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Dedicated to Acad. Maria Zaharescu
on the occasion of her 80th anniversary.
The authors acknowledge a long lasting friendship
and collaboration with Acad. Maria Zaharescu

INDOLIZINES AND AZAINDOLIZINES SUBSTITUTED WITH A PHENYLUREIDOBENZOYL MOIETY BY 1,3-DIPOLAR CYCLOADDITON OF THEIR CORRESPONDING *N*-YLIDES WITH ACETYLENES

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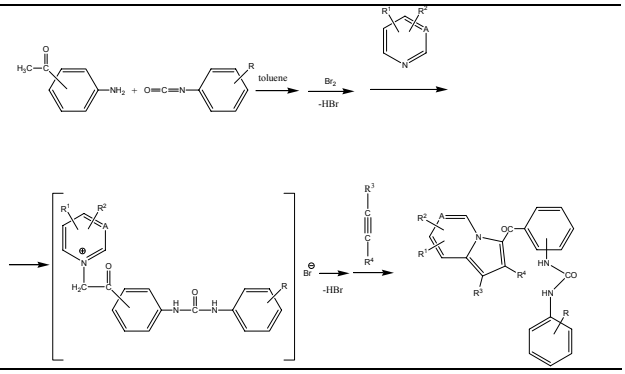
Reactions of 1-[4-(2-bromoacetyl)phenyl]-3-(R-phenyl)urea derivatives and 1-[3-(2-bromoacetyl)phenyl]-3-(R-phenyl)urea derivatives respectively, with pyridine, quinoline, or pyrimidine derivatives gave the corresponding *N*-heteroaryl quaternary salts. 1,3-Dipolar cycloaddition reactions of *in situ* generated *N*-heteroaryl-1-[3/4-(3-phenylureido)benzoyl]methylides with activated alkynes led to new indolizine, benzoindolizine or azaindolizine derivatives.



INTRODUCTION

Indolizine and azaindolizine derivatives are interesting *N*-bridgehead heterocyclic systems for both medicinal and material chemistry. By varying the type of substituents on indolizine and azaindolizine scaffolds fine tuning of a number of properties is possible. The importance of indolizine and azaindolizine derivatives has been demonstrated in the chemistry of natural products,[1-3] in materials science,[4-7] and in pharmaceutical chemistry.[8-12]

1,3-Dipolar cycloaddition reactions have long been utilized for developing novel lead structures of bio-active compounds and novel materials.[13-16] Offering both high yields and regioselectivity, 1,3-dipolar cycloaddition reactions represent a versatile synthetic method for obtaining a variety of indolizine and azaindolizine compounds. The 1,3-dipolar cycloaddition reactions between cycloimmonium ylides, usually generated *in situ* from the corespondin quaternary salts, and dipolarophiles is a widely used

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method for the synthesis of indolizines and azaindolizines.[17-27]

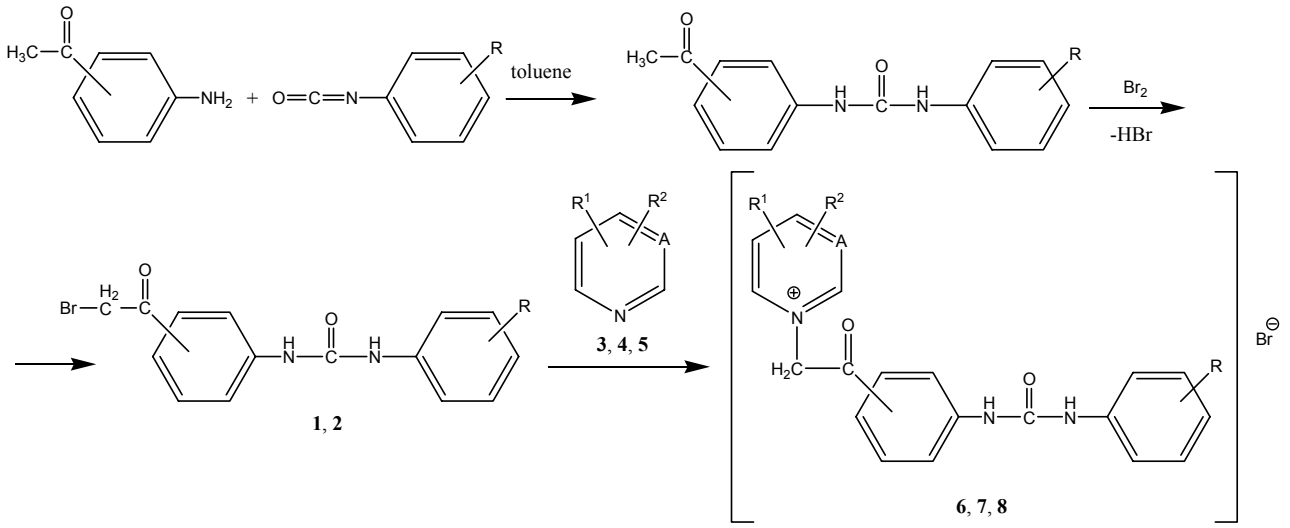
Herein, we report new indolizine and azaindolizine derivatives obtained *via* 1,3-dipolar cycloaddition reactions of pyridinium-, quinolinium- or pyrimidinium-1-[1-(3/4-carbonylphenyl)-3-phenylurea]methylides, generated *in situ* from the corresponding quaternary salts in the presence of 1,2-epoxybutane, with activated alkynes.

RESULTS AND DISCUSSION

By the reaction of 4-aminoacetophenone and 3-aminoacetophenone respectively, with substituted phenyl isocyanates in dioxane-toluene mixture and treating the resulting 1-(4-acetylphenyl)-3-(R-phenyl)-urea, respectively 1-(3-acetylphenyl)-3-(R-phenyl)-urea, with bromine in an acetic acid-dioxane mixture we have obtained 1-[4-(2-bromoacetyl)phenyl]-3-(R-phenyl)urea derivatives **1**, respectively 1-[3-(2-bromoacetyl)phenyl]-3-(R-phenyl)urea derivatives **2**.

Reactions of compounds **1** or **2** with 4-benzylpyridine **3**, substituted quinolines **4**, and 4-substituted pyrimidines **5** respectively, led easily to new *N*-[3/4-(3-phenylureido)-phenacyl] quaternary salts **6-8** in good yields (Scheme 1). Some of these quaternary salts have been separated, purified and characterized (compounds **7a-c** and **8a-c**, Table 1), while others have been used as crude products in the next step.

The isolated quaternary salts and their mp are presented in Table 1.



1: 4-$BrCH_2CO$; R = 3-CF_3
2: 3-$BrCH_2CO$; **a**: R = 3-CF_3
b: R = 4-Cl
c: R = 3-Cl

3: A = CH; R^1 = 4-CH_2Ph; R^2 = H
4: A = CH; R^1 = 5,6-benzo; **a**: R^2 = 4-CH_3
b: R^2 = 6-CH_3
5: A = N; R^1 = H; **a**: R^2 = 4-Ph
b: R^2 = 4-thienyl

6: A = CH
7: A = CH; R^1 = 5,6-benzo
8: A = N

Scheme 1 – Synthesis of new pyridinium, quinolinium and pyrimidinium salts.

Table 1

New quaternary salts and atom numbering for NMR assignment purposes

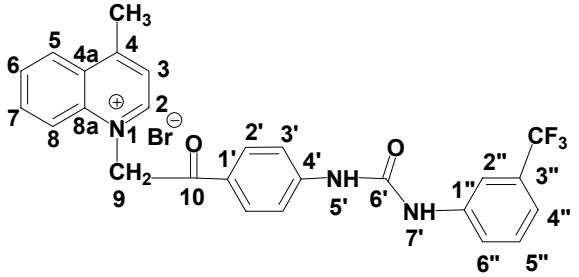
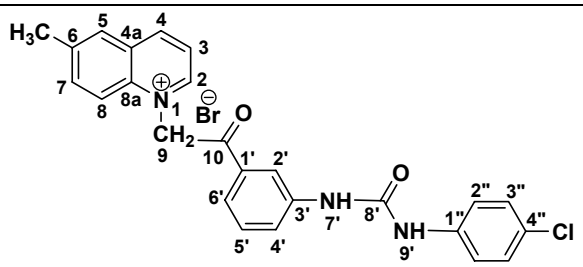
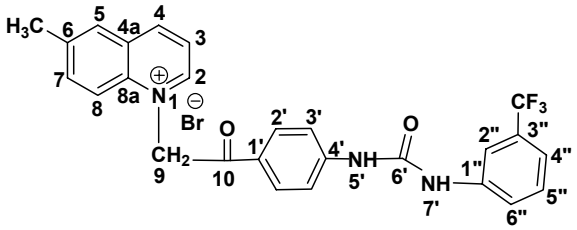
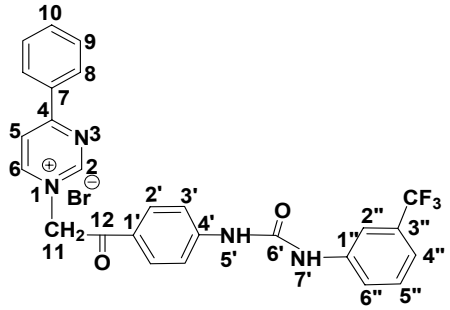
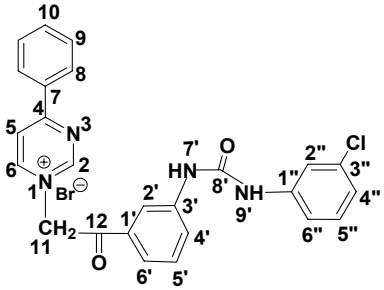
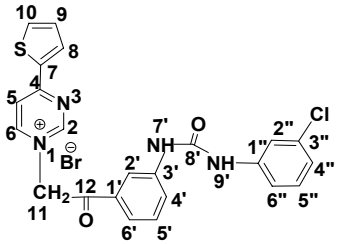
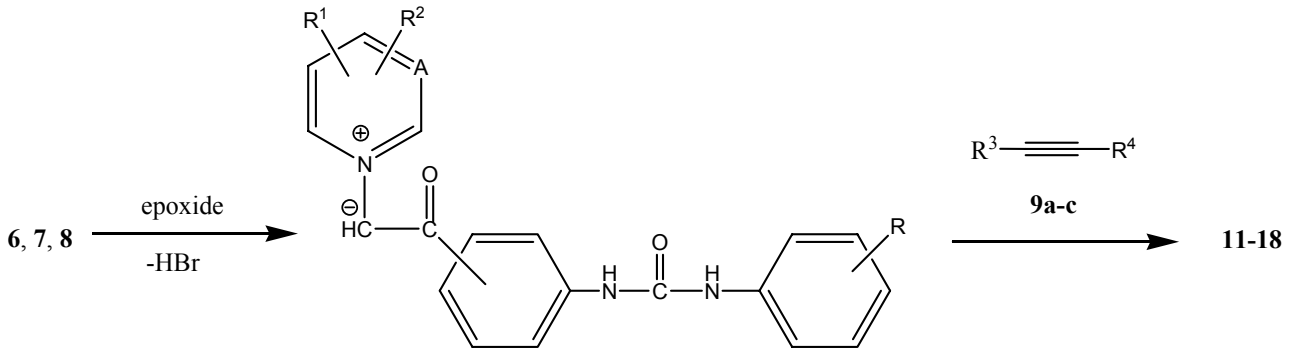
Starting compounds	Obtained quaternary salts	Formula	m.p. (°C)
1 + 4a	**7a**		254-256

Table 1 (continued)

2b + 4b	**7b**		178-180
1 + 4b	**7c**		269-271
1 + 5a	**8a**		254-256
2c + 5a	**8b**		239-241
2c + 5b	**8c**		172-175

The reaction of these intermediate quaternary salts **6-8** with activated alkynes, such as ethyl propiolate (**9a**), 3-butyn-2-one (**9b**) and dimethyl acetylenedicarboxylate (**9c**)**,** in an epoxide as acid acceptor and reaction solvent, led to the new indolizine **11**, pyrrolo[1,2-*a*]quinolines **12-14**, and pyrrolo[1,2-c]pyrimidines **15-18** respectively, substituted with a carbonyl-diphenylureido group on the pyrrolo ring. These new compounds have been obtained in good yields *via* 1,3-dipolar cycloadditions of pyridinium-, quinolinium- or pyrimidinium-1-methylides **10**, generated *in situ* from the corresponding quaternary salts **6-8** in the presence of an epoxide. (Scheme 2).

All new compounds **11-18** and their mp are presented in Table 2.



Scheme 2 – Synthesis of new compounds **11-18**.

Table 2

New indolizines and azaindolizines **11-18**, and atom numbering for NMR assignment purposes

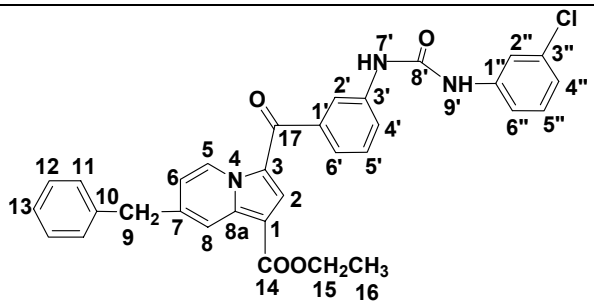
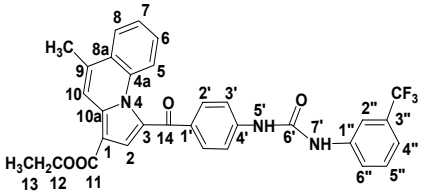
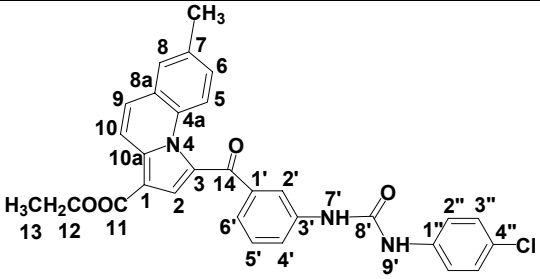
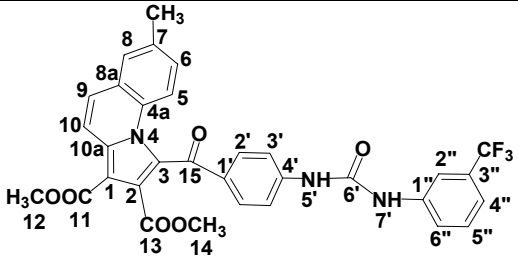
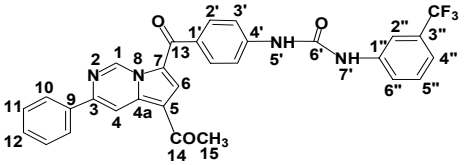
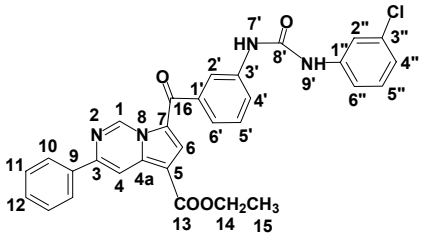
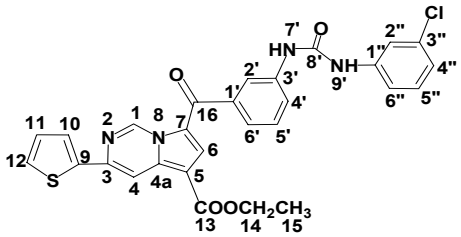
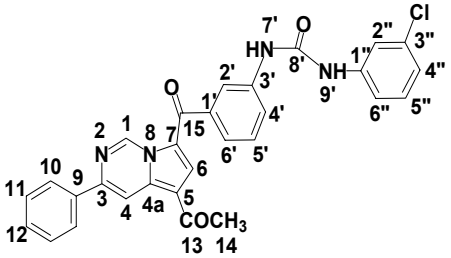
Compound	Formula	m.p. (°C)
11		227-229
12		245-247
13		255-258
14		227-229

Table 2 (continued)

15		279-281
16		318-320
17		240-242
18		236-238

Structures of all newly synthesized compounds, presented in Tables 1 and 2 were confirmed by chemical and spectral analysis. The IR spectra of these compounds exhibit the characteristic carbonyl and NH absorption bands. The ^{1}H-, ^{13}C- and ^{15}N-NMR chemical shifts for compounds **7**, **8**, **11**-**18** have been unambiguously assigned based on the following 2D NMR experiments: H,H-COSY, H,C-HSQC, H,C-HMBC, H,N-HMQC, H,N-HMBC, H,H-NOESY. For compound **14**, the two carbomethoxy residues were assigned based on their NOE response. Thus, the methyl protons from carbomethoxy group situated in position 1 were assigned based on their NOE cross peak with the proton in position 10. In a similar way, the methyl protons from carbomethoxy group situated in position 2 were assigned based on their NOE cross peaks with the protons from the *para*-substituted phenyl. The ^{1}H- ^{13}C- and ^{15}N- chemical shifts confirm all major structural elements of the new compounds. The unambiguous NMR assignments are useful references for the reported classes of compounds. Particularly the ^{15}N- chemical shifts for these classes are seldom reported in literature. Thus, as a general trend, the two N atoms in the Ar-NH-CO-NH-Ar fragment, deshielded to around 110 ppm reflect the nitrogen lone p electron involvement in an extended conjugation. The N-4/N-8 bridgehead nitrogen chemical shifts around 170-190 ppm confirm the sp2 hybridization

and planarity of the molecule allowing extended conjugation of π electrons in the indolizine, pyrrolo[1,2-*a*]quinoline, and pyrrolo[1,2-*c*]pyrimidine moieties respectively. These ^{15}N-NMR reference data are particularly useful for biological active compounds with related skeletons which are prone to selectively undergo biochemical *N*-transformations such as *N*-oxidation or *N*-complexation, when more than one nitrogen atom is present in molecule. Our data presented here here extend our previous interest in systematic studies of ^{15}N chemical shifts on series of compounds with biological activity relevance.[28-33]

EXPERIMENTAL

General information. Melting points were determined on a Boetius apparatus and are uncorrected. The IR spectra were recorded on a Nicolet Impact 410 spectrometer, in KBr pellets. The NMR spectra were recorded on a Bruker Avance III 400 instrument operating at 400, 100 and 40 MHz for ^{1}H, ^{13}C, and ^{15}N nuclei respectively. Samples were recorded with either a 5 mm multinuclear inverse detection z-gradient probe (^{1}H spectra and all 2D experiments) or with a 5 mm four nuclei direct detection z-gradient probe (^{1}H and ^{13}C spectra). Chemical shifts are reported in δ units (ppm) and were referenced to internal TMS for ^{1}H chemical shifts, to the internal deuterated solvent for ^{13}C chemical shifts (DMSO referenced at 39.4 ppm) and referenced to liquid ammonia (0.0 ppm) using nitromethane (380.2 ppm) as external standard for ^{15}N nuclei. Unambiguous 1D NMR signal assignments were made based on 2D NMR homo- and heterocorrelation. H,H-COSY, H,C-HSQC, H,C-HMBC and H,H-NOESY experiments, recorded using standard pulse sequences in the version with z-gradients, as delivered by Bruker with TopSpin 2.1 PL6 spectrometer control and processing software. The ^{15}N chemical shifts were obtained as projections from the 2D indirectly detected H,N-HMQC and H,N-HMBC spectra, employing standard pulse sequences in the version with z-gradients as delivered by Bruker (TopSpin 2.1 PL6). Satisfactory microanalyses for all new compounds were obtained: C ± 0.20, H ± 0.16, N ± 0.26.

1-[4-(2-Bromoacetyl)phenyl]-3-(R-phenyl)urea derivatives **1**, respectively 1-[3-(2-bromo-acetyl)phenyl]-3-(R-phenyl)urea derivatives **2** were obtained from 4-aminoacetophenone, respectively 3-aminoacetophenone and substituted phenyl isocyanates in dioxane-toluene, at 40-60 °C followed by the reaction of the resulting 1-(4-acetylphenyl)-3-(R-phenyl)-urea, respectively 1-(3-acetylphenyl)-3-(R-phenyl)-urea, with bromine in acetic acid-dioxane at room temperature. Substituted phenyl isocyanates, 4-benzylpyridine and quinolines were commercially available products (sigma Aldrich). 4-Phenyl- and 4-(2-thienyl)-pyrimidines were obtained according to a method described by Bredereck et al.[34]

General Procedure for Quaternary salts

A mixture of a *N*-heterocyclic compound **3-5** (5 mmol) and the corresponding α-bromocarbonyl compound **1**, **2** (5 mmol) in acetone (60 mL) was heated at reflux for 20 hours. The mixture was left overnight at the room temperature. The solid product was filtered, washed with acetone and recrystallised from methanol.

1-{3-[4-(3-Trifluoromethylphenyl)ureido]phenacyl}-4-methyl-quinolinium bromide **(7a). G**rey crystals (1.93 g, 71 %). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.07 (s, 3H, CH_3-4), 6.91 (bs, 2H, CH_2-9), 7.34 (bd, 1H, *J* = 7.6 Hz, H-4"), 7.52 (d, 1H, *J* = 7.6 Hz, H-5"), 7.62 (bd, 1H, *J* = 8.5 Hz, H-6"), 7.78 (d, 2H, *J* = 8.8 Hz, H-3'), 8.05 (bs, 1H, H-2"), 8.10 (d, 2H, *J* = 8.8 Hz, H-2'), 8.00-8.20 (m, 3H, H-3, H-6 and H-7), 8.36 (d, 1H, *J* = 8.9 Hz, H-5), 8.57 (dd, 1H, *J* = 8.5, 1.2 Hz, H-8), 9.39 (d, 1H, *J* = 6.2 Hz, H-2), 9.65 (s, 1H, NH-7'), 9.78 (s, 1H, NH-5'). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 19.7 (CH_3-4), 62.3 (CH_2-9), 113.9 (CH-2"), 117.1 (CH-3'), 118.4 (CH-4"), 119.3 (CH-8), 120.20 (q, $^{1}J_{C,F}$ = 273 Hz, CF_3), 121.6 (CH-6"), 122.5 (CH-6), 126.75 (CH-3), 126.87 (C-1'), 128.38 (C-4a), 129.3 (q, $^{2}J_{C,F}$ = 31 Hz, C-3"), 129.36 (CH-5), 129.8 (CH-5"), 130.0 (CH-2'), 135.1 (CH-7), 137.7 (C-4), 139.8 (C-1"), 145.3 (CH-2 and C-4'), 151.9 (C-8a), 159.6 (CO-6'), 188.8 (CO-10). IR (KBr, cm^{-1}`): 3253, 3040, 1720, 1680, 1591, 1560, 1535, 1447, 1316, 1229, 1164, 1126. Anal. Calcd. for $C_{26}H_{21}BrF_3N_3O_2$ (544.36): C, 57.36; H, 3.89; N, 7.72%. Found: C, 57.41; H, 3. 95; N, 7.68%.

1-{4-[3-(4-Chlorophenyl)ureido]phenacyl}-6-methyl-quinolinium bromide **(7b).** Brown crystals (1.94 g, 76 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.63 (s, 3H, CH_3), 7.00 (s, 2H, CH_2-9), 7.36 (d, 2H, *J* = 8.8 Hz, H-2"), 7.55 (d, 2H, *J* = 8.8 Hz, H-3"), 7.64 (t, 1H, *J* = 8.0 Hz, H-5'), 7.83 (d, 1H, *J* = 8.0 Hz, H-4'), 7.85 (d, 1H, *J* = 7.5 Hz, H-6'), 8.09 (dd, 1H, *J* = 9.3, 1.7 Hz, H-7), 8.29 (dd, 1H, *J* = 8.4, 5.6 Hz, H-3), 8.32 (bs, 2H, H-2' and H-5), 8.40 (d, 1H, *J* = 9.2 Hz, H-8), 9.28 (s, 1H, NH-9'), 9.33 (d, 1H, *J* = 8.4 Hz, H-4), 9.42 (s, 1H, NH-7'), 9.48 (d, 1H, *J* = 5.6 Hz, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 20.8 (CH_3), 63.2 (CH_2-9), 117.4 (CH-2'), 118.9 (CH-8), 119.6 (CH-2"), 122.1 (CH-3), 122.3 (CH-6'), 124.1 (CH-4'), 125.5 (C-4"), 128.6 (CH-3"), 128.9 (CH-5), 129.5 (CH-5' and C-4a), 134.2 (C-1'), 137.2 (C-8a), 137.8 (CH-7), 138.4 (C-1"), 140.3 (C-3' and C-6), 147.5 (CH-4), 149.8 (CH-2), 152.5 (CO-8'), 190.6 (CO-10). ^{15}N NMR (40 MHz, DMSO-d_6) δ (ppm): 107.9 (NH-9'), 109.2 (NH-7'), 188.7 (N-1). IR (KBr, cm^{-1}`): 3312, 3280, 1711, 1682, 1593, 1527, 1453, 1331, 1219, 1192, 1092. Anal. Calcd. for $C_{25}H_{21}BrClN_3O_2$ (510.81): C, 58.78; H, 4.14; N, 8.23%. Found: 58.84; H, 4.21; N, 8.18%.

1-{4-[4-(3-Trifluoromethylphenyl)ureido]phenacyl}-6-methyl-quinolinium bromide **(7c).** Orange crystals (2.1 g, 77 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.62 (s, 3H, CH_3), 6.95 (s, 2H, CH_2-9), 7.37 (d, 1H, *J* = 8.0 Hz, H-4"), 7.56 (t, 1H, *J* = 8.0 Hz, H-5"), 7.64 (d, 1H, *J* = 8.0 Hz, H-6"), 7.78 (d, 2H, *J* = 8.8 Hz, H-3'), 8.06 (s, 1H, H-2"), 8.07 (dd, 1H, *J* = 9.4, 1.7 Hz, H-7), 8.12 (d, 2H, *J* = 8.0 Hz, H-2'), 8.27 (dd, 1H, *J* = 8.4, 5.8 Hz, H-3), 8.31 (bs, 1H, H-5), 8.34 (d, 1H, *J* = 9.2 Hz, H-8), 9.31 (d, 1H, *J* = 8.4 Hz, H-4), 9.45 (d, 1H, *J* = 5.2 Hz, H-2), 9.60 (s, 1H, NH-7'), 9.74 (s, 1H, NH-5'). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 20.8 (CH_3), 62.8 (CH_2-9), 114.2 (q, $^{3}J_{C,F}$ = 5 Hz, CH-2"), 117.3 (CH-3'), 118.6 (q, $^{3}J_{C,F}$ = 4 Hz, CH-4"), 118.9 (CH-8), 121.9 (CH-6"), 122.1 (CH-3), 124.1 (q, $^{1}J_{C,F}$ = 273 Hz, CF_3), 127.1 (C-1'), 128.9 (CH-5), 129.5 (C-4a), 129.5 (q, $^{2}J_{C,F}$ = 31 Hz, C-3"), 130.0 (CH-5"), 130.2 (CH-2'), 137.2 (C-8a), 137.8 (CH-7), 140.0 (C-1"), 140.3 (C-6), 145.5 (C-4'), 147.5 (CH-4), 149.8 (CH-2), 152.1 (CO-6'), 188.8 (CO-10). ^{15}N NMR (40 MHz, DMSO-d_6) δ (ppm): 110.6 (NH-7'), 113.9 (NH-5'), 188.5 (N-

1). IR (KBr, cm^{-1}`): 3254, 3094, 3045, 1721, 1679, 1559, 1534, 1490, 1447, 1315, 1230, 1164, 1127. Anal. Calcd. for $C_{26}H_{21}BrF_3N_3O_2$ (544.36): C, 57.36; H, 3.89; N, 7.72%. Found: 57.29; H, 4.85; N, 7.77%.

1-{4-[4-(3-Trifluoromethylphenyl)ureido]phenacyl}-4-phenyl-pirimidinium bromide **(8a).** Yellow crystals (1.9 g, 68 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.39 (s, 2H, CH_2-11), 7.37 (d, 1H, *J* = 8.0 Hz, H-4"), 7.56 (t, 1H, *J* = 8.0 Hz, H-5"), 7.64 (d, 1H, *J* = 8.8 Hz, H-6"), 7.73 (t, 2H, *J* = 7.9 Hz, H-9), 7.78 (d, 2H, *J* = 8.9 Hz, H-3'), 7.83 (tt, 1H, *J* = 7.3, 2.0 Hz, H-10), 8.06 (bs, 1H, H-2"), 8.10 (d, 2H, *J* = 8.8 Hz, H-2'), 8.50 (dd, 2H, *J* = 7.2, 1.2 Hz, H-8), 9.00 (dd, 1H, *J* = 6.8, 0.6 Hz, H-5), 9.37 (dd, 1H, *J* = 6.9, 1.7 Hz, H-6), 9.60 (s, 1H, NH-7'), 9.74 (s, 1H, NH-5'), 9.76 (t, 1H, *J* = 1.2 Hz, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 62.1 (CH_2-11), 114.2 (q, $^3J_{C,F}$ = 4 Hz, CH-2"), 117.5 (CH-3'), 118.0 (CH-5),118.6 (q, $^3J_{C,F}$ = 3 Hz, CH-4"), 121.9 (CH-6"), 124.1 (q, $^1J_{C,F}$ = 273 Hz, CF_3), 126.8 (C-1'), 129.2 (CH-8), 129.5 (q, $^2J_{C,F}$ = 32 Hz, C-3"), 129.8 (CH-9), 130.0 (CH-5" and CH-2'), 132.9 (C-7), 134.8 (CH-10), 140.0 (C-1"), 145.5 (C-4'), 152.1 (CO-6'), 153.1 (CH-6), 154.4 (CH-2), 168.7 (C-4), 188.4 (CO-12). ^{15}N NMR (40 MHz, DMSO-d_6) δ (ppm): 110.3 (NH-9'), 113.5 (NH-7'), 190.4 (N-1), 283.6 (N-3). IR (KBr, cm^{-1}`): 3078, 3003, 1717, 1681, 1629, 1595, 1537, 1448, 1324, 1239, 1176, 1123, 1068. Anal. Calcd. for $C_{26}H_{20}BrF_3N_4O_2$ (557.36): C, 56.03; H, 3.62; N, 10.05%. Found: 56.12; H, 3.69; N, 9.98%.

1-{4-[3-(3-Chlorophenyl)ureido]phenacyl}-4-phenyl-pyrimidinium bromide **(8b).** Yellow crystals, (1.73 g, 66 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.44 (s, 2H, CH_2-11), 7.03-7.06 (m, 1H, H-4"), 7.32-7.34 (m, 2H, H-5" and H-6"), 7.62 (t, 1H, *J* = 7.9 Hz, H-5'), 7.73 (t, 2H, *J* = 7.3 Hz, H-9), 7.75-7.78 (m, 3H, H-4', H-6' and H-2"), 7.83 (t, 1H, *J* = 7.4 Hz, H-10), 8.36 (t, 1H, *J* = 1.7 Hz, H-2'), 8.50 (dd, 2H, *J* = 7.3, 1.3 Hz, H-8), 9.01 (d, 1H, *J* = 6.5 Hz, H-5), 9.34 (s, 1H, NH-9'), 9.37 (dd, 1H, *J* = 6.9, 1.6 Hz, H-6), 9.46 (s, 1H, NH-7'), 9.77 (s, 1H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 62.5 (CH_2-11), 116.6 (CH-6"), 117.2 (CH-2'), 117.5 (CH-2"), 118.0 (CH-5), 121.7 (CH-4"), 122.0 (CH-6'), 124.2 (CH-4'), 129.2 (CH-8), 129.7 (CH-5'), 129.8 (CH-9), 130.4 (CH-5"), 132.9 (C-7), 133.2 (C-3"), 134.0 (C-1'), 134.8 (CH-10), 140.3 (C-3'), 140.9 (C-1"), 152.4 (CO-8'), 153.2 (CH-6), 154.5 (CH-2), 168.8 (C-4), 190.1 (CO-12). ^{15}N NMR (40 MHz, DMSO-d_6) δ (ppm): 108.7 (NH-9' and NH-7'), 190.9 (N-1), 282.3 (N-3). IR (KBr, cm^{-1}`): 3266, 3079, 1702, 1627, 1594, 1544, 1473, 1451, 1337, 1308, 1249, 1221, 1192. Anal. Calcd. for $C_{25}H_{20}BrClN_4O_2$ (523.81): C, 57.32; H, 5.85; N, 10.70%. Found: 57.27; H, 3.90; N, 10.62%.

1-{4-[3-(3-Chlorophenyl)ureido]phenacyl}-4-thienyl)-pyrimidinium bromide **(8c).** Yellow crystals, (1.6 g, 61 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.32 (s, 2H, CH_2-11), 7.04-7.06 (m, 1H, H-4"), 7.31-7.33 (m, 2H, H-5" and H-6"), 7.51 (dd, 1H, *J* = 4.8, 4.1 Hz, H-9), 7.61 (t, 1H, *J* = 7.9 Hz, H-5'), 7.73-7.76 (m, 3H, H-4', H-6' and H-2"), 8.34 (t, 1H, *J* = 1.8 Hz, H-2'), 8.37 (dd, 1H, *J* = 5.0, 0.9 Hz, H-10), 8.57 (dd, 1H, *J* = 4.0, 0.8 Hz, H-8), 8.78 (d, 1H, *J* = 6.8 Hz, H-5), 9.17 (dd, 1H, *J* = 6.9, 1.5 Hz, H-6), 9.26 (s, 1H, NH-9'), 9.39 (s, 1H, NH-7'), 9.54 (bs, 1H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 62.2 (CH_2-11), 115.9 (CH-5), 116.6 (CH-6"), 117.2 (CH-2'), 117.5 (CH-2"), 121.7 (CH-4"), 121.9 (CH-6'), 124.2 (CH-4'), 129.7 (CH-5'), 130.4 (CH-5"), 130.9 (CH-9), 133.2 (C-3"), 133.9 (C-1'), 136.1 (CH-8), 138.8 (C-7), 139.5 (CH-10), 140.3 (C-3'), 141.0 (C-1"), 151.9 (CH-6), 152.4 (CO-8'), 154.7 (CH-2), 163.3 (C-4), 190.2 (CO-12). ^{15}N NMR (40 MHz, DMSO-d_6) δ (ppm): 109.2 (NH-9' and NH-7'), 185.7 (N-1), 276.6 (N-3). IR (KBr, cm^{-1}`): 3264, 3084, 1701, 1630, 1591, 1550, 1478, 1442, 1409, 1309, 1214, 1183. Anal. Calcd. for $C_{23}H_{18}BrClN_4O_2S$ (529.84): C, 52.14; H, 3.42; N, 10.57%. Found: 52.23; H, 3.46; N, 10.46%.

General Procedure for indolizines and azaindolizines

A mixture of a quaternary salt (2 mmol) and an activated alkyne (2.2 mmol) in 1,2-epoxybutane (60 mL) was heated at reflux temperature for 30 hours, then the major part of the solvent was removed under reduced pressure. The residue was treated with methanol (10 mL) and left overnight at room temperature. The solid was filtered and washed with cold methanol. All crude products were recrystallised from chloroform.

1-Carbethoxy-{3-[3-(3-chlorophenyl)ureido]benzoyl}-7-benzylindolizine **(11).** Yellow crystals, (0.44 g, 40 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.26 (t, 3H, *J* = 7.1 Hz, CH_3-16), 4.13 (s, 2H, CH_2-9), 4.25 (q, 2H, *J* = 7.1 Hz, CH_2-15), 6.98-7.03 (m, 1H, H-4"), 7.17 (dd, 1H, *J* = 7.3, 1.9 Hz, H-6), 7.25 (tt, 1H, *J* = 7.0, 1.6 Hz, H-13), 7.27-7.29 (m, 2H, H-5" and H-6"), 7.30 (d, 2H, *J* = 7.7 Hz, H-11), 7.32 (d, 2H, *J* = 7.0 Hz, H-12), 7.35-7.38 (m, 1H, H-6'), 7.47 (t, 1H, *J* = 7.8 Hz, H-5'), 7.66-7.70 (m, 1H, H-4'), 7.67 (bs, 1H, H-2), 7.72-7.74 (m, 1H, H-2"), 7.93 (t, 1H, *J* = 1.8 Hz, H-2'), 8.08-8.10 (m, 1H, H-8), 8.95 (s, 1H, NH-9'), 9.02 (s, 1H, NH-7'), 9.76 (d, 1H, *J* = 7.2 Hz, H-5). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 14.2 (CH_3-16), 40.5 (CH_2-9), 60.0 (CH_2-15), 104.7 (C-1), 116.6 (CH-6"), 117.2 (CH-8), 117.4 (CH-6), 117.6 (CH-2"), 118.4 (CH-2'), 121.3 (CH-4'), 121.5 (CH-4"), 121.6 (C-3), 122.3 (CH-6'), 126.4 (CH-13), 128.0 (CH-2), 128.5 (CH-5), 128.6 (CH-12), 128.9 (CH-5'), 129.0 (CH-11), 130.2 (CH-5"), 133.2 (C-3"), 139.1 (C-10), 139.3 (C-8a), 139.5 (C-3'), 139.8 (C-1'), 141.1 (C-1"), 142.9 (C-7), 152.4 (CO-8'), 162.9 (COO-14), 183.9 (CO-17). ^{15}N NMR (40 MHz, DMSO-d_6) δ (ppm): 108.6 (NH-9' and NH-7'), 193.2 (N-4). IR (KBr, cm^{-1}`): 3297, 1694, 1646, 1592, 1556, 1522, 1475, 1348, 1298, 1222, 1199, 1168. Anal. Calcd. for $C_{32}H_{26}ClN_3O_4$ (552.02) C, 69.62; H, 4.75; N, 7.61%. Found: C, 69.54; H, 4.69; N, 7.72%.

1-Carbethoxy-{3-[4-(3-trifluoromethylphenyl)ureido]benzoyl}-9-methylpyrrolo[1,2-a]quinoline **(12).** Yellow crystals, (0.47 g, 42 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.32 (t, 3H, *J* = 7.1 Hz, CH_3-13), 2.68 (s, 3H, CH_3-9), 4.29 (q, 2H, *J* = 7.1 Hz, CH_2-12), 7.35 (d, 1H, *J* = 7.6 Hz, H-4"), 7.41 (s, 1H, H-2), 7.54 (t, 1H, *J* = 7.8 Hz, H-5"), 7.57-7.67 (m, 2H, H-6 and H-7), 7.60 (d, 1H, *J* = 7.6 Hz, H-6"), 7.72 (d, 2H, *J* = 8.8 Hz, H-3'), 7.90 (dd, 1H, *J* = 8.4, 0.8 Hz, H-5), 8.02 (d, 2H, *J* = 8.8 Hz, H-2'), 8.04-8.06 (m, 2H, H-8 and H-2"), 8.09 (d, 1H, *J* = 0.8 Hz, H-10), 9.23 (s, 1H, NH-7'), 9.33 (s, 1H, NH-5'). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 14.3 (CH_3-13), 19.1 (CH_3-9), 59.7 (CH_2-12), 105.6 (C-1), 114.3 (q, $^3J_{C,F}$ = 4 Hz, CH-2"), 116.3 (CH-10), 117.6 (CH-3'), 118.4 (q, $^3J_{C,F}$ = 4 Hz, CH-4"), 120.2 (CH-5), 122.1 (CH-6"), 124.2 (q, $^1J_{C,F}$ = 274 Hz, CF_3), 124.5 (C-8a), 125.5 (CH-7), 125.6 (CH-8), 127.0 (CH-2), 127.5 (C-3), 128.7 (CH-6), 129.5 (q, $^2J_{C,F}$ = 31 Hz, C-3"), 129.9 (CH-5"), 130.9 (C-1'), 131.2 (CH-2'), 132.1 (C-4a), 136.9 (C-9), 138.7 (C-10a), 140.2 (C-1"), 144.2 (C-4'), 152.2 (CO-6'), 163.1 (COO-11), 183.1 (CO-14). ^{15}N NMR (40 MHz, DMSO-d_6) δ (ppm): 108.8 (NH-7'), 112.7 (NH-5'), 175.8 (N-4). IR (KBr, cm^{-1}`): 3326, 1715, 1667, 1624, 1592, 1557, 1540,

1522, 1445, 1314, 1204, 1168, 1119, 1093. Anal. Calcd. for $C_{31}H_{24}F_3N_3O_4$ (559.53): C, 66.54; H, 4.32; N, 7.51%. Found: C, 66.61; H, 4.36; N, 7.47%.

1-Carbethoxy-{3-[3-(4-chlorophenyl)ureido]benzoyl}-7-methylpyrrolo[1,2-a]quinoline **(13).** Yellow crystals (0.56 g, 53 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.31 (t, 3H, *J* = 7.1 Hz, CH_3-13), 2.47 (s, 3H, CH_3-7), 4.30 (q, 2H, *J* = 7.1 Hz, CH_2-12), 7.32 (d, 2H, *J* = 8.8 Hz, H-3"), 7.48 (s, 1H, H-2), 7.50 (d, 2H, *J* = 8.8 Hz, H-2"), 7.51 (d, 1H, *J* = 9.1 Hz, H-6), 7.54 (t, 1H, *J* = 7.9 Hz, H-5'), 7.64 (dt, 1H, *J* = 7.8, 1.3 Hz, H-6'), 7.78-7.81 (m, 2H, H-8 and H-4'), 7.85 (d, 1H, *J* = 8.8 Hz, H-5), 7.89 (d, 1H, *J* = 9.4 Hz, H-9), 8.19 (t, 1H, *J* = 1.8 Hz, H-2'), 8.22 (d, 1H, *J* = 9.3 Hz, H-10), 8.89 (s, 1H, NH-9'), 9.06 (s, 1H, NH-7'). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 14.3 (CH_3-13), 20.4 (CH_3-7), 59.8 (CH_2-12), 106.7 (C-1), 116.8 (CH-10), 119.1 (CH-2'), 119.9 (CH-2" and CH-5), 122.8 (CH-4'), 123.4 (CH-6'), 124.5 (C-8a), 125.5 (C-4"), 127.6 (C-3), 127.7 (CH-2), 128.4 (CH-8), 128.5 (CH-3"), 129.1 (CH-9), 129.2 (CH-5'), 130.2 (CH-6), 130.4 (C-4a), 135.1 (C-7), 138.3 (C-1'), 138.5 (C-10a), 139.9 (C-3'), 152.4 (CO-8'), 163.0 (COO-11), 183.9 (CO-14). ^{15}N NMR (40 MHz, DMSO-d_6) δ (ppm): 107.2 (NH-9' and NH-7'), 176.8 (N-4). IR (KBr, cm^{-1}`): 3370, 3291, 1705, 1641, 1597, 1548, 1487, 1427, 1305, 1279, 1228, 1181, 1083. Anal. Calcd. for $C_{30}H_{24}ClN_3O_4$ (525.98): C, 68.50; H, 4.60; N, 7.99%. Found: C, 68.58; H, 4.55; N, 8.11%.

1,2-Dicarbomethoxy-{3-[4-(3-trifluoromethylphenyl)ureido]benzoyl}-7-methylpyrrolo[1,2-a]quinoline **(14).** Yellow crystals (0.38 g, 43 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.40 (s, 3H, CH_3-7), 3.49 (s, 3H, CH_3-14) 3.84 (s, 3H, CH_3-12), 7.34-7.37 (m, 2H, H-6 and H-4"), 7.45 (d, 1H, *J* = 8.8 Hz, H-5), 7.54 (t, 1H, *J* = 7.8 Hz, H-5"), 7.61 (d, 1H, *J* = 7.6 Hz, H-6"), 7.64 (d, 2H, *J* = 8.8 Hz, H-3'), 7.77 (bs, 1H, H-8), 7.78 (d, 1H, *J* = 9.4 Hz, H-9), 7.82 (d, 2H, *J* = 8.8 Hz, H-2'), 8.03 (bs, 1H, H-2"), 8.12 (d, 1H, *J* = 9.2 Hz, H-10), 9.23 (s, 1H, NH-7'), 9.38 (s, 1H, NH-5'). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 20.3 (CH_3-7), 51.6 (CH_3-12), 52.1 (CH_3-14), 104.4 (C-3), 114.4 (q, $^3J_{C,F}$ = 4 Hz, CH-2"), 117.2 (CH-10), 117.6 (CH-3'), 118.1 (CH-5), 118.5 (q, $^3J_{C,F}$ = 3 Hz, CH-4"), 122.1 (CH-6"), 124.1 (q, $^1J_{C,F}$ = 272 Hz, CF_3), 124.7 (C-8a), 125.5 (C-2), 126.3 (C-1), 127.6 (CH-9), 128.9 (CH-8), 129.5 (q, $^2J_{C,F}$ = 31 Hz, C-3"), 129.8 (C-4a), 129.9 (CH-5"), 130.4 (C-1'), 130.5 (CH-6), 131.1 (CH-2'), 135.1 (C-10a), 135.4 (C-7), 140.0 (C-1"), 145.2 (C-4'), 152.1 (CO-6'), 162.9 (COO-11), 164.5 (COO-13), 186.0 (CO-15). ^{15}N NMR (40 MHz, DMSO-d_6) δ (ppm): 109.9 (NH-7'), 113.7 (NH-5'), 173.8 (N-4). IR (KBr, cm^{-1}`): 3376, 2953, 1708, 1593, 1558, 1523, 1448, 1321, 1282, 1226, 1173, 1153, 1092. Anal. Calcd. for $C_{32}H_{24}F_3N_3O_6$ (603.54): C, 63.68; H, 4.01; N, 6.96%. Found: C, 63.75; H, 4.09; N, 6.88%.

5-Acetyl-{7-[4-(3-trifluoromethylphenyl)ureido]benzoyl}-3-phenylpyrrolo[1,2-c]pyrimidine **(15).** Yellow crystals, (0.57 g, 53 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.60 (s, 3H, CH_3-15), 7.36 (d, 1H, *J* = 7.6 Hz, H-4"), 7.52-7.61 (m, 4H, H-5", H-12 and H-11), 7.64 (d, 1H, *J* = 8.8 Hz, H-6"), 7.73 (d, 2H, *J* = 8.4 Hz, H-3'), 7.94 (d, 2H, *J* = 8.8 Hz, H-2'), 8.06 (bs, 2H, H-2" and H-6), 8.20 (d, 2H, *J* = 6.8 Hz, H-10), 8.76 (d, 1H, *J* = 1.6 Hz, H-4), 9.28 (s, 1H, NH-7'), 9.35 (s, 1H, NH-5'), 10.42 (d, 1H, *J* = 1.6 Hz, H-1). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 28.3 (CH_3-15), 108.3 (CH-4), 114.3 (q, $^3J_{C,F}$ = 4 Hz, CH-2"), 114.7 (C-5), 117.7 (CH-3'), 118.4 (q, $^3J_{C,F}$ = 4 Hz, CH-4"), 122.1 (CH-6" and C-7), 124.1 (q, $^1J_{C,F}$ = 273 Hz, CF_3), 126.5 (CH-10), 129.0 (CH-6), 129.2 (CH-11), 129.5 (q, $^2J_{C,F}$ = 29 Hz, C-3"), 129.9 (CH-5"), 130.2 (CH-12), 130.6 (CH-2'), 131.6 (C-1'), 136.0 (C-9), 138.9 (C-4a), 140.2 (C-1"), 140.7 (CH-1), 143.6 (C-4'), 149.1 (C-3), 152.3 (CO-8'), 183.2 (CO-13), 193.4 (CO-14). ^{15}N NMR (40 MHz, DMSO-d_6) δ (ppm): 111.0 (NH-7' and NH-5'), 194.3 (N-8). IR (KBr, cm^{-1}`): 3291, 3097, 1678, 1643, 1620, 1599, 1538, 1512, 1480, 1444, 1412, 1334, 1230, 1200, 1177, 1109. Anal. Calcd. for $C_{30}H_{21}F_3N_4O_3$ (542.51): C, 66.42; H, 3.90; N, 10.33%. Found: C, 66.53; H, 3.95; N, 10.26%.

5-Carbethoxy-{7-[3-(3-chlorophenyl)ureido]benzoyl}-3-phenylpyrrolo[1,2-c]pyrimidine **(16).** Yellow crystals (0.45 g, 42 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.35 (t, 3H, *J* = 7.1 Hz, CH_3-15), 4.33 (q, 2H, *J* = 7.1 Hz, CH_2-14), 6.99-7.05 (m, 1H, H-4"), 7.28-7.30 (m, 2H, H-5" and H-6"), 7.44 (dt, 1H, *J* = 7.6, 1.4 Hz, H-6'), 7.50 (t, 2H, *J* = 7.7 Hz, H-11), 7.52-7.57 (m, 2H, H-5' and H-12), 7.68-7.71 (m, 1H, H-4'), 7.72 (bs, 1H, H-6), 7.72-7.74 (m, 1H, H-2"), 8.01 (t, 1H, *J* = 1.8 Hz, H-2'), 8.12-8.15 (m, 2H, H-10), 8.48 (d, 1H, *J* = 1.5 Hz, H-4), 8.97 (s, 1H, NH-9'), 9.07 (s, 1H, NH-7'), 10.38 (d, 1H, *J* = 1.5 Hz, H-1). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 14.2 (CH_3-15), 60.1 (CH_2-14), 106.2 (C-5), 107.5 (CH-4), 116.7 (CH-6"), 117.6 (CH-2"), 118.6 (CH-2'), 121.5 (C-4"), 121.9 (CH-4'), 122.1 (C-7), 122.4 (CH-6'), 126.4 (CH-10), 128.7 (CH-6), 129.0 (CH-11), 129.1 (CH-5'), 130.1 (CH-12), 130.3 (CH-5"), 133.2 (C-3"), 135.8 (C-9), 138.8 (C-1'), 139.6 (C-3'), 139.7 (C-4a), 140.6 (CH-1), 141.1 (C-1"), 148.4 (C-3), 152.4 (CO-8'), 162.6 (COO-13), 184.0 (CO-16). ^{15}N NMR (40 MHz, DMSO-d_6) δ (ppm): 108.4 (NH-9' and NH-7'), 193.7 (N-8), 259.0 (N-2). IR (KBr, cm^{-1}`): 3281, 1695, 1648, 1627, 1590, 1561, 1525, 1476, 1425, 1335, 1203, 1189. Anal. Calcd. for $C_{30}H_{23}ClN_4O_4$ (538.98): C, 66.85; H, 4.30; N, 10.39%. Found: C, 66.79; H, 4.23; N, 10.44%.

5-Carbethoxy-{7-[3-(3-chlorophenyl)ureido]benzoyl}-3-(2-thienyl)-pyrrolo[1,2-c]pyrimidine **(17).** Yellow crystals (0.42 g, 39 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.35 (t, 3H, *J* = 7.1 Hz, CH_3-15), 4.33 (q, 2H, *J* = 7.1 Hz, CH_2-14), 6.99-7.04 (m, 1H, H-4"), 7.24 (dd, 1H, *J* = 5.0, 3.8 Hz, H-11), 7.28-7.30 (m, 2H, H-5" and H-6"), 7.44 (dt, 1H, *J* = 7.7, 1.3 Hz, H-6'), 7.51 (t, 1H, *J* = 7.7 Hz, H-5'), 7.68-7.71 (m, 1H, H-4'), 7.71 (s, 1H, H-6), 7.72-7.74 (m, 1H, H-2"), 7.79 (dd, 1H, *J* = 5.0, 1.1 Hz, H-12), 7.90 (dd, 1H, *J* = 3.7, 1.1 Hz, H-10), 8.01 (t, 1H, *J* = 1.8 Hz, H-2'), 8.34 (d, 1H, *J* = 1.6 Hz, H-4), 8.97 (s, 1H, NH-9'), 9.07 (s, 1H, NH-7'), 10.29 (d, 1H, *J* = 1.5 Hz, H-1). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 14.3 (CH_3-15), 60.1 (CH_2-14), 105.5 (CH-4), 106.0 (C-5), 116.7 (CH-6"), 117.6 (CH-2"), 118.6 (CH-2'), 121.6 (C-4"), 121.9 (CH-4'), 122.3 (C-7), 122.4 (CH-6'), 126.7 (CH-10), 128.9 (CH-6), 129.1 (CH-11), 129.2 (CH-5'), 130.1 (CH-12), 130.3 (CH-5"), 133.2 (C-3"), 138.8 (C-1'), 139.5 (C-4a), 139.6 (C-3'), 140.8 (CH-1), 141.1 (C-1"), 141.5 (C-9), 144.4 (C-3), 152.4 (CO-8'), 162.6 (COO-13), 183.9 (CO-16). ^{15}N NMR (40 MHz, DMSO-d_6) δ (ppm): 108.0 (NH-9' and NH-7'), 192.3 (N-8), 258.1 (N-2). IR (KBr, cm^{-1}): 3295, 1697, 1644, 1622, 1590, 1562, 1525, 1472, 1422, 1333, 1259, 1189. Anal. Calcd. for $C_{28}H_{21}ClN_4O_4S$ (545.01): C, 61.70; H, 3.88; N, 10.28%. Found: C, 61.81; H, 3.93; N, 10.22%.

5-Acetyl-{7-[4-(3-chlorophenyl)ureido]benzoyl}-3-phenylpyrrolo[1,2-c]pyrimidine **(18).** Yellow crystals, (0.49 g, 48 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.58 (s, 3H, CH_3-14), 7.02-7.05 (m, 1H, H-4"), 7.28-7.32 (m, 2H, H-5" and H-6"), 7.52-7.58 (m, 5H, H-5', H-6', H-11 and H-12),

7.67-7.70 (m, 1H, H-4'), 7.77 (bs, 1H, H-2"), 8.07-8.09 (m, 1H, H-2'), 8.1 (s, 1H, H-6), 8.16 (d, 2H, *J* = 8.4 Hz, H-10), 8.72 (d, 1H, *J* = 1.6 Hz, H-4), 9.02 (s, 1H, NH-9'), 9.07 (s, 1H, NH-7'), 10.44 (d, 1H, *J* = 1.4 Hz, H-1). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 23.1 (CH_3-14), 108.3 (CH-4), 114.9 (C-5), 116.7 (CH-6"), 117.7 (CH-2"), 119.6 (CH-2'), 121.5 (C-4"), 121.8 (C-7), 122.2 (CH-4'), 122.7 (CH-6'), 126.5 (CH-10), 129.1 (CH-11), 129.2 (CH-5'), 129.9 (CH-6), 130.2 (CH-12), 130.3 (CH-5"), 133.2 (C-3"), 135.9 (C-9), 138.6 (C-1'), 139.2 (C-3'), 139.4 (C-4a), 140.6 (CH-1), 141.1 (C-1"), 149.5 (C-3), 152.6 (CO-8'), 184.0 (CO-15), 193.1 (CO-13). ^{15}N NMR (40 MHz, DMSO-d_6) δ (ppm): 108.3 (NH-9' and NH-7'), 194.4 (N-8), 261.7 (N-2). IR (KBr, cm^{-1}): 3342, 3061, 1671, 1653, 1608, 1552, 1513, 1480, 1410, 1333, 1297, 1192, 1077. Anal. Calcd. for $C_{29}H_{21}ClN_4O_3$ (508.95): C, 68.44; H, 4.16; N, 11.01%. Found: C, 68.36; H, 4.22; N, 10.93%.

CONCLUSIONS

New indolizine and azaindolizine derivatives, with a carbonyl-ureido substituent on the pyrrolo ring, otherwise difficult to obtain, were obtained by 1,3-dipolar cycloaddition reactions of pyridinium-, quinolinium- and pyrimidinium-1-diphenylureido-methylides, generated *in situ* from the corresponding quaternary salts, with activated alkynes in an epoxide. The variety of heterocyclic systems substituted with a diphenylureido moiety is a strong proof of the generality of this reaction which may be applied in obtaining large libraries of *N*-bridgehead heterocycles with such substitution pattern.

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