An Efficient and Simple Route to Prospective Biologically Active Isoindoloquinazoline, Pyrimidine and Thiazine Derivatives Using 2-Amino-N'-Arylbenzamidine and Related Compounds as Starting Materials

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The reaction of (*Z*)-2-amino-N'-arylbenzamidines **1**, 2-amino-4,5,6,7-tetrahydrobenzo[*b*]-thiophene-3-carboxamide (**4**) and 4-amino-5-substituted-2-(phenylamino)thiophene-3-carboxamides **12** with *o*-phthalaldehyde (**2**), terephthalaldehyde (**9**), and 4-formyl[2.2]paracyclophane (**16**) in ethanol under reflux conditions afforded isoindoloquinazoline, thienopyrimidine, pyrimidine and thiazine derivatives, respectively. The products were characterized based on their spectroscopic data and elemental analysis.

Key words: Amidines, Aldehydes, Quinazolines, Thienopyrimidines, Thiazines

Introduction

Quinazolines are undoubtedly of interest as topics of study because they are heterocyclic systems with multiple reactive centers. Among them are found a series of highly effective compounds used in agriculture, such as fungicides, bactericides, defoliants, and plant growth stimulants [1 – 3]. Compounds of this class are also used as medicinal drugs with various pharmacological activities [4 – 6]. Very recently quinazoline derivatives have been obtained by the reaction of (*Z*)-2-amino-N'-arylbenzamidines with tetracyanoethylene (TCNE) [7], isatoic anhydride [8], 4-formyl[2.2]paracyclophane [9], *p*-tolualdehyde [10], 2,3-dichloro-1,4-naphthoquinone (DCHNQ) [11], 7,7,8,8-tetracyanoquinodimethane (TCNQ) [12], and 2-di-cyanomethyleneindane-1,3-dione (CNIND) [13].

Fused pyrimidines continue to attract considerable attention of researchers because of their great practical usefulness due to a very wide spectrum of their biological activities. Thienopyrimidines occupy a special position among these compounds. Along with some other pyrimidine systems containing an annelated five-membered heteroaromatic ring, thienopyrimidines are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites. Earlier, various aspects of the chemistry and biology of isomeric thienopyrimidines have been reviewed [14 – 17].

Results and Discussion

We have found that on warming amidines **1a**, **b** and the thiophenecarboxamide derivative **4** with *o*-phthalaldehyde (**2**) reactions proceed with the formation of isoindoloquinazoline derivatives **3** and the thienopyrimidinone derivative **5** (Scheme 1).

The structure of the products **3** was deduced from their spectral data and elemental analysis. The ^{1}H NMR spectrum of compound **3a** revealed, beside signals of the aromatic protons in their expected positions, a singlet at δ = 6.09 ppm for the methylene protons. This peak existed in the lower field due to the inductive effect of both the adjacent nitrogen atom and the aromatic unit. The IR spectrum revealed no absorption maxima for either NH or C=O groups, but the C=N absorption was observed at 1621 cm^{-1}. On the other hand, both the mass spectrum and the elemental analysis confirm the molecular formula of the product **3a** as $C_{21}H_{15}N_3$. The formation of compounds **3a** could be explained as shown in Scheme 2.

We suggest that the aniline amino group of the reactant **1** adds one of the formyl carbon atoms of the aldehyde **2** losing a molecule of water to give the azomethine **6**. The lone pair of electrons of the azomethine nitrogen of **6** attacks the carbon atom of the second formyl group to give the intermediate **7** which undergoes rearrangement through 1,3-hydride shift to give the cycloadduct **8** which is suitable for an attack by the

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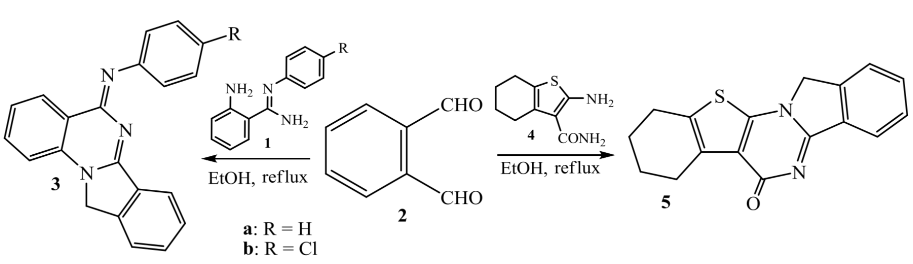


Scheme 1. Condensation of amidines **1a**, **b** and thiophenecarboxamide **4** with *o*-phthalaldehyde (**2**).

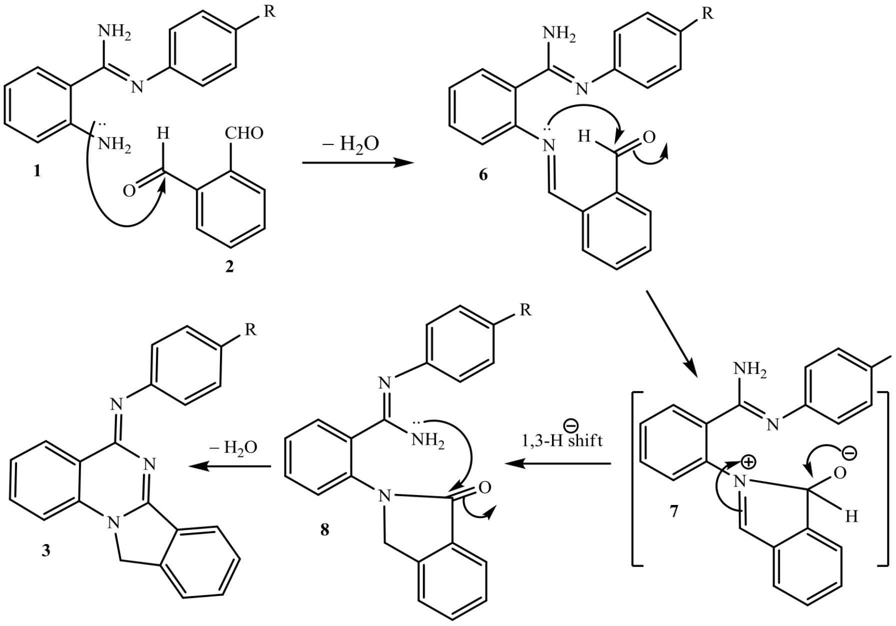
second amino group to form the end product **3** by losing a second molecule of water.

Mass spectrometry and elemental analysis confirm the molecular formula of the product **5** as $C_{17}H_{14}N_2OS$. However, the IR spectrum showed two absorption maxima at $\nu = 1632$ and 1600 as a result of (C=O) and (C=N) groups, respectively. The ^1H NMR spectrum of **5** revealed, beside the protons of both the aromatic and cyclohexyl groups which resonated as multiplets in their expected positions, a singlet at $\delta = 5.24$ ppm due to the N-CH_2-aryl protons.

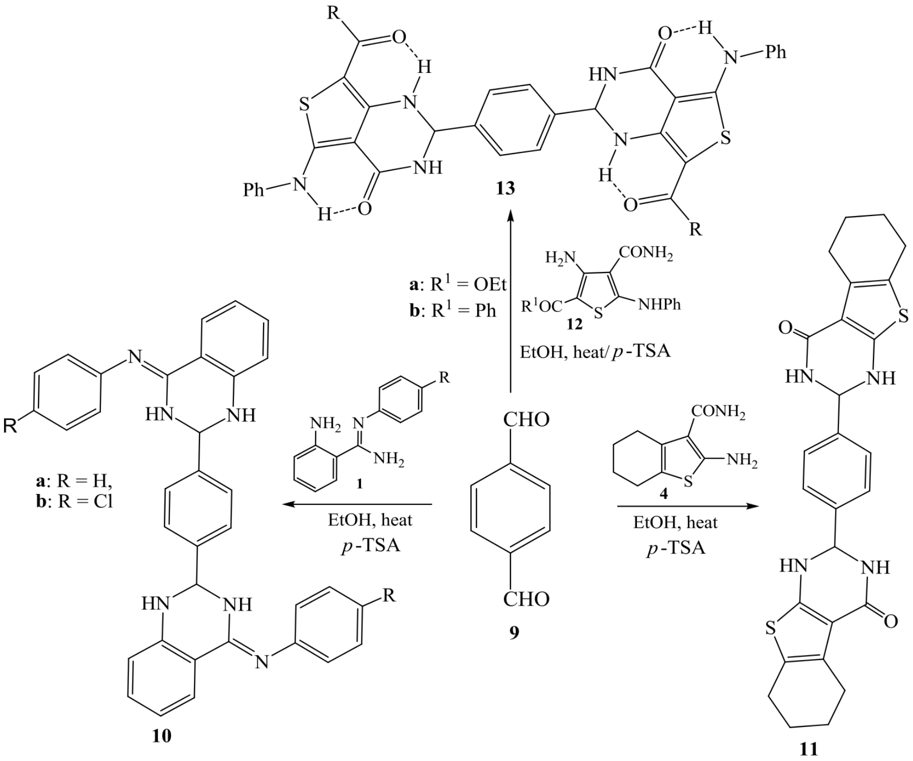
On the other hand, the reaction of amidines **1a**, **b** and terephthalaldehyde (**9**) in the molar ratio 2 : 1 in ethanol in presence of *p*-toluenesulfonic acid yielded quinazoline derivatives **10a**, **b** (Scheme 3).

The ^1H NMR spectrum of the product **10b** announced two exchangeable protons at $\delta = 7.93$ and 10.02 ppm related to the NH groups. The appearance of half the number of expected signals in the ^1H NMR data indicates that the product **10b** has a plane of symmetry. This was further confirmed by the appearance of half of the number of lines for the product carbon atoms in the ^{13}C NMR spectra. Mass spectrometry revealed the molecular ion peak of **10b** at $m/z = 588$.

Heating a mixture of thiophenecarboxamide derivative **4** and terephthalaldehyde (**9**) in molar ratio 2 : 1 in ethanol in the presence of a catalytic amount of *p*-toluenesulfonic acid for several hours under reflux conditions yielded the thienopyrimidinone derivative **11** (Scheme 3). The product was identified by its ^1H NMR spectrum where two singlets resonated at $\delta = 10.06$ and 8.59 ppm attributed to the two different NH groups. Furthermore, the presence of a singlet at $\delta = 7.41$ ppm for the pyrimidine C-2 protons strongly supports that idea. The IR spectrum showed two absorption bands at $\nu = 3390$ and 1629 cm^{-1} for NH and C=O groups, respectively. Both mass spectrum and elemental analysis confirm the molecular formula of the product **11** as $C_{26}H_{26}N_4O_2S_2$.



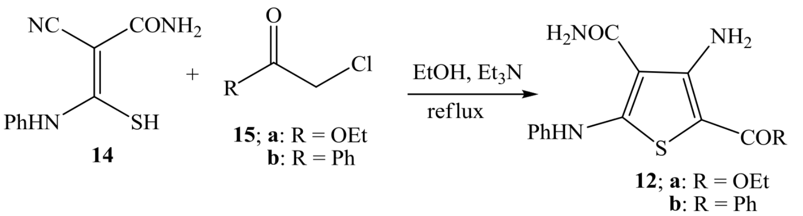
Scheme 2. A suggested mechanism for the formation of compounds **3**.



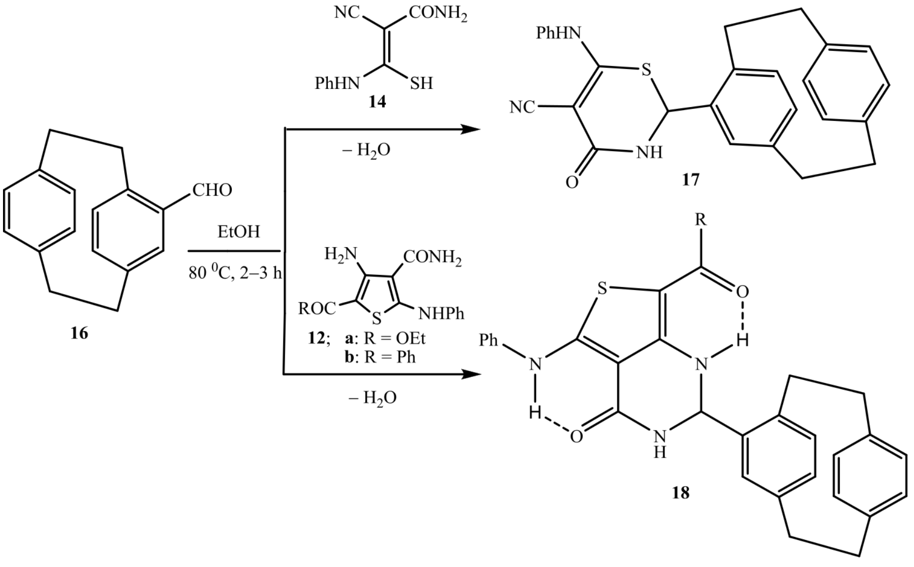
Scheme 3. Condensation of terephthalaldehyde (**9**) with aminoderivatives **1**, **4** and **12**.

The novel carboxamide reactants **12a, b** were obtained by heating a mixture of the acrylamide derivative **14** with either ethyl chloroacetate (**15a**) or ω-chloroacetophenone (**15b**) in the presence of triethylamine as a catalyst (Scheme 4). The compound **12a** as an example showed in its ^{1}H NMR spectrum the peaks of three exchangeable protons at δ = 10.12, 7.33 and 6.73 ppm for an -NH and two -NH_2 groups, respectively. Moreover, there are a quartet and a triplet at δ = 4.10 and 1.20 ppm, characteristic for both CH_2 and CH_3 groups of the -COOEt group, respectively.

The functional groups (NH, NH_2 and C=O) of the product **12a** absorbed in the IR spectrum at ν = 3373, 3329, 3197, and 1655 cm^{-1}, respectively. Mass spectrometry of compound **12a** revealed the molecular ion peak at m/z = 305. The products **12a, b** were used to complete our study dealing with the synthesis of novel heterocycles with prospective biological activity. We have found that on warming carboxamide derivatives **12a, b** with terephthalaldehyde (**9**) leads to the formation of the 2 : 1 adducts **13a, b** as shown in Scheme 3. The ^{1}H NMR spectrum of **13a** revealed, in addition to the peaks of the aromatic protons at their characteristic positions, three singlets at δ = 10.42, 8.57 and 7.65 ppm for three different NH groups. Their appearance at lower field may be the result of the presence of intramolecular hydrogen bonds. Furthermore, a triplet at δ = 5.83 ppm is related to pyrimidine C2 protons. The pyrimidine C2 protons appeared in the ^{1}H NMR spectrum as a triplet due to the splitting by the two adjacent NH groups. Moreover, the ester ethyl group resonated as a quartet and a triplet at δ = 4.15 and 1.21 ppm. The IR spectrum of this compound showed five characteristic bands at ν = 3387, 3273,



Scheme 4. Synthesis of thiophene-carboxamide derivatives **12**.



Scheme 5. Reaction of 4-formyl[2.2]paracyclophane (**16**) with **14** and **12a**, **b**.

3172, 3050, and 1646 cm^{-1} for NH and C=O groups, respectively. The molecular ion peak of the compound **13a** appeared in the mass spectrum at m/z = 708. However, we have found that the acrylamide derivative **14** and the thiophenecarboxamide derivatives **12a**, **b** react with 4-formyl[2.2]paracyclophane (**16**) under reflux conditions to give the thiazinone derivative **17** and the thienopyrimidinone derivatives **18a**, **b**, respectively (Scheme 5).

The ^{1}H NMR spectrum of the product **17** revealed, in addition to the signals of the aromatic protons, two singlets at δ = 10.01 and 8.59 ppm related to the two different NH groups, and a doublet at δ = 5.99 ppm characteristic for the thiazinone-C2 proton. The paracyclophane ethylene bridges appeared in the ^{1}H NMR as three multiplets at δ = 3.27 – 2.92 ppm. The NH groups absorbed in the IR spectrum at ν = 3211 and 3179 cm^{-1}, and the cyano and carbonyl groups at ν = 2196 and 1678 cm^{-1}, respectively. Both mass spectrometry and elemental analysis have confirmed the molecular formula of compound **17** as $C_{27}H_{23}N_3OS$.

The ^{1}H NMR spectrum of **18a** showed one singlet for an exchangeable proton at δ = 10.36 ppm related to the Ph-*NH* proton and two doublets at δ = 8.21 and 6.75 ppm for the two pyrimidine NH protons (two doublets due to coupling with the adjacent pyrimidine-C2 proton registered at δ = 5.97 ppm as a triplet). From the ^{1}H NMR spectrum we noticed that one of the pyrimidine NH groups resonated at a higher chemical shift value due to the presence of intramolecular hydrogen bonding as shown in Scheme 5. Furthermore, the ^{1}H NMR of **18a** revealed, in addition to signals for the ester-ethyl group, two multiplets at δ = 3.10 – 2.84 ppm for the protons of the paracyclophane ethylene bridges. The mass spectrum revealed a peak at m/z = 523 with intensity = 100 % representing the molecular ion peak.

Experimental Section

Melting points were measured in capillary tubes using a Büchi 530 melting point apparatus and are uncorrected. The infrared spectra were measured using a Bruker Tensor 27 instrument and a Jasco FT/IR-450 Plus infrared spectrophotometer. ^{1}H NMR (300 MHz) spectra were recorded in [D$_6$]DMSO on a Bruker AM 300 MHz spectrometer. Chemical shifts are quoted in δ and are referenced to TMS on measurements carried out in the Assiut Microanalysis Center at Assiut University and at the Microanalytical Center of Cairo University. Mass spectra were obtained with a Finnigan MAT 8430 instrument at 70 eV. Elemental analyses were performed on a Perkin-Elmer CHN-2400C analyzer model. Precoated silica gel plates (silica gel 0.25 mm, 60 GF$_{254}$; Merck) were used for thin layer chromatography.

Starting materials

All reagents were purchased from Alfa Aesar, Fluka and Aldrich companies and were used without further purification. (Z)-2-Amino-N'-arylbenzamidines **1a** and **1b** were prepared as reported in ref. [7].

*Reaction of 2-amino-N′-arylbenzimidamides **1a, b** with o-phthalaldehyde (**2**)*

Equimolar amounts of (*Z*)-2-amino-*N*′-arylbenzamidines **1a**, **b** and *o*-phthalaldehyde (**2**) were boiled in ethanol under reflux conditions for 4 – 6 h. After completion of the reaction (monitored by TLC), the resulting precipitate was filtered off and recrystallized from DMF/EtOH to yield **3a**, **b**.

*(Z)-N-(Isoindolo[2,1-a]quinazolin-5(11H)-ylidene)aniline (**3a**)* was obtained as a yellow solid; yield (176 mg, 57 %); m. p. = 284 – 285 °C. – IR (film): ν = 2928, 1621, 1551, 1474 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 6.09 (s, 2 H, N-CH$_2$), 7.14 – 7.24 (m, 6 H), 7.25 – 7.27 (m, 2 H), 7.32 (t, 2 H, *J* = 5.7 Hz), 7.48 (t, 1 H, *J* = 8.1 Hz), 8.06 – 8.16 (m, 2 H, Ar-H). – MS (EI, 70 eV): m/z (%) = 310 (28) [M+1]$^+$, 309 (100) [M]$^+$, 308 (89), 293 (13), 291 (14), 279 (18), 246 (13), 228 (14), 204 (19), 190 (16), 179 (19), 165 (16), 158 (14), 153 (20), 134 (12), 119 (17), 115 (19), 102 (29), 99 (14), 95 (16), 92 (24), 89 (31), 82 (20), 77 (78), 68 (20). – $C_{21}H_{15}N_3$ (309.36): calcd. C 81.53, H 4.89, N 13.58; found C 81.44, H 4.75, N 13.66.

*(Z)-4-Chloro-N-(isoindolo[2,1-a]quinazolin-5(11H)-ylidene)aniline (**3b**)* was obtained as a yellow solid; yield (189 mg, 55 %); m. p. = 273 – 275 °C. – IR (film): ν = 3068, 2922, 1604, 1549 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 6.09 (s, 2 H, N-CH$_2$), 7.14 – 7.24 (m, 5 H), 7.25 – 7.27 (m, 2 H), 7.32 (t, 2 H, *J* = 5.7 Hz), 7.48 (t, 1 H, *J* = 8.1 Hz), 8.06 – 8.16 (m, 2 H, Ar-H). – MS (EI, 70 eV): m/z (%) = 345 (20) [M+2]$^+$, 344 (12) [M+1]$^+$, 343 (38) [M]$^+$, 342 (43), 340 (25), 335 (30), 329 (34), 317 (25), 288 (30), 257 (29), 233 (33), 226 (28), 218 (25), 208 (32), 201 (37), 195 (41), 177 (47), 164 (28), 143 (38), 130 (10), 103 (20), 91 (29), 84 (36), 79 (47), 68 (38). – $C_{21}H_{14}ClN_3$ (343.81): calcd. C 73.36, H 4.10, Cl 10.31, N 12.22; found C 73.18, H 4.11, Cl 10.15, N 12.06.

*Reaction of 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**4**) with o-phthalaldehyde (**2**)*

2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**4**) and *o*-phthalaldehyde (**2**) in absolute ethanol were heated under reflux conditions for 2 h. A precipitate was formed and filtered off, washed with hot ethanol and recrystallized from DMF/EtOH to give *7,8,9,10-tetrahydrobenzo[4′,5′]thieno[3′,2′:5,6]pyrimido[2,1-a]isoindol-6(13H)-one (**5**)* as a violet solid; yield (159 mg, 54 %); m. p. > 304 °C. – IR (film): ν = 2927, 1632, 1600, 1443 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 1.03 (t, 2 H, CH$_2$), 1.78 (t, 2 H, CH$_2$), 2.67 – 2.94 (m, 4 H, 2 CH$_2$), 5.24 (s, 2 H, N-*CH$_2$*), 7.59 – 7.96 (m, 4 H, Ar-H). – MS (EI, 70 eV): m/z (%) = 295 (10) [M+1]$^+$, 294 (39) [M]$^+$, 293 (100), 291 (7), 278 (22), 266 (33), 252 (4), 237 (4), 216 (7), 186 (7), 179 (5), 160 (4), 133 (5), 115 (28), 99 (3), 82 (9), 73 (6), 69 (2). – $C_{17}H_{14}N_2OS$ (294.37): calcd. C 69.36, H 4.79, N 9.52, S 10.89; found C 69.23, H 4.73, N 9.37, S 10.71.

*Reaction of (Z)-2-amino-N′-phenylbenzimidamides (**1a, b**) with terephthalaldehyde (**9**)*

Equimolar amounts of **1a**, **b** and **9** were allowed to react in boiling ethanol in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) for 2 – 3 h. After completion of the reaction (monitored by TLC), the resulting precipitate was filtered off and recrystallized using a mixture of DMF/EtOH to give the products **10a**, **b**.

*N,N′-(2,2′-(1,4-Phenylene)bis(2,3-dihydroquinazoline-2(1H)-yl-4(1H)-ylidene))dianiline (**10a**)* was obtained as a yellow powder; yield (203 mg, 39 %); m. p. = 211 – 213 °C. – IR (film): ν = 3273, 3159, 1587 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 5.07 (s, 2 H, 2 CH), 6.91 – 7.47 (m, 5 H, Ar-H), 7.55 – 7.63 (m, 4 H, Ar-H), 7.64 – 7.67 (m, 5 H, Ar-H), 7.91 (s, 2 H, 2 NH), 7.69 – 7.93 (m, 5 H, Ar-H), 8.27 – 8.45 (m, 3 H, Ar-H), 10.04 (s, 2 H, 2 NH). – MS (EI, 70 eV): m/z (%) = 520 (64) [M]$^+$, 456 (7), 353 (17), 338 (20), 335 (6), 285 (15), 222 (21), 206 (5), 151 (4), 120 (9), 109 (8), 83 (11), 69 (18). – $C_{34}H_{28}N_6$ (520.63): calcd. C 78.44, H 5.42, N 16.14; found C 78.25, H 5.46, N 15.89.

*N,N′-(2,2′-(1,4-Phenylene)bis(2,3-dihydroquinazoline-2(1H)-yl-4(1H)-ylidene))bis(4-chloro-aniline) (**10b**)* was obtained as a pale-yellow solid; yield (295 mg, 61 %); m. p. > 300 °C. – IR (film): ν = 3224, 3052, 1563, 1506 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 5.02 (s, 2 H, CH), 7.55 – 7.63 (m, 4 H, Ar-H), 7.64 – 7.67 (m, 4 H, Ar-H), 7.93 (s, 2 H, 2 NH), 7.91 – 8.09 (m, 4 H, Ar-H), 8.37 – 8.58 (m, 8 H, Ar-H), 10.02 (s, 2 H, 2 NH). – MS (EI, 70 eV): m/z (%) = 592 (25) [M+4]$^+$, 590 (55) [M+2]$^+$, 588 (80) [M]$^+$, 583 (40), 297 (30), 296 (25), 293 (30), 291 (45), 201 (30), 192 (25), 137 (25), 118 (55), 102 (100), 85 (25), 76 (60). – $C_{34}H_{26}Cl_2N_6$ (589.53): calcd. C 69.27, H 4.45, N 14.26; found C 69.33, H 4.37, N 14.09.

*Reaction of 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**4**) with terephthalaldehyde (**9**)*

2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**4**) and **9** were heated in absolute ethanol for 3 – 4 h. A precipitate was formed. It was filtered off, washed with ethanol, dried and recrystallized from DMF/EtOH to give 2,2′*-(1,4-phenylene)bis(2,3,5,6,7,8-hexahydrobenzo[4,5]-thieno[2,3-d]pyrimidin-4(1H)-one) (**11**)*. This compound was obtained as an orange solid; yield (179 mg, 73 %); m. p. > 300 °C. – IR (film): ν = 3390, 2926, 2859, 1629, 1415 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 1.72 – 1.76 (m, 12 H), 2.51 – 2.70 (m, 4 H), 7.4 (s, 2 H, 2CH), 7.95 – 8.08 (m, 4 H, Ar-H), 8.59 (s, 2 H, 2

NH), 10.06 (s, 2 H, 2 NH). – MS (EI, 70 eV): m/z (%) = 490 (48) [M]$^+$, 489 (50), 468 (48), 427 (50), 383 (71), 359 (58), 342 (36), 306 (38), 294 (54), 253 (70), 244 (35), 238 (35), 226 (45), 214 (42), 193 (53), 189 (37), 171 (44), 152 (94), 149 (57), 136 (93), 100 (100), 91 (92), 80 (62), 77 (85). – $C_{26}H_{26}N_4O_2S_2$ (490.64): calcd. C 63.65, H 5.34, N 11.42, S 13.07; found C 63.49, H 5.31, N 11.28, S 12.92.

*Reaction of 2-cyano-3-mercapto-3-(phenylamino)acrylamide (**14**) with α-chloroketones **15a**, **b***

A mixture of (*Z*)-2-cyano-3-mercapto-3-(phenylamino)-acrylamide (**14**) (219 mg, 1 mmol) and 1.1 mmol of the α-chlorocarbonyl compound (ethyl chloroacetate or ω-chloroacetophenone) in the presence of five drops of triethylamine was refluxed in 20 mL ethanol for 2 h. The precipitate that was formed after cooling the reaction mixture was filtered off, dried, and recrystallized from ethanol to give **12a**, **b**.

*Ethyl 3-amino-4-carbamoyl-5-(phenylamino)thiophene-2-carboxylate (**12a**)* was obtained as colorless crystals; yield (253 mg, 80 %), m. p. = 202 – 203 °C. – IR (film): ν = 3373, 3329, 3197 (NH, NH$_2$), 1655 (CO), 1559 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 1.20 (t, 3 H, J = 6.9 Hz), 4.1 (q, 2 H, J = 7.2 Hz), 6.73 (s, 2 H, NH$_2$), 7.12 – 7.29 (m, 3 H, Ar-H), 7.33 (s, 2 H, NH$_2$), 7.35 – 7.40 (m, 2 H, Ar-H), 10.12 (s, 1 H, Ph-*NH*). – MS (EI, 70 eV): m/z (%) = 306 (11) [M+1]$^+$, 305 (51) [M]$^+$, 304 (22), 288 (24), 242 (100), 241 (41), 215 (26), 214 (34), 171 (11), 170 (14), 143 (36), 89 (18), 77 (24). – $C_{14}H_{15}N_3O_3S$ (305.08): calcd. C 55.07, H 4.95, N 13.76, S 10.50; found C 54.91, H 4.88, N 13.63, S 10.32.

*4-Amino-5-benzoyl-2-(phenylamino)thiophene-3-carboxamide (**12b**)* was obtained as orange crystals; yield (183 mg, 52 %); m. p. = 222 – 224 °C. – IR (film): ν = 3312, 3267, 3153, 1661, 1572 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 7.07 (t, 1 H, J = 6.80 Hz), 7.28 – 7.35 (m, 3 H, Ar-H), 7.40 – 7.44 (m, 4 H, Ar-H), 7.50 (s, 2 H, NH$_2$), 7.56 (d, 2 H, J = 7.59 Hz), 8.02 (s, 2 H, NH$_2$), 10.20 (s, 1 H, Ph-*NH*). – MS (EI, 70 eV): m/z (%) = 339 (4) [M+2]$^+$, 338 (16) [M+1]$^+$, 337 (57) [M]$^+$, 319 (100), 264 (3), 243 (4), 216 (3), 143 (12), 99 (16), 73 (34). – $C_{18}H_{15}N_3O_2S$ (337.09): calcd. C 64.08, H 4.48, N 12.45, S 9.50; found C 63.89, H 4.41, N 12.28, S 9.29.

*Reaction of **12a**, **b** with terephthalaldehyde (**9**)*

Refluxing of the thiophene-3-carboxamides **12a** or **12b** with **9** in the presence of a catalytic amount of *p*-TSA in boiling ethanol led to the formation of **13a** or **13b**.

*Diethyl 2,2′-(1,4-phenylene)bis(4-oxo-5-(phenylamino)-1,2,3,4-tetrahydrothieno[3,4-d]-pyrimidine-7-carboxylate) (**13a**)* was obtained as a colorless solid; yield (343 mg, 57 %); m. p. > 300 °C. – IR (film): ν = 3387, 3273, 3172, 3050, 1646, 1589 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 1.21 (t, 6 H, 2 CH$_3$, J = 7.2 Hz), 4.15 (q, 4 H, 2 CH$_2$, J = 5.7 Hz), 5.83 (t, 2 H, 2 pyrimidine C2, J = 3.9 Hz), 7.13 – 7.25 (m, 2 H, Ar-H), 7.29 (s, 4 H, Ar-H), 7.31 – 7.39 (m, 6 H, Ar-H), 7.40 – 7.44 (m, 2 H, Ar-H), 7.65 (s, 2 H, 2 NH), 8.57 (s, 2 H, 2 NH), 10.42 (s, 2 H, 2 Ph-*NH*). – MS (EI, 70 eV): m/z (%) = 708 (18) [M]$^+$, 354 (12), 333 (16), 331 (47), 330 (33), 305 (49), 288 (12), 259 (29), 242 (31), 214 (45), 200 (14), 189 (12), 171 (35), 148 (14), 130 (13), 119 (29), 104 (33), 94 (18), 93 (49), 91 (26), 77 (98). – $C_{36}H_{32}N_6O_6S_2$ (708.81): calcd. C 61.00, H 4.55, N 11.86, S 9.05; found C 60.87, H 4.53, N 11.73, S 8.92.

*2,2′-(1,4-Phenylene)bis(7-benzoyl-5-(phenylamino)-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-one) (**13b**)* was obtained as a pale-yellow solid; yield (356 mg, 54 %); m. p. > 300 °C. – IR (film): ν = 3274, 3181, 3048, 2907, 1649, 1581 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 6.01 (t, 2 H, 2 pyrimidine C2, J = 2.5 Hz), 7.15 (s, 4 H, Ar-H), 7.33 – 7.47 (m, 10 H, Ar-H), 7.49 – 7.52 (m, 2 H, Ar-H), 7.64 – 7.67 (m, 8 H, Ar-H), 8.63 (s, 2 H, 2 NH), 8.92 (s, 2 H, 2 NH), 10.50 (s, 2 H, 2 Ph-*NH*). – MS (EI, 70 eV): m/z (%) = 774 (17) [M+2]$^+$, 772 (24) [M]$^+$, 544 (8), 386 (10), 337 (32), 319 (100), 294 (20), 216 (9), 162 (12), 128 (11), 99 (22), 89 (6), 73 (40). – $C_{44}H_{32}N_6O_4S_2$(772.89): calcd. C 68.38, H 4.17, N 10.87, S 8.30; found C 68.21, H 4.11, N 10.67, S 8.12.

*Reaction of both acrylamide **14** and carboxamides **12a** and **12b** with 4-formyl[2.2]paracyclophane (**16**)*

General procedure

A mixture of either (*Z*)-2-cyano-3-mercapto-3-(phenylamino)acrylamide (**14**) or 4-amino-5-substituted-2-(phenylamino)thiophene-3-carboxamide **12a** or **12b** with 4-formyl-[2.2]paracyclophane (**17**) in dry EtOH (15 mL) was kept at 70 – 80 °C for 1 – 3 h. After completion of the reaction (monitored by TLC), the precipitate was collected by filtration, washed and recrystallized from DMF/EtOH to give the products **17** and **18a**, **b**.

*4-Oxo-2-paracyclophan-4-yl-6-(phenylamino)-3,4-dihydro-2H-1,3-thiazine-5-carbonitrile (**17**)* was obtained as a colorless solid; yield (191 mg, 87 %); m. p. = 189 – 192 °C. – IR (film): ν = 3211, 3179, 2196, 1678 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 2.78 – 2.92 (m, 2 H), 2.94 – 3.01 (m, 4 H), 3.11 – 3.27 (m, 2 H), 5.99 (d, 1 H, thiazine C2, J = 4.00 Hz), 6.42 – 6.61 (m, 5 H), 7.03 (d, 1 H, J = 8.40 Hz), 7.18 (t, 2 H, J = 7.40 Hz), 7.27 – 7.31 (m, 3 H, Ar-H), 7.42 (s, 1 H, Ar-H), 8.59 (d, 1 H, NH, J = 2.80 Hz), 10.01 (s, 1 H, Ph-*NH*). – MS (EI, 70 eV): m/z (%) = 437 (28) [M]$^+$, 410 (8), 352 (28), 333 (36), 329 (44), 272 (16), 238 (32), 207 (28), 186 (20), 139 (12), 131 (44), 121 (24), 99 (56), 84 (48), 73 (100), 69 (40), 65 (24). – $C_{27}H_{23}N_3OS$

(437.56): calcd. C 74.11, H 5.30, N 9.60, S 7.33; found C 73.92, H 5.21, N 9.47, S 7.17.

*Ethyl 2-(paracyclophan-4-yl)-4-oxo-5-(phenylamino)-1,2,3,4-tetrahydrothieno[3,4-d]pyrimidine-7-carboxylate (**18a**)* was obtained as a pale-yellow solid; yield (217 mg, 83 %); m. p. = 206 – 208 °C. – IR (film): ν = 3237, 3154, 1711, 1663, 1600, 1554 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 1.29 (t, 3 H, CH_3), 2.84 – 2.93 (m, 2 H), 2,96 – 3.10 (m, 6 H), 4.27 (q, 2 H, CH_2, J = 6.40 Hz), 5.97 (t, 1 H, CH, J = 10.80 Hz, pyrimidine C2), 6.41 – 6.57 (m, 4 H), 6.75 (d, 1 H, NH, J = 7.59 Hz), 7.14 (t, 2 H, J = 7.20 Hz), 7.25 – 7.54 (m, 6 H), 8.21 (d, 1 H, NH, J = 8.40 Hz), 10.36 (s, 1 H, Ph-*NH*). – MS (EI, 70 eV): m/z (%) = 525 (11) $[M+2]^+$, 523 (7) $[M]^+$, 509 (100), 466 (34), 425 (30), 412 (39), 365 (26), 311 (17), 273 (39), 238 (30), 207 (30), 195 (21), 170 (31), 142 (26), 114 (13), 104 (22), 99 (56), 84 (52), 73 (26). – $C_{31}H_{29}N_3O_3S$ (523.65): calcd. C 71.10, H 5.58, N 8.02, S 6.12; found C 70.87, H 5.53, N 7.89, S 5.97.

*7-Benzoyl-2-(paracyclophan-4-yl)-5-(phenylamino)-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-one (**18b**)* was obtained as a yellow solid; yield (205 mg, 74 %); m. p. = 246 – 247 °C. – IR (film): ν = 3291, 3187, 1680, 1604, 1577 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 2.84 – 2.93 (m, 2 H), 2.96 – 3.10 (m, 6 H), 6.18 (t, 1 H, pyrimidine C-2, J = 13.40 Hz), 6.49 – 6.57 (m, 6 H), 6.75 (d, 1 H, NH, J = 7.59 Hz), 7.14 (t, 2 H, J = 7.20 Hz), 7.25 – 7.58 (m, 7 H), 7.72 – 7.81 (m, 2 H), 8.30 (d, 1 H, CO*NH*, J = 7.20 Hz), 10.45 (s, 1 H, Ph-*NH*). – MS (EI, 70 eV): m/z (%) = 557 (5) $[M+2]^+$, 555 (7) $[M]^+$, 523 (4), 546 (58), 509 (9), 465 (4), 440 (50), 402 (13), 379 (5), 348 (15), 321 (51), 319 (100), 291 (14), 278 (10), 239 (17), 209 (8), 201 (12), 186 (46), 178 (22), 143 (17), 129 (31), 104 (4), 98 (77), 86 (60), 73 (77). – $C_{35}H_{29}N_3O_2S$ (555.69): calcd. C 75.65, H 5.26, N 7.56, S 5.77; found C 75.48, H 5.24, N 7.42, S 5.64.

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