 125.9, 119.9, 83.3, 78.9, 52.5,31.6, 28.1, 27.9, 26.8, 25.7, 22.6, 22.1 ppm; LRMS (ESI) Calculated for $C_{21}H_{34}N_3O_4$ *m/z* (M+H): 392.3, Obsd. 392.4.

*4.2.5.8. tert-butyl (2E,5Z)-4-benzyl-2-((tert-butoxycarbonyl)imino)-3-(cyclopropylmethyl)-5-(2-methylallylidene)imidazolidine-1-carboxylate (**7h**).* Prepared according to the general procedure 5, to give the 5-*exo-dig* cyclized guanidine as a white solid in 79% yield (5-*exo-dig*:6-*endo-dig* = >20:1), (0.381 g). R_f = 0.16 (20% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 3H), 7.15 (m, 2H), 4.92 (s, 1H), 4.87 (s, 1H), 4.80 (s, 1H), 4.06 (dd, *J* = 9.8, 3.8 Hz, 1H), 3.70 (dd, *J* = 14.6, 6.6 Hz, 1H), 3.11 (dd, *J* = 13.0, 3.8 Hz, 1H), 3.00 (dd, *J* = 14.6, 7.5 Hz, 1H), 2.48 (dd, *J* = 13.0, 9.9 Hz, 1H), 1.88 (s, 3H), 1.54 (s, 9H), 1.51 (s, 9H), 1.03 (m, 1H), 0.64 (m, 1H), 0.56 (m, 1H), 0.30 (m, 1H), 0.26 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.7, 151.6, 149.4, 140.0, 135.9, 130.7, 129.2, 128.4, 127.1, 121.0, 117.4, 83.6, 79.1. 62.1, 47.7, 38.8, 28.2, 28.1, 20.8, 9.4, 4.8, 3.3 ppm; LRMS (ESI) Calculated for $C_{28}H_{40}N_3O_4$ *m/z* (M+H): 482.3, Obsd. 482.3.

*4.2.6. General procedure 6 to form the cycloaddition of guanidine dienes **7a-h***

To a stirring solution of the desired 5-*exo-dig* cyclic guanidine (diene, 1 equiv) in CH_2Cl_2 (0.07 M) was added the appropriate triazoledione (dienophile, 1.2 equiv). The reaction was stirred at room temperature until judged complete by TLC. After completion, the reaction mixture was concentrated by rotary evaporation, and purified by column chromatography to yield polycyclic guanidine.

*4.2.6.1. tert-butyl (4R,10a′R,E)-1-benzyl-2-((tert-butoxycarbonyl) imino)-1′,3′-dioxo-2′-phenyl-2′,3′,8′,9′,10′,10a′-hexahydro-1′H,7′H-spiro[imidazolidine-4,5′-[1,2,4]triazolo[1,2-a]cinnoline]-3-carboxylate (**8a**).* Prepared according to the general procedure 6, to give the spiro-cyclic guanidine as white solid in 61% yield (0.118 g). R_f = 0.32 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.27 (m, 10H), 5.35 (s, 1H), 5.22 (d, *J* = 14.9 Hz, 1H), 4.40 (dd, *J* = 11.4, 3.5 Hz, 1H), 4.20 (d, *J* = 14.9 Hz, 1H), 3.88 (d, *J* = 11.2 Hz, 1H), 3.50 (d, *J* = 11.2 Hz, 1H), 2.46 (m, 1H), 2.40 (m, 1H), 2.14 (m, 1H), 1.96 (m, 1H), 1.90 (m, 1H), 1.60 (m, 1H), 1.49 (s, 9H), 1.42 (s, 9H), 1.37 (m, 1H), 1.30 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.1, 153.2, 151.6, 149.6, 148.7, 142.5, 135.6, 131.1, 129.2, 128.8, 128.7, 128.4, 127.8, 126.2, 115.8, 83.4, 78.5, 73.8, 56.8, 54.4, 49.9, 34.2, 31.1, 28.5, 28.2, 24.3 ppm; LRMS (ESI) Calculated for $C_{35}H_{43}N_6O_6$ *m/z* (M+H): 643.3, Obsd. 643.3.

*4.2.6.2. tert-butyl (4R,5R,10a′R,E)-1,5-dibenzyl-2-((tert-butoxycarbonyl)imino)-1′,3′-dioxo-2′-phenyl-2′,3′,8′,9′,10′,10a′-hexahydro-1′H,7′H-spiro[imidazolidine-4,5′-[1,2,4]triazolo[1,2-a]cinnoline]-3-carboxylate (**8b**).* Prepared according to the general procedure 6, to give the spiro-cyclic guanidine as white solid in 94% yield (0.207 g). R_f = 0.54 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.35 (m, 5H), 7.23–7.14 (m, 8H), 6.95 (m, 2H), 5.49 (s, 1H), 4.95 (dd, *J* = 9.2, 5.2 Hz, 1H), 4.76 (d, *J* = 15.6 Hz, 1H), 4.68 (d, *J* = 15.6 Hz, 1H), 4.22 (dd, *J* = 11.6, 3.6 Hz, 1H), 2.96 (dd, *J* = 15.6, 5.2 Hz, 1H), 2.75 (dd, *J* = 15.6, 9.2 Hz, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 2.00 (m, 1H), 1.69 (m, 1H), 1.61 (m, 1H), 1.49 (s, 9H), 1.40 (s, 9H), 1.28 (m, 1H), 0.79 (m, 1H), 0.68 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.0, 152.9, 151.0, 149.8, 148.2, 141.4, 136.2, 135.8, 131.0, 129.1, 128.7, 128.4, 128.3, 128.2, 127.4, 126.8, 126.0, 112.2, 83.6, 78.5, 77.3, 63.7, 54.1, 48.8, 35.7, 34.2, 30.5, 28.5, 28.1, 26.8, 23.9 ppm; LRMS (ESI) Calculated for $C_{42}H_{49}N_6O_6$ *m/z* (M+H): 733.4, Obsd. 733.4.

*4.2.6.3. tert-butyl (R,E)-1-benzyl-2-((tert-butoxycarbonyl)imino)-7′-methyl-1′,3′-dioxo-2′-phenyl-2′,3′-dihydro-1′H,8′H-spiro[imidazolidine-4,5′-[1,2,4]triazolo[1,2-a]pyridazine]-3-carboxylate (**8c**).* Prepared according to the general procedure 6, to give the spiro-cyclic guanidine as white solid in 56% yield (0.101 g). R_f = 0.16 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.26 (m, 10H), 5.45 (s, 1H), 5.14 (d, *J* = 14.9 Hz, 1H), 4.24 (d, *J* = 16.8 Hz, 1H), 4.22 (d, *J* = 14.9 Hz, 1H), 3.99 (d, *J* = 16.8 Hz, 1H), 3.80 (d, *J* = 11.3 Hz, 1H), 3.47 (d, *J* = 11.3 Hz, 1H), 1.90 (s, 3H), 1.49 (s, 9H), 1.42 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.0, 152.7, 151.1, 150.0, 149.4, 135.4, 133.5, 130.9, 129.2, 128.7, 128.6, 128.4, 127.8, 126.0, 120.6, 83.3, 78.5, 73.7, 56.0, 49.6, 45.0, 28.4, 28.1, 19.9 ppm; LRMS (ESI) Calculated for $C_{32}H_{39}N_6O_6$ *m/z* (M+H): 603.3, Obsd. 603.4.

4.2.6.4. tert-butyl (4R,5R,E)-1,5-dibenzyl-2-((tert-butoxycarbonyl) imino)-7′-methyl-1′,3′-dioxo-2′-phenyl-2′,3′-dihydro-1′H,8′H-spiro [imidazolidine-4,5′-[1,2,4]triazolo[1,2-a]pyridazine]-3-carboxylate

(***8d***). Prepared according to the general procedure 6, to give the spiro-cyclic guanidine as pale yellow solid in 75% yield (0.156 g). R_f = 0.23 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.12 (m, 13H), 5.61 (s, 1H), 5.04 (d, J = 15.6 Hz, 1H), 4.88 (dd, J = 11.2, 4.9 Hz, 1H), 4.49 (d, J = 15.6 Hz, 1H), 3.88 (d, J = 16.6 Hz, 1H), 3.14 (dd, J = 14.7, 4.4 Hz, 1H), 2.80 (d, J = 16.6 Hz, 1H), 2.54 (dd, J = 14.7, 11.2 Hz, 1H), 1.77 (s, 3H), 1.50 (s, 9H), 1.36 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.0, 151.9, 149.7, 149.5, 149.1, 135.4, 135.3, 134.1, 130.8, 129.2, 128.8, 128.7, 128.4, 128.3, 128.2, 127.7, 126.8, 125.6, 117.3, 83.6, 78.9, 77.2, 62.0, 47.5, 43.9, 34.7, 28.5, 28.0, 20.1 ppm; LRMS (ESI) Calculated for $C_{39}H_{45}N_6O_6$ *m/z* (M+H): 693.3, Obsd. 693.4.

*4.2.6.5. tert-butyl (R,E)-1-(benzo[d][1,3]dioxol-5-ylmethyl)-2-((tert-butoxycarbonyl)imino)-7′-methyl-1′,3′-dioxo-2′-phenyl-2′,3′-dihydro-1′H,8′H-spiro[imidazolidine-4,5′-[1,2,4]triazolo[1,2-a]pyridazine]-3-carboxylate (**8e**).* Prepared according to the general procedure 6, to give the spiro-cyclic guanidine as pale yellow solid in 87% yield (0.169 g). R_f = 0.17 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.34 (m, 5H), 6.83 (s, 1H), 6.74 (m, 2H), 5.92 (s, 2H), 5.46 (s, 1H), 5.01 (d, J = 14.6 Hz, 1H), 4.24 (d, J = 17.1 Hz, 1H), 4.13 (d, J = 14.6 Hz, 1H), 3.90 (d, J = 17.1 Hz, 1H), 3.78 (d, J = 11.4 Hz, 1H), 3.48 (d, J = 11.4 Hz, 1H), 1.90 (s, 3H), 1.49 (s, 9H), 1.42 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.9, 152.5, 151.0, 150.0, 149.3, 148.0, 147.3, 133.6, 130.9, 129.1, 129.0, 128.4, 125.9, 122.0, 120.5, 109.0, 108.2, 101.1, 83.2, 78.5, 73.6, 55.9, 49.3, 45.0, 28.4, 28.0, 20.0 ppm; LRMS (ESI) Calculated for $C_{33}H_{39}N_6O_8$ *m/z* (M+H): 647.3, Obsd. 647.4.

*4.2.6.6. tert-butyl (R,E)-1-(benzo[d][1,3]dioxol-5-ylmethyl)-2-((tert-butoxycarbonyl)imino)-2′-ethyl-7′-methyl-1′,3′-dioxo-2′,3′-dihydro-1′H,8′H-spiro[imidazolidine-4,5′-[1,2,4]triazolo[1,2-a]pyridazine]-3-carboxylate (**8f**).* Prepared according to the general procedure 6, to give the spiro-cyclic guanidine as pale yellow solid in 91% yield (0.163 g). R_f = 0.17 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.76 (m, 2H), 5.94 (s, 2H), 5.41 (s, H), 4.98 (d, J = 14.7 Hz, 1H), 4.17 (d, J = 14.7 Hz, 1H), 4.14 (d, J = 17.1 Hz, 1H), 3.81 (d, J = 17.1 Hz, 1H), 3.72 (d, J = 11.2 Hz, 1H), 3.63 (qd, J = 7.3, 2.1 Hz, 2H), 3.42 (d, J = 11.2 Hz, 1H), 1.88 (s, 3H), 1.48 (s, 9H), 1.39 (s, 9H), 1.28 (t, J = 7.3 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.0, 152.2, 152.0, 151.4, 149.5, 148.1, 147.3, 133.4, 129.2, 122.1, 120.9, 109.1, 108.3, 101.2, 83.1, 78.6, 73.4, 55.8, 49.3, 45.0, 34.5, 28.5, 28.1, 20.0, 13.5 ppm; LRMS (ESI) Calculated for $C_{29}H_{39}N_6O_8$ *m/z* (M+H): 599.3, Obsd. 599.3.

*4.2.6.7. tert-butyl (R,E)-2-((tert-butoxycarbonyl)imino)-1-(2,4-dimethoxybenzyl)-7′-methyl-1′,3′-dioxo-2′-phenyl-2′,3′-dihydro-1′H,8′H-spiro[imidazolidine-4,5′-[1,2,4]triazolo[1,2-a]pyridazine]-3-carboxylate (**8g**).* Prepared according to the general procedure 6, to give the spiro-cyclic guanidine as pale yellow solid in 97% yield (0.193 g). R_f = 0.13 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.25 (m, 6H), 6.41 (m, 2H), 5.44 (s, 1H), 4.85 (d, J = 14.5 Hz, 1H), 4.39 (d, J = 14.5 Hz, 1H), 4.21 (d, J = 16.9 Hz, 1H), 3.89 (d, J = 16.9 Hz, 1H), 3.87 (d, J = 11.3 Hz, 1H), 3.75 (s, 6H), 3.47 (d, J = 11.3 Hz, 1H), 1.88 (s, 3H), 1.48 (s, 9H), 1.40 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.6, 158.9, 158.7, 152.3, 150.7, 149.9, 149.4, 132.9, 131.5, 131.0, 129.0, 128.2, 125.8, 120.7, 115.6, 104.3, 98.2, 82.9, 78.1, 73.6, 55.7, 55.3, 55.2, 44.8, 43.2, 28.4, 27.9, 19.8 ppm; LRMS (ESI) Calculated for $C_{34}H_{43}N_6O_8$ *m/z* (M+H): 663.3, Obsd. 663.4.

*4.2.6.8. tert-butyl (4R,10a′R,E)-2-((tert-butoxycarbonyl)imino)-1-methyl-1′,3′-dioxo-2′-phenyl-2′,3′,8′,9′,10′,10a′-hexahydro-1′H,7′H-spiro[imidazolidine-4,5′-[1,2,4]triazolo[1,2-a]cinnoline]-3-carboxylate (**8h**).* Prepared according to the general procedure 6, to give the spiro-cyclic guanidine as pale yellow solid in 76% yield (0.127 g). R_f = 0.13 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.33 (m, 5H), 5.43 (s, 1H), 4.42 (dd, J = 11.3, 3.4 Hz, 1H), 4.00 (d, J = 11.0 Hz, 1H), 3.82 (d, J = 11.0 Hz, 1H), 3.00 (s, 3H), 2.53 (m, 1H), 2.42 (m, 1H), 2.16 (m, 1H), 2.00 (m, 1H), 1.94 (m, 1H), 1.61 (m, 1H), 1.49 (m, 1H), 1.46 (s, 9H), 1.41 (s, 9H), 1.36 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.8, 153.1, 151.5, 149.3, 148.5, 142.6, 130.9, 129.0, 128.2, 126.0, 115.5, 83.0, 78.0, 73.6, 58.7, 54.2, 34.2, 32.2, 30.9, 28.3, 28.1, 28.0, 24.2 ppm; LRMS (ESI) Calculated for $C_{29}H_{39}N_6O_6$ *m/z* (M+H): 567.3, Obsd. 567.4.

*4.2.6.9. tert-butyl (4R,5R,E)-5-benzyl-2-((tert-butoxycarbonyl)imino)-1-(cyclopropylmethyl)-7′-methyl-1′,3′-dioxo-2′-phenyl-2′,3′-dihydro-1′H,8′H-spiro[imidazolidine-4,5′-[1,2,4]triazolo[1,2-a]pyridazine]-3-carboxylate (**8i**).* Prepared according to general procedure 6, to give the spiro-cyclic guanidine as white solid in 88% yield (0.173 g). R_f = 0.30 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.13 (m, 10H), 5.57 (s, 1H), 5.24 (dd, J = 11.3, 4.3 Hz, 1H), 4.04 (dd, J = 14.6, 5.4 Hz, 1H), 3.92 (d, J = 16.6 Hz, 1H), 3.37 (dd, J = 14.6, 4.2 Hz, 1H), 2.88 (d, J = 16.6 Hz, 1H), 2.79 (dd, J = 14.6, 8.2 Hz, 1H), 2.67 (dd, J = 14.6, 11.3 Hz, 1H), 1.77 (s, 3H), 1.48 (s, 9H), 1.35 (s, 9H), 1.13 (m, 1H), 0.63 (m, 1H), 0.51 (m, 1H), 0.22 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.0, 151.8, 150.0, 149.8, 149.3, 135.9, 134.2, 131.0, 129.3, 129.0, 128.6, 128.4, 127.0, 125.8, 117.7, 83.4, 78.6, 77.2, 61.8, 48.0, 44.0, 34.8, 28.5, 28.1, 20.2, 8.5, 5.2, 2.5 ppm; LRMS (ESI) Calculated for $C_{36}H_{45}N_6O_6$ *m/z* (M+H): 657.3, Obsd. 657.4.

*4.2.7. (4R,10a′R)-1-benzyl-2-imino-2′-phenyl-8′,9′,10′,10a′-tetrahydro-1′H,7′H-spiro[imidazolidine-4,5′-[1,2,4]triazolo[1,2-a]cinnoline]-1′,3′(2′H)-dione (**9a**)*

A 50 mL round-bottom flask was charged with the appropriate polycyclic guanidine (0.2 mmol). The CH_2Cl_2/TFA mixture (1:1, 4.0 mL) was added. The reaction mixture was stirred at room temperature for 2 h. The crude mixture was taken up in MeOH and 2 M HCl in ethyl ether was added. The mixture was again concentrated and the resulting solid triturated with ethyl ether. The solid was then collected to give the title compound as white solid in 50% yield (48 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.81 (s, 1H), 8.56 (s, 2H), 7.52–7.32 (m, 10H), 5.56 (s, 1H), 4.79 (d, J = 12.4 Hz, 1H), 4.56 (d, J = 12.4 Hz, 1H), 4.42 (m, 1H), 4.15 (s, 1H), 3.79 (s, 1H), 2.37 (m, 1H), 2.18 (m, 2H), 1.83 (m, 1H), 1.75 (m, 1H), 1.55 (m, 1H), 1.37 (m, 1H), 1.21 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 156.7, 152.0, 149.1, 140.8, 134.1, 130.4, 128.9, 128.4, 128.3, 127.8, 127.6, 126.0, 116.5, 72.6, 57.0, 53.7, 47.8, 32.7, 29.8, 27.3, 23.2 ppm; HRMS (ESI) Calculated for $C_{25}H_{27}N_6O_2$ *m/z* (M+H): 443.2195, Obsd. 443.2197.

*4.2.8. General procedure 7 for the deprotection and fragmentation of **8a-i***

A 50 mL round-bottom flask was charged with the appropriate polycyclic guanidine (0.2 mmol). The CH_2Cl_2/TFA mixture (1:1, 4.0 mL) was added. The reaction mixture was stirred at room temperature for 2 h. The crude mixture was taken up in MeOH and 2 M HCl in ethyl ether was added. The mixture was again concentrated and the resulting solid triturated with ethyl ether. The solid was then collected to give the title compound.

*4.2.8.1. (R,Z)-1-(2-((2-amino-1-benzyl-1H-imidazol-4-yl)methylene)cyclohexyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (**10a**).* Prepared according to the general procedure 7, to give the polycyclic guanidine as white solid in 50% yield (48 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.61 (s, 1H), 10.51 (s, 1H), 7.96 (s, 2H), 7.51–7.30 (m, 10H), 7.08 (s, 1H), 6.09 (s, 1H), 5.15 (d, J = 14.6 Hz, 1H), 5.10 (d, J = 14.6 Hz, 1H), 4.80 (s, 1H), 2.61 (m, 1H), 2.30 (m, 1H), 2.23 (m, 1H), 1.79 (m, 2H), 1.54 (m, 2H), 1.36 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 153.1,

152.8, 145.6, 140.1, 134.8, 131.3, 128.5, 127.8, 127.6, 127.3, 125.9, 121.7, 113.9, 113.1, 55.0, 47.4, 32.7, 29.2, 26.3, 20.2 ppm; HRMS (ESI) Calculated for $C_{25}H_{28}N_6O_2$ *m/z* (M+H): 443.2195, Obsd. 443.2197.

*4.2.8.2. (R,Z)-1-(2-((2-amino-1,5-dibenzyl-1H-imidazol-4-yl)methylene)cyclohexyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (**10b**).* Prepared according to the general procedure 7, to give the polycyclic guanidine as white solid in 85% yield (97 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.59 (s, 1H), 10.53 (s, 1H), 7.99 (s, 2H), 7.46–6.99 (m, 15H), 6.17 (s, 1H), 5.06 (d, J = 17.5 Hz, 1H), 4.99 (d, J = 17.5 Hz, 1H), 4.89 (s, 1H), 3.82 (d, J = 17.5 Hz, 1H), 3.78 (d, J = 17.5 Hz, 1H), 2.54 (m, 1H), 2.42 (m, 1H), 2.28 (m, 1H), 1.82 (m, 2H), 1.64 (m, 1H), 1.54 (s, 9H), 1.36 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 153.5, 153.2, 147.2, 142.5, 136.7, 134.7, 131.8, 128.7, 128.6, 128.5, 127.9, 127.8, 127.6, 126.6, 126.4, 126.1, 123.4, 119.3, 118.9, 55.4, 45.3, 33.0, 30.1, 27.8, 27.3, 20.5 ppm; HRMS (ESI) Calculated for $C_{32}H_{34}N_6O_2$ *m/z* (M+H): 533.2665, Obsd. 533.2669.

*4.2.8.3. (Z)-1-(3-(2-amino-1-benzyl-1H-imidazol-4-yl)-2-methylallyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (**10c**).* Prepared according to the general procedure 7, to give the polycyclic guanidine as white solid in 80% yield (70 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.63 (s, 1H), 11.02 (s, 1H), 7.99 (s, 2H), 7.50–7.31 (m, 10H), 7.25 (s, 1H), 6.16, (s, 1H), 5.17 (s, 2H), 4.35 (s, 2H), 1.84 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 152.6, 152.1, 145.8, 136.0, 135.2, 131.6, 128.8, 128.7, 128.0, 127.8, 127.5, 126.0, 122.0, 114.6, 114.5, 47.6, 47.2, 21.1 ppm; HRMS (ESI) Calculated for $C_{22}H_{23}N_6O_2$ *m/z* (M+H): 403.1882, Obsd. 403.1888.

*4.2.8.4. (Z)-1-(3-(2-amino-1,5-dibenzyl-1H-imidazol-4-yl)-2-methylallyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (**10d**).* Prepared according to the general procedure 7, to give the polycyclic guanidine as white solid in 68% yield (72 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.73 (s, 1H), 11.05 (s, 1H), 7.96 (s, 2H), 7.52–7.02 (m, 15H), 6.30 (s, 1H), 5.05 (s, 2H), 4.12 (s, 2H), 3.82 (s, 2H), 1.83 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 152.8, 152.3, 147.2, 136.7, 136.6, 134.8, 131.8, 128.9, 128.7, 128.6, 128.0, 127.9, 127.7, 126.7, 126.2, 126.1, 123.6, 119.4, 114.9, 47.2, 45.3, 28.0, 21.3 ppm; HRMS (ESI) Calculated for $C_{29}H_{29}N_6O_2$ *m/z* (M+H): 493.2352, Obsd. 493.2363.

*4.2.8.5. (Z)-1-(3-(2-amino-1-(benzo[d][1,3]dioxol-5-ylmethyl)-1H-imidazol-4-yl)-2-methylallyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (**10e**).* Prepared according to the general procedure 7, to give the polycyclic guanidine as pale yellow solid in 81% yield (78 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.40 (s, 1H), 10.91 (s, 1H), 7.85 (s, 2H), 7.30–7.18 (m, 5H), 7.09 (s, 1H), 6.87 (s, 1H), 6.76–6.69 (m, 2H), 5.95 (s, 1H), 5.80 (s, 2H), 4.87 (s, 2H), 4.16 (s, 2H), 1.63 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 152.7, 152.3, 147.2, 145.7, 136.0, 131.7, 128.9, 128.8, 127.9, 126.1, 122.0, 121.8, 114.8, 114.4, 108.6, 108.4, 101.2, 47.5, 47.3, 21.2 ppm; HRMS (ESI) Calculated for $C_{23}H_{23}N_6O_4$ *m/z* (M+H): 447.1781, Obsd. 447.1785.

*4.2.8.6. (Z)-1-(3-(2-amino-1-(benzo[d][1,3]dioxol-5-ylmethyl)-1H-imidazol-4-yl)-2-methylallyl)-4-ethyl-1,2,4-triazolidine-3,5-dione (**10f**).* Prepared according to the general procedure 7, to give the polycyclic guanidine as white solid in 86% yield (75 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.58 (s, 1H), 10.63 (s, 1H), 8.01 (s, 2H), 7.24 (s, 1H), 7.05–6.88 (m, 3H), 6.09 (s, 1H), 6.00 (s, 2H), 5.05 (s, 2H), 4.24 (s, 2H), 3.42 (q, J = 7.3 Hz, 2H), 1.72 (s, 3H), 1.10 (t, J = 6.8 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 154.0, 153.6, 147.5, 147.2, 145.7, 136.2, 128.8, 122.0, 121.8, 114.5, 114.3, 108.6, 108.4, 101.2, 47.5, 47.1, 33.5, 21.1, 13.1 ppm; HRMS (ESI) Calculated for $C_{19}H_{23}N_6O_4$ *m/z* (M+H): 399.1781, Obsd. 399.1786.

*4.2.8.7. (Z)-1-(3-(2-amino-1-(2,4-dimethoxybenzyl)-1H-imidazol-4-yl)-2-methylallyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (**10g**).* Prepared according to the general procedure 7, to give the polycyclic guanidine as pale yellow solid in 80% yield (80 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.63 (s, 1H), 11.07 (s, 1H), 7.88 (s, 2H), 7.48–7.23 (m, 6H), 6.96 (s, 1H), 6.56–6.50 (m, 2H), 6.14 (s, 1H), 4.97 (s, 2H), 4.33 (s, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 1.82 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.9, 158.0, 152.7, 152.2, 145.8, 135.7, 131.6, 130.2, 128.8, 127.8, 126.1, 126.0, 121.5, 114.9, 114.8, 114.5, 104.6, 98.5, 55.5, 55.3, 47.2, 43.5, 21.2 ppm; HRMS (ESI) Calculated for $C_{24}H_{27}N_6O_4$ *m/z* (M+H): 463.2094, Obsd. 463.2094.

*4.2.8.8. (R,Z)-1-(2-((2-amino-1-methyl-1H-imidazol-4-yl)methylene)cyclohexyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (**10h**).* Prepared according to the general procedure 7, to give the polycyclic guanidine as white solid in 83% yield (67 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.57 (s, 1H), 10.59 (s, 1H), 7.77 (s, 2H), 7.46–7.37 (m, 5H), 7.02 (s, 1H), 6.09 (s, 1H), 4.81 (s, 1H), 3.43 (s, 3H), 2.63 (m, 1H), 2.37 (m, 1H), 2.23 (m, 1H), 1.82 (m, 2H), 1.53 (m, 2H), 1.37 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 153.1, 152.8, 145.8, 139.9, 131.4, 128.5, 127.6, 126.0, 121.1, 115.0, 113.0, 55.2, 32.8, 32.1, 29.4, 26.6, 20.3 ppm; HRMS (ESI) Calculated for $C_{19}H_{23}N_6O_2$ *m/z* (M+H): 367.1882, Obsd. 367.1880.

*4.2.8.9. (Z)-1-(3-(2-amino-5-benzyl-1-(cyclopropylmethyl)-1H-imidazol-4-yl)-2-methylallyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (**10i**).* Prepared according to the general procedure 7, to give the polycyclic guanidine as white solid in 80% yield (79 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.53 (s, 1H), 10.96 (s, 1H), 7.76 (s, 2H), 7.50–7.19 (m, 10H), 6.28 (s, 1H), 4.49 (s, 2H), 4.00 (s, 2H), 3.66 (d, J = 4.2 Hz, 2H), 1.82 (s, 3H), 0.89 (m, 1H), 0.35 (m, 2H), 0.27 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 152.8, 152.2, 146.7, 137.0, 136.1, 131.7, 128.8, 128.7, 128.0, 127.8, 126.7, 126.1, 123.4, 119.0, 114.8, 47.3, 46.0, 27.8, 21.2, 10.0, 3.3 ppm; HRMS (ESI) Calculated for $C_{26}H_{30}N_6O_2$ *m/z* (M+H): 458.2430, Obsd. 458.2430.

4.2.9. General procedure 8 for the hetero cycloaddition of cyclic guanidines

To a stirring solution of the preferred cyclic guanidine (diene, 1 equiv) and benzyl hydroxycarbamate **11** (dienophile, 1.2 equiv) in THF (0.07 M) was added CuCl (20 mol%) and pyridine (5 mol%). The reaction was stirred at room temperature open to the air until completed by TLC. Upon completion, the reaction was quenched with EDTA (0.5 M, pH 7.0), diluted with ethyl acetate and stirred for 30 min. The reaction was extracted with ethyl acetate three times and the combined organic layers were then dried over Na_2SO_4, filtered, and condensed by rotary evaporation. Purification was accomplished by flash chromatography to give the polycyclic guanidine.

*4.2.9.1. 6-Benzyl 1-(tert-butyl) (4aR,6aS,E)-2-((tert-butoxycarbonyl)imino)-3-methyl-3,4,4a,6a,7,8,9,10-octahydro-1H-benzo[c]pyrimido[4,5-e][1,2]oxazine-1,6(2H)-dicarboxylate (**12a**).* The general procedure 8 was used to give the polycyclic guanidine as pale yellow solid. (0.160 g, 72% yield). R_f = 0.52 (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.31 (m. 5H), 5.25 (d, J = 12.7 Hz, 1H), 5.20 (d, J = 12.7 Hz, 1H), 4.80 (br, 1H), 3.59 (dd, J = 14.07, 7.3 Hz, 1H), 3.25 (d, J = 13.7 Hz, 1H), 3.16 (d, J = 14.2 Hz, 1H), 2.98 (s, 3H), 2.10 (m, 1H), 1.85 (m, 2H), 1.68 (m, 2H), 1.51 (s, 9H), 1.45 (m, 1H), 1.41 (s, 9H), 1.32 (m, 1H), 1.27 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.4, 154.2, 151.7, 149.2, 136.0, 134.0, 128.7, 128.6, 128.4, 128.2, 82.6, 78.6, 76.6, 67.7, 56.4, 49.9, 37.5, 32.2, 28.3, 28.1, 28.0, 26.3, 24.8 ppm; LRMS (ESI) Calculated for $C_{29}H_{41}N_4O_7$ *m/z* (M+H): 567.3, Obsd. 567.4.

*4.2.9.2. 6-Benzyl 1-(tert-butyl) (4aR,6aS,E)-2-((tert-butoxycarbonyl) imino)-3-(2,4-dimethoxybenzyl)-3,4,4a,6a,7,8,9,10-octahydro-1H-benzo[c]pyrimido[4,5-e][1,2]oxazine-1,6(2H)-dicarboxylate (**12b**).* Prepared according to the general procedure 8, to give the polycyclic guanidine as pale yellow solid in 51% yield (0.141 g). $R_f = 0.33$ (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 5H), 7.13 (m, 1H), 6.39 (m, 2H), 5.17 (d, J = 14.2 Hz, 1H), 5.14 (d, J = 14.2 Hz, 1H), 5.05 (d, J = 14.7 Hz, 1H), 4.76 (br, 1H), 4.07 (d, J = 14.7 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.47 (dd, J = 14.7, 7.3 Hz, 1H), 3.32 (m, 1H), 3.22 (d, J = 14.7 Hz, 1H), 2.03 (m, 1H), 1.83 (m, 2H), 1.68 (m, 1H), 1.49 (s, 9H), 1.46 (m, 1H), 1.39 (s, 9H), 1.37 (m, 1H), 1.25 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.6, 159.6, 159.0, 158.7, 154.4, 152.3, 149.5, 135.8, 130.5, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 117.0, 104.4, 98.5, 82.8, 79.0, 77.2, 67.6, 55.5, 55.4, 47.2, 46.2, 32.4, 28.5, 28.4, 28.3, 28.1, 26.6, 24.9 ppm; LRMS (ESI) Calculated for $C_{37}H_{49}N_4O_9$ *m/z* (M+H): 693.3, Obsd. 693.5.

*4.2.9.3. 2-Benzyl 5-(tert-butyl) (R,E)-7-(benzo[d][1,3]dioxol-5-ylmethyl)-6-((tert-butoxycarbonyl)imino)-4-methyl-6,7,8,8a-tetrahydro-2H-pyrimido[4,5-e][1,2]oxazine-2,5(3H)-dicarboxylate (**12c**).* Prepared according to the general procedure 8, to give the polycyclic guanidine as white solid in 61% yield (0.155 g). $R_f = 0.38$ (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.74–6.67 (m, 3H), 5.90 (s, 2H), 5.22 (d, J = 12.2 Hz, 1H), 5.15 (d, J = 12.2 Hz, 1H), 4.81 (br, 1H), 4.68 (d, J = 15.2 Hz, 1H), 4.36 (d, J = 15.7 Hz, 1H), 4.33 (d, J = 15.2 Hz, 1H), 3.92 (d, J = 15.7 Hz, 1H), 3.38 (dd, J = 14.7, 7.3 Hz, 1H), 3.10 (d, J = 14.7 Hz, 1H), 1.95 (s, 3H), 1.52 (s, 9H), 1.43 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.9, 155.0, 151.8, 149.3, 148.0, 147.3, 135.8, 129.7, 128.7, 128.6, 128.3, 127.6, 123.9, 121.9, 108.9, 108.3, 101.1, 82.9, 79.3, 75.8, 68.1, 52.0, 48.3, 46.5, 28.3, 28.1, 14.8 ppm; LRMS (ESI) Calculated for $C_{33}H_{41}N_4O_9$ *m/z* (M+H): 637.3, Obsd. 637.4.

*4.2.10. General procedure 9 for the deprotection and salt exchange of **12a-c***

A 50 mL round-bottom flask was charged with the appropriate polycyclic guanidine (0.2 mmol). The CH_2Cl_2/TFA mixture (1:1, 4.0 mL) was added. The reaction mixture was stirred at room temperature for 2 h, then the solvent removed under reduced pressure. The crude mixture was taken up in MeOH and 2 M HCl in ethyl ether was added. The mixture was again concentrated and the resulting solid triturated with ethyl ether. The solid was then collected to give the title compound.

*4.2.10.1. (4aR,6aS)-3-methyl-4,4a,6,6a,7,8,9,10-octahydro-1H-benzo[c]pyrimido[4,5-e][1,2]oxazin-2(3H)-imine (**13a**).* Prepared according to general procedure 9 (0.3 mmol scale), to give polycyclic guanidine as yellow solid in 95% yield (74 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.08 (s, 2H), 5.07 (s, 1H), 3.78 (s, 1H), 3.69 (s, 1H), 3.30 (d, J = 12.2 Hz, 1H), 3.01 (s, 3H), 2.92 (d, J = 12.2 Hz, 1H), 2.10 (m, 1H), 1.78 (m, 3H), 1.71 (m, 1H), 1.51 (m, 2H), 1.15 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 151.7, 119.5, 111.1, 66.3, 54.7, 47.4, 37.2, 30.2, 26.1, 25.9, 23.7 ppm; HRMS (ESI) Calculated for $C_{11}H_{19}N_4O$ *m/z* (M+H): 223.1559, Obsd. 223.1561.

*4.2.10.2. (4aR,6aS)-3-(2,4-dimethoxybenzyl)-4,4a,6,6a,7,8,9,10-octahydro-1H-benzo[c]pyrimido[4,5-e][1,2]oxazin-2(3H)-imine (**13b**).* Prepared according to the general procedure 9 (0.3 mmol scale), to give polycyclic guanidine as pale yellow solid in 89% yield (105 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.28 (s, 2H), 7.21 (m, 1H), 6.61–6.52 (m, 2H), 4.98 (m, 1H), 4.55 (d, J = 15.7 Hz, 1H), 4.47 (d, J = 15.7 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.55 (m, 1H), 3.15 (t, J = 10.7 Hz, 1H), 2.95 (m, 1H), 2.10 (m, 1H), 1.77 (m, 3H), 1.50 (m, 2H), 1.17 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.8, 158.3, 151.5, 130.4, 119.7, 113.7, 104.7, 98.6, 66.4, 55.6, 55.3, 54.7, 48.0, 45.0, 30.2, 26.2, 25.9, 23.8 ppm; HRMS (ESI) Calculated for $C_{19}H_{27}N_4O_3$ *m/z* (M+H): 359.2083, Obsd. 359.2092.

*4.2.10.3. (R)-7-(benzo[d][1,3]dioxol-5-ylmethyl)-4-methyl-3,7,8,8a-tetrahydro-2H-pyrimido[4,5-e][1,2]oxazin-6(5H)-imine (**13c**).* Prepared according to general procedure 9 (0.3 mmol scale), to give polycyclic guanidine as yellow solid in 95% yield (96 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.40 (s, 2H), 6.94–6.82 (m, 3H), 6.01 (s, 2H), 4.97 (m, 1H), 4.59 (d, J = 16.1 Hz, 1H), 4.53 (d, J = 16.1 Hz, 1H), 3.77 (d, J = 15.7 Hz, 1H), 3.62 (m, 1H), 3.59 (d, J = 15.7 Hz, 1H), 3.13 (t, J = 10.3 Hz, 1H), 1.77 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 151.3, 147.6, 147.1, 127.9, 121.9, 121.5, 108.4, 108.3, 104.4, 101.2, 66.6, 51.9, 46.4, 45.4, 13.4 ppm; HRMS (ESI) Calculated for $C_{15}H_{19}N_4O_3$ *m/z* (M+H): 303.11457, Obsd. 303.1458.

*4.2.11. N-((E)-amino((cyclopropylmethyl)(4-methylpent-4-en-2-yn-1-yl)amino)methylene)cinnamamide (**14**)*

N-cyanocinnamamide (0.172 g, 1.0 mmol) was stirred in CH_2Cl_2 (10 mL). Chlorotrimethylsilane (0.152 mL, 1.2 mmol) and NEt_3 (0.209 mL, 1.5 mmol) were then added and the mixture stirred for 15 min. Secondary amine **S-2k** (0.149 g, 1.0 mmol) was then added. Upon completion (as judged by TLC on a basified reaction aliquot), the reaction mixture was washed 3 times with $NaHCO_3$ and then washed with a sat. brine solution. The combined organic layers were dried over Na_2SO_4, filtered and concentrated by rotary evaporation. Purification was accomplished by flash chromatography to yield the propagylguaniline as a pale yellow oil (0.209 g, 65% yield). $R_f = 0.44$ (60% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 16.2 Hz, 1H), 7.55 (m, 2H), 7.36–7.29 (m. 3H), 6.67 (d, J = 16.2 Hz, 1H), 5.29 (s, 1H), 5.24 (s, 1H), 4.50 (s, 2H), 3.46 (s, 2H), 1.86 (s, 3H), 1.08 (m, 1H), 0.59 (m, 2H), 0.34 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.8, 160.6, 139.9, 136.0, 129.2, 129.0, 128.7, 127.9, 126.1, 122.7, 86.1, 82.7, 51.4, 37.2, 23.4, 9.6, 4.0 ppm; LRMS (ESI) Calculated for $C_{20}H_{24}N_3O$ *m/z* (M+H): 322.2, Obsd. 322.2.

*4.2.12. (R,Z)-1-(cyclopropylmethyl)-3-(2-methylallylidene)-7-phenyl-2,3,6,7-tetrahydroimidazo[1,2-a]pyrimidin-5(1H)-one (**15**)*

To a stirring solution of propargylguanidine **14** (0.5 mmol) in acetonitrile (5.0 mL) was added silver nitrate (0.05 mmol, 10 mol%). After completion, the reaction mixture was concentrated by rotary evaporation, and purified by column chromatography to yield the bicyclic guanidine as pale yellow solid in 83% yield (0.133 g). $R_f = 0.43$ (60% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.22 (m, 5H), 5.67 (s, 1H), 4.99 (s, 1H), 4.75 (s, 1H), 4.74 (dd, J = 10.8, 4.4 Hz, 1H), 4.13 (d, J = 11.9 Hz, 1H), 4.05 (d, J = 11.9 Hz, 1H), 3.33 (dd, J = 14.0, 6.5 Hz, 1H), 3.22 (dd, J = 14.0, 6.5 Hz, 1H), 2.84 (dd, J = 17.7, 4.4 Hz, 1H), 2.47 (dd, J = 17.7, 10.8 Hz, 1H), 1.83 (s, 3H), 1.01 (m, 1H), 0.59 (m, 2H), 0.26 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.3, 151.6, 143.5, 141.1, 128.6, 127.2, 126.5, 126.4, 116.1, 114.9, 56.4, 50.9, 49.1, 40.6, 22.0, 8.8, 3.7, 3.5 ppm; LRMS (ESI) Calculated for $C_{20}H_{24}N_3O$ *m/z* (M+H): 322.2, Obsd. 322.2.

*4.2.13. (3R,7R)-1-(cyclopropylmethyl)-7′-methyl-2′,7-diphenyl-1,2,2′,6,7-pentahydro-1′H,5H,8′H-spiro[imidazo[1,2-a]pyrimidine-3,5'-[1,2,4]triazolo[1,2-a]pyridazine]-1′,3′,5-trione (**16**)*

To a stirring solution of the desired 5-*exo-dig* cyclic guanidine (diene, 1 equiv) in CH_2Cl_2 (0.07 M) was added the appropriate triazoledione (dienophile, 1.2 equiv). After completion, the reaction mixture was concentrated by rotary evaporation, and purified by column chromatography to give the polycyclic guanidine as white solid in 40% yield (0.060 g). $R_f = 0.33$ (40% ethyl acetate/*n*-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.22 (m, 10H), 5.54 (d, J = 1.5 Hz, 1H), 4.78 (dd, J = 11.7, 4.9 Hz, 1H), 4.37 (d, J = 16.6 Hz, 1H), 4.17 (d,

$J = 9.8$ Hz, 1H), 4.07 (d, $J = 16.6$ Hz, 1H), 3.73 (d, $J = 9.8$ Hz, 1H), 3.43 (dd, $J = 14.9$, 6.9 Hz, 1H), 3.16 (dd, $J = 14.9$, 6.9 Hz, 1H), 2.73 (dd, $J = 16.6$, 4.9 Hz, 1H), 2.40 (dd, $J = 16.6$, 11.7 Hz, 1H), 1.94 (s, 3H), 1.01 (m, 1H), 0.55 (m, 2H), 0.23 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.9, 151.1, 150.2, 149.4, 144.2, 132.5, 131.1, 129.4, 128.7, 128.5, 127.2, 126.5, 125.7, 119.7, 72.0, 57.0, 56.5, 49.8, 45.4, 40.2, 20.1, 8.8, 3.7, 3.6 ppm; HRMS (ESI) Calculated for $C_{28}H_{29}N_6O_3$ *m/z* (M+H): 497.2301, Obsd. 497.2309.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.08.052.

References

1. Forte B, Malgesini B, Piutti C, Quartieri F, Scolaro A, Papeo G. A submarine journey: the pyrrole-imidazole alkaloids. *Marine Drugs*. 2009;7(4):705–753.
2. Wang X, Ma Z, Wang X, De S, Ma Y, Chen C. Dimeric pyrrole-imidazole alkaloids: synthetic approaches and biosynthetic hypotheses. *Chemical Commun Camb Engl*. 2014;50(63):8628–8639.
3. (a) Harris TL, Worthington RJ, Melander C. Potent small-molecule suppression of oxacillin resistance in methicillin-resistant Staphylococcus aureus. *Angew Chem Int Ed*. 2012;51(45):11254–11257;
(b) Yeagley AA, Su Z, McCullough KD, Worthington RJ, Melander C. N-Substituted 2-aminoimidazole inhibitors of MRSA biofilm formation accessed through direct 1,3-bis(tert-butoxycarbonyl)guanidine cyclization. *Org Biomol Chem*. 2013;11(1):130–137;
(c) Worthington RJ, Richards JJ, Melander C. Non-microbicidal control of bacterial biofilms with small molecules. *Anti Infect Agents*. 2014;12(1):120–138.
4. Al Mourabit A, Potier P. Sponge's molecular diversity through the ambivalent reactivity of 2-aminoimidazole: a universal chemical pathway to the oroidin-based pyrrole-imidazole alkaloids and their Palau'amine congeners. *Eur J Org Chem*. 2001;2001(2):237–243.
5. Gainer MJ, Bennett NR, Takahashi Y, Looper RE. Regioselective rhodium (II)-Catalyzed hydroaminations of propargylguanidines. *Angew Chem*. 2011;123(3):710–713.
6. Schroif-Gregoire C, Travert N, Zaparucha A, Al-Mourabit A. Direct access to marine pyrrole-2-aminoimidazoles, oroidin, and derivatives, via new acyl-1,2-dihydropyridin intermediates. *Org Lett*. 2006;8(14):2961–2964.
7. (a) Frazier CP, Engelking JR, Read de Alaniz J. Copper-catalyzed aerobic oxidation of hydroxamic acids leads to a mild and versatile acylnitroso Ene reaction. *J Am Chem Soc*. 2011;133(27):10430–10433;
(b) Frazier CP, Bugarin A, Engelking JR, Read de Alaniz J. Copper-catalyzed aerobic oxidation of N-Substituted hydroxylamines: efficient and practical access to nitroso compounds. *Org Lett*. 2012;14(14):3620–3623;
(c) Chaiyaveij D, Cleary L, Batsanov AS, Marder TB, Shea KJ, Whiting A. Copper(II)-Catalyzed room temperature aerobic oxidation of hydroxamic acids and hydrazides to acyl-nitroso and azo intermediates, and their Diels–Alder trapping. *Org Lett*. 2011;13(13):3442–3443.