“Thioureidopeptide”: Novel Synthon for the Synthesis of *N*, *N'*, *N''*-Trisubstituted Guanidinopeptide Mimics

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Abstract The synthesis of *N*^α-protected *N,N,N''*-trisubstituted guanidinopeptide mimic molecules suitably decorated in peptide backbone has been delineated in one pot employing HgCl₂ as a desulphurizing agent. Chiral *N*^α-protected thioureidopeptide esters were employed as synthons for the synthesis of title molecules. The protocol is simple and the reaction conditions employed were mild, amenable to the amino acid chemistry.

Keywords Thioureidopeptide · HgCl₂ · Desulphurization · *N,N,N''*-trisubstituted guanidinopeptide mimics

Introduction

Guanidine functionality is widespread in many natural and synthetic biologically active molecules. Arginine rich peptide sequences such as HIV-1 TAT and penetratin are known to possess cell membrane translocating properties (Jadhav et al. 1998; Pepinsky et al. 1994). Guanidine head group of arginine is responsible for protein enzyme ion pairing, nitric oxide synthesis and insulin sensitivity (Zhang et al. 1997; Fast et al. 1997). The low bioavailability and cell membrane permeability of peptides limit their wider utility as tools in molecular biology. Many different types of unnatural biomimetics have been studied,

of which backbone modified guanidine tethered peptidomimetics is one of the subjects of our current interest (Farmer 1980; Spatola 1983; Lam et al. 1997; Ahn et al. 2002). Since the alkyl substituted guanidines are present in natural products and arginine containing peptide systems (Berlinck and Kossuga 2005; Berlinck et al. 2008; Heys et al. 2000), methods for the synthesis of guanidines with multiple substitution patterns are desirable.

Synthesis of substituted guanidines has been investigated both in solid phase and in solution phase. Detailed literature survey revealed several synthetic entries into substituted guanidine systems. These transformations include the reaction of alkyl or aryl guanidines with various electrophiles under basic conditions (Augstein et al. 1965; Stahle et al. 1980). Others involve the reaction of electrophilic precursor of guanidine moiety with a primary or secondary amine. Electrophilic imino centres generated from urea or thiourea and carbodiimide obtained by the dehydration or desulphurization of urea or thiourea respectively serve as suitable starting materials for the synthesis of trisubstituted guanidines (Barton et al. 1982; Barvian et al. 1997). In many of the above mentioned reactions, thiourea was employed as one of the precursors in the presence of EDCI, Sanger's reagent, Mukaiyama reagent, HgCl₂ to afford trisubstituted guanidines (Jefferson et al. 2004; Li et al. 2003). However, the most widely used method involves the addition of nucleophilic amine to the in situ generated active carbodiimide from the corresponding thiourea (Kurzer and Douraghi-Zadeh 1967; Shibaruma et al. 1977; Kim and Yi 1986a, b; Isobe and Ishikawa 1999). For the generation of carbodiimide from thiourea, heavy metal thiophiles such as Hg salt have been employed to effect the transformation (Li et al. 2002; Dudic et al. 2004; Luo et al. 2008). Guanylation of thiourea using HgCl₂ has long been reported in the literature and

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thus widely used protocol for guanylation reaction, as the work up procedure was simple. Also the yield was relatively promising.

The guanidine chemistry has not been much explored in the context of peptidomimetics except for the arginine analogs (Feichtinger et al. 1998a, b; Zapf et al. 2001; Schade et al. 2008; Martin et al. 2008; Balakrishnan et al. 2007). Recently Suhs and König (2006) reported the synthesis of functionalized guanidino amino acids which were structurally related to Arg and resembled a dipeptide having α - and γ -amino acid with a guanidinium group in the main chain. (Zhang et al. 2003; Zhang and Fan 2005) developed a strategy for the preparation of *N,N'*-bridged oligomeric guanidines bearing peptide side chains. Tri-functional amino acids and the corresponding peptides pose some limitations which otherwise will be useful if properly utilized by employing them as suitable synthons.

In continuation of our interest in synthesizing variety of backbone modified peptide surrogates such as ureidopeptides, thioureidopeptides, dithiocarbamate, trithiocarbonate, and heterocycles (Patil et al. 2003; Sureshbabu et al. 2009), we sought to synthesize another surrogate i.e., guanidinopeptide mimics. We envisaged that *N*-protected thioureidopeptides can be useful synthons for *N^z*-protected *N,N',N''*-trisubstituted guanidinopeptide mimics via desulphurization employing HgCl_2 .

Experimental

Materials and Methods

All solvents were freshly distilled before use. Amino acids were used as received from Sigma-Aldrich Company. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 300 MHz and 75 MHz respectively, with $\text{DMSO}-d_6$ as an internal standard. Mass spectra were recorded using high resolution mass spectrometer (HRMS) Q-T of mass spectrometer and the samples were dried under vacuum before analysis. All the reactions were monitored using TLCs with precoated silica gel plates purchased from Merck. Chiral HPLC analysis of isomers was carried out by Agilent 1100 series, Lux 5u Amylose-2, 250×4.60 mm.

Typical Procedure for the Preparation of Trisubstituted Guanidinopeptides (2a–k)

The starting thioureidopeptide (1.0 mmol) and amine (1.2 mmol) were dissolved in dimethylformamide (5 mL/mmol) at room temperature. The mixture was then charged with triethylamine (2.2 mmol) and cooled in an ice bath. Mercuric chloride (0.35 mmol) was then added at 0°C and the mixture was stirred for 20 min before it was warmed to

room temperature. When the reaction was completed as monitored through TLC, the reaction mixture was diluted with ethyl acetate (10 mL) and filtered through Celite. The Celite cake was then washed with additional ethyl acetate (5 mL). The filtrate was washed with water, then with brine and the organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo under reduced pressure. The crude product thus obtained was further purified on a silica gel column (EtOAc: Hexane).

Spectroscopic Data of Compounds 2a–j

(2*S*, 3*R*)-Methyl-2-(3-((*S*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)propyl)-2-phenylguanidino)-3-methylpentanoate (**2a**) 330 mg

^1H NMR (300 MHz, CDCl_3) δ 0.94 (t, $J = 4.2$ Hz, 3H), 0.99 (d, $J = 4.6$ Hz, 3H), 1.24–1.30 (m, 2H), 1.29 (d, $J = 6.8$ Hz, 3H), 2.04–2.07 (m, 1H), 2.94–3.03 (m, 2H), 3.71 (s, 3H), 4.02–4.07 (m, 1H), 4.42 (t, $J = 6.1$ Hz, 1H), 4.62 (d, $J = 7.1$ Hz, 2H), 4.89–4.93 (m, 1H), 5.41 (br s, 1H), 6.12 (br s, 1H), 6.73 (br, 1H), 7.10–7.75 (m, 13H); ^{13}C NMR (75 MHz, CDCl_3) δ 10.4, 16.3, 18.9, 28.6, 35.0, 42.4, 46.4, 48.2, 50.6, 52.3, 66.4, 120.6, 125.4, 125.8, 127.4, 127.6, 128.4, 128.8, 139.1, 141.0, 143.2, 155.2, 155.9, 172.1; HRMS calcd for $\text{C}_{32}\text{H}_{38}\text{N}_4\text{O}_4$ m/z 565.1796 ($\text{M}^+ + \text{Na}$), found 565.1702.

(*S,E*)-Methyl-2-(3-(2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)ethyl)-2-*m*-tolylguanidino)-3-phenylpropanoate (**2b**) 380 mg

^1H NMR (300 MHz, CDCl_3) δ 2.32 (s, 3H), 2.95–3.03 (m, 2H), 3.12–3.24 (m, 4H), 3.67 (s, 3H), 3.77–3.82 (m, 1H), 4.12–4.28 (m, 1H), 4.66 (d, $J = 5.6$ Hz, 2H), 5.17 (br s, 1H), 6.18 (br s, 1H), 6.54 (br s, 1H), 7.00–7.06 (m, 2H), 7.15–7.41 (m, 9H), 7.53 (d, $J = 7.2$ Hz, 2H), 7.68 (d, $J = 7.6$ Hz, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.1, 37.6, 39.8, 41.3, 47.7, 60.7, 67.3, 120.4, 125.1, 125.6, 127.5, 128.1, 129.4, 129.8, 134.9, 141.8, 144.4, 156.2, 158.1, 173.9; HRMS calcd for $\text{C}_{35}\text{H}_{36}\text{N}_4\text{O}_4$ m/z 599.2634 ($\text{M}^+ + \text{Na}$), found 599.2636.

(*S,E*)-Methyl-2-(3-(2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)ethyl)-2-benzylguanidino)-4-methylpentanoate (**2c**) 368 mg

^1H NMR (300 MHz, CDCl_3) δ 0.92 (d, $J = 5.4$ Hz, 6H), 1.45–1.71 (m, 3H), 2.52–2.63 (m, 2H), 2.79 (m, 2H), 2.97 (s, 2H), 3.31 (t, $J = 4.2$ Hz, 1H), 3.69 (s, 3H), 4.32 (t, $J = 2.9$ Hz, 1H), 4.49 (d, $J = 7.2$ Hz, 2H), 5.69 (br s, 1H), 6.24 (s, br, 1H), 6.75 (br s, 1H), 7.09–7.81 (m, 13H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.8, 22.5, 38.4, 41.1, 44.2,

46.9, 50.8, 52.0, 54.3, 67.2, 119.8, 125.0, 126.8, 126.9, 127.6, 128.3, 129.2, 136.2, 141.1, 143.7, 154.3, 156.6, 170.7; HRMS calcd for $C_{32}H_{38}N_4O_4$ m/z 565.1615 ($M^+ + Na$), found 565.1603.

(2*S*,3*R*)-Benzyl-2-(3-((*S*)-2-(benzyloxycarbonyl)-2-phenylethyl)-2-(3-chlorophenyl)guanidino)-3-methylpentanoate (**2d**) 406 mg

1H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, $J = 4.1$ Hz, 3H), 0.98 (d, $J = 4.4$ Hz, 3H), 1.26–1.31 (m, 2H), 2.11–2.17 (m, 1H), 3.56 (d, $J = 4.2$ Hz, 2H), 3.67–3.72 (m, 1H), 4.75–4.80 (m, 1H), 5.12 (s, 4H), 5.34 (br s, 1H), 5.89 (br s, 1H), 6.56 (br s, 1H), 6.96–7.55 (m, 19H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 18.7, 28.8, 38.5, 48.6, 50.9, 62.3, 66.1, 125.0, 126.3, 127.0, 127.5, 127.6, 128.4, 140.6, 141.4, 155.6, 158.79, 171.2; HRMS calcd for $C_{36}H_{39}ClN_4O_4$ m/z 649.2558 ($M^+ + Na$), found 649.2556.

(*S*)-Methyl-2-(2-benzyl-3-((*S*)-2-(benzyloxycarbonyl)-3-methylbutyl)guanidino) propanoate (**2e**) 304 mg

1H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, $J = 3.2$ Hz, 6H), 1.39 (d, $J = 5.6$ Hz, 3H), 2.11–2.16 (m, 1H), 3.52–3.57 (m, 2H), 3.71 (s, 3H), 3.87–3.91 (m, 1H), 4.42–4.52 (m, 1H), 5.12 (s, 2H), 5.28 (s, 2H), 5.36 (br s, 1H), 5.92 (br s, 1H), 6.52 (br s, 1H), 7.25–7.46 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 18.7, 34.8, 42.4, 53.1, 53.3, 57.9, 61.3, 67.6, 128.3, 128.4, 128.7, 129.0, 136.5, 138.9, 156.6,

X = Me or Bzl moiety; Pg = Fmoc, Cbz or Boc group.

Scheme 1 Synthesis of N^x -protected N,N',N'' -trisubstituted guanidino peptide mimics **2a-i**

159.2, 172.0; HRMS calcd for $C_{25}H_{34}N_4O_4$ m/z 477.2478 ($M^+ + Na$), found 477.2474.

(*S*)-Methyl-2-(3-((*S*)-2-(*tert*-butoxycarbonyl)-3-phenylpropyl)-2-(4-methoxyphenyl)guanidino)-4-methylpentanoate (**2f**) 362 mg

1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, $J = 5.4$ Hz, 6H), 1.45 (s, 9H), 1.47–1.71 (m, 3H), 2.79–2.88 (m, 2H), 2.00–2.20 (m, 1H), 3.51–3.56 (m, 2H), 3.63 (s, 3H), 3.74 (s, 3H), 3.85–4.00 (m, 1H), 4.80–4.95 (m, 1H), 5.24 (br s, 1H), 5.86 (br s, 1H), 6.57 (br s, 1H), 7.05–7.35 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 19.3, 21.5, 29.7, 30.2, 43.6, 48.2, 50.1, 63.4, 65.2, 82.3, 128.1, 128.3, 128.7, 129.1, 136.3, 138.7, 155.1, 160.1, 172.2; HRMS calcd for $C_{29}H_{42}N_4O_5$ m/z 549.3053 ($M^+ + Na$), found 549.3050.

(*S*)-Methyl-2-(3-((*S*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)propyl)-2-(3-chlorophenyl)guanidino)-3-methylbutanoate (**2 g**) 337 mg

1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, $J = 3.7$ Hz, 6H), 1.17 (d, $J = 6.4$ Hz, 3H), 2.12–2.20 (m, 1H), 2.41 (d, $J = 4.8$ Hz, 1H), 2.82 (d, $J = 7.1$ Hz, 1H), 2.89 (d, $J = 11.2$ Hz, 1H), 3.52 (s, 3H), 3.85–3.92 (m, 1H), 4.51 (t, $J = 6.6$ Hz, 1H), 4.81 (d, $J = 5.6$ Hz, 2H), 6.12 (br s, 1H), 6.93 (br s, 1H), 7.12–7.75 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 18.9, 30.9, 42.7, 46.9, 49.4, 55.4, 57.9, 66.6, 119.7, 124.9, 126.8, 127.5, 128.0, 128.3, 135.4, 141.0, 143.6, 143.7, 153.9, 156.6, 170.1; ES-MS calcd for $C_{31}H_{35}ClN_4O_4$ m/z 586.09 ($M^+ + Na$), found 586.07.

(*S,E*)-Methyl-2-(3-(2-(benzyloxycarbonyl)ethyl)-2-*p*-tolylguanidino)-4-methylpentanoate (**2 h**) 295 mg

1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, $J = 3.8$ Hz, 6H), 1.15–1.22 (m, 2H), 1.71–1.83 (m, 1H), 2.91–3.06 (m, 2H), 3.18–3.23 (m, 2H), 3.61 (s, 3H), 3.96–4.02 (m, 1H), 5.04

Scheme 2 Possible reaction pathway for the synthesis of N^x -protected N,N',N'' -trisubstituted guanidino peptide mimics from thioureido peptide

Table 1 List of N^Z -urethane protected N,N',N'' -trisubstituted guanidinopeptide mimics **2a–i**

Entry	Amine (R^2)	N^Z -protected trisubstituted guanidinopeptide mimics (2)	Mp ($^{\circ}\text{C}$)	Yield (%)
1			112–114	61
2			131–135	66
3			136–137	68
4			Gum	65
5			Gum	67
6			Gum	69
7			158–159	60
8			Gum	65
9			Gum	59

(s, 2H), 5.92 (br s, 1H), 6.51 (br s, 1H), 7.01–7.29 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ 23.2, 23.5, 34.23, 37.9, 41.2, 42.7, 51.1, 58.4, 67.1, 128.2, 128.5, 129.0, 129.2, 138.4, 140.6, 156.4, 159.8, 170.0; HRMS calcd for $\text{C}_{25}\text{H}_{34}\text{N}_4\text{O}_4$ m/z 477.2478 ($\text{M}^+ + \text{Na}$), found 477.2476.

(*S*)-Methyl-2-(2-benzyl-3-((*S*)-2-(*tert*-butoxycarbonyl)-3-phenylpropyl)guanidino)propanoate (**2i**) 276 mg

^1H NMR (300 MHz, CDCl_3) δ 1.24 (d, $J = 3.6$ Hz, 3H), 1.43 (s, 9H), 2.74 (d, $J = 4.0$ Hz, 2H), 3.41–3.46 (m, 2H), 3.62 (s, 3H), 3.72–3.79 (m, 1H), 3.98–4.02 (m, 1H), 4.93 (s, 2H), 5.26 (br s, 1H), 6.01 (br s, 1H), 6.89 (br s, 1H), 7.07–7.23 (m, 10H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.9, 29.5, 33.6, 38.7, 47.3, 53.3, 60.7, 66.6, 80.3, 126.6, 127.6, 127.9, 128.3, 128.5, 129.0, 136.1, 136.9, 156.2, 159.3, 172.5; HRMS calcd for $\text{C}_{26}\text{H}_{36}\text{N}_4\text{O}_4$ m/z 491.2634 ($\text{M}^+ + \text{Na}$), found 491.2631.

(9*H*-Fluoren-9-yl)methyl-(*S*)-1-(2-benzyl-3-((*S*)-1-phenylethyl)guanidino)-3-phenylpropan-2-ylcarbamate (**2j**) 376 mg

^1H NMR (300 MHz, CDCl_3) δ 1.48 (d, $J = 6.0$ Hz, 3H), 2.73–2.75 (m, 2H), 3.48–3.51 (m, 2H), 3.66–3.69 (m, 1H), 3.85–3.89 (m, 1H), 4.12 (t, $J = 3.8$ Hz, 1H), 4.24 (d, $J = 3.6$ Hz, 2H), 5.02 (s, 2H), 5.20 (br s, 1H), 5.92 (br s, 1H), 6.58 (br s, 1H), 7.01–7.49 (m, 23H); ^{13}C NMR (75 MHz, CDCl_3) δ 22.8, 38.5, 42.8, 45.8, 47.2, 52.3, 53.9, 66.8, 126.8, 127.2, 127.7, 128.2, 128.5, 128.6, 128.9, 129.0, 136.2, 136.6, 139.8, 156.9, 159.8; HRMS calcd for $\text{C}_{40}\text{H}_{40}\text{N}_4\text{O}_2$ m/z 631.3049 ($\text{M}^+ + \text{Na}$), found 631.3051.

Results and Discussion

Initially, a test reaction was carried out by taking Cbz-Val- $\psi\text{CH}_2\text{-NH-C(S)-NH-Ala-OMe}$ as thiourea component in the presence of HgCl_2 and benzyl amine. The reaction was performed in the presence of triethylamine (TEA) at 0 °C to r.t under mild conditions. The reaction afforded the desired trisubstituted guanidinopeptide, Cbz-Val- $\psi\text{CH}_2\text{-NH-C(NBn)-NH-Ala-OMe}$ in good yield (67 %). During the course of the reaction, an aliquot of the reaction mixture was taken and analysed by IR. A strong absorption peak in the region $2118\text{--}2138\text{ cm}^{-1}$ corresponding to --N=C=N-- stretch of the carbodiimide formed in situ by the desulphurization of thioureidopeptide was noticed. The conditions were then optimized with respect to the equivalence of amine and HgCl_2 required (Scheme 1). It was found that 1.2 equiv. of amine and 0.35 equiv. of HgCl_2 afforded the product in good yields. The product was

isolated after a simple work up and characterized by mass, ^1H and ^{13}C NMR analyses.

Zhang and Fan (2005) reported that the Fmoc protected amino acid derived thiourea prepared by the reaction of Fmoc protected vicinal diamine with Pbf-NCS on desulphurization in presence of EDCI resulted in cyclic guanidine as major product. The reaction was mediated through the highly electrophilic carbodiimide (attached to Pbf) which can trap adjacent weakly nucleophilic carbamate nitrogen and undergoes intramolecular cyclization resulting in cyclic guanidine. However, in case of thioureidopeptides due to the lack of such electron withdrawing groups, the formed carbodiimide is comparatively less reactive than the aryl counterparts. To our delight intramolecular cyclization did not occur (ES-MS analysis of the obtained crude product revealed only the presence of trisubstituted guanidine and not the cyclized product), as the nucleophilicity of carbamate nitrogen is inefficient for addition to the less electrophilic carbodiimide. During the course of reaction, the amine component will preferably added to the carbodiimide in presence of base rather than the carbamate nitrogen, as illustrated in Scheme 2.

The generality of the protocol was further exemplified with a series of *N*-protected thioureidopeptides with different urethane protections such as Fmoc, Cbz and Boc, which on guanidinylation employing seven different aromatic amines with or without other substitutions resulted in trisubstituted guanidinopeptides in good yields (Table 1). Further, the structural analyses of the products were carried out through mass, ^1H and ^{13}C NMR spectroscopic analyses.

Also the protocol employed for the synthesis of title molecules was proved to be racemisation free as evidenced by the HPLC analysis of diastereomeric trisubstituted guanidinopeptides, **2j** and **2k** obtained by the reaction of corresponding chiral thioureidopeptides, Fmoc-Phe- $\psi[\text{CH}_2\text{NC(S)NH}]\text{-(S)-1-phenethylamine}$ and Fmoc-Phe- $\psi[\text{CH}_2\text{NC(S)NH}]\text{-(R)-1-phenethylamine}$ with benzylamine, which exhibited R_f values 12.4 and 12.7 min respectively. Whereas the equimolar mixture of **2j** and **2k** exhibited the R_f values 12.2 and 12.5 min, which indicated the presence of two different isomers.

Conclusion

In conclusion herein we described a simple and mild protocol for an efficient one pot transformation of thioureidopeptides into hitherto unreported class of *N*²-urethane protected *N,N',N''*-trisubstituted guanidinopeptide mimics in relatively good yields employing HgCl_2 as a desulphurizing agent. The protocol is simple and the reaction conditions employed were mild in affording products in moderate to good yields.

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Compliance with Ethical Standards

Conflict of interest Basavaprabhu, Girish Prabhu, Krishnamurthy M, Nageswara Rao P and Vommina V. Sureshbabu declare that they have no conflict of interest.

Informed consent Authors declare that there is no informed consent in the article.

Human and animal rights This article does not contain any studies with human or animal subjects performed by any of the authors.

References

- Ahn JM, Boyle NA, MacDonald MT, Janda KD (2002) Peptidomimetics and peptide backbone modifications. *Mini Rev Med Chem* 2:463–473
- Augstein J, Green SM, Monro AM, Potter GWH, Worthing CR, Wrigley TI (1965) Adrenergic neurone blocking agents derived from 1,4-benzodioxan. *J Med Chem* 8:446–456
- Balakrishnan S, Zhao C, Zondlo NJ (2007) Convergent and stereospecific synthesis of molecules containing alpha-functionalized guanidiniums via alpha-guanidino acids. *J Org Chem* 72:9834–9837
- Barton DHR, Elliot JD, Gero SD (1982) Synthesis and properties of a series of sterically hindered guanidine bases. *J Chem Soc Perkin Trans 1*:2085–2090
- Barvian MR, Showalter HDH, Doherty AM (1997) Preparation of N, N'-bis(aryl)guanidines from electron deficient amines via masked carbodiimides. *Tetrahedron Lett* 38:6799–6802
- Berlinck RGS, Kossuga MH (2005) Natural guanidine derivatives. *Nat Prod Rep* 22:516–550
- Berlinck RGS, Burtoloso ACB, Kossuga MH (2008) The chemistry and biology of organic guanidine derivatives. *Nat Prod Rep* 25:919–954
- Dudic M, Colombo A, Sansone F, Casnati A, Donofrio G, Ungaro RA (2004) general synthesis of water soluble upper rim calix[n]arene guanidinium derivatives which bind to plasmid DNA. *Tetrahedron* 60:11613–11618
- Farmer PS (1980) In: Ariens EJ (ed). *Drug design*, Academic Press, San Diego 10:119–143
- Fast WF, Levsky ME, Marletta MA, Silverman RB (1997) N^ω-Propargyl-L-arginine and N^ω-hydroxy- N^ω-propargyl-L-arginine are inhibitors, but not Inactivators of Neuronal and Macrophage Nitric Oxide Synthases. *Bioorg Med Chem* 5:1601–1608
- Feichtinger K, Zapf C, Sings HL, Goodman M (1998a) Diprotected triflylguanidines: a new class of guanidinylation reagents. *J Org Chem* 63:3804–3805
- Feichtinger K, Sings HL, Baker TJ, Matthews K, Goodman M (1998b) Triurethane-protected guanidines and triflyldiurethane-protected guanidines: new reagents for guanidinylation reactions. *J Org Chem* 63:8432–8439
- Heys L, Moore CG, Murphy PJ (2000) The guanidine metabolites of *Ptilocaulis spiculifer* and related compounds; isolation and synthesis. *Chem Soc Rev* 29:57–67
- Isobe T, Ishikawa T (1999) 2-Chloro-1,3-dimethylimidazolinium chloride: a powerful dehydrating equivalent to DCC. *J Org Chem* 64:6984–6988
- Jadhav PK, Woerner FJ, Lam PY, Hodge CN, Eyermann CJ, Man HW, Daneker WF, Bacheler LT, Rayner MM, Meek JL, Erickson-Vitanen S, Jackson DA, Calabrese JC, Schadt M, Chang CH (1998) Nonpeptide cyclic cyanoguanidines as HIV-1 protease inhibitors: synthesis, structure-activity relationships, and X-ray crystal structure studies. *J Med Chem* 41:1446–1455
- Jefferson EA, Seth PP, Robinson DE, Winter DK, Miyaji A, Osgood SA, Swayze EE, Risen LM (2004) Biaryl guanidine inhibitors of in vitro HCV-IRES activity. *Bioorg Med Chem Lett* 14:5139–5143
- Kim S, Yi KY (1986a) Di-2-pyridyl sulfite: a new useful reagent for the preparation of N-sulfinylamines, nitriles, isocyanides, and carbodiimides under mild conditions. *Tetrahedron Lett* 27:1925–1928
- Kim S, Yi KY (1986b) 1,1'-Thiocarbonyldi-2,2'-pyridone: a new useful reagent for functional group conversions under essentially neutral conditions. *J Org Chem* 51:2613–2615
- Kurzer F, Douraghi-Zadeh K (1967) Advances in the chemistry of carbodiimides. *Chem Rev* 67:107–152 and references therein
- Lam KS, Lebl M, Krchnak V (1997) The one-bead-one-compound combinatorial library method. *Chem Rev* 97:411–448
- Li H, Shimizu H, Flinspach M, Jamal J, Yang W, Xian M, Cai T, Wen EZ, Jia Q, Wang PG, Poulos T (2002) The novel binding mode of N-alkyl-N'-hydroxyguanidine to neuronal nitric oxide synthase provides mechanistic insights into NO biosynthesis. *Biochemistry* 41:13868–13875
- Li J, Zhang Z, Fan E (2003) TFA-sensitive arylsulfonylthiourea-assisted synthesis of N, N'-substituted guanidines. *J Org Chem* 68:1611–1614
- Luo G, Mattson GK, Bruce MA, Wong H, Murphy BJ, Longhi D, Antal-Zimanyi I, Poindexter GS (2008) Isosteric N-arylpiperazine replacements in a series of dihydropyridine NPY1 receptor antagonists. *Bioorg Med Chem Lett* 14:5975–5978
- Martin AL, Bernas L, Foster PF, Rutt BK, Gillies ER (2008) Enhanced cell uptake of superparamagnetic iron oxide nanoparticles functionalized with dendritic guanidines. *Bioconjugate Chem* 19:2375–2384
- Patil BS, Vasanthakumar GR, Sureshbabu VV (2003) Isocyanates of N^ω-[(9-fluorenylmethyl)oxy]carbonyl amino acids: synthesis, isolation, characterization, and application to the efficient synthesis of urea peptidomimetics. *J Org Chem* 68:7274–7280
- Pepinsky RB, Androphy EJ, Corina K, Brown R, Barsoum JG (1994) Specific inhibition of a human papillomavirus E2-trans activator by intracellular delivery of its repressor. *DNA Cell Biol* 13:1011–1019
- Schade D, Kotthaus J, Clement B (2008) Efficient synthesis of optically pure N^ω-alkylated L-arginines. *Synthesis* 15:2391–2397
- Shibaruma T, Shiono M, Mukayama T (1977) A convenient method for the preparation of carbodiimides using 2-chloropyridinium salt. *Chem Lett* 6(5):575–576
- Spatola AF (1983) In chemistry and biochemistry of amino acids, peptides, and proteins: a survey of recent developments; Weinstein B (ed), Marcel Dekker, New York 7:267–357
- Stahle H, Daniel H, Kobinger W, Lillie C, Pichler L (1980) Chemistry, pharmacology, and structure-activity relationships with a new type of imidazolines exerting a specific bradycardic action at a cardiac site. *J Med Chem* 23:1217–1222
- Suhs T, König B (2006) Synthesis of functionalized guanidino amino acids. *Chem Eur J* 12:8150–8157
- Sureshbabu VV, Naik SA, Narendra N, Hemantha HP (2009) N-Urethane-protected amino alkyl isothiocyanates: synthesis, isolation, characterization, and application to the synthesis of thioureidopeptides. *J Org Chem* 74:5260–5266
- Zapf CW, Creighton CJ, Tomioka M, Goodman M (2001) A novel traceless resin-bound guanidinylation reagent for secondary amines to prepare N, N'-disubstituted guanidines. *Org Lett* 3:1133–1136

- Zhang Z, Fan E (2005) Solid-phase and solution-phase syntheses of oligomeric guanidines bearing peptide side chains. *J Org Chem* 70:8801–8810
- Zhang HQ, Dixon RP, Marletta MA, Nikolic D, van Breemen R, Silverman RB (1997) Mechanism of Inactivation of Neuronal Nitric Oxide Synthase by N^ω-Allyl-L-arginine. *J Am Chem Soc* 119:10888–10902
- Zhang Z, Carter T, Fan E (2003) Oligomeric guanidine synthesis assisted by TFA-sensitive arylsulfonylthiourea. *Tetrahedron Lett* 44:3063–3066