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One-Pot Regio- and Chemoselective Synthesis of Thiaazatricyclododecane

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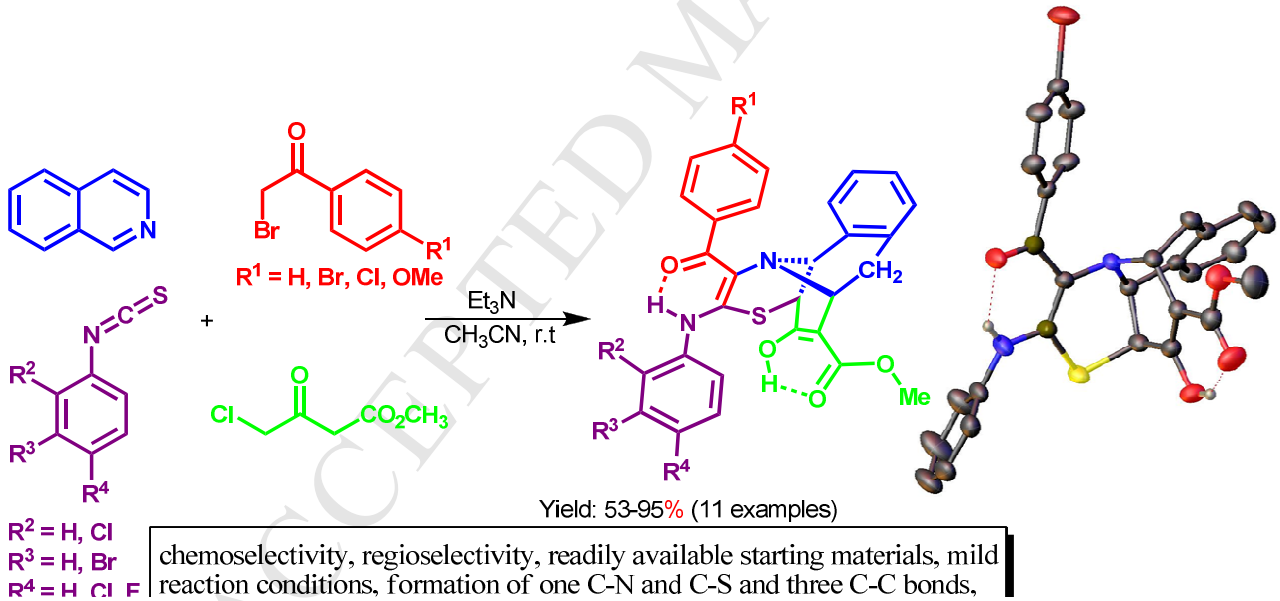

chemoselectivity, regioselectivity, readily available starting materials, mild reaction conditions, formation of one C-N and C-S and three C-C bonds,

One-Pot Regio- and Chemoselective Synthesis of Thiaazatricyclododecane

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Abstract— A highly regio- and chemoselective heteroannulation protocol for the synthesis of unreported polysubstituted thiaazatricyclododecanes has been developed by a sequential four-component reaction of isoquinoline, 2-bromoacetophenones, aryl isothiocyanates, and methyl 4-chloro-3-oxobutanoate under mild conditions in CH_3CN. To the best of our knowledge there are no previous reports for the synthesis of these classes of thiaazatricyclododecanes. The method features formation of various C−N, C−S, and C−C bonds, low-cost and readily available substrates, as well as simple one-pot operation, which makes this process highly profitable. This synthesis serves as a nice addition to chemistry in which purification *via* chromatography and recrystallization can be avoided, and the pure products were obtained simply by washing the crude products with hexane-ethyl acetate (10:1).

Keywords: isoquinoline, 2-bromoacetophenones, aryl isothiocyanates, methyl 4-chloro-3-oxobutanoate, thiaazatricyclododecane, multicomponent reaction

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1. Introduction

Bridged tricyclic *N*-heterocycles are interesting because they occur in many natural products. Several alkaloids like the C_{20}-diterpenoid alkaloid racemulsonine, calyciphylline A, and daphniglaucins D are known to possess an azatricyclic core as part of their structures.[1]

Most of these frameworks have interesting biological properties. For example, FR901483 isolated from the fermentation broth of Cladobotryum, is a new immunosuppressant containing a novel azatricyclododecane ring system.[2] Thiourea derivatives of 4-azatricyclo[5.2.2.$0^{2,6}$]undec-8-ene-3,5-dione inhibitors malarial aspartic protease plasmepsin II.[3] From the another point of view tricyclo[6.4.0.$0^{4,9}$]dodecane structure demonstrates a fascinating ring structure that features an 1,5-ethano-bridged cis decalin. Therefore, they have drawn some attention from both theoretical and synthetic points of view.[4] Despite the advances described above; there is a lack of convenient synthetic access to bridged tricyclic *N*-heterocycles. Kibayashi and co-workers developed a route to azatricyclic core skeleton based on vinylation at the bridgehead position of 2-azabicyclo[3.3.1]nonane *via* an anti-Bredt iminium ion using vinylaluminum reagents.[5] Coates synthesized bridgehead aza-tricyclic frameworks by starting from ent-beyeran-16-one.[6] Most of the reported methods suffer from disadvantageous like low yields, require longer reaction times, limited substrate scopes, expensive catalysts, and many tedious isolation steps.

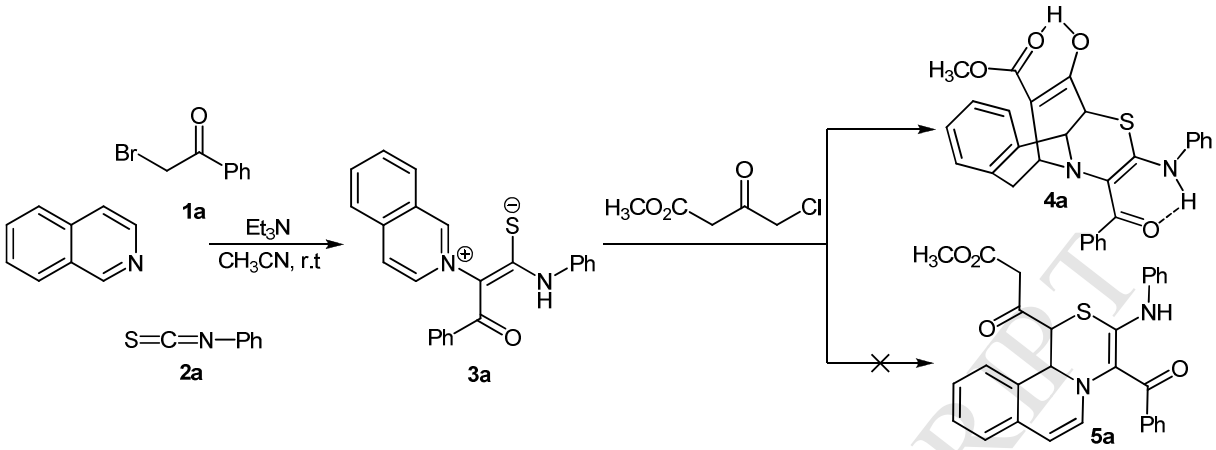
The construction of architecturally complex molecules by a short pathway from inexpensive and available starting materials is of much attention to organic chemists due to the benefits such as generation of multiple bonds in a single transformation, avoiding the isolation of intermediates, and saving in cost and time. So the methods which involve domino, tandem and cascade processes are more important.[7] Pyridinium, quinolinium, and isoquinolinium ylides have emerged as interesting synthetic intermediates in the construction of numerous nitrogen heterocycles, most of which include 1,3-cycloaddition reactions of ylides with electron-deficient

alkenes and alkynes.[8] [3+2] Annulation of isoquinolinium ylides with allenoates or enals yields pyrroloisoquinolines.[9] Ley et al. reported the sequential condensation of an isoquinolinium salt with isothiocyanates and isocyanides to yield the pyrrole structures.[10] Recently, we established a sequential four-component domino reaction of isoquinoline, 2-bromoacetophenones, aryl isothiocyanates, and dimethyl acetylenedicarboxylate for the formation of thiazepino[5,4-*a*]isoquinolines.[11]

2. Results and Discussion

In continuation of our interest in innovative one-pot reactions that offer easy access to some nitrogen tricyclic skeletons,[12] in this study, we developed a novel one-pot construction of bridged tricyclic *N*-heterocycle from readily available isoquinoline, 2-bromoacetophenones **1**, aryl isothiocyanates **2**, and methyl 4-chloro-3-oxobutanoate based on the factors that the sequential addition of isoquinoline to 2-bromoacetophenones **1** and aryl isothiocyanates **2** could generate in situ betaines, which may react with methyl 4-chloro-3-oxobutanoate.

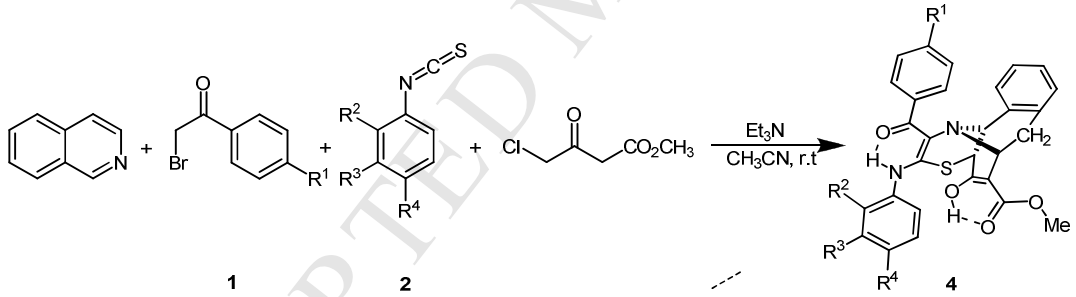
For this purpose, we investigated the reaction of isoquinoline, 2-bromoacetophenone **1a**, phenyl isothiocyanate **2a**, and methyl 4-chloro-3-oxobutanoate in CH_3CN at room temperature in the presence of Et_3N. Quite surprisingly, instead of the anticipated [1,4]thiazino[3,4-*a*]isoquinoline **5a** (Scheme 1), we observed an unexpected process leading to thiaazatricyclododecane **4a** (thiazinoisoquinoline having an ethano bridge) in excellent yields. Then we investigated the reaction of isoquinoline, 2-bromoacetophenone **1a**, phenyl isothiocyanate **2a**, and methyl 4-chloro-3-oxobutanoate in different solvents like CH_2Cl_2, $CHCl_3$, THF, CH_3CN, and DMF in the presence of Et_3N and K_2CO_3. The best result was obtained using Et_3N in CH_3CN.



Scheme 1. The reaction of betaine, resulted from isoquinoline, 2-bromoacetophenone **1a**, and phenyl isothiocyanate **2a**, and methyl 4-chloro-3-oxobutanoate

With the established optimal conditions, the scope of this sequential four-component reaction was examined by applying a variety of 2-bromoacetophenones **1** and aryl isothiocyanates **2** (Table 1).

Table 1: Scope of regio- and chemoselective synthesis of thiaazatricyclododecane 4a-k



Entry	R^1	R^2	R^3	R^4	Compound **4**	Yield (%)
1	H	H	H	H	**4a**	95
2	Br	H	H	H	**4b**	87
3	Cl	H	H	H	**4c**	66
4	OMe	H	H	H	**4d**	85
5	H	H	Br	H	**4e**	87
6	H	Cl	H	Cl	**4f**	53
7	H	H	H	F	**4g**	77
8	Br	H	Br	H	**4h**	76
9	Br	H	H	F	**4i**	75
10	Cl	H	Br	H	**4j**	82
11	Cl	Cl	H	Cl	**4k**	70

Applying pyridine instead of isoquinoline and phenyl isocyanate as a replacement for phenyl isothiocyanate produced the betain intermediate but unfortunately did not yield the final product.

The structures of the resultant products **4** have been confirmed by mass spectrometric analyses and by IR, ^{1}H NMR, and ^{13}C NMR spectral analysis. In addition, one of them (**4b**) has been unambiguously determined by X-ray diffraction analysis (Figure 1).

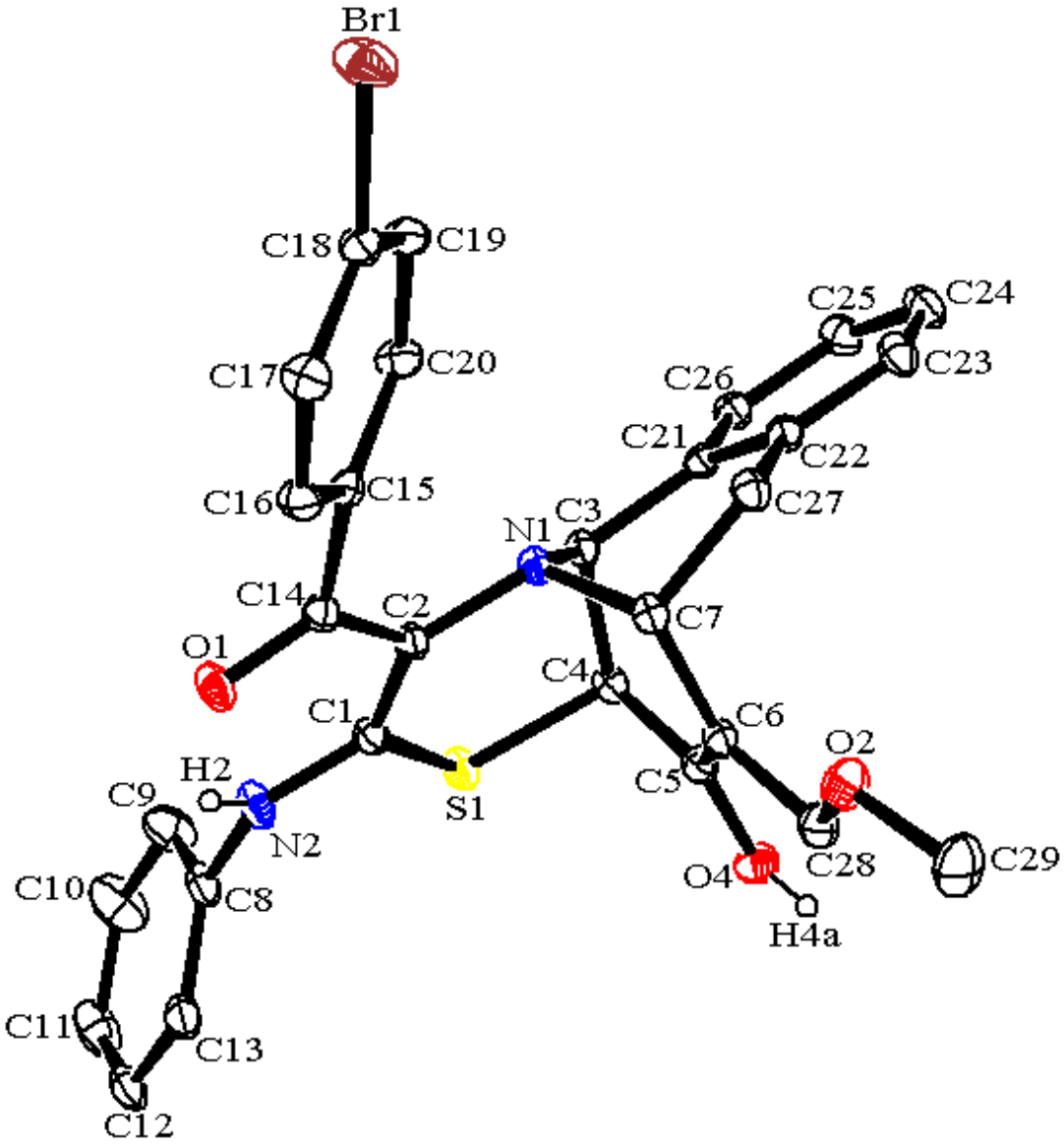


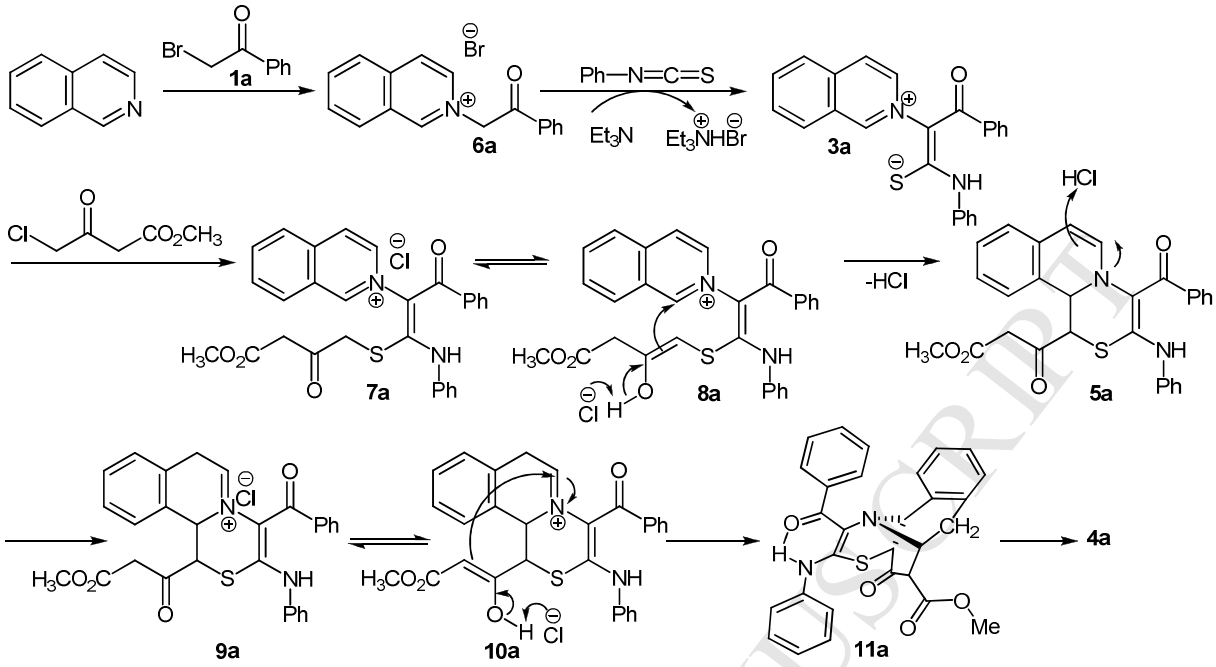
Figure 1. The Ortep Diagram of Compound **4b**

The mass spectrum of **4a** displayed the molecular ion peak at *m/z* = 496. In the IR spectrum of **4a** absorption bands at 3465 (NH and OH), 1653 (C=O), and 1620 (C=C) cm^{-1} are the most significant stretching frequencies. In ^{1}H NMR spectrum of **4a** a doublet and a doublet of doublet at δ = 2.34 and 2.49 ppm are ascribed to diastereotopic protons of CH_2 group. Three CH groups appeared at δ = 3.38, 4.03, and 4.52 ppm. A singlet signal at δ = 3.62 ppm is related to the methoxy group. The NH and OH were assigned at δ = 11.52 and 12.6 ppm, respectively. The fourteen aromatic hydrogen atoms gave rise to characteristic resonances in the aromatic region of the spectrum. Observation of 26 distinct signals in the ^{1}H- decoupled ^{13}C NMR spectrum of **4a** is in agreement with the proposed structure.

On the basis of our results, we propose the mechanism shown in Scheme 2 (exemplified for **4a**). The reaction of isoquinoline with 2-bromoacetophenone **1a** led to the isoquinolinium salt **6a**. Subsequent addition of phenyl isothiocyanate **2a** and triethylamine gave the corresponding betaine **3a**. Then nucleophilic addition of betaine **3a** to methyl 4-chloro-3-oxobutanoate happened to produce the *S*-alkylated intermediate **7a**. Then Enolic form of **7a** (**8a**) underwent an intramolecular cyclization to produce [1,4]thiazino[3,4-*a*]isoquinoline **5a** followed by transformation to iminium salt **9a**. Enolic form of **9a** (**10a**) was altered to **11a** through the second chemoselective intramolecular cyclization. Finally by keto-enol tautomerization the product **4a** is produced.[13-15]

3. Conclusion

In conclusion, we have synthesized thiaazatricyclododecanes through the reaction of methyl 4-chloro-3-oxobutanoate with betaine generated in situ from reaction of isoquinoline, 2-bromoacetophenones, and aryl isothiocyanates. The mild reaction conditions and formation of multiple bonds make this strategy highly viable.



Scheme 2. Mechanistic rationalization for the formation of **4a**

4. Experimental

Melting points measured on an Electrothermal 9100 apparatus. IR spectra were recorded as KBr pellets on a NICOLET FT-IR 100 spectrometer. ^{1}H NMR (400 and 300 MHz) and ^{13}C NMR (100 and 75 MHz) spectra were obtained using Bruker DRX-400 AVANCE and Bruker DRX-500 AVANCE spectrometers. All NMR spectra at room temperature were recorded in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: bs (broad singlet), s (singlet), d (doublet), t (triplet), td (triplet of doublets), dd (doublet of doublets), m (multiplet). Elemental analyses for C, H and N performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 or 70 eV. All chemicals were purchased from Merck or Aldrich and were used without further purification.

4.1. General procedure for the preparation of compounds 4a-k.

A solution of 2-bromoacetophenone **1** (1 mmol) and isoquinoline (1 mmol) in CH_3CN was magnetically stirred for 3 h and then aryl isothiocyanate **2** (1 mmol) was added followed by the drop wise addition of a solution of triethylamine (1.1 mmol) in CH_3CN at r.t over 10 min. The mixture was stirred for 20 min and subsequently methyl 4-chloro-3-oxobutanoate was added to the reaction mixture. After completion of reaction, the solvent was removed under reduced pressure, and the residue was washed with hexane-ethyl acetate (10:1) to afford the pure product **4a-k**.

4.1.1. Methyl 15-anilino-16-benzoyl-12-hydroxy-14-thia-1-azatetracyclo[8.6.0.0^{2,13}.0^{3,8}]hexadeca-3,5,7,11,15-pentaene-11-carboxylate (4a). Yellow powder, mp = 145-147 °C, 0.5 g, yield: 95%. IR (KBr) (ν_{max}, cm^{-1}): 3465 (OH and NH), 1653 (C=O), 1620 (CO_2Me), 1527 and 1442 (Ar), 1288, 1244 and 1192 (C-O). Anal. Calcd. for $C_{29}H_{24}N_2O_4S$ (496.58): C, 70.14; H, 4.87; N, 5.64%. Found: C, 70.10; H, 4.86; N, 5.48%. MS (EI, 70 eV): *m/z* (%) = 496 (11), 464 (13), 439 (60), 405 (4), 361 (9), 333 (5), 308 (8), 279 (7), 129 (48), 105 (100), 77 (94), 51 (16). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 2.34 (1H, d, $^2J_{HH}$ = 16.0 Hz, CH_2), 2.49 (1H, dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 4.8 Hz, CH_2), 3.38 (1H, s, CH^{13}), 3.62 (3H, s, OMe), 4.03 (1H, d, $^3J_{HH}$ = 5.2 Hz, CH^{10}), 4.52 (1H, s, CH^2), 6.96 (1H, d, $^3J_{HH}$ = 6.8 Hz, CH of Ar), 7.14-7.58 (11H, m, 11CH of Ph and Ar), 7.78 (2H, d, $^3J_{HH}$ = 7.2 Hz, $2CH_{ortho}$ of Ph), 11.52 (1H, s, NH), 12.6 (1H, s, OH). ^{13}C NMR (100.00 MHz, $CDCl_3$): δ_C 33.7 (CH_2), 40.6 (CH^{13}), 52.5 (OMe), 55.4 (CH^{10}), 56.4 (CH^2), 98.4 (C^{11}), 120.2 (C^{16}), 124.6 ($2CH_{ortho}$ of Ph), 126.5 (CH^6), 127.7 (CH^4), 127.8 ($2CH_{meta}$ of Ph), 128.2 (CH_{para} of Ph), 129.1 ($2CH_{meta}$ of Ph), 129.7 ($2CH_{ortho}$ of Ph), 130.5 (CH^7), 130.5 (CH_{para} of Ph), 132.7 (CH^5), 133.6 (C^3), 135.4 (C^8), 135.8 (C_{ipso}–CO), 138.6 (C_{ipso}-NH), 140.7 (C^{15}), 167.4 (C-OH), 170.7 (CO_2Me), 190.8 (C=O).

4.1.2. Methyl 15-anilino-16-(4-bromobenzoyl)-12-hydroxy-14-thia-1-azatetracyclo [8.6.0.0^{2,13}.0^{3,8}]hexadeca-3(8),4,6,11,15-pentaene-11-carboxylate (4b). Yellow powder, mp =

210-213 °C, 0.5 g, yield: 87%. IR (KBr) (ν_{max}, cm^{-1}): 3436 (OH and NH), 1739 (C=O), 1653 (CO_2Me), 1583, 1513 and 1444 (Ar), 1286, 1246 and 1196 (C-O). Anal. Calcd. for $C_{29}H_{23}BrN_2O_4S$ (575.47): C, 60.53; H, 4.03; N, 4.87%. Found: C, 60.48; H, 4.06; N, 4.84%. MS (EI, 70 eV): *m/z* (%) = 516 (3), 333 (2), 255 (6), 230 (8), 202 (3), 183 (73), 155 (45), 129 (100), 102 (29), 77 (91), 51 (42). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 2.40 (1H, d, $^2J_{HH}$ = 16.0 Hz, CH_2), 2.61 (1H, dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 4.8 Hz, CH_2), 3.54 (1H, s, CH^{13}), 3.72 (1H, d, $^3J_{HH}$ = 4.0 Hz, CH^{10}), 3.75 (3H, s, OMe), 4.49 (1H, s, CH^2),7.02 (1H, t, $^3J_{HH}$ = 4.8 Hz, CH of Ar), 7.22-7.42 (8H, m, 8CH of Ar and Ph), 7.50 (2H, d, $^3J_{HH}$ = 8.4 Hz, 2CH of Ar), 7.76 (2H, d, $^3J_{HH}$ = 8.4 Hz, 2CH of Ar), 11.86 (1H, s, NH), 13.06 (1H, s, OH). ^{13}C NMR (100.00 MHz, $CDCl_3$): δ_C 33.9 (CH_2), 40.1 (CH^{13}), 51.9 (OMe), 56.2 (CH^{10}), 56.3 (CH^2), 98.5 (C^{11}), 118.5 (C^{16}), 124.4 (C_{ipso}-Br), 125.6 ($2CH_{ortho}$of Ph), 126.3 (CH^6), 126.5 (CH^4), 126.6 (CH_{para} of Ph), 128.0 (CH^7), 129.1 ($2CH_{meta}$ of Ph), 129.8 (CH^5), 130.7 (2CH of Ar), 130.9 (2CH of Ar), 132.8 (C^3), 135.1 (C^8), 137.9 (C_{ipso}-CO), 139.3 (C_{ipso}–NH), 153.8 (C^{15}), 167.5 (C-OH), 171.3 (CO_2Me), 189.1(C=O). Crystal data for **3b** $C_{33}H_{33}BrN_2O_5S$ (CCDC 1425334): M_W = 649.57,monoclinic, P21/n,a = 12.170(5) Å, b = 10.609(5) Å, c = 23.592(5) Å, α = 90.00, β = 94.030(5), γ= 90.00, V = 3039(2) $Å^3$, Z = 4, Dc = 1.420 mg/m^3, F (000) = 1344, crystal dimension 0.48×0.42×0.38 mm radiation, Mo Kα (λ = 0.71073Å), $2.99 \leq 2\theta \leq 25.10$, intensity data were collected at 293(2) K with a Bruker APEX area-detector diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of $-14 \leq h \leq 14$, $-10 \leq k \leq 12$, $-28 \leq l \leq 22$; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 4062 observed reflections with R (into) = 0.0743 by a full-matrix least-squares technique converged to R = 0.0504 and Raw = 0.1192 [I>2sigma(I)].

4.1.3. Methyl 15-anilino-16-(4-chlorobenzoyl)-12-hydroxy-14-thia-1-azatetracyclo[8.6.0.0^{2,13}.0^{3,8}]hexadeca-3(8),4,6,11,15-pentaene-11-carboxylate (4c). Orange

powder, mp = 164-166 °C, 0.35 g, yield: 66%. IR (KBr) (ν_{max}, cm^{-1}): 3430 (OH and NH), 1657 (C=O), 1586 (CO_2Me), 1531 and 1443 (Ar), 1247, 1197 and 1127 (C-O). Anal. Calcd for $C_{29}H_{23}ClN_2O_4S$ (531.02): C, 65.59; H, 4.37; N, 5.28%. Found: C, 65.40; H, 4.26; N, 5.20%. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H 2.39 (1H, d, $^2J_{HH}$ = 15.9 Hz, CH_2), 2.61 (1H, dd, $^2J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 5.1 Hz, CH_2), 3.53 (1H, s, CH^{13}), 3.71 (1H, d, $^3J_{HH}$ = 4.2 Hz, CH^{10}), 3.74 (3H, s, OMe), 4.49 (1H, s, CH^2), 7.01 (1H, d, $^3J_{HH}$ = 4.5 Hz, CH of Ar), 7.23-7.42 (10H, m, 10CH of Ar and Ph), 7.82 (2H, d, $^3J_{HH}$ = 8.1 Hz, 2CH of Ar), 11.76 (1H, s, NH), 12.81 (1H, s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 33.9 (CH_2), 40.1 (CH^{13}), 51.9 (OMe), 56.2 (CH^{10}), 56.3 (CH^2), 98.5 (C^{11}), 111.5 (C^{16}), 125.6 ($2CH_{ortho}$ of Ph), 126.2 (CH^6), 126.5 (CH^4), 126.6 (CH_{para} of Ph), 127.7 (2CH of Ar), 128.0 (CH^5), 129.1 ($2CH_{meta}$ of Ph), 129.8 (CH^7), 130.7 (2CH of Ar), 132.8 (C^3), 135.1 (C^8), 135.9 (C_{ipso}–Cl), 137.9 (C_{ipso}–CO), 138.8 (C_{ipso}-NH), 153.7 (C^{15}), 167.5 (C-OH), 171.3 (CO_2Me), 187.6 (C=O).

4.1.4. Methyl 15-anilino-12-hydroxy-16-(4-methoxybenzoyl)-14-thia-1-azatetracyclo [8.6.0.0^{2,13}.0^{3,8}]hexadeca-3(8),4,6,11,15-pentaene-11-carboxylate (4d). Cream powder, mp = 167-170 °C, 0.45 g, yield: 85%. IR (KBr) (ν_{max}, cm^{-1}): 3430 (OH and NH), 1630 (C=O), 1604 (CO_2Me), 1538 and 1445 (Ar), 1248, 1170 and 1113 (C-O). Anal. Calcd. for $C_{30}H_{26}N_2O_5S$ (526.60): C, 68.43; H, 4.98; N, 5.32%. Found: C, 68.40; H, 4.96; N, 5.30%. MS (EI, 70 eV): *m/z* (%) = 523 (M^+, 2), 494 (2), 368 (2), 281 (4), 236 (6), 203 (5), 183 (13), 135 (100), 115 (4), 97 (18), 77 (53), 57 (38). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 2.31 (1H, d, $^2J_{HH}$ = 16.4 Hz, CH_2), 2.05 (1H, dd, $^2J_{HH}$ = 16.4 Hz, $^3J_{HH}$ = 5.2 Hz, CH_2), 3.45 (1H, s, CH^{13}), 3.64 (3H, s, OMe), 3.68 (1H, d, $^3J_{HH}$ = 4.0 Hz, CH^{10}), 3.77 (3H, s,OMe),4.42 (1H, s, CH^2), 6.78 (2H, d, $^3J_{HH}$ = 8.8 Hz, 2CH of Ar), 6.92 (1H, t, $^3J_{HH}$ = 4.8 Hz, CH of Ar), 7.12-7.31 (8H, m, 8CH of Ar and Ph), 7.84 (2H, d, $^3J_{HH}$ = 8.8 Hz, 2CH of Ar), 11.76 (1H, s, NH), 12.81 (1H, s, OH). ^{13}C NMR (100.00 MHz, $CDCl_3$): δ_C 33.9 (CH_2), 40.0 (CH^{13}), 51.8 (OMe), 55.3 (CH^{10}), 56.1 (OMe), 56.2 (CH^2), 98.7 (C^{11}), 112.7 (2CH of Ar), 119.1 (C^{16}), 125.3 ($2CH_{ortho}$ of Ph), 125.9 (CH^6), 126.2 (CH^4),

126.7 (CH_{para} of Ph), 127.9 (CH^{7}), 129.0 ($2CH_{meta}$of Ph), 129.8 (CH^{5}), 131.4 (2CH of Ar), 132.8 (C^{3}), 133.0 (C^{8}), 135.4 (C_{ipso}–CO), 138.4 (C_{ipso}–NH), 151.6 (C^{15}), 161.2 (C_{ipso}–OMe), 167.6 (C-OH), 171.4 (CO_2Me), 189.7 (C=O).

4.1.5. Methyl 16-benzoyl-15-(3-bromoanilino)-12-hydroxy-14-thia-1-azatetracyclo [8.6.0.0^{2,13}.0^{3,8}]hexadeca-3(8),4,6,11,15-pentaene-11-carboxylate (4e). Yellow powder, mp = 135-139 °C, 0.50 g, yield: 87%. IR (KBr) (ν_{max}, cm^{-1}): 3435 (OH and NH), 1657 (C=O), 1622 (CO_2Me), 1531 and 1441 (Ar), 1244, 1198 and 1069 (C-O). Anal. Calcd. for $C_{29}H_{23}BrN_2O_4S$ (574.47): C, 60.53; H, 4.03; N, 4.87%. Found: C, 60.31; H, 3.96; N, 4.80%. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H 2.34 (1H, d, $^2J_{HH}$ = 15.9 Hz, CH_2), 2.52 (1H, dd, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 4.9 Hz, CH_2), 3.58 (1H, s, CH^{13}), 3.73 (3H, s, OMe), 3.81 (1H, d, $^3J_{HH}$ = 4.5 Hz, CH^{10}), 4.49 (1H, s, CH^{2}), 6.98 (1H, d, $^3J_{HH}$ = 5.1 Hz, CH of Ar), 7.24-7.28 (6H, m, 6CH of Ar), 7.36 (2H, t, $^3J_{HH}$ = 7.2 Hz, $2CH_{meta}$ of Ph), 7.42 (1H, t, $^3J_{HH}$ = 7.2 Hz, CH_{para} of Ph), 7.53 (1H, s, CH of Ar), 7.83 (2H, d, $^3J_{HH}$ = 7.2 Hz, $2CH_{ortho}$ of Ph), 11.86 (1H, s, NH), 12.93 (1H, s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 33.7 (CH_2), 40.1 (CH^{13}), 51.9 (OMe), 56.1 (CH^{10}), 56.2 (CH^{2}), 98.6 (C^{11}), 119.7 (C^{16}), 122.5 (C_{ipso}-Br), 123.5 (CH of Ar), 126.2 (CH of Ar), 126.7 (CH^{6}), 127.5 ($2CH_{ortho}$ of Ph), 127.8 (CH^{4}), 127.9 (CH of Ar), 128.7 (CH of Ar), 129.1 ($2CH_{meta}$ of Ph), 129.7 (CH^{5}), 130.1 (CH_{para} of Ph), 130.3 (CH^{7}), 132.9 (C^{3}), 135.0 (C^{8}), 139.7 (C_{ipso}–CO), 140.1 (C_{ipso}–NH), 151.3 (C^{15}), 167.3 (C–OH), 171.3 (CO_2Me), 191.4 (C=O).

4.1.6. Methyl 16-benzoyl-15-(2,4-dichloroanilino)-12-hydroxy-14-thia-1-azatetracyclo[8.6.0.0^{2,13}.0^{3,8}]hexadeca-3(8),4,6,11,15-pentaene-11-carboxylate (4f). Yellow powder, mp = 165-167 °C, 0.30 g, yield: 53%. IR (KBr) (ν_{max}, cm^{-1}): 3438 (OH and NH), 1670 (C=O), 1642 (CO_2Me), 1529 and 1477 (Ar), 1251, 1174 and 1083 (C-O). Anal. Calcd. for $C_{29}H_{22}Cl_2N_2O_4S$ (565.47): C, 61.60; H, 3.92; N, 4.95%. Found: C, 61.31; H, 3.66; N, 4.70%. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H 2.36 (1H, d, $^2J_{HH}$ = 16.2 Hz, CH_2), 2.53 (1H, dd, $^2J_{HH}$ = 16.5 Hz, $^3J_{HH}$ = 4.9 Hz, CH_2), 3.61 (1H, s, CH^{13}), 3.74 (3H, s, OMe), 3.87 (1H, d, $^3J_{HH}$ = 5.1 Hz, CH^{10}),

4.48 (1H, s, CH^{2}), 6.98 (1H, d, $^{3}J_{HH}$ = 5.1 Hz, CH of Ar), 7.24-7.28 (4H, m, 4CH of Ar), 7.36 (2H, t, $^{3}J_{HH}$ = 7.2 Hz, $2CH_{meta}$ of Ph), 7.43 (1H, d, $^{3}J_{HH}$ = 7.5 Hz, CH of Ar), 7.45 (1H, s, CH of Ar), 7.52 (1H, d, $^{3}J_{HH}$ = 8.4 Hz, CH of Ar), 7.87 (2H, d, $^{3}J_{HH}$ = 8.4 Hz, $2CH_{ortho}$ of Ph), 11.88 (1H, s, NH), 12.58 (1H, s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 33.6 (CH_2), 40.2 (CH^{13}), 51.9 (OMe), 55.9 (CH^{10}), 56.1 (CH^{2}), 98.7 (C^{11}), 104.9 (C^{16}), 126.1 (CH^{6}), 126.3 (CH^{4}), 126.7 (CH of Ar), 127.1 (CH of Ar), 127.5 ($2CH_{meta}$ of Ph), 128.0 (CH of Ar), 129.4 ($2CH_{ortho}$ of Ph), 129.7 (CH^{5}),129.8 (C_{ipso}-Cl), 129.9 (CH^{7}), 130.5 (CH_{para} of Ph), 130.9 (C_{ipso}-Cl), 132.9 (C^{3}), 134.9 (C^{8}), 139.8 (C_{ipso}–CO), 144.5 (C_{ipso}–NH), 154.2 (C^{15}), 167.4 (C-OH), 176.8 (CO_2Me), 194.4 (C=O).

4.1.7. Methyl 16-benzoyl-15-(4-fluoroanilino)-12-hydroxy-14-thia-1-azatetracyclo[8.6.0.0^{2,13}.0^{3,8}]hexadeca-3(8),4,6,11,15-pentaene-11-carboxylate (4g). Yellow powder, mp = 166-169 °C, 0.4 g, yield: 77%. IR (KBr) (ν_{max}, cm^{-1}): 3438 (OH and NH), 1655 (C=O), 1620 (CO_2Me), 1516 and 1442 (Ar), 1289, 1236 and 1190 (C-O). Anal. Calcd. for $C_{29}H_{23}FN_2O_4S$ (514.57): C, 67.69; H, 4.51; N, 5.44%. Found: C, 67.58; H, 4.49; N, 5.42%. MS (EI, 70 eV): *m/z* (%) = 514 (9), 482 (9), 456 (62), 423 (3), 390 (3), 367 (12), 346 (6), 326 (12), 297 (9), 269 (6), 235 (10), 211 (6), 185 (6), 153 (11), 130 (60), 105 (100), 77 (99), 51 (21). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 2.31 (1H, d, $^{2}J_{HH}$ = 16.4 Hz, CH_2), 2.53 (1H, dd, $^{2}J_{HH}$ = 16.4 Hz, $^{3}J_{HH}$ = 4.8 Hz, CH_2), 3.54 (1H, s, CH^{13}), 3.73 (1H, d, $^{3}J_{HH}$ = 3.2 Hz, CH^{10}), 3.74 (3H, s, OMe), 4.48 (1H, s, CH^{2}), 6.98 (1H, t, $^{3}J_{HH}$ = 4.8 Hz, CH of Ar), 7.09 (2H, t, $^{3}J_{HH}$ = 8.8 Hz, 2CH of Ar), 7.23-7.43 (8H, m, 8CH of Ph and Ar), 7.84 (2H, d, $^{3}J_{HH}$ = 8.0 Hz, $2CH_{ortho}$ of Ph), 11.87 (1H, s, NH), 12.87 (1H, s, OH). ^{13}C NMR (100.00 MHz, $CDCl_3$): δ_C 33.8 (CH_2), 40.2 (CH^{13}), 51.9 (OMe), 56.2 (CH^{10}), 56.2 (CH^{2}), 98.6 (C^{11}), 115.9 (d, $^{2}J_{CF}$ = 22.5 Hz, 2CH of Ar), 118.6 (C^{16}), 126.2(CH^{6}), 126.6 (CH^{4}), 127.5 ($2CH_{meta}$ of Ph), 127.8 (d, $^{3}J_{CF}$ = 8.5 Hz, 2CH of Ar), 127.9 (CH^{7}), 129.0 ($2CH_{ortho}$ of Ph), 129.7 (CH^{5}), 129.9 (CH_{para} of Ph), 133.0 (C^{3}), 134.1 (C^{8}), 135.2

(C_{ipso}–CO), 140.4 (C_{ipso}–NH), 153.5 (C^{15}), 161.1 (d, $^{1}J_{CF}$ = 245.3 Hz, C_{ipso}–F), 167.5 (C-OH), 171.4 (CO_2Me), 190.9 (C=O).

4.1.8. Methyl 15-(3-bromoanilino)-16-(4-bromobenzoyl)-12-hydroxy-14-thia-1-azatetracyclo [8.6.0.0^{2,13}.0^{3,8}]hexadeca-3,5,7,11,15-pentaene-11-carboxylate (4h). Orange powder, mp = 197-199 °C, 0.50 g, yield: 76%. IR (KBr) (ν_{max}, cm^{-1}): 3427 (OH and NH), 1658 (C=O), 1622 (CO_2Me), 1578 and 1442 (Ar), 1241, 1194 and 1113 (C-O). Anal. Calcd. for $C_{29}H_{22}Br_2N_2O_4S$ (654.37): C, 53.23; H, 3.39; N, 4.28%. Found: C, 53.15; H, 3.26; N, 4.20%. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H 2.40 (1H, d, $^{2}J_{HH}$ = 16.2 Hz, CH_2), 2.60 (1H, dd, $^{2}J_{HH}$ = 16.2 Hz, $^{3}J_{HH}$ = 4.8 Hz, CH_2), 3.78 (1H, s, CH^{13}), 3.70 (1H, d, $^{3}J_{HH}$ = 4.0 Hz, CH^{10}), 3.74 (3H, s, OMe), 4.48 (1H, s, CH^{2}), 7.02 (1H, d, $^{3}J_{HH}$ = 5.1 Hz, CH of Ar), 7.24-7.38 (6H, m, 6CH of Ar), 7.50 (2H, d, $^{3}J_{HH}$ = 8.4 Hz, 2CH of Ar), 7.52 (1H, s, CH of Ar), 7.75 (2H, d, $^{3}J_{HH}$ = 8.4 Hz, 2CH of Ar), 11.85 (1H, s, NH), 12.98 (1H, s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 33.8 (CH_2), 40.1 (CH^{13}), 51.9 (OMe), 56.1 (CH^{10}), 56.3 (CH^{2}), 98.5 (C^{11}), 119.3 (C^{16}), 122.5 (C_{ipso}-Br), 123.7 (CH of Ar), 124.7 (C_{ipso}-Br), 126.3 (CH of Ar), 126.7 (CH^{6}), 128.0 (CH of Ar), 128.1 (CH^{4}), 129.0 (CH of Ar), 129.8 (CH^{5}), 130.3 (CH^{7}), 130.7 (2CH of Ar), 130.9 (2CH of Ar), 132.7 (C^{3}), 134.9 (C^{8}), 138.9 (C_{ipso}–CO), 139.5 (C_{ipso}–NH), 152.3 (C^{15}), 167.3 (C-OH), 171.3 (CO_2Me), 189.6 (C=O).

4.1.9. Methyl 16-(4-Bromobenzoyl)-15-(4-fluoroanilino)-12-hydroxy-14-thia-1-azatetracyclo [8.6.0.0^{2,13}.0^{3,8}]hexadeca-3,5,7,11,15-pentaene-11-carboxylate (4i). Yellow powder, mp = 184-188 °C, 0.45 g, yield: 75%. IR (KBr) (ν_{max}, cm^{-1}): 3422 (OH and NH), 1657 (C=O), 1619 (CO_2Me), 1512 and 1441 (Ar), 1232, 1190 and 1131 (C-O). Anal. Calcd. for $C_{29}H_{22}BrFN_2O_4S$ (593.46): C, 58.69; H, 3.74; N, 4.72%. Found: C, 58.60; H, 3.96; N, 4.65%. MS (EI, 70 eV): *m/z* (%) = 592 (26), 562 (28), 536 (19), 445 (5), 406 (3), 377 (9), 349 (5), 312 (9), 221 (19), 183 (100), 155 (56), 129 (85), 95 (32), 69 (27). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 2.40 (1H, d, $^{2}J_{HH}$ = 16.4 Hz, CH_2), 2.61 (1H, dd, $^{2}J_{HH}$ = 16.4 Hz, $^{3}J_{HH}$ = 5.2 Hz, CH_2), 3.53 (1H,

s, CH^{13}), 3.71 (1H, d, $^{3}J_{HH}$ = 4.0 Hz, CH^{10}), 3.75 (3H, s, OMe), 4.47 (1H, s, CH^{2}), 7.02 (1H, t, $^{3}J_{HH}$ = 4.8 Hz, CH of Ar), 7.09 (2H, t, $^{3}J_{HH}$ = 8.4 Hz, 2CH of Ar), 7.22-7.33 (5H, m, 5CH of Ph and Ar), 7.50 (2H, d, $^{3}J_{HH}$ = 8.4 Hz, 2CH of Ar), 7.76 (2H, d, $^{3}J_{HH}$ = 8.4 Hz, 2CH of Ar), 11.86 (1H, s, NH), 12.91 (1H, s, OH). ^{13}C NMR (100.00 MHz, $CDCl_3$): δ_C 33.9 (CH_2), 40.2 (CH^{13}), 51.9 (OMe), 56.2 (CH^{10}), 56.3 (CH^{2}), 98.5 (C^{11}), 116.0 (d, $^{2}J_{CF}$ = 21.5 Hz, 2CH of Ar) 118.4 (C^{16}), 124.4 (C_{ipso}-Br), 126.3 (CH^{6}), 126.6 (CH^{4}), 127.9 (CH^{7}), 128.0 (d, $^{3}J_{CF}$ = 8.8 Hz, 2CH of Ar), 129.9 (CH^{5}), 130.7 (2CH of Ar), 130.9 (2CH of Ar), 132.8 (C^{3}), 133.85 (C^{8}), 135.0 (C_{ipso}–CO), 139.2 (C_{ipso}-NH), 154.3 (C^{15}), 161.2 (d, $^{1}J_{CF}$ = 245.6 Hz, C_{ipso}–F), 167.4 (C-OH), 171.3 (CO_2Me), 189.2 (C=O).

4.1.10. Methyl 15-(3-bromoanilino)-16-(4-chlorobenzoyl)-12-hydroxy-14-thia-1-azatetracyclo [8.6.0.0^{2,13}.0^{3,8}]hexadeca-3,5,7,11,15-pentaene-11-carboxylate (4j). Orange powder, mp = 207-213 °C, 0.50 g, yield: 82%. IR (KBr) (ν_{max}, cm^{-1}): 3431 (OH and NH), 1659 (C=O), 1621 (CO_2Me), 1546 and 1438 (Ar), 1245, 1193 and 1087 (C-O). Anal. Calcd. for $C_{29}H_{22}BrClN_2O_4S$ (609.92): C, 57.11; H, 3.64; N, 4.59%. Found: C, 56.95; H, 3.26; N, 4.50%. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H 2.40 (1H, d, $^{2}J_{HH}$ = 16.2 Hz, CH_2), 2.60 (1H, dd, $^{2}J_{HH}$ = 16.2 Hz, $^{3}J_{HH}$ = 5.1 Hz, CH_2), 3.58 (1H, s, CH^{13}), 3.69 (1H, d, $^{3}J_{HH}$ = 4.8 Hz, CH^{10}), 3.74 (3H, s, OMe), 4.48 (1H, s, CH^{2}), 7.02 (1H, d, $^{3}J_{HH}$ = 4.2 Hz, CH of Ar), 7.24-7.28 (6H, m, 6CH of Ar), 7.34 (2H, d, $^{3}J_{HH}$ = 7.2 Hz, 2CH of Ar), 7.52 (1H, s, CH of Ar), 7.82 (2H, d, $^{3}J_{HH}$ = 7.2 Hz, 2CH of Ar), 11.85 (1H, s, NH), 12.97 (1H, s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 33.8 (CH_2), 40.0 (CH^{13}), 51.9 (OMe), 56.1 (CH^{10}), 56.3 (CH^{2}), 98.5 (C^{11}), 119.3 (C^{16}), 122.5 (C_{ipso}-Br), 123.7 (CH of Ar), 126.3 (CH of Ar), 126.7 (CH^{6}), 127.8 (2CHof Ar), 127.9 (CH^{4}), 128.0 (CH of Ar), 128.9 (CH of Ar), 129.8 (CH^{5}), 130.3 (CH^{7}), 130.7 (2CH of Ar), 132.7 (C^{3}), 135.0 (C^{8}), 136.2 (C_{ipso}–Cl), 138.5 (C_{ipso}–CO), 139.5 (C_{ipso}-NH), 152.2 (C^{15}), 167.3 (C-OH), 171.3 (CO_2Me), 189.5 (C=O).

4.1.11. Methyl 16-(4-chlorobenzoyl)-15-(2,4-dichloroanilino)-12-hydroxy-14-thia-1-azatetracyclo[8.6.0.0^{2,13}.0^{3,8}]hexadeca-3,5,7,11,15-pentaene-11-carboxylate (4k). Yellow powder, mp = 213-217 °C, 0.45 g, yield: 79%. IR (KBr) (ν_{max}, cm^{-1}): 3437 (OH and NH), 1670 (C=O), 1624 (CO_2Me), 1532 and 1477 (Ar), 1247, 1197 and 1084 (C-O). Anal. Calcd. for $C_{29}H_{21}Cl_3N_2O_4S$ (599.91): C, 58.06; H, 3.53; N, 4.67%. Found: C, 58.01; H, 3.46; N, 4.50%. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H 2.42 (1H, d, $^2J_{HH}$ = 16.2 Hz, CH_2), 2.62 (1H, dd, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 5.1 Hz, CH_2), 3.60 (1H, s, CH^{13}), 3.72 (1H, d, $^3J_{HH}$ = 4.5 Hz, CH^{10}), 3.75 (3H, s, OMe), 4.47 (1H, s, CH^2), 7.02 (1H, d, $^3J_{HH}$ = 5.1 Hz, CH of Ar), 7.25-7.28 (4H, m, 4CH of Ar), 7.34 (2H, d, $^3J_{HH}$ = 8.4 Hz, 2CH of Ar), 7.47 (1H, d, $^4J_{HH}$ = 1.8 Hz, CH of Ar), 7.51 (1H, d, $^3J_{HH}$ = 8.4 Hz, CH of Ar), 7.86 (2H, d, $^3J_{HH}$ = 8.4 Hz, 2CH of Ar), 11.87 (1H, s, NH), 12.98 (1H, s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 33.7 (CH_2), 40.1 (CH^{13}), 51.9 (OMe), 56.1 (CH^{10}), 56.2 (CH^2), 98.6 (C^{11}), 120.6 (C^{16}), 126.3 (CH^6), 126.4 (CH^4), 126.7 (CH of Ar), 127.2 (CH of Ar), 127.8 (2CH of Ar), 128.1 (CH of Ar), 129.78 (C_{ipso}-Cl), 129.8 (CH^5), 129.9 (CH^7), 130.9 (2CH of Ar), 131.2 (C_{ipso}-Cl), 132.7 (C^3), 134.6 (C^8), 134.7 (C_{ipso}–Cl), 136.5 (C_{ipso}–CO), 138.1 (C_{ipso}-NH), 150.5 (C^{15}), 167.1 (C-OH), 171.2 (CO_2Me), 189.9 (C=O).

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